SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description
Administrative information		
Title	1	**Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym** A Single-Center, Randomized Study to Evaluate the Effectiveness of the Systematic Identification of Genetic Health Testing (SIGHT) in Prompting Clinical Decision-Making for Genetic Testing in Pediatric Patients
Trial registration	2a	**Trial identifier and registry name. If not yet registered, name of intended registry** Clinicaltrials.gov – **NCT06744543**
	2b	**All items from the World Health Organization Trial Registration Data Set** See table 1.
Protocol version	3	**Date and version identifier** Issue Date: 12-9-2024 Protocol number 1 Authors: LDR, DMR Revision chronology: Amendment 2, version 3 9-9-2025 – Amended language around SIGHT probability vs scores, and secondary outcomes
Funding	4	**Sources and types of financial, material, and other support** This study is being conducted without any external financial funding. All resources, including manpower, materials, and operational costs, are being provided by Vanderbilt University Medical Center (VUMC). This includes the use of existing facilities, equipment, and staff time, which are being allocated as part of the regular functioning of VUMC. No specific funding or material support has been received from external commercial, governmental, or non-governmental organizations. The study relies on the participation of the research team and the use of existing infrastructure at the participating centers. This statement acknowledges the lack of external funding while highlighting the contributions made by the participating institutions in terms of existing resources and efforts.

Roles and responsibilities	5a	**Names, affiliations, and roles of protocol contributors**

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DMR conceived of the study. TM built and validated the predictive model. DMR initiated the study design and LR, LB, BS, aided with design and implementation. DMR and QC, provided statistical expertise in clinical trial design and is conducting the primary statistical analysis. All authors contributed to refinement of the study protocol.

	5b	**Name and contact information for the trial sponsor**

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5c **Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities**

This study had no external funding source. Funding played no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

5d **Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)**

Principal investigator
Design
Preparation of protocol and revisions
Preparation of provider documentation and educational materials
Managing CTO [clinical trials office]
Publication of study reports
(see above for members)
Agreement of final protocol
Audit of interim analysis for power calculation revisions
Reviewing progress of study and if necessary, agreeing changes to the protocol.
Trial manager - Lucas Day Richter, MGC CGC
Study planning
Organization of committee meetings
Responsible for trial master file
Audit of 1 year monthly feedback.
Assistance with internal review, board/independent ethics committee applications
Data verification
Randomization
Data collection
Data manager - Theodore Morley
Randomization
Allocation
Maintenance of trial IT system and data entry
Data verification

Introduction

Background and rationale	6a	**Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention**

Roughly 5% of the world's population is afflicted with rare diseases, the majority of which are genetic. Genetic testing represents a standard means to diagnose a patient with a genetic disease. However, current approaches that determine which patients receive a genetic test are inconsistent, inequitable and incomplete.

The first step in determining which patients might benefit from genetic testing is risk identification and prognostication. Researchers like our team have developed and validated predictive models that use routinely collected Electronic Health Record (EHR) data like past diagnoses to predict individuals at risk of having genetic disease. Our machine-learning model is known as the Systematic Identification of Genetic Health Testing (SIGHT). SIGHT has been validated internally and externally and shown to identify more patients needing a genetic test while maintaining or increasing the proportion having a putative genetic disease compared to the current nonsystematic approach (Morley et al, 2021).

6b **Explanation for choice of comparators**

The trial adopts a superiority framework to assess the effectiveness of SIGHT in improving clinical decision-making regarding genetic testing. Participants will be randomized into one of two arms: the standard care arm, which follows the traditional approach to genetic testing, and the SIGHT-guided intervention arm, which uses a data-driven strategy facilitated by SIGHT.

Healthcare providers of the patients in the SIGHT-guided intervention arm will receive alert messages, recommending consideration of genetic testing and referral to the genetics clinic. In contrast, providers of the patients in the standard care arm will not receive such alerts and will proceed with usual care practices. Patients with a score greater than equal to 0.30 and who have a scheduled visit at POD-C will be randomized in a 1:1 ratio to either the usual care or SIGHT-guided arm. Randomization will be stratified within the VUMC pediatric POD-C clinic. Patients will be excluded if they have already undergone Chromosomal Microarray testing at VUMC.

Objectives	7	**Specific objectives or hypotheses**

This study will evaluate the effectiveness of SIGHT as a clinical support system to prompt provider/patient discussion and shared decision making regarding the need for genetic testing in form of a chromosomal microarray. We seek to study if identifying patients with high SIGHT scores will decrease the duration of time to testing and increase diagnostic yield. SIGHT only relies on data already collected in routine clinical encounters and is calculated prior to a clinical visit at VUMC.

SIGHT does not replace clinical judgment in determining the necessity for genetic testing, but we seek to measure whether SIGHT increases the rates at which the important problem of elucidating the genetic etiology of disease is addressed. Our SIGHT-guided intervention group will be patients with high SIGHT scores where their provider receives a clinical communication recommending ordering of a genetic test and referral to the genetics clinic. Our comparison group will be patients with equivalently high SIGHT scores that receive usual care (i.e., do not receive a provider message). Patients will be from the POD-C pediatric primary care clinic at the Vanderbilt University Medical Center (VUMC) One Hundred Oaks location (OHO).

Trial design	8	**Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)** This study is a randomized, controlled trial with a parallel group design, focusing on the utilization of SIGHT in a pediatric clinical setting. The trial employs a superiority framework to evaluate the effectiveness of SIGHT in enhancing clinical decision-making regarding genetic testing. Randomization will be assigned in a 1:1 allocation ratio to either the intervention group, receiving a SIGHT-prompted provider message, or the control group, receiving usual care without the SIGHT-prompted message. The randomization process will be automated with SIGHT scores generated prior to regular scheduled patient visits at the POD-C pediatric primary care clinic at the Vanderbilt University Medical Center (VUMC) One Hundred Oaks location (OHO). This trial design allows for a robust comparison between the standard approach to genetic testing and an innovative, data-driven strategy facilitated by SIGHT. The primary objective is to assess whether the SIGHT model can effectively increase the number of patients who receive a genetic diagnosis, while potentially decreasing the time to genetic testing and increasing diagnostic yield in pediatric patients.

Methods: Participants, interventions, and outcomes

Study setting	9	**Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained** The study will take place in Nashville TN and consist of pediatric patients visiting the POD-C pediatric primary care clinic at the Vanderbilt University Medical Center (VUMC) One Hundred Oaks location (OHO as part of the usual course of care.

Eligibility criteria	10	**Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)**

Inclusion criteria will consist of patients > 1 year old, < 20 years of age with a visit to the POD-C pediatric primary care clinic at the Vanderbilt University Medical Center (VUMC) One Hundred Oaks location (OHO.

Exclusion criteria will consist of patients who have been programmatically excluded due to having already received a chromosomal microarray at VUMC, and patients > 20 years of age and < 1 year of age

All ordering providers (i.e. APRN's and physicians) in the POD-C pediatric primary care clinic at the Vanderbilt University Medical Center (VUMC) One Hundred Oaks location will be receive an intervention in form of a SIGHT prompted message from a genetic counsellor for each patient meeting criteria (see below). No direct patient interventions will be provided from the study team.

Interventions	11a	**Interventions for each group with sufficient detail to allow replication, including how and when they will be administered**

Eligible patients will be randomized to the intervention or comparator arm with the intervention arm having a SIGHT predicted score of 0.3 or greater. For patients randomized to the SIGHT- prompted provider message, the clinician responsible for care in that encounter (determined in the usual course of care) will receive a message showing the relevant diagnostic codes contributing to the high score.

Providers screening for or otherwise aware of SIGHT- predicted risk will have full discretion to offer genetic testing and/or refer to genetics providers. The management of screening will follow usual care at VUMC.

Patients will experience usual care until providers screen for the need of genetic testing which they might not otherwise do without the SIGHT-prompted provider message for those identified at highest risk.

11b **Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)**

This protocol presents minimal risks to participants, adverse events or other problems are not anticipated. Risks include discomfort among both providers and patients in discussing the sensitive but important topic of being at risk of genetic disease. The risk model is not perfect and might not identify patients who are at risk – it is not intended to pre-empt providers screening any patient for genetic disease if they choose to do so. The risk model might also identify those not at risk, leading to questions of genetic susceptibility being asked unnecessarily.

Providers may dismiss the SIGHT – prompted provider message and not act on its recommendations at any time. No other intervention is planned. Patients would be unaware of the providers' decisions in that case unless the provider chooses independently to discuss the SIGHT score with them.

11c **Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)**

Adherence meetings are held prior to study implementation with POD-C physicians. These providers will be more likely to provide constant care in the clinic over the duration of the study as opposed to those physicians who have interim appointments. The Directors of the POD-C clinic can also request an education session at any time or new provider training if needed. Additionally, training materials will be readily accessible via all SIGHT provider prompted messaging. Strategies to improve adherence for the pediatric patients flagged by the SIGHT model is not applicable as they will follow usual care at VUMC and will not be consented and enrolled by the study team.

11d **Relevant concomitant care and interventions that are permitted or prohibited during the trial**

Usual pediatric care and treatments that are unrelated to genetic testing are permitted and expected to continue as normal. Interventions and treatments necessary for the immediate health and well-being of the patient, regardless of their relation to genetic testing, are anticipated as part of usual care. Any intervention by the study team that could influence the healthcare provider's decision-making process regarding genetic testing, outside of the SIGHT model's recommendations will be avoided. Interventions specifically aimed at influencing the study outcomes, such as additional prompts or incentives for genetic testing are prohibited.

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

Primary Outcome:
Specific Measurement Variable: Number of patients diagnosed via a Chromosomal Microarray.
Analysis Metric: Chi-square test.
Method of Aggregation: Direct case control comparison of the raw count of patients diagnosed, presented as a percentage.
Time Point: Assessed after one year to include enough time for patients to undergo testing through usual care.

Secondary Outcomes:
Specific Measurement Variable: Duration of time to genetic testing.
Analysis Metric: Time to event, measured from the initial patient visit to the time genetic testing is conducted.
Method of Aggregation: Median time in days

Specific Measurement Variable: Rates of genetic testing.
Analysis Metric: Proportion of patients who received testing
Method of Aggregation: Proportion of patients, presented as a percentage
Time Point: Assessed after one year to include enough time for patients to undergo testing through the usual course of care.

Specific Measurement Variable: Diagnosis via any genetic testing.
Analysis Metric: Proportion of patients diagnosed with a genetic disease following molecular testing or clinical evaluation.
Method of Aggregation: Proportion of patients, presented as a percentage.
Time Point: Assessed after one year to include enough time for patients to undergo additional testing through usual care.

Specific Measurement Variable: Adherence to the SIGHT-prompted provider message.
Analysis Metric: Frequency of provider actions via referral to genetics and ordering a patient CMA following receipt of a SIGHT-prompted message.
Method of Aggregation: Proportion of instances where the provider follows the SIGHT recommendation.
Time Point: Information will be collected at the end of the study.

Participant timeline	13	**Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)**

1. **Enrollment Process:** Eligibility Screening: Conducted at the initial patient visit. Consent Process: Following eligibility screening, informed consent will not be obtained as patients are following usual care.
2. **Interventions:** SIGHT-Prompted Provider Message: Initiated following screening for patients who meet the predefined risk threshold.
3. **Assessments:** Baseline Assessment: Conducted during the initial visit, including collection of patient health data. Follow-up Assessments: Scheduled after initial visit to monitor the outcomes, such as number of patients receiving a diagnosis, time to genetic testing, and diagnostic yield.
4. **Visits:** Initial Visit: SIGHT prompted provider message followed by review of referrals and documentation attributable to the initial patient visit. Subsequent Visits: Regular follow-ups as per usual pediatric care, during which recommendations and any genetic testing decisions are documented and assessed.
5. **Study Close-Out:** Final Assessment: Conducted at the end of the study period to collect the final data on all outcomes.

Sample size	14	**Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations**

Previous data suggest that, under the usual course of care, 9% of high-risk patients (those with a predicted score of ≥ 0.3) had genetic testing. Of those, 9% received a genetic diagnosis, resulting in a genetic diagnosis rate of 0.81% (0.09 * 0.09) among high-risk patients

One thousand high-risk patients (score ≥0.3) will be randomized 1:1 (500 per arm). This sample size provides 80% power to detect an increase in the genetic diagnosis rate from 0.81% under standard care to at least 3.6% with the SIGHT intervention (chi-square test, α=0.05)

Recruitment	15	**Strategies for achieving adequate participant enrolment to reach target sample size**	
			The VUMC POD-C pediatric clinic has had over 200,000 patient encounters from over the last five years with more than 30,000 unique patients and over 10,000 unique patients in 2023. The clinic averages 144 visits per day (median = 165). Estimates indicate potentially 1-2 patients flagged per day which should readily provide enough patients for an adequate sample size over a two to three-year period.

Methods: Assignment of interventions (for controlled trials)

Allocation: Sequence generation	16a	**Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions**.

The SIGHT study will utilize a computer-generated assignment schedule for all patients seen in the POD-C pediatric clinic with a score greater than or equal to 0.3 for allocation into the intervention group. A computer-generated randomization schedule will be used for assigning participants to the control group. This is completed using the built-in random module of python, assigning patients with equal scores either 0 (control) or 1 (intervention) to each patient who has met all previously defined criteria, with assignments saved to a log file.

The allocation will be done with a 1:1 ratio. This randomization process is designed to ensure that patients surpassing a previously defined threshold for predicted risk of needing genetic testing are randomly selected for the intervention group. A SIGHT-prompted provider message will be generated for patients in the intervention group, while patients in the control group will receive usual care without this prompted message.

Patients who exceed a predefined risk threshold and are scheduled for their first visit within a year will be eligible for randomization to the intervention group. An estimated 500 patients will be randomly selected to receive a SIGHT-prompted provider message as part of the intervention.

The comparator arm will consist of the random eligible patients who do not receive the intervention. These patients will not be a typical control group to avoid ethical concerns related to withholding potentially important care but will follow usual care and may still get genetic testing.

To maintain the integrity of the randomization process, the study will employ random allocation to intervention and comparator arms with the expectation of a 1:1 ratio over time.

This method of randomization aligns with ethical standards and the goal of the study to evaluate the effectiveness of the SIGHT intervention while ensuring that all patients receive the usual care appropriate to their clinical needs.

Allocation concealment mechanism	16b	**Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned.** The allocation sequence will be implemented using a secure, computerized system to ensure allocation concealment. This system will generate the allocation sequence and assign patients who surpass the predefined risk threshold to either the intervention or the comparator group. The allocation system will maintain concealment by ensuring that randomization is not processed until a patient has been identified as eligible. This process occurs after the patient's eligibility is confirmed but before any intervention is assigned, to prevent selection bias and to maintain the integrity of the randomization process.

Implementation 16c **Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions**

Allocation Sequence Generation
The allocation sequence will be generated by the study's data management team using a computer-based randomization function. Any pediatric patient scheduled for a visit in the POD-C pediatric primary care clinic at VUMC One Hundred Oaks (OHO) who meets or exceeds the predefined risk threshold will be flagged as eligible. These flagged patients will then be randomly assigned to either the intervention arm (SIGHT-prompted provider message) or the usual care arm (no provider message).

Participant Enrollment
Patients aged 1 to 20 years who have not previously undergone chromosomal microarray testing at VUMC will be automatically included in the randomization pool once they have a scheduled visit at the OHO clinic. As this study follows standard clinical care, patients themselves do not undergo a separate consent process for randomization. Instead, their providers will be informed of any SIGHT alerts only if the patient is randomized to receive them.

Assignment of Participants to Interventions
For those randomized to the intervention arm, a SIGHT-prompted provider message is generated within EPIC by a genetic counselor on the research team. This message indicates the patient's increased risk level and recommends considering a chromosomal microarray and referral to genetics. The provider maintains full discretion to act upon or dismiss this recommendation. By contrast, providers in the usual care arm receive no automated messages about SIGHT risk, and patients continue under routine care practices.

Concealment of Allocation
The randomization process is integrated into the workflow so that neither providers nor the study team can predict a patient's assignment prior to the system's automated allocation. This design ensures there is no foreknowledge of group assignment—preventing selection bias and preserving the trial's integrity.

Blinding (masking)	17a	**Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how** There will be no blinding of participants or physicians as patients and providers will follow usual care. Providers may dismiss the SIGHT – prompted provider message and not act on its recommendations at any time. No other intervention is planned. Patients would be unaware of the providers' decisions in that case unless the provider chooses independently to discuss the SIGHT score with them. A sample size re-estimation will be conducted after 250 patients have been randomized to account for uncertainty, and adherence rates for the initial test-referral rate used in the sample size calculation. An independent analyst, who will be blinded to the randomization assignment, will calculate the observed test-referral rate across all patients. This analysis will focus on updating the test-referral rate parameter to ensure the study is adequately powered. The updated test-referral rate will be used to reassess and, if necessary, adjust the total sample size to maintain the study's power at 80%. This process will ensure the trial remains robust and capable of detecting meaningful differences between the usual care and SIGHT-guided intervention arms.
	17b	**If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial** NA

Methods: Data collection, management, and analysis

Data collection methods	18a	**Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol** The trial will utilize the SIGHT predictive model to generate a score for all POD-C patients. Data collection will include baseline and outcome data assessed via EHR data queries for internal genetic test orders in form of a CMA, referrals to pediatric genetics, and attributable dates. All queried metrics and additional metrics related to genetic testing results will be assessed and verified through chart review performed by a clinician (genetic counselor or geneticist) for the intervention and comparator arm for patients seen in the POD-C clinic. The validity and reliability of the SIGHT predictive model, as well as the data collection methods, have been ensured through pilot testing and chart review prior to study implementation. All data collected and related documentation will be available in the trial master file with data availability based upon institutional policy.
	18b	**Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols** There will be no plan to promote participant retention and complete follow-up as patients are following usual care and may or may not undergo genetic testing as per the choice of the patient and family.
Data management	19	**Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol** Data will be extracted EPIC's Clarity and then stored on VUMC's ACCRE cluster, which is designed for secure handling of export-controlled data, PHI, and human genotype and phenotype data. EPIC's Clarity and the ACCRE cluster feature rigorous backup protocols ensuring data integrity and recovery. Details of data management procedures, including security protocols, access controls, and data backup schedules, are detailed at https://www.vanderbilt.edu/accre/overview/.

Statistical methods

20a **Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol**

The primary and secondary outcomes of this trial will be analyzed using appropriate statistical tests to compare the intervention arm (SIGHT-prompted provider message) against the control (patients receiving usual care provided through the POD-C pediatric primary care clinic at the Vanderbilt University Medical Center (VUMC) One Hundred Oaks location (OHO). The primary outcome measure will be the difference in number of patients who receive diagnoses via a Chromosomal Microarray between the two groups.

The statistical analysis will utilize a chi-square test for binary outcomes such as the presence or absence of a genetic diagnosis as identified by the test or provider adherence to SIGHT message recommendations. For continuous secondary outcomes, such as the time to genetic testing, a T-test or Mann-Whitney U test will be used depending on data distribution. Subgroup analyses will involve regression methods to assess the differential effects of the intervention across subgroups defined by baseline demographic characteristics (e.g. age, sex, race). Multivariate analyses will be conducted using logistic regression for binary outcomes and linear or Cox proportional hazards regression for continuous or time-to-event outcomes, respectively. Model assumptions will be checked through the assessment of residuals and model fit will be evaluated accordingly.

When indicated, a two-sided p-value of less than 0.05 will be considered statistically significant. The Bonferroni correction will be applied to account for multiple comparisons when analyzing multiple outcomes. R will be used to perform all analyses. The analysis plan will follow the intention-to-treat principle, with all randomized participants included in the analysis according to the group to which they were allocated.

Variable/outcome	Hypothesis	Outcome measure	Methods of analysis
Primary			R will be used to perform all analysis.
Number of diagnoses via CMA	More patients are diagnosed being flagged by SIGHT via a Chromosomal Microarray	Number of patients flagged by SIGHT who receive a diagnosis via CMA over one year vs controls [binary]	Chi-square test
Secondary			
a. Time to genetic test	Patients in the intervention arm will receive genetic testing faster than those in the control arm.	Duration in days for which patients flagged by SIGHT receive a genetic test vs control [continuous]	Cox proportional Hazards to compare the time to event (in this case genetic testing) between two groups while controlling for covariates.
b. Rates of genetic testing	Increased rates of genetic testing in the intervention arm	Rates of genetic testing ordered by providers between cases and controls over a one-year period after POD-C visit [continuous'	Binary logistic regression to calculate the odds ratio for the likelihood of receiving a genetic test in the intervention arm compared to the controls
c. Diagnosis via any test (molecular confirmation)	More patients will receive a diagnosis from molecular confirmation outside of firs tier testing via a CMA.	Number of patients flagged by SIGHT who receive a diagnosis via any test over one year vs controls [binary]	Chi-square test
d. Adherence to Intervention	Providers who Receive SIGHT prompts demonstrate higher adherence recommendations compared to controls	Proportion of eligible patients where providers ordered a CMA and place genetics referrals after receiving a prompt [binary]	Chi-square test; logistic regression adjusting for covariates

	20b	**Methods for any additional analyses (eg, subgroup and adjusted analyses)** Subgroup analysis within demographic groups (sex, race, age) will be performed as described in the primary analysis but within each group or stratified by age.
	20c	**Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)** Non-adherence and missing data for the SIGHT protocol are non-applicable in this context as patients will follow usual care. Patients who are lost to follow up or have no follow up care during the duration of the study will remain included in the analysis.
Methods: Monitoring		
Data monitoring	21a	**Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed.** This study does not require a DMC as the protocol presents minimal risks to participants and adverse events or other problems are not anticipated. In the unlikely event that such events occur, unanticipated problems involving risks to subjects or others will be reported immediately to the PI and and within 7 days of the PI's notification of the event to the IRB.
	21b	**Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial** As stated in item 21a the SIGHT study will not have a DCM but rather report all outcomes to the IRB. Given that the study maintains low risk for patient harm, stoppage of the study is not anticipated but in the event of unforeseen circumstances the PI has full authority to end the study. An interim analysis for sample size re-estimation will be conducted after approximately 250 patients have been enrolled to refine the test-referral rate and ensure the study is adequately powered. An independent analyst, blinded to arm assignment, will perform this recalculation. This is not an efficacy or early-stopping analysis but a parameter update.
Harms	22	**Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct**

This protocol presents minimal risks to participants and adverse events, or other problems are not anticipated. Risks include discomfort among both providers and patients in discussing the sensitive but important topic of being at risk of genetic disease. The risk model is not perfect and might not identify risk in those who are at risk – it is not intended to pre-empt providers screening any patient (or all patients) for genetic disease if they choose to do so. The risk model might also identify risk in those not at risk, leading to questions of genetic susceptibility being asked unnecessarily.

Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

The study coordinator, with PI oversight, is responsible for ensuring protocol compliance, data integrity, and participant safety. This protocol presents minimal risks to participants and adverse events, or other problems are not anticipated. In the unlikely event that such events occur, unanticipated problems involving risks to subjects or others will be reported immediately to the PI, and in writing within 7 days to the IRB. The PI will apprise fellow investigators and study personnel of all adverse events that occur during the conduct of this research project through regular study meetings. Annual reports will be submitted to the IRB summarizing study progress, adverse events, complaints about the research, and any protocol violations.

Auditing	23	**Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor** Given the SIGHT study's design, including data management and monitoring processes, small scale and low risk to patients, independent auditing is not required or necessary.

Ethics and dissemination

Research ethics approval	24	**Plans for seeking research ethics committee/institutional review board (REC/IRB) approval** This protocol, including all materials such as provider educational materials, clinical letter of support, and methodology, will undergo thorough review and approval by VUMC institutional review boards/ethical committees (IRBs/ECs) for adherence to scientific standards and compliance with research and human subject regulations. All materials related to the SIGHT study will be subjected to ethical review. Any modifications to these documents will also require re-approval. Following initial approval, the local IRBs/ECs will conduct an annual review of the protocol. The principal investigator is responsible for submitting annual safety and progress reports to the IRBs/ECs and within three months of study termination or completion at their site.
Protocol amendments	25	**Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)** Modifications to the SIGHT study protocol that impact study conduct, patient safety, or potential benefits, including changes in study objectives, design, patient population, or significant administrative aspects, will require a formal amendment. These amendments will be agreed upon by the PI and study team and approved by the Ethics Committee/IRB prior to implementation. Such amendments will also be notified to health authorities in accordance with local regulations. For administrative changes that are minor and do not affect the study conduct, these will be documented in a memorandum. The Ethics Committee/IRB may be notified of these changes at the discretion of the study team.
Consent or assent	26a	**Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)** Patients are following usual care and do not require specific informed consent for participation. Providers will be responsible for deciding whether to act on SIGHT recommendations.
	26b	**Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable** NA

Confidentiality	27	**How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial**

We will deploy the model via Vanderbilt's ACCRE cluster to HealthIT's secure, PHI-approved managed platform Clarity This will allow us to configure a nightly job that will process the billing codes stored in the Clarity data warehouse to identify patients that are eligible for the order and referral.

In the SIGHT study, the confidentiality of personal information for all participants is paramount. Therefore, the following measures will be implemented:

1. **Documentation:** No documents with personal identifiers will be obtained.
2. **Coded Identification:** All study-related records will be identified only by a unique coded ID number to ensure participant anonymity.
3. **Password-Protected Databases:** Digital databases containing participant data will be password-protected and accessible only to authorized personnel.
4. **Staff Confidentiality Agreements:** All study staff will be required to undergo HIPPA training for compliance and sign agreements to uphold the privacy of participants.
5. **Controlled Information Release:** Participant information will not be released outside the study except as required for monitoring by regulatory authorities or as mandated by law.
6. **Data Transmission Security:** When transmitting data (i.e. SIGHT prompted messages) from genetic counselor to physicians, secure methods such as virtual private networks (VPN) and electronic health record communication via EPIC will be utilized to preserve data confidentiality. All other data will be stored via ACCRE as mentioned above.

Declaration of interests	28	**Financial and other competing interests for principal investigators for the overall trial and each study site**

Dr. Ruderfer has served on advisory boards for Illumina and Alkermes and has received research funds unrelated to this work from PTC Therapeutics. There is no external funding source for this trial.

Access to data	29	**Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators** Summary level data regarding genetic testing prompted by SIGHT will be available via supplementary materials. All requests for raw (for example temporal data regarding genetic testing for cases and controls) are reviewed by Vanderbilt University Medical Center to determine whether the request is subject to any intellectual property or confidentiality obligations. For example, patient-related data not included in the paper may be subject to patient confidentiality. Any such data and materials that can be shared will be released via a material transfer agreement.
Ancillary and post-trial care	30	**Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation** This protocol presents minimal risks to participants and adverse events, or other problems are not anticipated. Provisions for trial care will not be necessary as patients are following usual care at VUMC and will not be directly enrolled in the study.
Dissemination policy	31a	**Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions** The PI will submit the results of the study for publication even in the absence of statistically significant results.
	31b	**Authorship eligibility guidelines and any intended use of professional writers** All SIGHT study team personnel will be listed as authors with appropriate contributions. No professional writers will be used for publication.
	31c	**Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code** Summary level data regarding genetic testing prompted by SIGHT will be available via supplementary materials. All requests for raw (for example temporal data regarding genetic testing for cases and controls) are reviewed by Vanderbilt University Medical Center to determine whether the request is subject to any intellectual property or confidentiality obligations. For example, patient-related data not included in the paper may be subject to patient confidentiality. Any such data and materials that can be shared will be released via a material transfer agreement.

Appendices

Informed consent materials	32	**Model consent form and other related documentation given to participants and authorised surrogates** The only documentation generated will be educational material and SIGHT provider prompted messages for providers. All, material has undergone an internal review and will be approved by the clinical directors and the VUMC IRB before implementations of the SIGHT study.
Biological specimens	33	**Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable** No specimens will be collected by the study team or stored for future use. All, study related data will be collected via the electronic health record by following patients being seen at VUMC via usual care.

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov – **NCT06744543**
Date of registration in primary registry	**11 February, 2025**
Secondary identifying numbers	NA
Source(s) of monetary or material support	No funding source
Primary sponsor	NA
Secondary sponsor(s)	NA
Contact for public queries	Lucas Day Richter, MGC CGC lucas.richter@vumc.org
Contact for scientific queries	Lucas Day Richter, MGC CGC lucas.richter@vumc.org Vanderbilt University Medical Center Department of Medicine, Division of Genetic Medicine, Nashville TN Center for Digital Genomic Medicine Vanderbilt Genetics Institute
Public title	Clinical Decision Support to Find Individuals at Risk of Genetics Disease
Scientific title	*Integrating Machine Learning into Clinic: Systematic Identification of Genetic Health Testing (SIGHT) Randomized control trial.*
Countries of recruitment	United States
Health condition(s) or problem(s) studied	Genetics Disease in the Pediatric Population
Intervention(s)	Active comparator: Patients having a SIGHT predicted score greater than equal to 0.30 with a score less than 0.30 seen in the POD-C pediatric primary care clinic at the Vanderbilt University Medical Center (VUMC) One Hundred Oaks location (OHO .
	Controls: Randomized pediatric patients who meet criteria without intervention seen at POD-C pediatric primary care clinic at the Vanderbilt University Medical Center (VUMC) One Hundred Oaks location (OHO)..
Key inclusion and exclusion criteria	Ages eligible for study: >1 years and < 20 years of age Sexes eligible for study: both
	Inclusion criteria: Inclusion criteria will consist of patients > 1 year old, < 20 years of age with a visit to POD-C pediatric primary care clinic at the Vanderbilt University Medical Center (VUMC) One Hundred Oaks location (OHO).
	Exclusion criteria: Exclusion criteria will consist of patients who have been programmatically excluded due to having already received a chromosomal microarray at VUMC, and patients > 20 years of age.
Study type	Interventional
	Allocation: Randomized intervention model.
Date of first enrolment	February 2025
Target sample size	1000
Recruitment status	Recruiting
Primary outcome(s)	Number of cases diagnosed via a Chromosomal Microarray compared to the controls

Data category	Information
Key secondary outcomes	1. Time to patients receiving genetic testing 2. Rate of genetic testing 3. Satisfaction of physicians who received a SIGHT prompted provider message 4. Number of patients receiving a diagnosis via any test (molecular confirmation), or a clinical diagnosis by a pediatric geneticist following the course of usual care.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.