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NYCKidSeq: Incorporating genomics into the clinical care of diverse NYC children

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***English and Spanish translations**

I. BACKGROUND AND SIGNIFICANCE

Approximately 3% of children are born with genetic disorders that result in poor health or mortality. Genomic diagnostics has the potential to transform the lives of affected families and communities and impact human health on a global scale. The NIH-funded Clinical Sequencing Evidence-Generating (CSER) Consortium is tasked with evaluating and quantifying the clinical utility of genomic medicine. NYCKidSeq is a multi-institutional program (Mount Sinai/MS, Einstein Montefiore/EM, and the New York Genome Center/NYGC) and one of the newest members of CSER.

Fundamental to exploiting genomics for improved care in health systems is the quality of the underlying knowledge. Simply put, knowledge of genetic variants is not equal across different populations. The past decade of large-scale genomic data generation has been conducted predominantly in individuals of European ancestry. [1] Evidence suggests that this bias is likely to persist in the ongoing and upcoming efforts to sequence people's entire genomes. [2] As clinical sequencing becomes routine, the common experience among medical professionals is that the number of candidate variants for a suspected genetic disorder is significantly higher in non-European populations. This presents challenges to clinical laboratories for determining the pathogenicity of rare variation, particularly for putatively deleterious non-synonymous calls, which instead are labeled as variants of unknown significance (VUS). Therefore, it is imperative that geneticists sequence and investigate a much broader ensemble of populations that are representative of the rich diversity of patients in NYC and the world. If we do not, a biased picture will emerge of which variants are important, and genomic medicine will have limited benefit for underserved populations. Thus, in NYCKidSeq, we are working with children, young adults and their families from Harlem and the Bronx, communities that represent low-income and minority populations, are underrepresented in the genomic datapool, and are frequently the last to benefit from advances in research and technology

NYCKidSeq is focused on three broad areas of hereditary childhood disease. We will sequence the genomes of 1,130 children and young adults from Harlem and the Bronx with suspected genetic etiology of their neurologic disorders, primary immunodeficiencies, and cardiovascular disorders with the goal of detecting the mutated gene responsible for their disorder. Whole genome sequencing (WGS) has the potential to capture all classes of genetic variation in one analysis, and WGS interpretation has recently shown identification of clinically relevant variants in ~40% of autism [3,4] and ~60% of intellectual disability cases. [5] However, little is known about the clinical utility of WGS in other clinical settings, with WGS posing challenges in today's health systems, including cost, clinical interpretation and data storage. A nuanced understanding of the clinical utility of WGS compared to other first-line genetic modalities used across clinical settings, and in different communities, will be vital for evidence-based integration of genomics in health systems. Another advantage of WGS is that it offers the possibility of serially revisiting the data as the genetic elucidation of diseases progresses, with future progress expected to identify pathogenic variants. Of course, if underserved people and communities are not included in these genomic sequencing studies, they are less likely to benefit from our improved understanding of the genetic architecture of disease.

This challenge has been encountered at Mount Sinai, where >65,000 carrier couples have been tested using a pan-ethnic NGS carrier screening panel developed for genetic traits (the 281 gene NextStep™). In one example, a case of galactosemia was missed in an offspring where the carrier status of the Hispanic/Latino mother was not detected due to the inability to assign pathogenicity to her rare, non-synonymous *GALT* variant. To level the playing field, we will need expedited strategies for exploiting genomics for health in under-represented populations. We need new research models that bridge genetic research and clinical care, specific to these populations. We

have therefore assembled experts in population genetics/genomics and data scientists, with clinical labs and treating physicians, to work together as a team to develop infrastructure for updating the annotation pipelines and gene sets, and promulgating new positive findings. We will investigate the important contributions and interrelations of ancestry as a biological concept, and race as a social construct, and how these impacts clinical care. This proposal is uniquely poised to achieve these goals, and will focus on communication and stakeholder engagement as a means of achieving them.

Communication

Many children with underlying genetic disorders targeted in this proposal are subjected to diagnostic and/or therapeutic odysseys that could be avoided with early, precise genetic diagnostics. For instance, congenital heart defects remain the commonest class of birth defect and the one with the highest newborn mortality, while primary immunodeficiency disorders as well as the cardiomyopathies and channelopathies are also associated with substantial morbidity and mortality. Epilepsy can be a clinically challenging condition, with adequate control of seizures being elusive for some patients. Intellectual and developmental disabilities are increasingly recognized as prevalent and, for some diagnostic entities such as the autism spectrum disorders, rising in population frequency. Collectively, children with these disorders represent the largest patient group referred for genetic evaluation, and in full service pediatric clinical settings, genetic testing is routinely offered.

However, the complexity of genomics information remains a significant barrier to health care delivery. This is intimidating even for the clinical geneticist, and more so for primary care physicians or non-geneticist subspecialists, to whom children with genetic conditions initially present. In overcoming barriers to adoption of genetic testing, it will be of major importance to help all health care providers and patients/families to understand the meaning of these test results. We are therefore developing a novel GUIA that will be used by our genetic counselors to facilitate the delivery of genomic results to families. This GUIA is a primary focus of our research; we will compare parental understanding of and satisfaction with receiving genetic test results for their child among those who randomized to the tool versus those randomized to usual care. We will also develop a suite of software resources that allow web-based exploration of the results of genetic testing. These unique tools will enable caregivers to explore the significance of VUS identified by DNA sequencing, creating the opportunity for these caregivers to request follow up on specific VUS that may be relevant to their patient's phenotype. This empowerment of caregivers, with whom families have built trusted relationships, is designed to enhance the uptake of testing and the comfort with its interpretation.

Stakeholder Engagement

Efforts to develop effective, sustainable, scalable interventions that advance equity and advance genomics in diverse populations have met with insufficient success.[6] In part, because there is inadequate engagement of the stakeholder groups who understand and can impact root causes of disparities. Research traditionally takes place in disciplinary, disease and demographic silos, and low-income, minority communities most disproportionately impacted by disparities are too often marginalized or excluded from contributing to research, other than as subjects. Building teams of trans-disciplinary experts within health systems (team science), has begun to challenge traditional ways of thinking about and conducting scientific endeavors.[7,8] Building a culture of trans-disciplinary research includes increased familiarity, participatory goal setting, and encouraging feelings of inclusiveness among team members to foster social cohesiveness.[9-12] Diverse stakeholders can provide additional insights, approaches and resources, and spark innovation by merging expertise in qualitative, secondary data, clinical trial, digital health, community and clinical research. This can facilitate understanding of, access to, and implementation of genomic medicine.

Our team has significant experience in stakeholder engagement, partnership with patients from underserved communities, clinicians and advocates in Harlem and the Bronx, and has informed the field of stakeholder-engaged genomics research. We have engaged the Genomics Stakeholder Board at Mount Sinai to review and advise about our study design and materials.

We will also engage with health care administrators and other hospital organizational leaders. By participating in a questionnaire to assess organizational readiness for clinical sequencing implementation, we will capture current perspectives of healthcare systems leadership as they prepare for the adoption of genomic sequencing in a variety of clinical settings, particularly those serving underserved populations and those underrepresented in genomic research.

Summary
Taken as a whole, the NYCKidSeq program will significantly advance the implementation of genomic medicine, particularly for children, young adults and their families in Harlem and the Bronx. We will assess the clinical utility of genomic medicine in three broad areas of pediatric disorders, while engaging a range of providers and community advisors to overcome the well-documented barriers to inclusion of underserved and under-represented populations in genomic research. We will also test, analyze, and implement a novel GUIA to facilitate the return of genomic test results and enhance understanding of these results by families and patients, and care providers at all levels of expertise, in two health systems. Healthcare systems leadership will be engaged to provide insights into their readiness for genomic implementation. Overall, this work will inform the genomics and clinical communities about how to implement genomic medicine in a diverse population in a clinically useful, technologically savvy, culturally sensitive, and ethically sound manner.

II. STUDY DESIGN

II.a. Study Objectives

As described above, NYCKidSeq is multifaceted and has elements that involve human subject research and elements that do not. The *overall* Specific Aims of our project are shown below for clarity. This proposal, however, is only focused on Specific Aims 1, 2 and 3 (*i.e.,* those that involve human subject research).

Aim 1. Evaluate the clinical utility of whole genome sequencing (WGS) and targeted gene panels (TGP) for diagnostic purposes, and compare the diagnostic yield of both.

Aim 2. Engage stakeholders at various levels of the genome sequencing process to facilitate healthcare implementation**.**

Aim 3. Evaluate the use of a novel Communication Tool ("GUIA", Genomic Understanding, Information and Awareness") to facilitate the delivery of complex genomic results using a randomized controlled trial of traditional genetic counseling vs counseling with GUIA, and evaluating parental understanding, satisfaction, and feelings about the results, and their subsequent behavior.

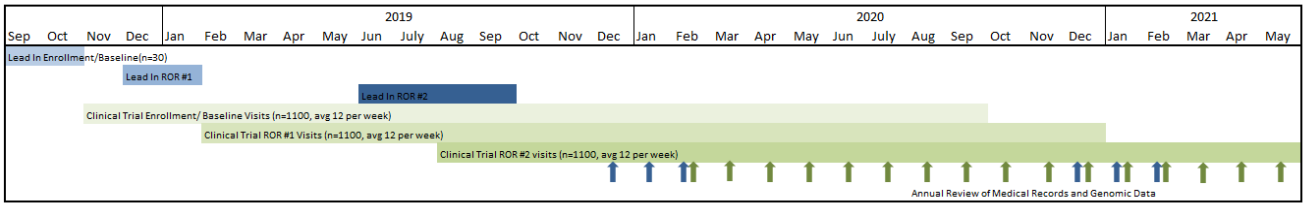
Aim 4. Overcome barriers to implementation using novel Electronic Health Record based resources and assessing their translation across medical centers.

II.b. Duration of Participation

Recruitment for the Lead-In Phase (n=30) will commence in approximately January 2019 and will finish in approximately February 2019. Recruitment for the full Clinical Trial (n=1100) using GUIA

will commence in about February 2019, using the results of the Lead-In Phase, after a modified IRB application highlighting these changes has been submitted/approved. We will continue to recruit until September 2020. Participants will have three study visits (Baseline, Return of results (ROR1), and ROR2) over a nine-month period. The length of a subject's participation will be a minimum of nine months to a maximum of 27 months, depending on the time of study entry; participation after the initial nine months will consist solely of chart and data review. Aside from the required Baseline, ROR1 and ROR2 visits, it is unlikely that the participants will have to come back for additional visits unless something novel and relevant is detected in either their annual medical record or annual genomic data review. Should that occur, the participants will review the new findings in an additional genetic counseling visit as part of the study; any additional testing or medical visits that are deemed necessary because of the new findings will be part of clinical care.

Fig. 1: Clinical Study Timeline



II.c. Study Population

We have chosen to study children and young adults with several disorders across clinical settings in order to ensure that we would maximize our reach into the ethnocultural and ancestral diversity in our population. In addition, these disorders tend to be challenging and expensive to diagnose, allowing us to readily define the clinical utility and economic impact of WGS.

Our targeted diseases are as follows:

Neurologic disorders: The genetic basis of **idiopathic seizure disorders** is well described, and the number of causative genes continues to expand.[13,14]We will focus on children with prolonged, clustered, or repetitive seizures so as not to duplicate the extensive work already being done in the Epilepsy Phenome Genome Project. Children with seizure disorders will be recruited from EM under the direction of clinical specialist Dr. Elissa Yazowitz, a board-certified child neurologist and clinical neurophysiologist, and from MS under the direction of Dr. Steven Wolf. **Intellectual disability** affects about 2-3% of the general population, and genetic causes may be present in 25-50%, although this number increases with severity. To increase our diagnostic rate, we will focus our recruitment efforts on children who have idiopathic, non-syndromic, severe to profound intellectual disability with or without autistic spectrum disorder, syndromic intellectual disability, idiopathic intellectual disability with a strong family history of the same, and idiopathic intellectual disability with receptive language abnormalities. Children with intellectual disability will be recruited from the Children's Evaluation and Rehabilitation Center (CERC) under the direction of Dr. Lisa Shulman, the clinical arm of The Rose F. Kennedy Center at EM, as well as from EM's and MS's Neurology and Genetics programs. The primary study geneticists are Drs. Melissa Wasserstein and John Greally (EM), and Dr. George Diaz (MS).

Immunologic disorders: Primary immune deficiency disorders arise due to genetic abnormalities of one or more genes important in human immunity.[15] More than 200 different primary immune deficiency disorders are known, with an estimated incidence between 1:500 to about 1:500,000. Dr. Cunningham-Rundles' group has previously demonstrated that ~0.4% of MS's

hospitalized patients had complications suggestive of primary immune deficiency. These subjects were younger, sicker, more often Hispanic or African American, and more likely to have Medicaid. There are currently 290 known causative genes, although that number is increasing rapidly. We expect to find an underlying molecular diagnosis in 50 to 69% of patients in targeted populations. The primary study immunologists are Dr. Charlotte Cunningham-Rundles (MS) and Dr. Arye Rubenstein (EM).

Cardiac disorders: Congenital heart diseases constitute the commonest class of birth defects and, despite substantial progress in clinical care, remain the leading cause of newborn mortality among birth defects.[16] Mendelian traits and aneuploidy underline approximately 10% of cases, and pathologic copy number variations (CNVs) and *de novo* single nucleotide variations (SNVs)/indels each explain another 10% of cases .[17-20] Affected children with congenital heart disease will be recruited from MS and EM. We will focus on recruiting children with congenital heart disease plus extra-cardiac anomalies and/or intellectual disabilities as they are more likely to have likely causal *de novo* SNVs/indels or CNVs.[19,20] In addition, we will recruit those likely to have Mendelian disease (e.g., secundum atrial septal defects with some degree of atrio-ventricular block, affected first degree relatives). Genetic **cardiac arrhythmias** such as long QT syndrome are characterized by cardiac conduction abnormalities that can result in sudden cardiac death in otherwise healthy individuals. Long QT syndrome is characterized by delayed repolarization of the myocardium and QT prolongation, resulting in syncope and cardiac arrest. Familial hypertrophic **cardiomyopathy** is the most common genetic heart disease in the United States, whereas familial dilated cardiomyopathy affects approximately 375,000 Americans [21]Children with cardiomyopathies, arrhythmias, and channelopathies will be recruited from the MS and the EM Cardiogenetics Clinic. The population who attends Cardiogenetics clinic is quite diverse, largely African-American and Hispanic/Latino (approximately 60-70%) with significant additional representation by South Asian (Indian, Bengali, and Pakistani) patients. The primary study cardiologists are Dr. Bruce Gelb (MS) and Dr. Tom McDonald (EM).

In addition to the aforementioned patients, our study population includes medical providers and healthcare systems leadership as part of Specific Aim 2, which focuses on engaging stakeholders within the medical system. First, **study providers** at MS and EM will be engaged throughout the study, from patient referral and study introduction through ROR. A subset of study providers will be surveyed 0-6 weeks post-ROR1 to assess their level of confidence and perceived utility with their referred patient's genomic results, and subsequent recommended actions that were attributed to the genomic testing. Participants (N=115-230) who receive positive (n=57-115), and negative and uncertain (n=57-115) primary and/or secondary results across EM and MS will be included in the request for provider assessment. These specialty providers will be sub-investigators in the clinical trial as well as other primary or specialty care providers involved in the downstream care and management of the patient within the EM or MS system. The Non-Study Provider Survey Informed Consent must be completed by non-study primary or specialty care providers prior to participation.

Healthcare systems leadership will be engaged 0-8 weeks after the main study phase initiation (approximately October – November 2018) to assess organizational readiness to implement clinical sequencing within their healthcare systems using the Clinical Sequencing Evidence-Generating Research (CSER)-harmonized survey. We aim to enroll 6-10 executives, administrators, managers, and/or clinicians at EM and MS, for a total of 12 to 20 participants across both sites. Respondents of interest include hospital or healthcare system executives, administrators, and managers in roles such as chief executive officer, chief operating officer, chief of staff, vice president of patient care, chief financial officer, service chief, director, manager, supervisor, and/or clinician. Information

from this questionnaire will be pooled among CSER sites to evaluate organizational readiness to change across multiple healthcare systems, hospitals, and communities across the nation. The survey (See Appendix h) will be administered online via SurveyMonkey and the responses will remain anonymous.

II.d. Primary, Secondary and Exploratory Outcomes

Primary outcome

1) Perceived understanding of genomic testing results, with comparison of results in traditional GC group vs GUIA group (ROR1 and ROR2, Q3).

Secondary outcomes

Understanding genomic results

2) Objective understanding of genomic testing results, with comparison of results in traditional Genetic Counseling (GC) group vs GUIA group (as measured by surveys ROR1 Q1, 2, 13 and ROR2 Q1, 2, 13);

3) Understanding of medical follow up and the actionability of genomic results (ROR1 Q4, 5, 6) and adherence to medical follow up recommendations (ROR2 Q4), and

Diagnostic results and comparison of WGS to TGP

4) Overall diagnostic yield as the percentage of NYCKidSeq participants with definitive or likely positive diagnoses;

5) Diagnostic yield of WGS overall and by disease category (neurology, cardiology, primary immunodeficiency), as the percentage of participants with definitive or likely positive diagnoses;

6) Diagnostic yield of TGP overall and by disease category (neurology, cardiology, primary immunodeficiency), as the percentage of participants with definitive or likely positive diagnoses;

7) Time to diagnosis of TGP vs WGS;

8) Concordance of TGP vs WGS results;

9) Diagnostic yield of WGS between different race/ethnic groups, as the percentage of participants with definitive or likely positive diagnoses;

10) Diagnostic yield of TGP between different race/ethnic groups, as the percentage of participants with definitive or likely positive diagnoses;

CSER Harmonized Measures

11) Comparison of parental satisfaction with mode of delivery in control vs GUIA group ("Satisfaction with mode of communication of results") (ROR1, Q7);

12) Comparison of parental overall satisfaction with results in control vs GUIA group (ROR1, Q8);

13) Parental feelings about genomic testing results in control vs GUIA group (FACToR) (ROR1 and ROR2, Q9);

14) Perceptions of Uncertainties in genomic sequencing in control vs GUIA group (PUGs)(ROR1 and ROR2, Q10);

15) Parental personal utility scale in control vs GUIA group (PrU) (ROR1 and ROR2, Q11);

16) Information seeking in control vs GUIA group and Perceived Usefulness of GUIA ("Information seeking") (ROR1, Q14) (ROR2, Q7,16);

17) Comparison of behavioral changes in control vs GUIA group ("Patient-Initiated Actions Attributable to Genetic Testing") (ROR2, Q5);

18) Comparison of patient QOL in control vs GUIA group (Quality of Life Ascertainment Visual Analog Scale and PedsQL Generic Core Scale) (ROR2, Q14,15);

19) Family communication in control vs GUIA group ("Family Communication") (ROR2, Q6);

20) Decision regret in control vs GUIA group ("Decision Regret") (ROR1 and ROR2, Q12);

21) Economic impact of child's health status (Baseline and ROR2, Q8);

22) Provider confidence in handling genomic results and perceived utility of genomic results in patient care in control vs GUIA group ("Health Provider Confidence") (PROV ROR1, Q2);

23) Provider perceived utility of genomic results in control vs GUIA group ("Healthcare Provider Perceived Utility") (PROV ROR1, Q3);

24) Comparison of provider's recommended actions for the patient ("Recommended Actions Attributable to Genomic Testing,") (PROV ROR1, Q7) to report of patient follow through on medical actions attributable to genomic testing for patients receiving primary and/or secondary findings and an equal number of patients receiving negative results, in control vs GUIA group ("Follow through on medical actions attributable to genomic testing") (PROV ROR-FU2, Q1);

Exploratory outcome

25) For study subjects with active disease (i.e., neurology, cardiology, primary immunodeficiency), physician recommended change in treatment (medication, prophylaxis, or therapy) in children with a positive genomic diagnosis compared to those with a negative genomic diagnosis, based on Referring Physician Opinion and Recommendations; to be assessed at ROR1 (see Appendix x);

26) Number of diagnoses in study subjects who received results following standard clinical analysis, or clinical analysis that uses the enhanced HPO terms and other data made available through GenomeDiver with, and without, ClinPhen;

27) Compare the ClinPhen generated HPO terms with the pre-test clinician generated phenotype terms in children with positive results to assess concordance.

II.e. Clinical Trial Design

The overall design is a Randomized Controlled Trial (RCT), evaluating the use of a novel Communication Tool, "GUIA," to facilitate the return of WGS genomic results and comparing it to return of results using routine genetic counseling. The RCT will occur in the context of our performing WGS and TGP for diagnostic purposes in 1,130 children in an effort to assess clinical utility. Children and young adults with specific disorders (see Section II.c.) will be recruited from MS and EM.

GUIA will be an enhanced, personalized electronic version of a flip chart, which is the type of tool most commonly used in routine genetic counseling. In the third year of the study, we hope to have the tool integrated into EPIC. There are no tools yet focused on this complex information, specifically on helping patients understand their own genomic results. The tool is currently under development and will continued to be developed during the "Lead-In" phase of this study, when some of the first 30 NYCKidSeq participants will share their impressions of the tool to enable us to refine it. We anticipate that GUIA will be completed by approximately January 2019, and we will then begin to enroll the remaining 1100 NYCKidSeq patients into the RCT, with half receiving their results via routine genetic counseling, and half with the use of GUIA as a supplement to genetic counseling.

III. Study Procedures

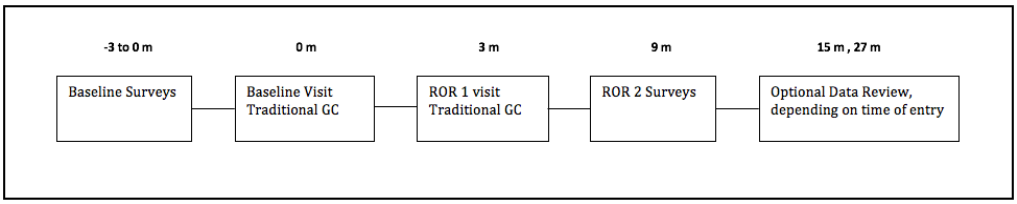


Fig. 2a. Study flow chart, Lead-in phase (N=30), anticipated enrollment from September-October 2018.

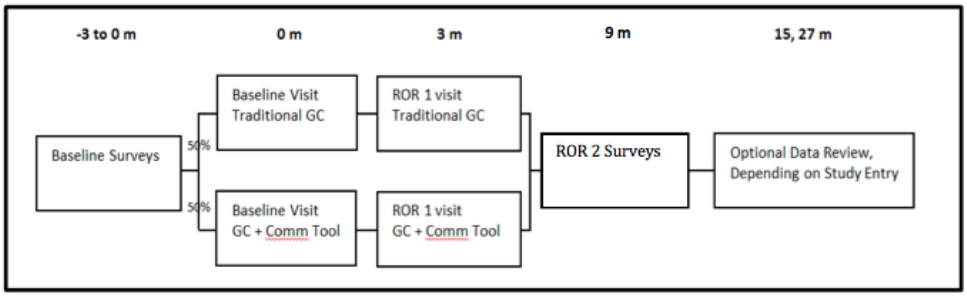


Fig. 2b. Study flow chart, Clinical trial (N=1100), anticipated enrollment starting October 2018.

III.a. Pre-Screening of referred patient's eligibility prior to study team contact (HIPAA Waiver)

Upon receipt of the referral for a potential participant, the study team will review and confirm the child's eligibility in EPIC prior to contact with the family. Alternatively, study coordinators may attend specific clinics after invitation by our study physicians. The study physicians and/or physician colleagues (i.e. treating physicians) will provide the coordinators with a list of that week or that day's patients who they deem to be potential NYCKidSeq participants. The coordinator will enter and review the patients' medical records to check if they meet inclusion and exclusion criteria. If a patient does fulfill criteria, the coordinators will notify the physicians before the visit starts. The physicians will then introduce the study to the family, if they are interested and agree to be contacted by the study team, the child's MRN and phenotype checklist (Appendix w. 'Physician

phenotype checklist') will securely be sent to the study team *(see 'Recruitment' Section V.a.)*. The CRC will review the referred child's pre-screening Inclusion and Exclusion criteria in EPIC and input minimal data points (e.g., age, race/ethnicity, prior genetic testing time/result, language, and phenotype) into RedCap under a recruitment study ID.

If approved, the CRC will contact (in-person or on phone) the family to discuss the study and answer questions, review and re-confirm eligibility (e.g., parents have not participated in genomic testing and/or counseling within 6-months, English- or Spanish-speaking, available for study visits) and determine level of interest (e.g., administer baseline consent (in-person), schedule visit to review baseline consent/survey (phone), and/or administer decliner survey) (see 'Recruitment Scripts' Appendix j and k). If the referral is NOT eligible, the referring physician and family will be informed of the decision. If the family is NOT eligible or declines to participate, the RedCap record will be reviewed and purged of any personal identifiers (e.g., name and MRN). The site-specific project manager will have access to this information in a secure file linking to the recruitment ID.

Although the coordinators will have access to all variables in the charts, sensitive material/variables that are not necessary for this study will not be considered. Once eligibility has been reviewed, the patient's medical record will be closed. The purpose of pre-screening through accessing the medical record and viewing relevant clinical information is to not burden the patients family who would not be eligible for the study.

This study could not be practiacably carried out without this waiver as patients being recruited may be unsure of genomic testing eligiblity criteria due to the nature of these conditions' complicated etiology. Therefore, we need to look into the child's medical record to ensure this information is correct. We would like to minimize stress on the parents due to the nature of their child's disorder, and minimize the risk that they are introduced to a study for which they may not be eligible.

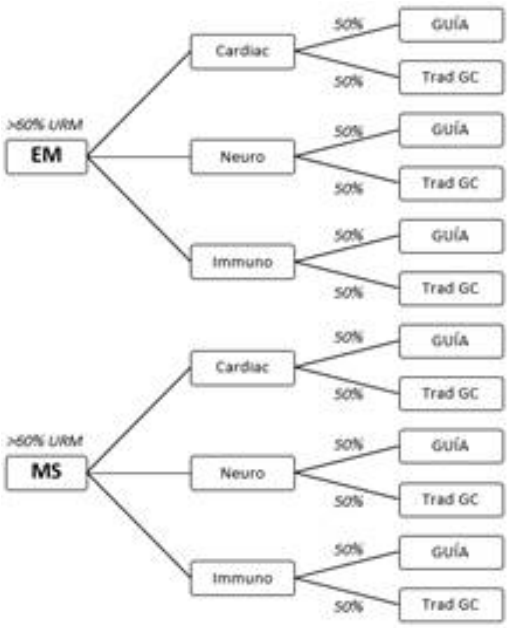
III.b. Randomization and Baseline Survey

Randomization into GUIA or Routine Genetic Counseling Arms

Families that agree to participate after the initial discussion with the CRC (see Sec III.a.) will be scheduled for their baseline visit. They will, at this time (i.e., prior to signing informed consent), be randomized to participate in GUIA or routine genetic counseling visit using the RedCap randomization tool. This randomization will take place before their initial visit so they can be scheduled with the appropriate GUIA-specific or routine genetic counselor. The CRC will tell the parents that they will meet with a genetic counselor who will deliver their results using standard of care, or using standard of care with a new educational tool, but they will not be told which group they are assigned to until they show up for their visit. The purpose of doing this is to minimize the chance that parents will research genomic educational tools prior to their visit, which might affect how they answer the study's baseline surveys.

In the routine GC group, participants will receive standard of care, routine genetic counseling for the Baseline and Return of Results (ROR1) visits. In the GUIA group, they will receive routine GC for the Baseline visit, and routine GC plus GUIA for the ROR1 visit.

Because some of the clinical practices at EM and MS might have different patient characteristics, and because the disease categories might have varying severities of illness that might impact the study outcome, we have chosen to use a stratified randomization scheme by disease category (cardiac, neurologic, immunologic) and clinical site as follows:



For Lead-In and RCT Groups: Baseline Surveys

After parents sign the *Informed Consent: Baseline Survey (see Section VI.a.)*, a site-specific clinical research coordinator (CRC) will administer a 45-60 minute baseline survey. All CRCs are bilingual and will administer the survey in the parent's preferred language (English or Spanish). Participants will have the option to take the survey in-person (preferred) or by phone if the parent(s) is unable to be present in person. Of note, the survey needs to be administered before the parent consents to genomic testing, as it is designed to measure pre-testing/pre-education knowledge and the genomic consenting process includes extensive education. For this reason, there is a separate informed consent (*Informed Consent: Baseline Survey*) for the survey that will be signed before it is administered. If the baseline survey is in-person, parents/guardians may choose to complete the baseline survey in a separate visit before their baseline/enrollment visit (in which case they would have four study visits), or at the time of the recruitment (i.e., in clinic or as an inpatient). CRCs will use tablets to enter survey answers directly into our RedCap database. Baseline survey questions (English and Spanish versions) are attached in Appendix b.

Lead-In Phase Group: The participants of the Lead-In phase (N=30) will not be randomized into the GUIA vs traditional genetic counseling groups. Instead, we will be asking them to provide parental feedback on 1) the surveys and 2) the GUIA. The first 15 participants will be asked to provide feedback on the GUIA at ROR1 (see below). For the baseline visit, they will take the current version of the baseline survey, and will be scheduled to meet with a Genetic Counselor from the GUIA for the baseline visit.

The next 15 participants will be asked to provide parental input about our baseline survey. The goal of this input is to ensure that the flow and content of our questions are clear and not likely to be misinterpreted, and to review the timing and order of the questions. We will use a think out loud feedback approach. The CRCs will be trained on how to obtain and record the parent's input. The participants of this group will receive an additional $20 gift card after this feedback survey

session. The CRC will then give his/her contact information, discuss next steps, and schedule the Baseline visit with a genetic counselor from the "traditional" arm.

If the parents and/or young adults decline to participate after reviewing the *Informed Consent: Baseline Survey*, they will be asked a few optional questions regarding this decision to help us better assess any barriers to study participation (Appendix e 'Decliner Survey'). The RedCap record will be reviewed and purged of any personal identifiers (e.g., name, MRN). Any unidentifiable data recorded up to this point will be stored under the study ID, which was assigned after the physician referral was made.

III.c. Baseline Visit

The baseline visit will be the same for the Lead-In and RCT phases of the study.

Informed consent and Pre-Test Genetic Counseling: At this visit, the parent/guardian will review the *Informed Consent: Main study* with the genetic counselor and will sign the informed consent and child assent when appropriate. If the child is a young adult (18-21 years of age) with intact cognitive abilities, they will sign an Informed Consent for testing, while the parent(s) sign an Informed Consent for surveys and parental blood draw. During the consenting process, the family will be educated about the study, as well as extensively educated about the risks, benefits, and limitation of genomic testing. As part of the pre-test genetic counseling, the genetic counselor will obtain a medical and family history. They will then provide education on the type and purpose of genomic testing, possible results of genomic testing, and potential implications for other family members. Genetic counselors will also describe the potential to identify ACMG secondary findings[22] (i.e., a published list of 59 medically actionable genes; mutations in one of more of these genes may be identified by genomic sequencing and may have medical implications for the patient and family). Consistent with ACMG guidelines for pediatrics[23] participants will have the option to choose whether or not they want to receive those results. The genetic counselor will also review the risks of sharing genomic data through dbGaP, as well as current protections against discrimination based on genetic information established by GINA (Genetic Information Nondiscrimination Act). At the end of the Baseline Visit, the GC will give the family a $20 gift card.

Sample collection and processing: We will collect whole blood from all study participants, including from each available biological parent to assist with interpretation of genomic results. If a biological parent is involved with the child but not available at the visit, we will mail saliva kits to the home. We will not obtain samples from legal guardians who are not biological parents. After collection, samples from each patient will be bar-coded on site and ordered either via paper requisitions (initially) or through a custom interface built within Epic (estimated in 2019). Samples will be initially sent to Sema4 Genomics Laboratory for DNA extraction. An aliquot will be sent to our collaborating institute, the New York Genome Center (NYGC), for whole genome sequencing, and the remainder will be retained at Sema4 for targeted gene panel (TGP) analysis and Sanger validation. Both Sema4 and NYGC are CLIA-certified and approved by New York State to perform targeted gene panels and whole genome sequencing for clinical purposes. (See Appendix cc)

If the parents and/or young adults decline to participate after reviewing the *Informed consent: Main Study,* they will be asked a few optional questions regarding this decision to help us better assess any barriers to study participation (Appendix e 'Decliner Survey'). The RedCap record will be reviewed and purged of any personal identifiers (e.g., name, MRN). Any data recorded up to this point will be stored under the study ID.

III.d. Return of Results (ROR)/Follow Up (FU) Visit 1, aka ROR1:

Result reporting will occur approximately three months after the samples are obtained (Visit 2 – see Schedule of Assessments), and is a required study visit regardless of whether results were abnormal or not. It will always be done by the assigned genetic counselor they met with during the Baseline Visit. The referring physicians, who will be active participants in the interpretation of results, will have the option to participate in the result reporting session, depending on their individual current practice and the specific results of the study subject. However, as this is an intervention that adds to usual care, we will not interfere with what providers prefer or choose to do in terms of their involvement in ROR. Regardless of their choice about whether or not to participate in the session, all results will be reviewed by the referring physician, and they will share their opinion about the significance of the genomic findings as well as their medical recommendations with the GC, using "NYCKidSeq Referring Physician Opinion and Recommendations" (see Appendix x). This form will either be filled out directly by the physician, or communicated with the GC by phone or email.

Lead-In Phase (n=30)

GUIA Feedback Group (First 15 participants): These participants will meet with their assigned genetic counselor from the GUIA GC group to review their results (as described below for the main RCT). After their ROR1 session, a different genetic counselor (and/or a trained study team member) will collect participant feedback on the GUIA, which will be under development at the time of their participation. A think out loud feedback approach will be used with the goal of addressing and clarifying wording/phrasing, use of images, order of information, amount and detail of information, pace, and potential Spanish translational issues. These sessions will be recorded and transcribed. At the end of the feedback session, the CRC will administer the ROR1 survey and provide $40 gift card, in addition to the $20 study visit gift card.

Survey Feedback Group (Second 15 participants): These participants will meet with their assigned genetic counselor from the routine GC group to review their results (as described below for the main RCT). After the ROR1 session, the CRC will administer the ROR1 survey and ask for their feedback on the survey to ensure that the flow and content of our ROR1 questions are clear and not likely to be misinterpreted, and that timing of the survey is not over burdensome. We will use a think out loud feedback approach. At the end of this survey feedback session, the CRC will receive a $20 gift card in addition for their feedback, to the $20 study visit gift card.

RCT Phase (n=1100)

The RCT is divided into two arms, the Routine Genetic Counseling (GC) arm, and the GUIA Arm. The routine GC arm will mimic what is routinely done as part of clinical care.

Routine GC Arm (n=550 study wide): During the ROR1 genetic counseling session, the genetic counselor will review the purpose of the genomic testing and disclose the child's test results. For positive test results, the genetic counselor will describe the diagnosis, associated symptoms, management recommendations, and life expectancy, if known. The genetic counselor will then discuss the inheritance pattern, recurrence risks, and identify at-risk family members who may also require/consider testing. In the case of negative results, the genetic counselor will discuss the implications of such a result, such as the possibility that there is a genetic cause for the child's symptoms that was unable to be identified at this time by this testing. For ambiguous results, the genetic counselor will explain the meaning and uncertainty associated with these types of results and provide recommendations for continued disease management. The genetic counselor will also

disclose any secondary findings to participants who opted to receive those results. Psychosocial concerns will be addressed throughout the encounter. Lastly, the genetic counselor will provide medical and support referrals, when appropriate, using suggestions made by the physician via the "NYCKidSeq Referring Physician Opinion and Recommendations for ROR1." As the WGS and TGP are NYS-approved for clinical purposes, reports will be given to the families and incorporated into their medical records, and shared with referring physicians. They will also be provided a standard clinical letter which simply explains the findings for their physicians and/or insurance for additional services. At the end of the visit, parents will take the ROR1 survey, and then receive a $20 gift card.

GUIA Arm (n=550 study wide): Genetic counselors in this arm will follow the same procedures as those outlined for the Routine GC Arm and will also utilize GUIA during the genetic counseling session. GUIA will be filled out prior to the session, incorporating the genomic results and the medical and support referrals made by the MD via the "NYCKidSeq Referring Physician Opinion and Recommendations for ROR1." During the ROR1 genetic counseling session, the genetic counselor will review the purpose of the genomic testing and disclose the child's test results. For positive test results, the genetic counselor will describe the diagnosis, associated symptoms, management recommendations, and life expectancy, if known. The genetic counselor will then discuss the inheritance pattern, recurrence risks, and identify at-risk family members who may also require/consider testing. In the case of negative results, the genetic counselor will discuss the implications of such a result, such as the possibility that there is a genetic cause for the child's symptoms that was unable to be identified at this time by this testing. For ambiguous results, the genetic counselor will explain the meaning and uncertainty associated with these types of results and provide recommendations for continued disease management. The genetic counselor will also disclose any secondary findings to participants who opted to receive those results. Psychosocial concerns will be addressed throughout the encounter. Lastly, the genetic counselor will provide medical and support referrals, when appropriate. At the end of the ROR1 the genetic counselor will print a copy of the GUIA and clinical laboratory report for the participant to take home with them. At the end of the session, parents will take the ROR1 survey and will then receive a $20 gift card.

Standardization of Genetic Counseling Sessions: In order to ensure that all genetic counseling sessions address the topics described above in the Baseline and ROR1 Visits, genetic counselors will utilize a pre- and post-test checklist, which is attached in Appendix w and z.

III.e. Return of Results Follow Up Visit 2, aka ROR 2 Visit

The ROR2 visit will be the same for the Lead-In and RCT phases of the study. This visit will occur about six months after the ROR1 visit, at ~9 months after study entry, and will occur either in-person or by phone if a visit is too difficult for the family. At this visit, the CRC will administer the ROR2 survey (see Appendix d). We anticipate greater challenges with retaining subjects at this visit, so we will increase the gift card amount to $40 for this visit.

Lead-In Phase (Second 15 participants): The CRC will administer the ROR2 to the survey feedback participants and asked for their input on the flow and content of the questions to ensure they are clear and not likely to be misinterpreted, in addition they will be asked about the timing of the survey. We will use a think out loud feedback approach. At the end of this survey feedback session, the CRC will receive the $40 gift card for this study visit.

To maximize follow-up, CRCs will begin calling parents 4 weeks before the visit to begin to arrange follow-up. For those whose contact information is no longer accurate, alternate numbers collected

at baseline will be called, and CRCs will query if patients have any appointments within the health system during which they can intercept patients, update contact information and arrange follow-up. They will text, email and/or mail reminders of upcoming visits. If it is not possible for the parents to come in, the ROR2 survey will be administered by phone.

III.f. After the Study Visits: Reviews of DNA Sequencing Results and Medical Records

We are constantly learning how to interpret DNA changes, and we are likely to acquire new, possibly useful information during the course of the study. Because of this, we will review the subject's genetic results every twelve months for the duration of the study (until May 2021) using new knowledge to re-interpret results. If we find something important, a study team member will call the subject and ask for them to come back for another visit to review the new finding. The visit to review the results will be performed by a study genetic counselor; any additional medical visits that are required because of the new results will be considered part of clinical care.

Similarly, we will review electronic medical records annually for quantifiable or objective clinical utility endpoints related to the study entry diagnosis. Specifically, we will look for changes in medications, number and causes for hospitalizations, physiologic studies such as EEG and echocardiogram, and radiographic studies. We will also review the subject's medical record every year to see if there are any changes in their health status during the course of the study (see Appendix g).

III.g. Provider Surveys

Provider ROR1 Survey

A subset of referring providers across EM and MS will be asked to complete a brief questionnaire between 0 to 6 weeks after their referred patients' results are returned (n=115-230 participants). If the provider is not a study co-investigator physician, they will be consented to participate in this survey using the Non-study Provider Survey Informed Consent. A CRC coordinator will email the consent form to the provider, review the survey and consent over the phone (or in-person, if available), and answer any questions. If the provider agrees to participate in the ROR1 provider survey, they will sign the consent form and send back a copy for our records. The CRC will then send a RedCap survey link to the provider to complete. The questions in this survey have been harmonized across the CSER sites and will query providers on their level of confidence in handling genomic results and the perceived utility of the genomic results in their patients' care and management. The survey will also ask providers to recount the medical recommendations they offered to their patients based on the genomic result (see Appendix f). Providers will be asked to answer these surveys on participants who receive positive results and an equal number of negative results (which in this analysis includes uncertain results).

Study Staff EHR Extraction and/or Provider ROR2 Survey

Five to seven months after ROR1 (study time 11-13 months) study staff will review patients' medical records to assess follow through with providers' medical recommendations based on any primary or secondary findings identified through genomic testing. Approximately 3.5-5.5 months after ROR1 Provider Survey administration, providers who participated in that survey will also be asked to complete a brief follow-up ROR2 survey that will help determine patient adherence to recommendations. These measures have been harmonized across all CSER sites (see Appendix g.).

III.h. Healthcare Leadership Survey

Healthcare executives, administrators, managers, and/or clinicians at EM and MS will be engaged 0-8 weeks after the main study phase initiation (approximately October-December 2018) to assess organizational readiness to implement clinical sequencing within their healthcare systems using a CSER harmonized survey (see Appendix h.). Information from this questionnaire will be pooled among CSER2 sites to evaluate organizational readiness to change across multiple healthcare systems, hospitals, and communities across the nation. We aim to enroll 6-10 participants at both sites (N=12-20). Respondents of interest include hospital or healthcare system executives, administrators, and managers in roles such as chief executive officer, chief operating officer, chief of staff, vice president of patient care, chief financial officer, service chief, director, manager, supervisor, and/or clinician. A study member will reach out to the potential participants through email to invite them to participate with a link to the survey. The introduction page of the survey will inform them of the purpose, benefits, and any risks to participating (which are none).

As this is an anonymous survey that will not collect identifiers or be linked to participant emails, we will have the following "Statement of Consent" prior to entering the survey:

> **Statement of Consent:**
> "I have read the above description of this survey and I understand it. I have been informed of the risks and benefits involved. Furthermore, I have been assured that any future questions that I may have will also be answered by the principal investigator or the research team. I voluntarily agree to participate in this research survey."
>
> By clicking "Next" you agree to the "Statement of Consent" and voluntarily agree to participate in the survey.
> Note: By clicking "Next", you have not waived any of legal rights to which you would otherwise be entitled. You do not have to participate, it is your choice. You do not have to answer all the questions and you may stop at any time.

III.i. ClinPhen

We currently use HPO terms in NYCKidSeq as part of the process of making a diagnosis based on the patient's DNA sequencing data. When we send the genetic test requests to Sema4 and the NY Genome Center clinical labs, we include a checklist of findings in the patient (phenotype checklist) that correspond to HPO terms. When the laboratory finds DNA sequence variants and likely mutations in the patient's DNA, they test whether the same or similar sequence changes have caused other patients to have had similar presentations, using HPO terms. The greater the number and the more accurate the terms provided, the more likely it is that a diagnosis will be made.

By using the natural language processing capabilities of ClinPhen, we can extract HPO terms directly from the caregiver notes in the patient's electronic health record. This results in a tabular output as shown below:

HPO ID	Phenotype name	No. occurrences in note
HP:0001650	Aortic valve stenosis	2

We anticipate that we will be able to add much larger numbers of HPO terms to the patient description than manual curation or the use of checklists will allow, thus improving our potential for making diagnoses.

We will work with the Clinical Research Informatics team at EM and the Informatics and Information Technology team at MS. Assigned staff will download the notes from the patient records of all patients being tested as part of the NYCKidSeq project. Personnel from the group of Drs. John Greally and Eimear Kenny will run ClinPhen in the secure environments of EM and MS. The resulting tab-separated variable (tsv) table for each patient will be stored with its medical record number. Assigned staff from EM and MS will work with the staff of the clinical laboratory at the NY Genome Center to arrange the data's secure transfer to their secure, HIPAA-and New York State-compliant computing environment where the rest of the NYCKidSeq patient data will already reside. Analyses using these HPO data will only be performed locally at that site, by NYCKidSeq investigators from the NY Genome Center, Einstein-Montefiore and Mount Sinai. Importantly, all ClinPhen-related data will only be accessible to and analysed by NYCKidSeq investigators at Einstein-Montefiore, Mount Sinai, and the NYGC.

ClinPhen takes only seconds to run per note, so we can process thousands of notes within a day. We plan to perform quarterly runs of ClinPhen for the remainder of the NYCKidSeq project. We do not need a license to run ClinPhen, as it is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License and freely available for academic, nonprofit, and personal use.

The NYCKidSeq project will use the ClinPhen data in three ways:

1. We will test the comprehensiveness and accuracy of ClinPhen's extraction of HPO terms from NYCKidSeq notes by replicating a comparable study performed by NYCKidSeq researchers at Mount Sinai, involving a comparison of HPO term extraction from patient notes by ClinPhen and by clinicians.
2. We will implement the filtering strategy performed by the developers of ClinPhen[24], removing the phenotypes that occur frequently in a large unselected patient population. This work is currently under way, extracting HPO terms from the notes of all patients ≤18 years old seen in the Montefiore health system over the last 18 months.
3. We will provide these filtered HPO terms to the NY Genome Center clinical lab when re-analysis is performed of whole genome sequencing data, testing how our diagnostic rates improve (see Exploratory Outcome above). Before doing this, we plan to add an option to our GenomeDiver laboratory software tool which will allow the caregiver the ability to curate the new HPO terms into categories of definitely present in the child, definitely not present, or uncertain. This should further improve the accuracy and utility of the data.

The ClinPhen workflow will be as follows: Two weeks before each quarter, a project manager will contact the Clinical Research Informatics team and the Informatics and Information Technology team to provide the medical record numbers and other identifiers of the Montefiore and Sinai patients enrolled in NYCKidSeq. Staff will extract all of the clinical notes for each patient and store them locally on a protected server controlled by these research groups and already qualified for personal health information storage. A member of the Greally group at Einstein and a member of the Sinai group will run ClinPhen locally on the same servers, generating TSV files of HPO terms for each patient. The files will then be transferred securely to the NY Genome Center. The HPO terms from each patient assigned to the GenomeDiver arm will be used as described above, passing them through an intermediate GenomeDiver step for manual curation prior to performing clinical analysis of the patient's whole genome sequencing data. HPO terms from each patient with an initial positive result will be manually compared with the primary phenotypic indication at study enrollment, as noted on the phenotype checklist.

III.j. Discrepancy Committee

At the request of the study Genetic Counselors, we will hold *ad hoc* discrepancy committee meetings to review any NYCKidSeq cases that have confusing, discrepant, or unsatisfying results. The committee will consist of NYCKidSeq medical geneticists, genetic counselors, lab directors, and referring providers. Each case will be presented to the group and then opened for discussion to determine the significance of the genomic results. We will use the decision of the discrepancy committee as our final diagnostic determination.

IV. Patient Population

IV.a. Sample Size

The total number of subjects expected to participate is 1,130 with approximately 50-70% from EM and 30-50% from MS. Across both hospital centers, we expect to enroll 30 children between September-October 2018 in the Lead-In Phase. We then anticipate enrolling a total of 1100 children for the clinical trial between October 2018-September 2020 for the Randomized Clinical Trial.

IV.b. Inclusion Criteria

- Infants, children and young adults up to and including 21 years of age; young adults (18-21) who are cognitively intact may participate in this study, but their parent(s) or legal guardian(s) must also agree to participate.
- English- or Spanish-speaking parent or legal guardian capable of providing informed consent, participating in surveys, and able to see GUIA;
- Currently undiagnosed, likely genetic* cause of neurologic, immunologic, or cardiac disorders (*as determined by disorder-specific criteria in Section IIIc. and phenotype checklist Appendix w.);
- Followed by a physician in the MS or EM systems;
- Willing and able to return for each study visit (not moving out of the area within nine months);
- If targeted gene panels and/or whole exome sequencing were previously done, results must have been returned at least three months before enrollment;
- If targeted gene panels and/or whole exome sequencing were previously done, results must have been negative, or identified only one variant in a potentially causative autosomal recessive gene, and
- If the parents received genetic counseling about this child, themselves, or a family member, the last genetic counseling session must have been at least three months before enrollment (*if testing was within 3-months their recruitment will be held until they 3-months or after)
- If patients have undergone karyotyping alone, we do <u>not</u> have to wait 3 months prior to inclusion.

IV.c. Exclusion Criteria

Individuals will be excluded if:

- The referred child is currently participating in a different genetic sequencing study that includes genetic counseling and/or return of results before the participant's ROR2 visit, and
- If they have a known or likely molecular genetic diagnosis for their neurologic,

immunologic, or cardiac disorder.
- They have had a bone-marrow transplant.

IV.d. Sex of Subjects

While we anticipate having equal numbers of genetically male and female participants, this may vary if a significant number of participants have X-linked genetic disorders, which typically have more pronounced phenotypes in genetic males. No sex is being excluded.

IV.e. Age of Subjects

For all phenotypes, infants, children and young adults who are 21 years of age or under are included in this study.

IV.f. Racial and Ethnic Origin

Subjects of all racial and ethnic backgrounds are included in this study, with the following distribution of race/ethnicity: approximately 1/3 Black/African ancestry; 1/3 Latino/Hispanic ancestry, and 1/3 White/ European ancestry. If this expectation is incorrect, we will cap inclusion of White children at <40% of total participants, to ensure at least 60% are from underserved populations, consistent with the requirements of this funding opportunity.

IV.g. Vulnerable Subjects

This study is a pediatric and young adult study; therefore infants, children and teenagers will have the opportunity to enroll with a parental/guardian who is capable of providing informed consent. Young adults (18-21) with intellectual disability whose parents have legal guardianship and are capable of providing informed consent are also able to participate. Cognitively intact teens or young adults who are pregnant or who have a pregnant partner may also be included but they will be counseled against use of this research testing for prenatal purposes and will be immediately referred to a non-study related prenatal genetic counselor, with whom our study team will retain close communication.

All of our potential subjects are children or young adults with a likely genetic etiology of their illness. Their participation is justified as there is a potential of direct benefit (diagnosis) with minimal risk.

V. Recruitment and Retention

V.a. Recruitment Overview

In general, our participants will be under the care of one of our study physicians or one of their colleagues. Prior to first enrollment, a member of the study team will meet with each Division (Neurology, Cardiology, and Immunology at MS and EM) to teach them about the study and discuss how to inform their Division's study physician about a potential participant. The study physician will be in frequent contact with the CRC, and will regularly update him/her about all potential participants.

Prior to any contact with the study team, potential (referred) participants will be pre-screened to ensure eligibility. A HIPAA waiver is being requested to assist with the pre-screening EPIC review (see Section III.a.).

There are three main scenarios for recruitment:

- *During a routine clinic visit:* The CRC will find out from the physician or Epic when the referred participant is next due in clinic and will plan to meet with them at that time. The study physician is responsible for introducing the study to the family, and if the family is interested, will then introduce the CRC to them for further discussion. Bullet points for the physician are attached in Appendix v. The CRC will discuss the study with the family (English and Spanish scripts are attached in Appendix j) and will provide them with study brochures (English and Spanish versions) are attached in Appendix i);
- *During a phone call:* If no clinic visits are scheduled, the physician will contact the family by telephone or email to introduce the study, and ask the family if they are interested in being contacted by the study team. After the family agrees to have the CRC contact them, the CRC will call the family to discuss the study using the script (Appendix j), and will share the study brochure with them by mail or email. The CRC will then call the family several days later to answer and questions and discuss next steps, and
- *During an inpatient admission:* Other participants may be identified through inpatient admission. In this case, the admitting service will notify the appropriate study physician, who will then notify the CRC. Again, the CRC will use the script and brochure.

V.b. Recruitment and retention strategies

We have assembled an outstanding team of seasoned clinicians, respected medical center and school leaders, and NIH-funded researchers with outstanding records for recruiting children and families in their respective specialties into clinical trials. The Genomics Stakeholder Board, situated at Mount Sinai, has been working with our team to devise sensitive, effective strategies for recruiting and retaining study subjects. The Board has reviewed and provided feedback about our informed consents, study brochures, and recruitment scripts.

Carefully trained, bilingual, dedicated site-specific research coordinators that are from the same demographic groups and neighborhoods as participants will work with the pediatric subspecialists to recruit patients, and will facilitate retention using relationship building, continuity with specific participants, sending personalized birthday and holiday cards, calling between study visits to check in and having multiple contacts and modes of contact (e.g., phone, mail, text, email, intercepting at upcoming clinical appointments).

VI. Informed Consent

VI.a. Overview of Informed Consent Versions and Processes

Informed Consent: Baseline Survey

The baseline survey consent will be reviewed with all parents/legal guardians of potential participants.

Our research focus of the surveys is only on parental responses, and as the surveys are appropriate for parents of individuals up to 21 years of age, we will only consent parents (i.e., there is no need to consent young adults (18-21) for this part).

Versions of *Informed Consent: Baseline Survey*
Lead-in Phase (N=30):

- Parents of children 0-17 years old – *Baseline surveys and feedback*
- Parents adult children (18-21) with diminished capacity – *Baseline surveys, feedback*
- Parents of adult cognitively intact children (18-21) – *Baseline survey, feedback*

Main RCT Phase (N=1100):

- Parents/Legal Guardians of all study participants

Informed Consent: Main Study

The main study consent will be obtained at the Baseline visit by our dedicated study genetic counselors and will include assent from capable minors. The informed consent process will include extensive pre-test education, including descriptions of the research study, the risks and benefits of WGS and TGP, and will offer parental choice about ACMG secondary findings, consistent with current ACMG recommendations . [25]We have worked closely with the clinical testing laboratories (NYGC and Sema4) to incorporate the appropriate CLIA- and NYS-approved language for genomic testing. We have ensured that our informed consent documents and include the Core Elements suggested by Jamal *et al*. [26]In addition, we have worked closely with the Genomics Stakeholder Board, study bioethicists and genetic counselors to ensure that the consent is understandable by our population and at the appropriate literacy level. [27]

Versions of *Informed Consent: Main study*
Lead-in Phase (N=30):

- Parents of children 0-17 years old – *Main study (genomic testing, blood draws, parental ROR1 and ROR2 surveys and/or tool feedback)*
- Parents adult children (18-21) with diminished capacity – *Main Study (genomic testing, blood draws, parental ROR1 and ROR2 surveys and/or tool feedback)*
- Adults (cognitively intact 18-21) – *Genomic testing, no surveys*
- Parent of adult cognitively intact children (18-21) – *Parental blood draw, ROR1 and ROR2 surveys and/or tool feedback*
- Assent – *Main study (testing)*

RCT Phase (N=1100):

- Parents of children 0-17 years old – *RCT main study*
- Parents adult children (18-21) with diminished capacity – *RCT main study*
- Adults (cognitively intact 18-21) – *Genomic testing, no surveys*
- Parent of adult cognitively intact children (18-21) - *Parental ROR1 and ROR2 surveys, and parental blood draw*
- Assent – *RCT main study*

When parents choose to receive their child's secondary findings, the parents will be able to decide if they would like to receive their own secondary finding results. This option will be given to the parents of cognitively intact young adults as well. As such, parents will be asked to sign a clinical laboratory consent form regarding their preference for release of secondary findings for themselves.

Pediatric assent will be taken on all cognitively intact children who are of appropriate age. The assent includes language informing the children that their parents may choose to share their de-identified data with secure, public research databases, and that if they disagree with that plan after they turn 18, they should contact the study team. The study team will check if it is possible to retrieve and destroy data at that point, although it may not be possible because of de-identification.

Children who turn 18 during the study and who are capable of providing informed consent will be re-consented at that time using the adult (cognitively intact 18-21) consent form. The informed consent and pre-test education session will always be performed by a study genetic counselor during the Baseline visit. If we are unable to contact the 18-year-old, and if we have not yet shared their de-identified data with secure, public research databases, we will not share it

Our informed consent documents have been reviewed with our Genomics Stakeholder board and study bioethicists for their input about language, appropriateness, and inclusivity.

VI.b. Parental Approval and Child Assent

Child assent will be obtained in all cognitively appropriate children who are capable of doing so.

VI.c. Remuneration and Costs

There will be no cost to participate in this study. The costs of study-related genomic testing (WGS and TGP) are covered by the study and will not be billed to patients. Similarly, they will not be billed for study visits (Baseline, ROR1, ROR2). If additional consultations or clinical studies are needed based on the results of genomic testing, they will be billed as part of routine clinical are, as they would be done for clinical purposes.

Lead-in Phase (n=30): Study participants of the Lead-In phase will receive an additional $40 for the for participation in the survey and/or GUIA feedback sessions. They will also receive the main study gift cards as outlined below.

Study subjects will receive $20 gift cards (choice of Amazon, Target, or CVS) at the Baseline and ROR1 visits, and $40 for the ROR2 visit. This amount will be paid to the 'family' as a whole, meaning if a cognitively intact adult child (18-21) participates with his/her parent(s), this amount will be paid to the 'family', not individual 'subjects'. If the subject withdraws from the study before all visits are completed, they will be paid for the completed visits.

VI.d. Provisions to Protect Patient Privacy

All contact with the patient regarding the research will be done privately in a room with the door closed. Only authorized personnel will be present when discussing the research. No sensitive issues will be discussed in a public area. Every effort will be put in place to limit the amount of information left on a phone message and/or email. The subject will be asked what their preference will be in communicating with them (phone, email, etc.) and this will be recorded by the CRC.

VII. Risks and Benefits

VII.a. Risks and Protection Against Risks

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. In addition to what is described below, there may be unforeseeable risks that occur as a result of exome sequencing and its clinical interpretation.

Risks related to randomization: We cannot fathom any risks specifically related to participation in either the traditional or GUIA arm. This is important as this randomization will take place prior to informed consent.

Risks related to blood draw: Rarely, the vein where we inserted the needle will become sore or

red. Sometimes, a temporary harmless "black and blue" may develop. Very rarely, fainting may occur.

Risks related to learning genetic information: There is a chance that the subject may learn that they carry a gene mutation that may increase their risk for a specific medical condition. Although they will be referred for medical help or risk management as appropriate, this knowledge might be upsetting and may cause you anxiety or psychological distress. As described above, some of these conditions may have treatment or screening options available, while others may not. Some of these conditions may also be potentially stigmatizing. The subject will be asked to think about if they want this information long before the data is available. However, even if they decide to receive this information, it can be upsetting.

Subjects may also learn that a family member is at risk to develop certain medical conditions or diseases. They may also learn that their ancestry or parentage is different than they thought. This may also cause some psychological distress.

This test may suggest that biological relationships of family members are not as reported, such as non-paternity (the man identified as the father of the child is not the biological father). The lab report will not directly state that there is a question about paternity, but people reading the report may be able to figure it out nonetheless. If the child is found to carry a pathogenic variant in a gene, this may affect their reproductive decisions. The family will have the opportunity to discuss this with the study's genetic counselor, and will be offered additional genetic counseling resources for your future use.

Risks associated with genomic testing: These tests may not generate accurate results in instances that cannot be predicted. Such instances include but are not limited to: incomplete medical and/or family history, unavailability of critical family members for help with interpretation, inaccurate reporting of family relationships, or technical problems. The results of this test may have significant medical, psychological, and social implications for you and your family. You and your family members may experience anxiety before, during, and after testing.

Risks related to privacy: Privacy is very important to us, and we will use many safety measures to protect it. However, in spite of all of these protections, there is the possibility that the exome sequence data derived may, even when presented without other identifying factors, allow a subject to be re-identified, and therefore this research study cannot promise anonymity, particularly if they choose to publish or share exome sequence data. The risk of this happening is very small, but may grow in the future. We will share all genetic information with dbGaP database, and a break in security may also pose a potential risk to blood relatives as well as the participant. For example, it could be used to make it harder for the participant (or a relative) to get or keep a job or insurance. If private information was misused it is possible participants may also experience other harms, such as stress, anxiety, stigmatization, or embarrassment from revealing information about family relationships, ethnic heritage, or health conditions.

Specific illnesses and known genetic problems may be found by examining DNA. In the future, insurance companies may use this information to determine if someone is able to be insured by their company. The genetic results from this study will become part of the participant's medical record. Insurance companies routinely have access to such records. We will not release information about participants or their family to anyone unless authorized to do so.

There is a small risk that participants may face discrimination on the basis of genetic

predispositions that are identified through this project. Sometimes patients have been required to furnish information from genetic testing for health insurance, life insurance, and/or a job. There is a Federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers of over 15 people to discriminate against individuals based on their genetic information. However, it does not protect against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

A risk of taking part in this study is the possibility of a loss of confidentiality or privacy. Loss of privacy means having personal information shared with someone who is not on the study team and was not supposed to see or know about information.

Risks related to answering questionnaires: Participants may feel uncomfortable answering questions about knowledge and understanding of genetic testing. They can choose not to answer questions that make them feel uncomfortable.

New findings: If we learn any significant new findings during the study that might influence an individual's decision to participate, we will contact them and explain those findings to them.

VII.b. Potential Benefits to the Subjects

There is no guarantee that the subject will get any direct benefit from being in this study. However, we may learn about the subject's diagnosis, which may improve their treatment. Moreover, some may feel benefit from knowing their diagnosis even if it does not improve care *per se*. There are possible benefits from learning about the subject's secondary findings, such as identifying future disorders that can be prevented or treated. Others might potentially benefit from the subject's participation in this study. Understanding genetic diversity can help all people benefit from the genomic medicine. Helping us learn how we can best communicate information about WGS may help individuals who might choose to have WGS in the future.

VIII. Data Analysis

The analysis team will be led by the project PI and will include interviewers, statisticians, computational genomicists and members of the clinical research team (all key personnel in NYCKidSeq and CITI credentialed).

Descriptive statistics will be calculated for quantitative survey instruments in the baseline, ROR1 and ROR2 surveys. In the case of missing data, when survey measures contain summary scores, a mean score will be calculated based on the responses provided. We will adjust for covariates, including age, sex, and race/ethnicity where appropriate. Repeated measures of analyses of variance (ANOVAs), chi-squared test or regression models will be fit to the data in a simple paired design (N=550 on each arm) to assess and identify significant improvements in parental understanding, satisfaction, and feelings about the results, and their subsequent behavior in the traditional GC group vs GUIA group. A statistical significance criterion of $p< 0.05$ will be used for all analysis.

We will also analyze the data from the think out loud feedback sessions of parents performed during the lead-in phase of the study (N=30) to learn about the GUIA (N=15) and to identify any issues with the survey (N=15). Any useful feedback from these sessions will be incorporated into the tool and the survey.

We will also perform analysis to compare the clinical utility and diagnostic yield of WGS compared to TGP by comparing the results status (+/-/uncertain) via each modality. We anticipate that WGS may underperform compared to TGP for rare variant detection, and to observe regional differences in coverage due to issues of capture, and genome mapping. We expect that WGS will show improvement over chromosomal arrays for detecting smaller Copy Number Variants, more precise breakpoint resolution, and better location and orientation of duplicate sequences. We will focus our analysis on concordance, accuracy and reproducibility as being most important for clinical utility. We will also examine differences in diagnostic yield of pathogenic, likely pathogenic or uncertain variants across race/ethnicity groups.

IX. Study Monitoring

IX.a. Study operating procedures

Appendices a-cc includes:

- Training materials and manual for recruiters that will delivered by the project manager, including all study protocols, background on genomics and the clinical conditions under study, use of REDCap, consent, recruitment, survey and retention techniques. The CRCs will be observed in role plays for all study aspects (i.e., responding to common reasons for study resistance, mistakes obtaining surveys) until they are functioning confidently and accurately.
- Patient/family and clinician surveys with data dictionaries and references
- Training materials for physicians detailing a communication plan for referral within their practice, bulleted recruitment scripts, the phenotype checklist, and options about return of results. Genetic counselor training with study information, and opportunities to practice consenting, pre-test and post-test counseling.

lX.b. Database

Data will be entered and stored in a REDCap database to track and monitor patients. The database was adapted from the data dictionary from the GUARDD study to include MRNs and patient IDs, inclusion criteria, baseline, 3- and 9-month patient contact logs and surveys, calendar and reminder functions, and ability for recruiters, managers and investigators to track workflow and perform queries to assess the status of patients (i.e., who is outstanding for a 3-month ROR1 visit).

IX.c. Data and Safety Monitoring

As this is a non-interventional study, there will not be a separate Data Safety Monitoring Board. However, the weekly phone calls, led by Drs. Wasserstein and Kenny will address any questions/concerns raised by families, parents, or study personnel. Additionally, they will review all data at their respective sites with the appropriate study personnel to ensure completeness and accuracy.

X. Privacy and Data Sharing

X.a. Sharing Results with Subjects

The purpose of this NIH-funded study is to assess the clinical utility of genomic sequencing. Therefore, the results of whole genome sequencing as well as the targeted gene panel will be disclosed to the subject. Pre-testing counseling will be done by a genetic counselor and will include subject preferences with regards to returning secondary findings. Results will be returned by the

genetic counselor during the ROR1 visit, and the subjects will have a ROR2 visit approximately six months after the return of results. In addition, genomic results (variant calls) will automatically be re-analyzed every six months at the clinical laboratories as per CLIA-approved protocols, and subjects will be informed of any significant findings; depending on their preferences regarding secondary findings. Our study team will review the subject's genetic results every twelve months for the duration of the study (until May 2021) using new knowledge to re-interpret results. If a study or referring physician feels that a change in the patient's phenotype prompts a re-analysis, a request will be placed with the clinical laboratories with these additional filters.

X.b. Information and Specimen Banking

If participants consent to part in this study, they are voluntarily agreeing to the indefinite storage of their and their child's blood and sequencing information by the research study, including NYCKidSeq research teams at Sema4, NYGC, EM, and MS. EM requires that medical records are kept for 25 years; these (clinical reports) will be stored at EM with personal identifiers such as the child's name. The child's identifiable data may be used by the NYCKidSeq research team for reasons related to, and for reasons unrelated to, the current research project. Samples may be used for either research or for clinical purposes if additional testing is needed.

Participant can decide that they do not want the NYCKidSeq research teams to keep their and their child's biological samples, and may withdraw consent to storage and use of such samples at any time by contacting the PI, Dr. Melissa Wasserstein at 3411 Wayne Avenue, Bronx, NY 10467, in writing. If this happens, we will promptly destroy the sample(s) or the portions thereof that have not already been used. However, the parent(s) and their child's sample may have already been distributed to other researchers within NYCKidSeq before the request to destroy was received, and we may not be able to retrieve it and stop future research.

We will ask participants their permission to allow their and their child's de-identified blood, saliva (if collected) and DNA samples, and sequencing information (data) to be shared with other researchers (i.e., those who are not associated with NYCKidSeq). These biological samples and the sequencing data may be used in future research, including future genetic testing, to learn about, prevent, or treat health problems.

To protect participants privacy, Montefiore Medical Center has policies and procedures in place that are overseen and monitored by the Institutional Review Board. Montefiore Medical Center requires its staff who may use or have access to participant samples (parent(s) and child) or data to receive training on its privacy and data security policies, and to follow those policies with care.

X.c. Sharing Results with Scientific Community

Public Sharing of genome data

One purpose of this study is to help researchers around the world learn about the genomes of people from diverse populations. If the participants agree to take part in this study, some of the child's genetic and related health information will be entered into one or more scientific databases available to other researchers inside and outside of EM, MS, Sema4, and the NYGC.

Participants will have the option to share such data with secure, public research databases like The Database of Genes and Phenotypes ("dbGAP"), an NIH-maintained database which has restricted access. Only researchers who apply and are approved can access to these restricted databases, like dbGAP, dbVar, and other databases. The NYCKidSeq program will limit sharing of data to only

restricted databases, which require approval to access. Additionally, we are one of six CSER consortium sites where researchers across the Consortium may apply for access to survey and health data, and residual samples collected from our study. A member of the CSER consortium must submit their request to an ethics board for approval. Any approved CSER consortium requests will be require written ethics approval which will then be reviewed by all MPI's including site bioethicists and consulting with our site IRBs prior to release of any de-identified information.

Please note that identifying information about the participants, such as name, address, telephone number, or social security number, will NOT be put into these scientific databases. However, because the child's genetic information is unique to them, there is a chance that it could be traced back to the participant. The risk of this happening is very small and is explained in the *Risks* section of the protocol and consent. Researchers will always have a duty to protect your privacy and to keep your information confidential.

We have also included language in the pediatric assent that informs teens that their parents may choose to share the teen's sequencing data in secure, public research databases and/or their de-identified samples with outside researchers. When the child turns 18, if s/he does not agree with the parental decision plan, s/he may contact the study team to share their previously unshared data/sample. Conversely, if their parents chose to share their data/sample and they disagree, we will not share it, although if the data/sample has already been de-identified and shared, it will not be possible to retrieve it.

For those participants who have already enrolled and signed earlier versions of informed consent that mandated sharing data with secure, public research databases and sharing samples with outside researchers, we will contact them either in person, by email, or by phone to offer them the opportunity to **opt out** of sharing their de-identified data with these secure, public research databases *prior to* data upload and sharing de-identified sample with outside researchers, if it hasn't been shared already. We will record their decision and note it in our database.

X.d. Data Storage and Confidentiality

Hardcopies of data
All hard copies of source documents will be locked in a secure cabinet while they are unsupervised. Only authorized research study personnel will have access to this information.

Storage and security of electronic data
Any email correspondence between the research teams will be secured using institutionally approved encryption and identifiable patient information will be limited to the minimum necessary in order to uphold protection of patient privacy. Coded documents and specimens will be stored indefinitely unless the participant withdraws from the study.

X.e. HIPAA Authorization

The researchers and study staff will follow federal and state laws to protect participants' privacy. We will institute rigorous data confidentiality and privacy protections, in accordance with HIPAA, to minimize the chance of risk for the participants. The following procedures will be used at MS and EM safeguard data: 1) train staff on data sensitivity and safeguards; 2) store and process sensitive hard copy in a centralized location; 3) secure sensitive hard copy in locked files when not in use; 4) remove names, addresses, and other direct identifiers from hard copy and computer-readable data if they are not necessary for participant tracking; 5) destroy all identifiable links to data after accuracy has been verified and final analyses have been completed; and 6) protect the patient

information file, secured in our file server, by Microsoft NT encrypted password and a separate password to access the database file on the server.

The health information that we may use or disclose for the research described in this protocol includes information from the child's entire medical record, such his/her name, phone number, email, medical diagnoses, dates, test results, social security number, medical record numbers, etc.

The only people who can see the participant's research records are:

- Researchers at Montefiore Medical Center and other individuals who work with the researchers
- Organizations and institutions involved in this research, including those that fund the research, including: *The National Institutes of Health, the Clinical Sequencing Evidence-Generating Research Consortium, Albert Einstein College of Medicine/Montefiore Medical Center, the Icahn School of Medicine/Mount Sinai Health System, Sema4, and the New York Genome Center*
- Groups that review research such as central reviewers, Institutional Review Boards, the Office for Human Research Protections, the US Food and Drug Administration, data coordinating centers, and domestic and foreign agencies that regulate research.

The purposes of these uses and disclosures are to (1) conduct the study and (2) make sure the study is being done correctly. The information covered under this section may no longer be protected by federal privacy laws (such as HIPAA) once disclosed, and those persons who receive the participant's health information may share it with others without the participant's additional permission. All of these groups have been asked to keep the participant's information confidential.

Medical information collected during the research, such as the genomic test results, will be entered into the child's Montefiore electronic medical record and will be available to clinicians and other staff at Montefiore who provide care to them.

X.f. Certificate of Confidentiality

As this is an NIH-funded study, we have added the following statement to all consent forms:

"As a way to protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health, which is funding this study. If information from this study were requested or subpoenaed by government agencies or the courts, we would use the Certificate to attempt to legally refuse to provide that information. These requests are rare – in only a few cases did researchers have to use the Certificate, and it was honored most of the time, but not every time. There are several kinds of situations to which the Certificate does not apply. For example, we are still required to report child abuse and some diseases, and we must make data available to the government for review or evaluation of our research. The Certificate does not prevent you or a member of your family from voluntarily sharing information. Similarly, if an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information."

XI. Data Quality Control & Database Management

XI.a. Data entry

A REDCap database will be developed to track and monitor patients, adapting the data dictionary from previous studies. This includes MRNs and patient IDs, inclusion criteria, baseline, 3- and 9-month patient contact logs and surveys, calendar and reminder functions, and ability for recruiters,

managers and investigators to track workflow and perform queries to assess the status of patients (i.e., who is outstanding for a 3-month visit). Surveys will be piloted with patients/parents using think out loud feedback techniques, revised accordingly, and entered into REDCap so recruiters can use tablet PC's to survey and directly enter data.

Once a week, the project manager will review the data as part of quality control. The check will review the data for errors, outliers, missing fields, inconsistencies, etc. A REDCap 'operations manual' will be created for this study.

XI.b. Plan for management of identifiers

Limited identifying information of consented participants will be stored in a web-based REDCap database. The REDCap server is managed by Mount Sinai IT and is firewall protected. User access to the database for study personnel will be managed by the Study Project Managers, Nicole Kelly (EM) and Michelle Ramos (MS). Data access for study personnel will be limited to their site participants and what is required for their roles on the project.

The link between identifying information and the research code (recruitment ID and Global study ID), MRN and subject's initials will be stored in a secure file in a password-protected networked drive that sites behind Institutional firewalls. This drive is only accessible to those with approved access determined by their required roles. This linking file will only be accessible to the site project manager and principal investigator. Computerized data will be encrypted to enhance protection of confidentiality.

Any paper source documents (e.g., consent forms, phenotype checklists, physician outcomes report Pre- and post-GC checklists, copies of the educational tool, results, surveys, CRC notes), anything that is printed linked to the patient, will be kept in the subject's research study binder. Subject binders will be kept in a locked cabinet in the project managers locked office, to which only authorized research study personnel will have access to.

Subject documents will be identified by their study numbers when applicable, with the exception of any clinical documents that are part of their permanent medical record. The data obtained and stored for this research study will also be used for standard clinical care for each subject. Only personnel directly involved in the research study will have access to this information.

Clinical research records (source documents) will be reviewed quarterly by the site project manager to ensure identifiers have been removed, as deemed necessary. Coded documents and specimens will be stored indefinitely unless the participant withdraws from the study. In the even that a subject withdraws or declines to participate at any time, their research records (source and electronic REDCap) will be purged of PHI (e.g., name, MRN, address, contact information). The site project manager will maintain the above-mentioned subject linking file (initials, MRN, and study IDs) in the event re-identification is ever needed.

As this study involves genetic testing done for clinical (diagnostic) purposes, and the results are entered into EPIC along with the GC session notes, will be maintained in the participant's permanent medical record, and up to 25 years as required by Einstein Montefiore as per Institutional policy. The remaining clinical research records including IRB documentation will be retained for at least three years after the clinical research study is completed consistent with NIH and FDA policies, or longer if required by Einstein. Documents will be shredded and disposed of in accordance with hospital guidelines.

XI.d. Data Backups

Disk-to-disk backups of the operational database will be made four times daily to a warm spare server in the Data Center that is not connected to the Internet. Monthly off-line backups will be stored on DVD in the locked backup cabinet in the Health Evidence and Policy's IT facility in Room IMI L4-57. These backups will be destroyed after 90 days. Analytical data sets with de-identified data will be stored in the same facility for the duration of the project. The EM research team will only have access to their site-specific subject data.

XII. *References*

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XIII. Appendices

a. Schedule of Assessments

Visit	Recruitment	Baseline	Return of Results Visit 1 (ROR1)	Return of Results Visit 2 (ROR2)	Data Review
	-3m to 0	*0*	*3m*	*8-10m*	*5m/27m***
Informed Consent: Baseline Survey	x				
Baseline Survey Set	x				
Randomization: ET or SOC	x*				
Phenotype/ Inclusion-Exclusion	x				
Informed Consent: Clinical Trial		x			
Pre-test Genetic Counseling		x			
Blood draw for WGS/TGP		x			
Review results of WGS/TGP with family (SOC or ET)			x		
ROR1 Survey Set			x		
ROR2 Survey Set				x	
Re-analysis of WGS data for subjects with negative and uncertain results					x
Electronic Health Record Analysis					x

See labeled study attachments:

b. **Baseline Parent Survey ***
c. **ROR1 Parent Survey ***
d. **ROR2 Parent Survey ***
e. **Decliner Parent Survey ***
f. **ROR1 Provider Survey**
g. **EHR Extraction Site Survey/ROR2 Provider Survey**
h. **Healthcare Administration Survey**
i. **Recruitment/Study Information Brochure***
j. **In-Person Recruitment script for clinical research coordinators*…**
k. **Phone Recruitment script for clinical research coordinators*…**
l. **Baseline consent/survey reminder letter***
m. **Baseline GC visit reminder letter***
n. **R0R1 reminder letter***
o. **R0R2 reminder letter***
p. **Baseline consent/survey no show letter***
q. **Baseline GC visit no show letter***
r. **R0R1 no show letter***
s. **ROR2 no show letter***
t. **Holiday card***
u. **Birthday card***
v. **Physician study bullet points**
w. **Physician phenotype checklist**
x. **Referring physician opinion and recommendations**
y. **Pre-test GC checklist**
z. **Post-test GC checklist**
aa. **Participant package inserts**
bb. **GUIA mock-up**
cc. **NYGC and Sema4 CLIA certificates**