TeleKidSeq: Incorporating Telehealth into Clinical Care of Diverse NYC Children Undergoing Whole Genome Sequencing

1. **Background**

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) for our CSER site called NYCKidSeq.

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. Evidence suggests that this bias is likely to persist in the ongoing and upcoming efforts to sequence people’s entire genomes. 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 data pool, and are frequently the last to benefit from advances in research and technology. This study will also accumulate data on how this population reacts to the incorporation of one of two different educational models (share screen vs. no share screen) through telehealth.

TeleKidSeq is a pilot study that is part of NYCKidSeq. The study is focused on three broad areas of hereditary childhood disease. By the completion of this one-year project, we will sequence the genomes of 496 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 as high as ~40% of autism and ~60% of intellectual disability cases. 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.

We have, therefore, assembled experts in population genetics/genomics and data scientists, with clinical lab personnel 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 this 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.

With the continued threat of COVID-19, the medical profession has had to adapt many of its current practices to cope with the increased stress on the hospital system, as well as protecting patients and providers from possible exposure (Rosenbaum, 2020; <https://doi.org/10.1056/NEJMms2009984>). As the previous NYCKidseq clinical trial was significantly interrupted by these changes to patient care as laid forward by each individual institution, we recognize the opportunity to assess alternative forms of genomic communication with families from underserved populations. Therefore we launch this new pilot study called TeleKidSeq to evaluate two different modes of delivering genetic results via telehealth.

**Telehealth and 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 the advent of COVID-19, most healthcare professionals have had to adjust the way they triage, evaluate, care for patients, and discuss genetic testing and results. Instead of in-person services, many medical specialties including genetics, have adopted telehealth to reduce staff and patient/family exposure to ill persons, preserve personal protective equipment, and minimize the impact of patient surges on facilities. Wosick *et al*., 2020 define telehealth as the entire spectrum of activities used to deliver care at a distance—without direct physical contact with the patient. Telehealth encompasses both provider-to-patient and provider-to-provider communications, and can take place synchronously (telephone and video), asynchronously (patient portal messages, e-consults), and through virtual agents (chatbots) and wearable devices (<https://doi.org/10.1093/jamia/ocaa067>). While telehealth technology and its use are not new, widespread adoption among healthcare professionals and patients has been relatively slow (CDC, 2020; <https://www.cdc.gov/coronavirus/2019-ncov/hcp/telehealth.html>). The current COVID-19 event is not the first time that government agencies and healthcare providers have turned to telehealth in response to disaster situations. In 2000, the North Atlantic Treaty Alliance (NATO) developed a Multinational Telemedicine System that has been deployed with their military forces during various crises, and has provided areas in need with health support from medical experts located in other countries (CDC, 2020). There are many examples prior to COVID-19 where healthcare professionals used telehealth to provide healthcare services to victims of hurricane disasters, severe prolonged droughts, and past pandemics like Severe Acute Respiratory Syndrome (SARS) in 2003 (Smith, 2020; <https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/32196391/>). In the midst of “stay-at-home” orders and physical distancing, telehealth programs can overcome physical barriers to provide patients access to medical care. However, the complexity involved in educating and discussing genetic-related concepts, especially during a return of result appointment, may be challenging through telehealth. Currently, there is not enough data on how complex subject matters like genetic testing and results disclosure are conducted via telehealth. One important component of a genetic consult is educating patients on certain genetic concepts like genes, inheritance, variants of uncertain significance, and other genetic terminology. During this education process, Genetic Counselors (GCs) hope to help patients understand how their genetics can impact future healthcare management, screening, and surveillance. During this education process, some healthcare professionals may use visual aids, diagrams, charts, and other figures to help facilitate learning and understanding of such genetic concepts.

The rapid and widespread dissemination of telehealth was prompted by the need to continue to provide outpatient care when COVID-19 shelter-in-place and social distancing measures forced clinics and physician practices to close to in-person visits. It will be critical to understand whether telehealth provides comparable or higher quality of care and whether expansions in telehealth exacerbate health disparities among certain patient populations. (Ekeland AG, Bowes A, Flottorp S. Methodologies for assessing telehealth: a systematic review of reviews. International journal of medical informatics. 2012;81(1):1-11.) Differences in implementation will affect telehealth uptake and impact. Thus, it is important that patients and families receive enough technical assistance to overcome barriers in receiving telehealth visits, and that the information provided in these visits is culturally and linguistically appropriate, and not at a high reading level. Understanding patient and provider experiences is essential to determining the continued value of telehealth in primary care and its impact on disparities. Addressing this suite of critical questions requires both qualitative and quantitative methods, as well as close collaboration with stakeholders.

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 will compare parental understanding of and satisfaction with receiving genetic test results for their child among those who receive results via telehealth with screen-sharing capabilities versus those receiving results via telehealth without screen-share capabilities. With the increased need for telegenetics services in the age of COVID-19, many secure systems are not equipped with screen-sharing capabilities, requiring genetic professionals to send resources or results before or after the visit. We would like to explore the effectiveness of using screen-sharing technologies in telehealth and how it impacts genomic understanding. For each participant we will generate a personalized results report via a genomics communication tool called GUÍA previously developed by our group, and a PDF handout of the GUÍA mailed, or a digitized copy emailed, to participants after post-test genetic counseling. During the post-test genetic counselling session, the digitized copy of the GUÍA report will be shared on the screen for one group, while the other group will simply be shown visual images, similar to those contained in the report, over a camera. The study will compare these two groups by assessing participant understanding of and satisfaction with receiving genetic test results for their child.

**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 advise about our study design.

**Summary**

Taken as a whole, the TeleKidSeq 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 collect data points related to telehealth delivery methods by testing, analyzing, and implementing screen-share technology. We will standardize the participants experience by using a novel, digitized communication tool GUÍA to communicate genetic test results after the post-test genetic counselling in both arms. During the post-test genetic counselling session, the digitized copy of the GUÍA report will be shared on the screen for one group, while the other group will simply be shown visual images, similar to those contained in the report, over a camera. We will evaluate understanding of these results by families and patients, and care providers at all levels of expertise, in two health systems through telehealth in an urban setting. 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.

1. **Study Design**

***II.a. Study Objectives***

As described above, TeleKidSeq 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) for diagnostic purposes.

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

**Aim 3.** Evaluate the use of live videoconferencing telehealth platforms with and without screen-sharing capabilities to facilitate the delivery of complex genomic results, and assess evaluating parental understanding, satisfaction, and feelings about the results, and their subsequent behavior.

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

***II.b. Duration of Participation***

Recruitment will begin in approximately 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 approximately 9 months. The study has been approved to recruit through May 31, 2021 by the funder (see “Projected Enrollment Schedule” below).

**Projected Enrollment Schedule:**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Oct ‘20 | Nov ‘20 | Dec ‘20 | Jan ‘21 | Feb ‘21 | Mar ‘21 | Apr ‘21 | May ‘21 | Total |
| Monthly Target Enrollment | 48 | 56 | 32 | 72 | 72 | 72 | 72 | 72 | **496** |
| Per Site | 24 | 28 | 16 | 36 | 36 | 36 | 36 | 36 | **248** |

***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. 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. 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.

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. 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.

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. Mendelian   traits   and   aneuploidy   underlie approximately 10% of cases, and pathologic copy number variations (CNVs) and *de novo* single nucleotide variations (SNVs)/indels each explain another 10% of cases. 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. 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

***II.d. Primary, Secondary and Exploratory Outcomes***

**Primary outcome**

1)Perceived understanding of genomic testing results, with comparison of results from genetic counseling visits completed via video telehealth visit with screen-share capabilities versus no screen-share capabilities. (ROR1 and ROR2, Q3);

**Secondary outcomes**

**Understanding genomic results**

1)    Objective understanding of genomic testing results, with comparison of results in Screen-share group vs no screen-share group (as measured by surveys ROR1 Q1, 2, 13 and ROR2 Q1, 2, 13);

2)    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

                  **Role of telehealth platform**

3)    Patients' satisfaction with and preference for telehealth visits with screen-sharing capabilities or no screen-sharing capabilities versus in-person counseling and compare the two groups;

4)    Ease of use of telehealth platform/preference for telehealth platform over in-person visits in control vs screen-share group (specific questions to include the role of images in counseling)

 **Diagnostic results of WGS**

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

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

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

**CSER Harmonized Measures**

13)    Comparison of parental satisfaction with mode of delivery in control vs screen-share group (“Satisfaction with mode of communication of results”) (ROR1, Q7);

14)    Comparison of parental overall satisfaction with results in control vs screen-share group (ROR1, Q8);

15) Parental feelings about genomic testing results in control vs screen-share group (FACToR) (ROR1 and ROR2, Q9);

16) Parental personal utility scale in control vs screen-share group (PrU)(ROR1 and ROR2, Q11);

17) Information seeking in control vs screen-share group and Perceived Usefulness of GUIA (“Information seeking”) (ROR1, Q14) (ROR2, Q7,16);

18) Comparison of behavioral changes in control vs screen-share group (“Patient-Initiated Actions Attributable to Genetic Testing”) (ROR2, Q5);

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

20) Family communication in control vs screen-share group (“Family Communication”) (ROR2, Q6);

21) Decision regret in control vs screen-share group (“Decision Regret”) (ROR1 and ROR2, Q12);

22) Economic impact of child’s health status (Baseline and ROR2, Q8);

23) Access to care (Baseline and ROR2), modified to address access if using telehealth mechanisms;

**Exploratory outcomes**

1) 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.

2) Compare comfort with computers/technology with satisfaction with return of results and with understanding of genomic results in screen-share vs. non-screen-share arms

3) Compare previous telehealth experience with satisfaction with return of results and with understanding of genomic results in screen-share vs. non-screen-share arms.

4) Describe the frequency and types of technical difficulties during study telehealth visits (if any) between the screen-share vs. non-screen-share arms.

5)  GC/provider satisfaction with and preference for telehealth visit with screening sharing capabilities or no screen-sharing capabilities vs. in-person counseling and compare the two groups.

***II.e. Clinical Trial Design***

The overall design is a pilot study, evaluating the use of video plus screen-sharing capabilities as compared to use of video but no screen-sharing capabilities via a teleconferencing platform to facilitate pre- and post-test counseling for WGS. The study will occur in the context of our performing WGS for diagnostic purposes in approximately 500 children in an effort to assess clinical utility. Children and young adults with specific disorders (see Section II.c.) will be recruited from MS, EM, and other specialty providers.

1. **Study Procedures**

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

For study subjects recruited from within the EM/MS systems, 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 CRCs may attend specific clinics after invitation by the clinics’ physician. The study physicians, physician colleagues (*i.e*., treating physicians), and/or nursing staff will provide the CRCs with a list of patients scheduled for the day or week who they deem to be potential TeleKidSeq participants. The study team member (CRC or GC) will enter and review the patients’ medical records to check if they meet inclusion and exclusion criteria. If a patient does fulfill criteria, the CRCs will notify the physicians prior to the scheduled appointment.  With the study physicians’ permission, study GCs may also pre-screen a physicians’ clinic schedule one week before the scheduled clinic day on EPIC to review patients’ medical records to see if they meet inclusion and exclusion criteria and, in this way, identify potentially eligible patients prior to their visit.

For study subjects who are referred to the study by specialists external to the MS/EM systems, study CRCs will perform eligibility screening via phone or in-person with potential TeleKidSeq participants. The role of physicians, physician colleagues (*i.e*., treating physicians), and/or nursing staff at external sites will be restricted to informing prospective subjects about the availability of the study and/or providing information about study.

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 s. ‘Physician phenotype checklist’) will securely be sent to the study team *(see ‘Recruitment’ Section V.a.)*. Phenotype checklists may be completed in printed form, electronic (PDF) form, or included as part of the patient’s chart note in EPIC. 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 the family (in-person or by phone) 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 3-months, English- or Spanish-speaking, available for study visits), and determine level of interest (*e.g*., administer baseline consent (phone), schedule visit to review baseline consent/survey (phone), and/or administer decliner survey) (see ‘Recruitment Scripts’ Appendix f and g). CRCs will also administer the “Telehealth Access” screener (Appendix g) to assess ability and comfort in using telehealth platforms for this study and to evaluate if the child and their biological mother and/or father, if available, are able to provide saliva samples via saliva kit or, if not, to provide blood samples using outpatient services within three weeks of signing Informed Consent: Main Study.

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 CRC and GCs will have access to all variables in the charts, sensitive material/variables that are not necessary for this study will not be considered. Once the CRC/GC has reviewed the patient’s eligibility, 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 practicably carried out without this waiver as patients being recruited may be unsure of genomic testing eligibility 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 Telehealth with Screen Sharing or Telehealth without Screen Sharing**

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: Baseline Survey), be randomized to participate in either the (1) Telehealth With Screen Sharing arm or (2) Telehealth Without Screen Sharing arm, using the REDCap randomization tool. The CRC will tell the parents that the results will be disclosed using Telehealth With Screen Sharing or Telehealth Without Screen Sharing, but they will not be told to which group they are assigned until their Baseline visit. CRC will inform them which arm they have been randomized to at that time.

In the Telehealth Without Screen Sharing group, participants will receive standard of care, routine genetic counseling via secure teleconferencing platform with video capability (no screen sharing) for the Baseline and Return of Results (ROR1) genetic counseling appointments. These participants will receive a PDF copy of GUIA as a resource via mail or email after the ROR1 visit is complete. In the Telehealth With Screen Sharing group, they will receive routine genetic counseling for the Baseline visit via secure teleconferencing platform with video capability (no screen sharing), and routine genetic counseling plus GUÍA using screen sharing 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:



Baseline Surveys

If the participant is able to complete the visit from their home, based on the responses to the “Telehealth Access Screener,” the baseline survey, consent, and baseline visit will all be completed via telehealth. We will be using the secure, HIPAA-compliant version of the application, “Zoom.” The clinical research coordinator (CRC) will provide the link to the informed consent that will be obtained electronically through REDCap via text or email at the visit. Parents will be able to view and sign the informed consent while the CRC discusses it with them through Zoom. If there are technical difficulties in this process, the CRC can alternatively call the parents to discuss the consent while the parent reviews and signs the consent on REDCap.

Should the family be unable to access appropriate technology for the Baseline survey, consent, and Baseline visit (as determined by the “Telehealth Access Screener”), they will come to the institution for their visit, where they will have access to a private patient area such as the Clinical Research Unit at EM. This will be conducted over Zoom using a provided tablet or computer, where e-consent can be completed.

Should e-consenting fail due to technical difficulties of any kind, whether on-site or at the participant’s home, the CRC can use a paper-copy to consent. This will be mailed to the parents or alternatively provided in-person.

After parents sign the *Informed Consent: Baseline Survey (see Section VI.a.)* electronically via REDCap or in-person, a site-specific 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 via secure video conferencing platform (preferred) or by phone if the parent(s) is unable to use secure video conferencing platform for the baseline survey. CRCs will **not** use screen-sharing capabilities when completing this informed consent and administering the survey. Of note, the survey needs to be administered before the parent consents to genomic testing by signing the Informed Consent: Main Survey consent, 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. For the baseline survey, parents/guardians may choose to complete the baseline survey in a separate visit before their baseline/enrollment telehealth-visit (in which case they would have four separate study visits), or at the time of the recruitment (*i.e*., longer first visit).  CRCs will use tablets or work computers to enter survey answers directly into our REDCap database. Baseline survey questions (English and Spanish versions) are attached in Appendix a.

***III.c. Baseline Visit***

**Informed consent and Pre-Test Genetic Counseling:** Participants will have the option to take part in the main study consenting process by using a secure video conferencing platform, either off-site (*i.e*., at home or at the family’s preferred secure location) or in the hospital setting in a private patient area (using a tablet or computer provided by the study). Although off site is preferred, the purpose of offering participants the ability to use this technology in a hospital setting is to reduce any disparities in access to this research.

At this visit conducted via secure video conferencing platform, the parent/guardian will review the *Informed Consent: Main study* with the GC and will electronically sign the informed consent and child assent when appropriate using the REDCap secure e-consenting platform.

The GC will provide the link to the informed consent that will be obtained electronically through REDCap via the chat function of Zoom, email, or text at the time of the visit. The consent form will not be sent to the participant before the visit, as this has the potential to bias the responses to the baseline survey. Parents will be able to view and sign the informed consent while the GC discusses it with them through Zoom. If there are technical difficulties in this process, the GC can alternatively call the parents to discuss the consent while the parent reviews and signs the consent on REDCap.

Should the family be unable to access appropriate technology for the Baseline survey, consent, and Baseline visit (as determined by the “Telehealth Access Screener”), they will come to the institution for their visit. This will be conducted over Zoom using a provided tablet or computer, where e-consent can be completed.

Should e-consenting fail due to technical difficulties of any kind, whether on-site or at the participant’s home, the GC can use a paper-copy to consent. This will be mailed to the parents or alternatively provided in-person.

If the child is a young adult (18-21 years of age) with intact cognitive abilities, they will electronically sign a separate 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 limitations of genomic testing. For participants randomized to the Telehealth Without Screen-Sharing arm, GCs will have the option to display standardized images on paper to participants by holding up these images to the webcam for the participant to view. For participants randomized to the Telehealth With Screen-Sharing arm, GCs will have the option to display digitized images and text from the GUÍA tool using screen sharing via teleconferencing platform. Images available to be displayed during the baseline visit will be the same for both arms and must be approved by the study GC team before use.As part of the pre-test genetic counseling, the GC 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. GCs will also describe the potential to identify American College of Medical Genetics (ACMG) secondary findings22 (*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 GC 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 CRC will send the family with a $20 gift card either electronically or by post.

**Sample collection and processing**: We will have several modes of collecting samples for this testing. Samples (whole blood, saliva, or buccal swab) will be collected from study participants, including from each available biological parent, to assist with interpretation of genomic results. We will not obtain samples from legal guardians who are not biological parents.

Sample collection method will be determined on a case by case basis as a part of the “Telehealth Access and Sample Collection screener” that will be completed with the CRC before the first study visit. This will determine the participant and family’s 1) ability to complete a saliva collection from home and 2) preference for sample collection. Outlined below are the procedures for each sample collection method.

*Whole Blood Collection:*

If the family opts for a blood draw and/or if the child is unable to cooperate for the completion of a saliva sampling kit, we will coordinate a blood draw to occur within three weeks of the baseline telehealth appointment. Should the participant not arrive to clinic within three weeks for a blood draw, this will be considered a withdrawal from the study.

After collection, blood samples from each patient will be labelled/bar-coded on site and ordered via paper requisitions. Samples will be mailed to the New York Genome Center (NYGC) Laboratory using pre-labeled FedEx packaging.

*Saliva Collection:*

Child and biological parents may opt to receive saliva kits mailed to their home for saliva collection. Families will receive a pre-addressed package and instructions to mail saliva samples to the NYGC laboratory.

*Buccal Swab Collection:*

Similar to saliva sample collection, buccal swab kits will be mailed to the participants’ home for buccal cell collection. Families will receive a pre-addressed package and instructions to mail saliva samples to the NYGC laboratory.

For families, who elect to provide saliva/buccal swab samples, the GC will explain the process of sample collection during the pre-test visit. A hard copy with instructions and link to videos demonstrating the collection. *E.g*.: buccal swab <https://www.youtube.com/watch?v=azj5b0vA2Hk>; saliva <https://www.youtube.com/watch?v=tNHY3f_dExA>

All samples will be sent to the NYGC laboratory. Accompanying materials including signed test requisition forms, pedigree, and chart note will be provided to the NYGC laboratory using a shared, secure content management platform, Box. NYGC is a CLIA-certified and approved by New York State to perform WGS for clinical purposes.  (See Appendix y)

Declining at baseline visit: 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 d. ‘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 when the results are obtained from the testing laboratory (Visit 2), and is a required study video visit regardless of whether results were abnormal or not.  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. In the case of results that will benefit input from a geneticist, GCs will involve a geneticist in the interpretation of the results.  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 “TeleKidSeq Referring Physician Opinion and Recommendations” (see Appendix t). This form will either be filled out directly by the physician, or communicated with the GC by phone or email if the provider prefers. GC will fill the recommendations in RedCap. The ROR1 visit will occur by videoconference, using a secure, HIPAA compliant platform, with or without screen sharing. Instructions to assist participants on how to use the video conference platform will be shared by the CRCs via email.

Pilot Study, “TeleKidSeq” (n=496)

The Pilot is divided into two arms, the Telehealth Without Screen Sharing arm (“Telehealth”), and the Telehealth With Screen Sharing arm (ScreenShare”). In both arms, results will be returned using a secure video conferencing platform.

    Telehealth Without Screen Sharing Arm (n=248 study wide): During the ROR1 genetic counseling session, the GC will review the purpose of the genomic testing and disclose the child’s test results. For positive test results, the GC will describe the diagnosis, associated symptoms, management recommendations, and life expectancy, if known. The GC 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 GC 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 GC will explain the meaning and uncertainty associated with these types of results and provide recommendations for continued disease management.  The GC will also disclose any secondary findings to participants who opted to receive those results.  Psychosocial concerns will be addressed throughout the encounter. Lastly, the GC will provide medical and support referrals, when appropriate, using suggestions made by the physician via the “Referring Physician Opinion and Recommendations for ROR1.”  As the WGS is NYS-approved for clinical purposes, reports will be given to the families and incorporated into their medical records, and shared with referring physicians. All discussions will be performed via video conferencing without the use of screen sharing. **For participants in the Telehealth Without Screen Sharing Arm, GC may show standardized images and WGS reports to participants by holding up these documents (on paper) to the webcam. All images used during the ROR1 visit must be approved by the study GC** **team.** If the GCs use pen and paper to draw/educate the patients, the details should be documented in RedCap. Following ROR, patients will receive (either via email or by post, based on participants’ preference) a GUÍA report and WGS laboratory report for the participants’ records. A copy of these documents will be uploaded to the Media tab in the electronic medical record (EPIC). At the end of the visit, parents will take the ROR1 survey, and then receive a $20 gift card.

    Telehealth With Screen Sharing Arm (n=248 study wide): GCs in this arm will follow the same procedures as those outlined for the Telehealth Without Screen Sharing Arm and will also utilize GUÍA with screen sharing during the genetic counseling session.  **For participants in the Telehealth With Screen Sharing arm, GCs will show GUÍA and WGS reports to participants using screen sharing capabilities.** During the ROR1 genetic counseling session, the GC will review the purpose of the genomic testing and disclose the child’s test results. For positive test results, the GC will describe the diagnosis, associated symptoms, management recommendations, and life expectancy, if known. The GC 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 GC 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 GC will explain the meaning and uncertainty associated with these types of results and provide recommendations for continued disease management.  The GC will also disclose any secondary findings to participants who opted to receive those results.  Psychosocial concerns will be addressed throughout the encounter. Lastly, the GC will provide medical and support referrals, when appropriate.  At the end of the ROR1 the GC will confirm with the participant if they would like the results to be sent via mail or e-mail, and share a copy of GUÍA and WGS laboratory report for the participants’ records.  A copy of these documents will be uploaded to the Media in the electronic medical record (EPIC). 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, GC will utilize a pre- and post-test checklist, which is attached in Appendix u and v. GUÍA will be filled out prior to all sessions, incorporating the genomic results and the medical and support referrals made by the MD via the “Referring Physician Opinion and Recommendations for ROR1” and/or via email with the MD, all participants will receive a PDF copy of the GUÍA report after the post-test counseling by mail or email.

**Hard to reach/Lost-to-follow up:** We have developed the following approach to address cases where we are unable to reach the family to return the genetic results (ROR1 visit). The study team will contact the family up to 6 times over a ~45-day window after the results are ready to return. This includes phone calls, emails and texts (where applicable) and mailing of a hard to reach letter (see ‘Final Hard to Reach ROR1 letter’). In our final attempt to contact, we will remind the family that they consented to having their child’s results shared with their child’s physician and these results become part of their medical record. If we do not hear from them, we will proceed with informing the child’s referring provider and upload the results to EPIC. We will also let the family know that they can contact the study team if they wish to receive counseling about the results at a later date, if the study is still active. Our study team will create a note in EPIC stating “that we attempted to reach the family and were unsuccessful. The results are in the Media section and we interpret them as follows…”. We will inform the referring provider of this by email as well as routing the note and results to them via EPIC.

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

This visit will occur about six months after the ROR1 visit, at ~9 months after study entry, and will occur either by secure teleconferencing platform or by phone if a visit is too difficult for the family.  At this visit, the CRC will administer the ROR2 survey (see Appendix c). We anticipate greater challenges with retaining subjects at this visit, so we will increase the gift card amount to $40 for this 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 (using Google voice number), email and/or mail reminders of upcoming visits. If it is not possible for the parents to join via secure teleconferencing platform, the ROR2 survey will be administered by phone.

***III.i. Discrepancy Committee***

At the request of the study GCs, we will hold *ad hoc* discrepancy committee meetings to review any TeleKidSeq cases that have confusing, discrepant, or unsatisfying results. The committee will consist of TeleKidSeq medical geneticists, GCs, 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.

1. **Patient Population**

***IV.a. Sample Size***

The total number of subjects expected to participate is 496.

***IV.b. Inclusion Criteria***

* Infants, children and young adults up to and including 21 years of age at the time of enrollment; 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 video;
* Currently undiagnosed, likely genetic\* cause of neurologic, immunologic, or cardiac disorders (\*as determined by disorder-specific criteria in Section IIIc. and phenotype checklist Appendix s);
* 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, or identified variant(s) of uncertain significance, 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 not have to wait 3 months prior to inclusion.
* Participating parent(s)/guardian(s) must have access to a secure teleconferencing platform.

***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.
* Families who do not have access to video conferencing capabilities and decline to come to EM or MS for ROR1 using the iPad. These individuals will instead be referred to clinical genetics at either EM or MS for follow-up.

***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 at the time of enrollment 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 European ancestry 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 partnermay 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 GC, 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.

1. **Recruitment and Retention**

***V.a. Recruitment Overview***

Many of our participants will be under the care of physicians at MS or EM. We will also recruit from local specialty practices that focus on patients with the indications in Section II.c.

Prior to first enrollment, a member of the study team will meet with each referring division or practice to teach them about the study and discuss how to inform their physician about a potential participant.  The referring physicians 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 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 r).  The CRC will discuss the study with the family (English and Spanish scripts are attached in Appendix f) and will provide them with study brochures (English and Spanish versions) are attached in Appendix e.
* *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 g), 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 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 research. 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 CRCs 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).

1. **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*

*Pilot (n=496):*

* Parents/legal guardians of all study participants

*Informed Consent: Main Study*

The main study consent will be obtained at the Baseline visit by our study GCs 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 will offer parental choice about ACMG secondary findings, consistent with current ACMG recommendations. We have worked closely with the clinical testing laboratory (NYGC) 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*. In addition, we have worked closely with the Genomics Stakeholder Board, study bioethicists and GCs to ensure that the consent is understandable by our population and at the appropriate literacy level.

Versions of *Informed Consent: Main study*

*Pilot (n=496):*

* + Parents of children 0-17 years old – *Pilot main study*

Parents adult children (18-21) with diminished capacity – *Pilot 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 – *Pilot 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 GC 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 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.

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.

1. **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 screen-share vs non-screen-share arms.  This is important as this randomization will take place prior to informed consent. The study’s randomization scheme focuses on how results will be delivered (telehealth with screen share vs telehealth without screen share), so any theoretical risks would relate to understanding of results. As there are currently no established practices or standards of care for how genetic counseling is performed by telehealth, so we do not believe that participants in either arm are at greater risk because of randomization. Both arms will have results delivered by experienced and trained GCs who will use their professional expertise to ensure maximal comprehension. GCs will use either standardized images or the GUÍA tool to explain genetic results, and images deployed in both approaches will be very similar across both arms. The only difference will be the *delivery* of those images (ie, over screen-share capabilities or over video capabilities).

**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 GC, and will be offered additional genetic counseling resources for 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 participants and their families. Participants and their 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 WGS 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 WGS data.  The risk of this happening is very small, but may grow in the future.  We will share all genetic information with the 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. Use of telehealth platforms is associated with the risk of unauthorized individuals gaining access to personal data, for example, due to security incidents like data breaches and cyberattacks. Although participants are asked to find a secure and private physical location to conduct telehealth visits, there is the chance that these visits may be held in a place where relatives or others may hear information discussed during these study visits.

**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 Participants***

There is no guarantee that the subject will get any direct benefit from being in this study. However, we may learn about the participant’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 participant or their family members secondary findings, such as identifying future disorders that can be prevented or treated. Others might potentially benefit from 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.

1. **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 TeleKidSeq are 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=248 in each arm) to assess and identify significant improvements in parental understanding, satisfaction, and feelings about the results, and their subsequent behavior in the screen-share group vs. non-screen-share group. A statistical significance criterion of p< 0.05 will be used for all analysis.

1. **Study Monitoring**

***IX.a. Study operating procedures***

Appendices a-y 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. GC training with study information, and opportunities to practice consenting, pre-test and post-test counseling.
	+ CRC Phone Script: includes Telehealth Access & Sample Collection Screener
	+ Advertisement to External (non-EM/non-MS) Healthcare Providers

***IX.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 with the other study PIs 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.

1. **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 WGS will be disclosed to the participants. Pre-testing counseling will be done by a GC and will include participants preferences with regards to returning secondary findings. Results will be returned by the GC during the ROR1 visit, and participants will have a ROR2 visit approximately six months after the return of 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 laboratory 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 TeleKidSeq research teams at 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 TeleKidSeq 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 TeleKidSeq 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. Eimear Kenny, at 1468 Madison Avenue, Annenberg 18th Floor, Room 18-80D or at 212-241-8288. 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 TeleKidSeq 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 sequencing information (data) to be shared with other researchers (i.e., those who are not associated with TeleKidSeq). 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, the Icahn School of Medicine at Mount Sinai and the Mount Sinai Hospital system has policies and procedures in place that are overseen and monitored by the Institutional Review Board. The Icahn School of Medicine at Mount Sinai and the Mount Sinai Hospital system 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, 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 TeleKidSeq 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, health, and genomic data collected from our study, which we will provide under the term of a data use agreement co-signed by our IRB.

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.

***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 MS, EM, 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, 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 electronic medical record and will be available to clinicians and other staff at 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.”

1. **Data Quality Control & Database Management**

***XI.a. Data entry***

A REDCap databasewill 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 event 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 EM 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 EM. 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 research team will only have access to their site-specific subject data.

1. **Appendices**
	1. **Baseline Parent Survey**
	2. **ROR1 Parent Survey**
	3. **ROR2 Parent Survey**
	4. **Decliner Parent Survey \***
	5. **Recruitment/Study Information Brochure\***
	6. **In-Person Recruitment Script for Clinical Research Coordinators\*…**
	7. **Phone Recruitment Script/Telehealth Screener for Clinical Research Coordinators\*…**
	8. **Baseline consent/survey reminder letter\***
	9. **Baseline GC visit reminder letter\***
	10. **R0R1 reminder letter\***
	11. **R0R2 reminder letter\***
	12. **Baseline consent/survey no show letter\***
	13. **Baseline GC visit no show letter\***
	14. **R0R1 no show letter\***
	15. **ROR2 no show letter\***
	16. **Holiday card\***
	17. **Birthday card\***
	18. **Physician study bullet points**
	19. **Physician phenotype checklist**
	20. **Referring physician opinion and recommendations**
	21. **Pre-test GC checklist**
	22. **Post-test GC checklist**
	23. **Participant package inserts**
	24. **GUIA mock-up**
	25. **NYGC CLIA certificate**