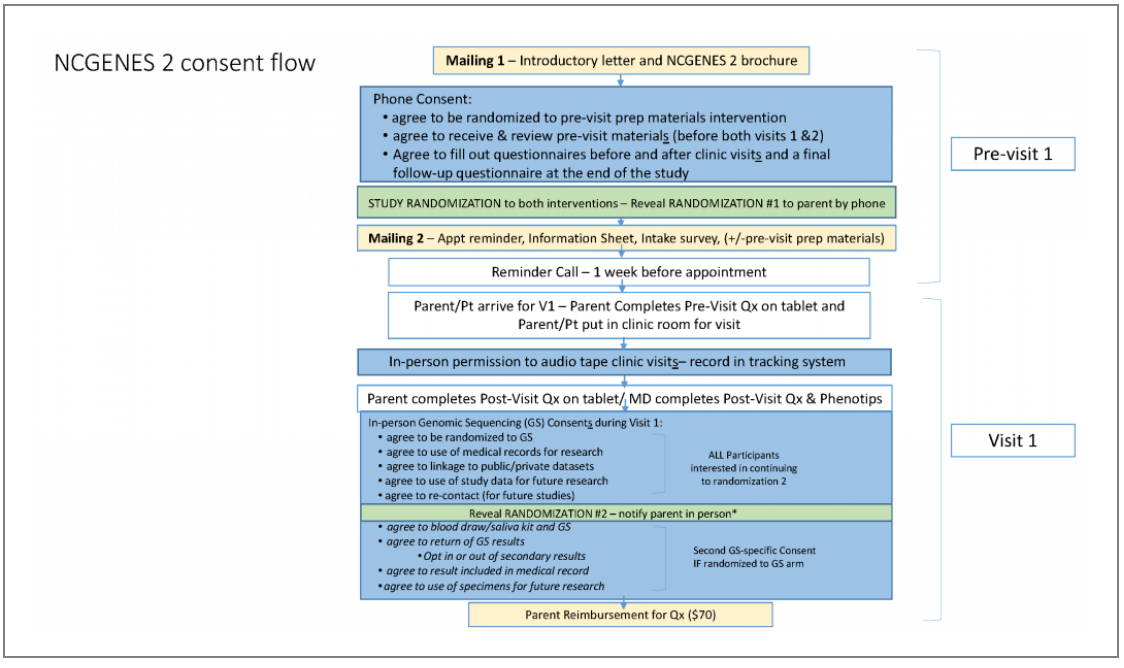
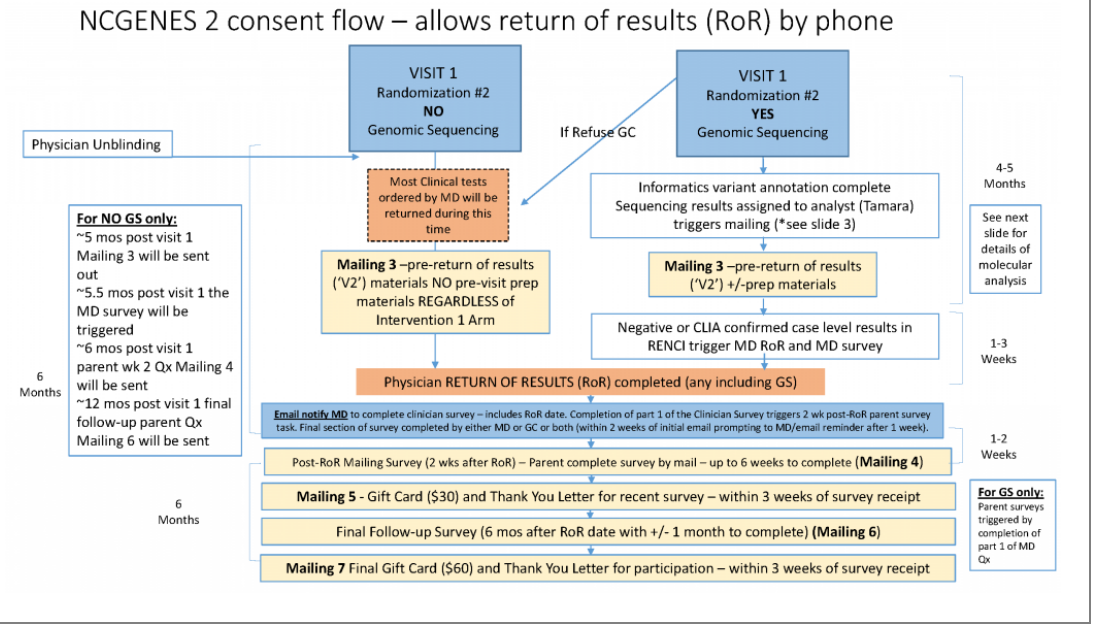
Protected: NCGENES 2 Study Protocol

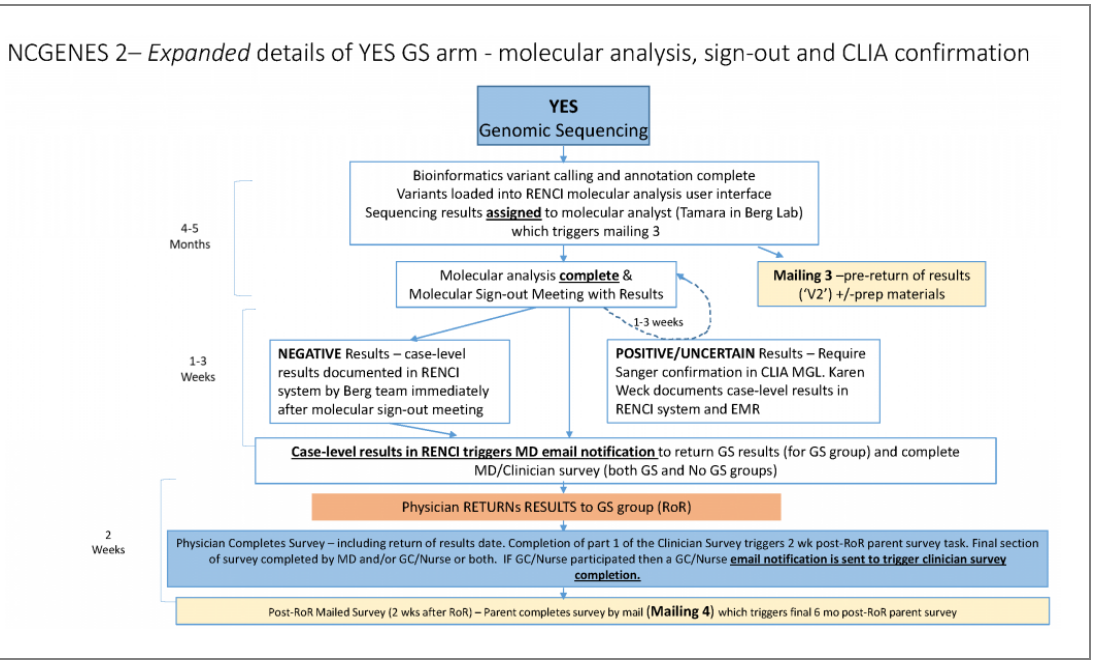
NCGENES 2 Overview

NCGENES 2 stands for the North Carolina Genomic Evaluation by Next-gen Exome Sequencing, phase 2. The research study investigates ways parents understand what to expect at their child's doctor visit and resources that might allow parents to speak more easily with their child's doctor. Parents who decide to take part in this research will be paid up to $170 for their time and their child may be offered a special test called exome sequencing, free of charge. This special test may help clinicians identify a reason for their child's condition. Understanding a child's condition may, in turn, help providers and parents/legal guardians plan for the child's care. Importantly, this study also attempts to understand differences between people who have an easy time getting health care and people who do not. The diagrams on the next few pages illustrate the overall flow of the NCGENES 2 study, from participant referral to follow-up surveys. New users should study these pages in detail to understand the structure of the study.

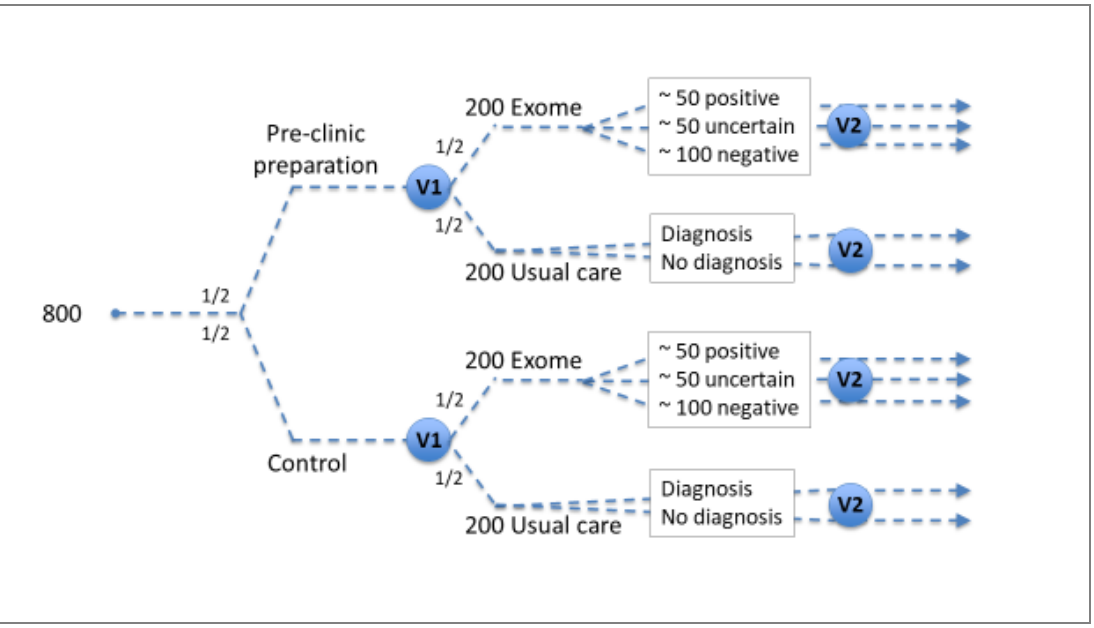
Study Flow







Overview of NCGENES 2 Clinical Protocol Interventions



*Planned enrollment is 850, for ease of distribution across groups 800 was used here.

**Clinic Visit 2 (V2) is now called Return of Results (RoR) because the vast majority of participants do not return to clinic for a second visit, instead results are provided by phone.

NCGENES 2 Clinical Study Roles

Study task in NCGENES are distributed between team members with distinct roles. These roles are based in part on the various blinding statuses necessary to perform each task. Different roles also have access to different data within the study tracking system. The principal distinction in roles exists between the Study Coordinator (SC) and Research Assistant (RA). The table below lists all the clinical roles, their level of blinding, and the tasks they perform.

Role[1]	**Blinding Status**	**Tasks**[2]
Study Coordinator	– Unblinded to participant randomizations as the occur	Eligibility and Selection, Enrollment, Mailing 2 & 3, Consents/Assents, Biospecimen Collection
PI/Clinical Project Director	– Unblinded throughout	Oversee study design, resolve implementation issues
Research Assistant	– Blinded to Intervention 1 randomization through clinic visit – Unblinded to intervention 2	Mailing 1, Pre- and Post-Visit Surveys, Audio Recordings, RoR Parent Mailings, Biospecimen Collection
Data Analyst/Programmer	– Unblinded throughout	Generates enrollment reports, ensures clean data
Lab Staff	– Blinded to identifying information on participants	Analyzes biospecimens and records results
Genetic Counselor	– Blinded to Intervention 1 randomization through clinic visit – Unblinded to intervention 2	Post-RoR Provider surveys, Consents/Assents (if necessary)

Clinicians	– Blinded to Intervention 1 randomization through clinic visit – Unblinded to intervention 2	Post-Visit and Post-RoR Provider Surveys, PhenoTips, Return results

1. The same person can hold multiple different roles across sites and therefore have different blinding statuses at each site.↑
2. Not exhaustive, may vary by site.↑

NCGenes

Protected: Enrollment

Participant Referral

The set of all potential participants in the NCGENES 2 study is comprised of children (less than 16 years of age) referred for a disorder with unknown but suspected genetic etiology, who are scheduled in the Pediatric Neurology or Pediatric Genetics and Metabolism clinics at the University of North Carolina at Chapel Hill, the Pediatric Genetics clinic at East Carolina University in Greenville, NC, or the Pediatric Genetics and Metabolism clinic at Mission Health in Asheville, NC. Each participant will have an initial status of **REFERRED** in the NCGENES 2 Tracking System. Referred participants' scheduling and demographic information will either be populated nightly from the UNC Carolina Data Warehouse for Health (CDW)[1] or will be entered manually into the study's tracking system following review of scheduling information in the Electronic Medical Record (EMR). Study staff will use this tracking system throughout the enrollment and data collection process, starting with manual entry or auto-population of patient scheduling data and the identification of eligible participants.[2]

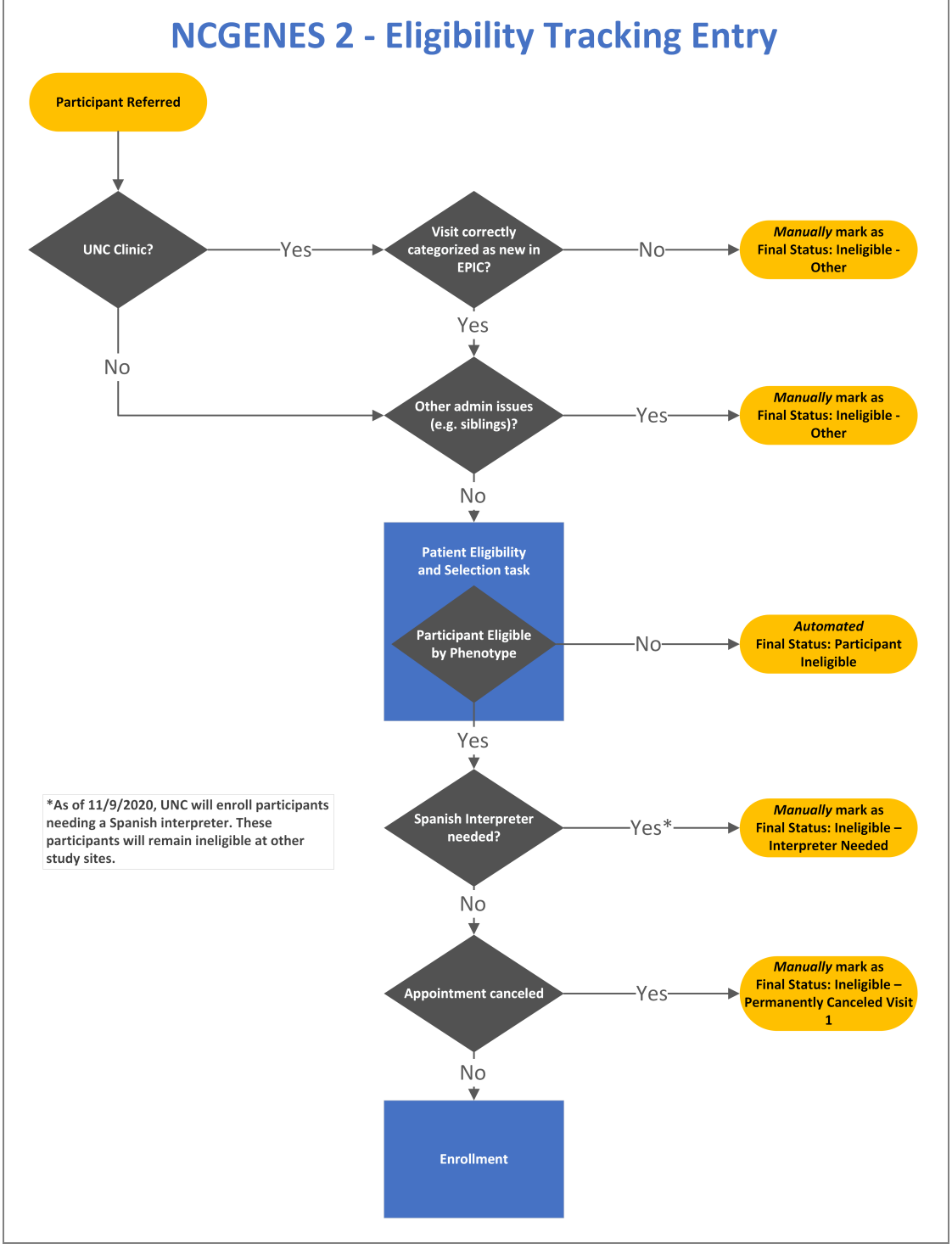
Participant Eligibility

Eligible participants must:

- Be less than 16 years of age at the time eligibility is determined
- Be referred to a participating clinic with an appointment at least 3 weeks away with one of the study physicians
- Have an unknown but likely genetic etiology for their disorder

These criteria should be evaluated in the order they appear above. The study **Clinical Criteria** document provides a thorough explanation of patient screening. This diagram outlines the usual process for determining eligibility.

Note: This chart assumes that, at non-UNC sites, the referrer performs proper reveiw of all administartive eligibility criteria prior to entering the participant into tracking. See the **Clinical Criteria** for more detail on administrative v. phenotypic screening.



If the study coordinator cannot determine the eligibility of a child due to inconclusive data on their condition, they should consult directly with the primary study physician at their respective site. If eligibility is still in question, staff should contact ☑ **Dr. Jonathan Berg** for a final determination of eligibility. Once a determination is made, participant eligibility information should be entered in the tracking system by completing the

Mark Participant as INELIGIBLE Manually[3]

In some cases, a participant status may need to be changed to **INELIGIBLE** manually. Detailed instructions for changing a participant's status manually can be found ~~**here**~~.

~~Patient eligibility and selection~~ task for that participant.

Status Update: Participants who meet the eligibility criteria will be given the status of **PARTICIPANT ELIGIBLE**. Participants who do not meet the criteria will be given the status of **PARTICIPANT INELIGIBLE**. **This flowchart** provides further detail on the cascade of tracking statuses.

The following situations require a participant be marked ineligible manually:

1. If prior to completion of the ~~Patient eligibility and selection~~ task[4], EMR review reveals the patient/family
    a. permanently canceled their

Participant Selection

Eligible participants are "selected" in or out of the study using a method called randomized recruitment (~~**See here for more detail**~~). Selection into the study will be based on an algorithm designed to create a cohort with 60% from under-served or under-represented populations and 40% from served populations at enrollment. In NCGENES 2, under-served and under-represented populations are defined by race, ethnicity and insurance status. Specifically, under-served and under-represented are defined as either Non-White OR Hispanic OR having Medicaid, charity care, or no insurance. Participants with one or more of the defining characteristics will automatically be selected to the study. Randomized recruitment is used to designate all other eligible participants as **SELECTED** or **NOT SELECTED** and is done in the background of the tracking system. This process is prompted by completion of the ~~Patient eligibility and selection~~ task.

For Participants with a status of NOT SELECTED or PARTICIPANT INELIGIBLE	This is a final study status for this participant and no further action is required.

For Participants with a status of SELECTED	Mail the Introductory Letter (~~**Mailing 1**~~). Participants that have been selected into the study will have a status of "pending" in the tracking system for their enrollment call (or for their enrollment call with selection) until they are approached for enrollment into the study. Ideally, enrollment calls with and without selection should be placed about 7 days after Mailing 1 to obtain initial consent to randomization 1. In unique cases, enrollment calls may be placed closer to Mailing 1 (i.e. less than 7 days after) in order to allow sufficient time to for recruitment.
For Participants with missing selection criteria that must be obtained on the enrollment call	When participant study selection criteria are completely unknown or the known information is insufficient to determine whether the participant is under-served/under-represented, participants will still have the status of **PARTICIPANT ELIGIBLE** . In this case, the Introductory Letter and Study Brochure should be mailed (See ~~**Mailing 1**~~ for more details). An ~~Enrollment call (with selection)~~ should then be placed 7 days after Mailing 1 has been sent. During this call, the parents of these participants will be asked to provide the missing selection criteria and selection will be completed during the call. The participant's status will change when selection is completed. If the participant is selected, the tracking system will prompt the staff member to proceed with enrollment. If the participant is not selected, the tracking system will prompt the staff member to conclude the call.

Enrollment Call

The Study Coordinator will use the parent's contact information from the tracking system to facilitate the enrollment call to determine parent eligibility and invite the parent and child into the study. In NCGENES 2, both the parent and child are participants.
The primary components of the enrollment call are to:

1. Determine the parent's eligibility for the study
2. Verbally consent the parent into the study – focused on intervention 1
3. Randomize the parent to an arm of the first intervention (pre-visit education or no pre-visit education)
4. Confirm the parent's mailing address

5. Inform the parent of parking/travel assistance to the study-related clinic visit, and of compensation for completion of study surveys

This section details practical instructions for completing the enrollment call. The enrollment call should be completed in concert with the ~~Enrollment call (with selection)~~ task in the tracking system.

(See **IRBIS** for the Enrollment Call Scripts)

Enrollment Call Strategy

Attempts to reach the parent or legal guardian should be spread throughout the day with calls during the morning (9am to Noon), afternoon (Noon to 5pm), and evening (7 to 8pm). In some cases, weekend calls may be needed and should focus on Saturdays, 9am to 4pm. Over a period of approximately 5-14 days, up to 5 attempts should be made to reach the parent on file. If the parent has not been reached after 5 attempts, they will be marked **NO APPROACH**. Attempts to enroll a participant should conclude 3 weeks before their scheduled clinic visit, unless the participant has been reached prior to that point or in special circumstances. After every attempt to contact the parent for the enrollment call, a note should be recorded in the ~~**communication log**~~ with any relevant information (e.g. parent unavailable, no answer, call disconnected, wrong number, phone disconnected).

If the study staff member does not feel comfortable contacting a person because of personal conflict, it is their responsibility to find another study staff member who is willing to approach the participant and follow the enrollment protocol.

Early Phase Enrollment

During roll-out at each site, enrollment may need to be restricted based on the capacity of the clinic to handle multiple participants in a short time period. In these cases, all eligible participants should be screened as such. From the list of eligible participants, the study coordinator should begin contacting parents gradually. If the study coordinator reaches their enrollment capacity, they should immediately stop contacting eligible participants. If a previously approached parent calls the

Mark Participant as FAILED APPROACH Manually[6]

Participants will have a status of **FAILED APPROACH** if the participant's parents are:

- not able to be reached (e.g. bad contact information)
- not reached within the number of attempts per protocol (max = 5 calls)
- not reached by phone 3 or more weeks prior to the participant's outpatient clinic visit.

study coordinator back expressing interest after this point, the study coordinator should say the following:

> *Thank you very much for returning our call. Unfortunately, at this time, we are only able enroll one patient each day in this research study and someone else has been scheduled to participate on the same day as your appointment. Again, we really appreciate your call back. Please remember that your child is still scheduled to see Dr. {NAME} on {VISIT DATE/TIME} in the Genetics Clinic. Dr. {NAME} and the clinic staff are looking forward to seeing you and your child on that date. Goodbye.*

Parent Eligibility

The study coordinator will use the participant tracking system and enrollment script to determine eligible parents and enroll parents into the study. Parents/legal guardians eligible for invitation to the NCGENES 2 study will be:

1. 18 years of age or more
2. able to sign legal documents for your child (excludes foster parents)[8]
3. willing and able to attend the study-related clinic visit
4. able to complete surveys in English (or Spanish, if at the UNC site)

If the study coordinator reaches the parent and performs the parent eligibility screening, the enrollment status will automatically update to **PARENT ELIGIBLE** or **PARENT INELIGIBLE** . **PARENT INELIGIBLE** is a final study status and no further action is required. Those parents determined to be eligible will continue to the next step: parent consent to intervention/randomization 1.[9]

Parent Consent

Eligible parents will be invited to participate in the study and consented. If the study coordinator consents the parent, the enrollment status will be updated to **PARENT CONSENTED** . Parents who refuse or decline to consent will have an updated

The **FAILED APPROACH** status should be manually applied in the tracking system by the study coordinator. Detailed instructions for changing a participant's status manually can be found in the ~~**here**~~.

Mark Participant as NO APPROACH Manually[7]

Participants will have a status of **NO APPROACH** if study staff does not attempt to enroll an *eligible* participant. This can happen if

- insufficient staffing prevents enrollment from being conducted 3 or more weeks before the visit
- the patient completes their visit before being enrolled due to
  - the visit being rescheduled unbeknownst to staff
  - the visit being scheduled as telemedicine or while staff cannot perform in-clinic research activities, e.g. during the COVID-19 pandemic

status of **REFUSED** with a type of "at enrollment (intervention I)". The status change is triggered when a parent answers "No" to the question: Do you want to join the first part of the NCGENES research study? All parents who decline/refuse participation will be asked if they would like to indicate a reason for their decision. If a reason is provided, it should be recorded in the tracking system when the participant's status is changed.

Randomization 1

Parents who consent to be in the first part of the study will be randomized into either the **PRE-VISIT PREP** or **NO PRE-VISIT PREP** groups (i.e. intervention 1). The group assignment will be based on a block randomization scheme. A participant is randomized into a group automatically when a parent's consent is recorded in tracking as part of the ~~Enrollment call (with selection)~~ task. The participant's randomization arm will automatically appear on the next page of the task.[10] Based on this randomization (and after conclusion of the call), the study coordinator or another unblinded study staff person should mail a Visit 1 Appointment Packet (~~**Mailing 2**~~) to the participant with or without pre-visit prep materials.

Provider Notification of NCGENES 2 Participant

After a participant has been enrolled, study staff must notify the clinician of their patient's status as an NCGENES 2 participant. The protocol for this notification varies by clinic.

UNC Genetics and Metabolism Clinic	For patients seen in the UNC Genetics and Metabolism Clinic, the Study Coordinator will place the phrase "NCGENES Participant" in the clinic calendar in MEDGIS (the Genetics and Metabolism EMR system).
UNC Pediatric Neurology Clinic	For patients seen in the UNC Pediatric Neurology clinic, the study coordinator emails the neurology nurse at least two times a month, informing them of the patients whose parents have agreed to participate in NCGENES 2. These actions allow clinicians and clinical teams to know that the patient-parent pair are NCGENES 2 participants.
Mission Health Fullerton Genetics Clinic	For patients seen in the Mission Health Fullerton Genetics Clinic, the Study Coordinator will enter the phrase "NCGENES2 Participant" in the clinic calendar in Cerner (the Mission EMR system).

Reminder Call

Study staff should call to remind a participant about their study research visit 1 week prior to the clinic visit. This event is captured in the tracking system as the ~~Reminder Call for Visit 1~~ task and should also be recorded in the participant's **~~Communication Log~~**. Once the parent is reached or the caller succesfully leaves a message, the reminder call is complete. The script can also be found in **IRBIS**.

The purpose of this call is to:

1. Remind the parent about their research visit
2. Remind the parent to complete the documents mailed to them and bring them to the clinic
3. Discuss travel to the clinic
4. Answer any questions the parent may have about their pending study visit

Notes

1. If the participant data is uploaded to the tracking system automatically from the EMR, the primary guardian is set as the primary guarantor (i.e. the insurance policy holder). For this study, the primary guardian must be the consenting parent/caregiver. If the consenting parent is not the primary guarantor, this information should be corrected by study staff during the introduction to the Enrollment Call task by entering the correct parent's name where prompted. ↑
2. The process for entering participants manually into the tracking system is explained **~~here~~**. ↑
3. All statuses entered manually are final statuses. Only tracking system administrators can change these statuses once they are set. ↑
4. This set of circumstances applies only at sites where patients are automatically referred into the tracking system. At sites where patient data is entered into the tracking system manually, such situations should not arise, as these cases will not be entered into tracking in the first place. See **Clinical Criteria** for more detail. ↑
5. Such situations usually occur during the enrollment call. ↑
6. All statuses entered manually are final statuses. Only tracking system administrators can change these statuses once they are set. ↑
7. All statuses entered manually are final statuses. Only tracking system administrators can change these statuses once they are set. ↑
8. For questions of parental eligibility at UNC due to ability to consent, please contact **Alyssa Draffin**, the Pediatric Genetics Clinic Social Worker. If you have questions they should be directed towards her. Please "cc" the group on responses so that all can be aware of the most current info available on the topic of parent eligibility.The best way to reach Alyssa is to **PAGE HER**. Her number is 919-216-4537. This functions like a text, so you can type a message to her. Staff at partner sites should contact their site's social worker. ↑

9. If the parent is determined to be eligible **BUT** the enrollment call is not completed, the participant's status will be **PARENT ELIGIBLE** until the call is completed. This situation can occur if the parent does not have time to complete the enrollment call and the remainder of the call is scheduled for a different date/time. ↑
10. If the tracking system fails at this point in the call, the enrolling researcher should complete the call and inform the parent they will learn their group assignment when they receive the study materials. They should then inform ✉ **Peter Newman-Matthews** of the tracking system failure and ask for the randomization 1 assignment. Once this information is obtained the Visit 1 Appointment Packet (~~**Mailing 2**~~) should be sent and the tracking system should be updated once the failure has been resolved. ↑

NCGenes

Protected: Visit 1

This section of the protocol outlines the procedures that should be followed before, during and after the clinic visit. The visit 1 protocol includes information for preparing for a clinical visit, confirming the participant's clinic date, document collection, conducting pre-visit surveys, facilitating audio recording of clinic visit, conducting post-visit surveys, invitation to and consenting for intervention/randomization #2 (genomic sequencing), and distribution of reimbursement. This section also covers special topics for clinic visit 1 which include participant distress and no-show protocols and information for physician surveys and entry of PhenoTips information. Most of the tasks in visit 1 are conducted by the study RA and Study Coordinator. The RA greets the families and handles all tasks up to the post-visit survey after which the RA transitions the participants to the SC.

Preparation for Visit 1

Prior to each participant visit, the study coordinator and research assistant sould complete all the tasks on the corresponding **Visit 1 Checklist**. To prepare for a clinic visit, both the Study Coordinator and RA should ensure that all electronic devices needed for clinic are fully charged, including audio recorders, tablets and iPads. Additionally, study staff should download movies/cartoon content on the iPad/tablet for child participants weekly. Prior to the clinic visit, the Study Coordinator compiles a hard copy folder for each participant and, if necessary, books a consultation room in the clinic where randomization, payment, child gift/snack distribution and genomic sequencing-related consenting will take place.

Compiling the Participant Folder

The participant folder contains a complete set of Visit 1 documents (used if electronic system fails). ***No indication of study randomization status should be included in or on the participant's folder.*** This folder is then given to the RA so that it can be brought to the clinic for use. The participant folder should be compiled as follows:

1. Label a Manila Folder with the participant's NCG ID.
2. With the folder open flat and label positioned in the top right corner, place a sticky note on the left side of the folder with the parent and child's name, child's age, and provider's name.

3. On the right side of the folder, clip the following items:
    a. Envelope with parent participant cash compensation ($70)
    b. Blood draw bag with the following items:
        i. Study ID Labels (5)
        ii. 2 Lab requisition form (BSP should be printed on Blue Paper and CLIA will be printed on white paper)
        iii. Blood draw tubes (2)
        iv. Additional blood draw bag (1)
4. Gather the following study documents and place them in the order indicated:
    a. Baseline intake[1] with stamped return envelope and ID label
    b. Parent Pre-visit survey
    c. Permission to Audio Tape form
    d. Parent Post-visit survey
    e. Clinician Post-Visit Survey
    f. Blank Blue Sheet to Separate RA and SC forms
    g. Consent to Randomization 2 form (3 copies)
    h. If necessary, Assent to Randomization 2 (3 copies)
    i. HIPAA Authorization (3 copies)
    j. Yellow paper with reminder to get signature for compensation [2]
    k. Consent to Genomic Sequencing (3 copies)
    l. If necessary, Assent to Genome Sequencing (3 copies)
    m. Post-genomic sequencing consent brochure
    n. Blank CLIA Order Form
5. Once compiled, these documents should be placed inside the manila folder, and the folder should be closed and secured with a binder clip.

What to Bring to Clinic

In addition to the participant folder, there are several items that the RA and the Study Coordinator should bring with them to the clinic. These items are placed in rolling bags for secure transport to clinic.

RA Clinic Bag Contents

- iPad tablet for child participants with updated videos/cartoons
- Study tablet, power cord and mouse (ensure stylus is in tablet and bring an extra stylus)
- Charged, numbered audio recording device with charger
- Participant research folder secured with binder clips (**See above**)
- Laminated card with instructions for Clinician on completing survey and PhenoTips
- Laminated sheet with MDs and genetic counselor names (Optional)
- Hard copy of site-specific**RA checklist**
- Post-it notes
- Pens

Study Coordinator Clinic Bag Contents

- Study tablet, power cord and mouse (ensure stylus is in tablet and bring an extra stylus)
- iPad tablet for child participants with updated videos/cartoons
- Charged, numbered audio recording device with charger
- Snacks
- Hard copy receipt book for parent compensation in the event electronic tablet version fails
- Pens
- Post-it notes
- Children's gifts (age appropriate)

To make sure the audio recorder is charged:

1. Turn on the recorder by sliding the POWER/HOLD switch toward "POWER."
2. Check that the battery has three bars.
3. If the battery doesn't have three bars, charge the battery.

To charge the battery:

1. Connect the USB cable to the USB port of a computer.
2. While the recorder is turned off, connect the USB cable to the bottom of the recorder.
3. Press the PLAY/OK button to start charging, which takes about three hours.
4. Charging Is complete when the battery says "F".

Visit 1 Procedures

Arrival to Visit 1

The RA will be blinded to the participant's randomization statuses (pre-visit preparation and genomic sequencing). She will coordinate with anyone who will be assisting with the clinic/research visit (e.g., study coordinator, student volunteer, and/or other research and clinical staff). Prior to leaving for the research appointment, the RA should inform the SC in

preson, by text, or by phone that they are on their way to clinic or have arrived at clinic. The RA should arrive at the clinic at least 15 – 20 minutes prior to the research visit. Upon arrival, the RA should begin looking for the patient and their parent.

About 20 – 30 minutes before the research appointment, the SC will check EPIC or Cerner to learn if the patient has arrived and will continue to monitor EPIC/Cerner until the patient arrives. The SC will text the RA with the patient's status per EPIC at the time of the initial EPIC review and periodically until the patient's arrival.

The first portion of the research visit is typically conducted in the waiting room. Upon participant arrival and after the parent checks the child in at the clinic reception desk, the RA should greet the participants (child and parent) in the clinic waiting room. The RA should introduce themselves and confirm the parent's and child's names. When the RA is with the family in the waiting area or has escorted the family to a consultation room (depending on clinic) and prior to the child seeing the iPad, they should ask the parent if they may offer pre-recorded videos to the child. The RA may have a student volunteer who accompanies them to the clinic to entertain the child and any sibling(s) with the video/waiting room toys.

Wrong parent? If the parent who brings the child to the clinical encounter is **NOT** the parent who consented by phone, the parent who is with the child MUST be consented to the study to complete all subsequent surveys and consents. A ~~Note~~ must be placed in the tracking system for the participant to document this event, and an email sent to the Study Biostatistician **Laura Farnan**.

Participant late? If a participant shows up 20 minutes late for a clinic appointment, the clinic check-in staff must obtain provider approval for the participant to have the clinic appointment. Therefore, if a participant is 15-20 minutes late for their clinic appointment, the RA should ask the provider/genetic counselor if the participant will be seen upon arrival. If so, the RA should ask if they can also complete the study pre-visit survey. If so, the RA should continue to wait for the participant and complete their usual study actions as quickly as possible when the participant eventually arrives. The RA should keep the SC informed about all this, either by text, in-person, or by email. If the provider/genetic counselor informs the RA that a participant will not be seen or that the study pre-visit survey cannot be completed, the RA should obtain the reason for this event and relay this information to the SC. When possible the SC will contact the RA via text or phone to remind them to check with the provider/genetic counselor if the participant is running late.

Participant missed the clinical appointment? See **No Show Protocol**.

Confirming Visit 1

When the parent has checked into the clinic and the child has been offered the iPad (if parent(s) allow), the RA should complete the ~~Confirm Visit 1 Appointment Date and Provider~~ task in tracking. The purpose of this task is to confirm the participant's appointment date and provider. This is particularly important if a participant ends up being seen by a different physician in a particular clinic. Confirmation of this sets the NCGENES visit 1 date for the study. Following the appointment date and provider confirmation, the RA should turn their attention to the parent and remind the parent about what will happen during the visit and should ask the parent if they have brought their completed baseline intake.

Collecting the Intake Survey

Participants should have completed the baseline intake prior to their research visit and should have brought the completed document with them to the clinic. If the participant has their completed form, collect it at the beginning of the research appointment. When you collect the document briefly check for its completion (especially for the child's partial social security number). This step can also be done while the parent is completing the pre-visit survey.

Parent forgot their completed baseline intake? If the participant completed the baseline intake at home but failed to bring it with them to the study visit, provide the parent with a labeled envelope with prepaid postage and a blank copy of the intake (in case the parent cannot locate the completed form). Inform the parent that they should use the provided envelope to return the intake by mail.

Parent didn't complete baseline intake? If the participant did not complete the baseline intake, two things can be done:

1. If the participants arrive with substantial time before their doctor visit, the parent can complete an intake form in the clinic after completing the pre-visit survey.
2. If the participant cannot complete the survey in clinic, they should be provided with another baseline intake with a labeled envelope with prepaid postage. Inform the parent that they should use the provided envelope to return the baseline intake by mail.

Record the collection of the completed baseline intake in the participant tracking system by completing the ~~Visit 1 – Collect Info about Intake Completion~~ task. Additionally, if the baseline intake is *not* collected during the clinic visit, a ~~Note~~ should be made in the tracking system for the participant that includes information about whether the baseline intake was completed or not prior to the visit.

Additional Notes on Document Collection

The ~~Questionnaires – Collection Method~~ task documents the type of questionnaire collected for the baseline intake, pre-visit parent, post-visit parent, and post-visit clinician surveys. This task should be completed by the RA but may be completed by other study staff members. The RA or staff member should record if the questionnaire was completed by phone, on the tablet, or by paper.

Parent attempts to give RA QPL? The parent has been provided with instructions to give their question prompt list (QPL) ("Visiting a pediatric specialist: It's OK to ask questions.") to their child's physician. If the parent tries to hand the QPL to the RA, the RA should inform them to give the QPL to their child's physician. If this happens, the RA may say the following:

> *You may ask anyone on your child's medical team these questions, but please make sure to give this list to the doctor.*

Pre-visit Survey

After addressing the baseline intake, the RA will administer the ~~Pre-Visit 1 Parent Questionnaire~~ using the tablet. Before handing the tablet to the parent, the RA should read the instructions on the initial page of the survey and let them know they can consult you if they have any questions. The pre-visit survey should take most parents about 15-20 minutes. When the parent has finished the survey, the system should automatically log off the user so that the parent cannot get to other software to on the tablet. **The RA should ensure that the parent has clicked on finish and finalize and close the survey window.** The RA should then access the tracking system and go to the participant's individual page to ensure that the ~~Pre-Visit 1 Parent Questionnaire~~ status is "Completed" (if you fail to close the initial participant task list menu, you will need to refresh the screen to see the completed status for that task).

Tracking system down? If the tracking system is down, the parent should complete a paper copy of the survey that has a participant study ID label placed in the upper right-hand corner. Read the instructions on the initial page of the survey and let them know they can consult you if they have any questions. Within 24 hours of the visit (and when the tracking system is working again), upload this paper version to the ~~participant documents~~ tab. The parent's answers should also be manually entered into the ~~Pre-Visit 1 Parent Questionnaire~~ task. (If a hardcopy is received on a Friday, it must be manually entered by 5:00 pm the following Monday.)

When the parent has finished the survey the RA should check to see that the survey has been finished and the tablet is back on the appropriate home screen.

Audio Recording and the Clinic Visit

Prior to the visit, the RA should ensure the audio recorder is properly charged and in the clinic bag.

Consenting the Parent to Audio Recording

The RA should consent the parent to audio recording by completing the ~~Parent Permission to Audio Tape Clinic Visit~~ task. This consenting should occur in the clinic waiting room or after you enter the clinic room with the participants for the appointment.

> **Tracking system down?** If the tracking system is down, consent the parent to audio recording using the paper version of the consent in the participant's folder. Within 24 hours of the visit (and when the tracking system is working again), upload this paper version to the ~~Participant Documents~~ tab. Then, complete the ~~Parent Permission to Audio Tape Clinic Visit~~ task and, if the parent consented, write "Completed Document on Paper" in the signature field.

Once the consent process is complete, the RA should remind the parent of what to expect after their clinic visit before setting up the audio recording. To do so, the RA should tell the parent the following:

> *When you are done, I'll bring you to meet with Tracey [or whoever is helping that day], the study coordinator/genetic counselor, where you will receive your reimbursement, some snacks and a gift for [child's name]. This is also where you will get a chance to hear more about the special research test that your child may have a chance to get. You might remember that we mentioned this test to you when we spoke to you by phone a few weeks ago*

Setting-up in the Clinic Room to Collect Audio

If the parent consents to audio recording, the RA will be responsible for initiating audio recording in the clinic room ideally immediately before the genetic counselor OR the physician, if no counselor will be seeing the patient. If, however, this is not possible, audio recording can be initiated after the patient has been placed in a clinic room.

To begin recording with an Olympus DS-2500 recorder:

1. Turn on the recorder by sliding the POWER/HOLD switch toward "POWER."
2. Press the NEW button on the side of the recorder to create a new file.
3. Press the REC button to start recording.
4. The indicator light will glow orange and the record symbol will appear on the display.
5. Place the recorder near the sound source.

The RA should state the audio recorder number immediately after beginning recording. The RA should exit the room once the audio recording has been set up and should wait outside the room until the end of the

visit. *During the visit, regardless of whether the parent has consented to audio recording, the RA should text or call the Study Coordinator to let them know the parent has completed the pre-visit activities.*

At the Conclusion of the Clinic Visit

Once the visit is over and all medical staff has left the room, the recorder should be turned off and stored in the RA's rolling bag. At the earliest, this can occur after the physician leaves the room but before they return with the hard copy version of the patient's clinic summary.

To stop recording with an Olympus DS-2500 recorder:

1. Press the STOP button to stop recording.
2. If you want to append additional recordings to the same file, press the REC button again.
3. Turn off the recorder by sliding the POWER/HOLD switch toward "POWER" and holding it for 0.5 seconds or longer.

If you have any additional questions, please consult **the instruction manual for the recorder**.

After returning to the office, the RA should upload the audio recording to the secure folder to the general ~~Documents~~ page in tracking. If the battery power is low (< 2 bars), the RA should wait to upload the file until after charging the device.

Post-visit Survey

Once the visit is completed, the RA will administer the post-visit survey. Based upon available space, the post-visit survey will be completed in the exam room, clinic waiting room or the assigned NCGENES consultation room. Consulting the clinic nurse/genetic counselor/observing overall clinic flow, the RA should establish the location for the post-visit survey while the participant is in their visit. The RA will escort the family to this location and then provide an iPad with pre-recorded videos to the child. Next, the RA will log in to their tablet and begin the ~~Post-Visit 1 Parent Questionnaire~~ task for the parent. Before handing the tablet to the parent, the RA will read the instructions on the initial page of the survey and let the parent know they can consult the RA if they have any questions. Before the RA leaves the parent with survey, they should remind them of the coming study visit:

> *When you are done, I'll bring you to meet with Tracey (or whoever is helping that day), the study coordinator/genetic counselor, where you will receive your reimbursement, some snacks and a gift for patient's name. This is also where you will get a chance to hear more about the special research test that your child may have a chance to get. You might remember that we mentioned this test to you when we spoke to you by phone a few weeks ago.*

The RA should stay nearby as the parent completes the survey in case they have questions or difficulties. While the parent is completing the survey, the RA should notify the study coordinator that the participants will be ready soon (10 – 20 mins) for the second part of the research visit (i.e. intervention 2). When the parent has finished the survey, the system should automatically log off the user so that the parent cannot get to other software to on the tablet. The RA should ensure that the parent has clicked on "Finish and Finalize" and close the survey window. The RA should then access the tracking system and go to the participant's page to ensure that the ~~Post-Visit 1 Parent Questionnaire~~ status is "Completed" (you may need to refresh the page).

When the post-visit survey is completed, the RA will escort the family to the assigned NCGENES consultation room if necessary. While walking to this room (or waiting for the SC), the RA can orient the family to the next steps of the research visit (e.g., introduce opportunity to be in the second part of the study, compensation, etc.). Once the SC, RA, and family are all in the consultation room, the RA will introduce the study coordinator (or unblinded study staff member) and give them the participant's research folder. If necessary (and there are no scheduling conflicts) the student volunteer or RA will stay to help entertain the child/sibling while the SC talks with the family and/or help escort the family to phlebotomy.

RA Notifications

Before the SC begins their portion of the research visit, the RA must notify the SC either via text or in-person of the following:

- If the physician has ordered bloodwork for the patient
- Of any non-standard clinic operations, such as time sensitive blood work or another clinic appointment that is scheduled for the same day as the research visit
- The physician's determination of the participant's developmental age (for participants 7 years of age or older)
- Feedback provided by any of the providers regarding the project

Determining Developmental Age

Since participants who are *developmentally* age 7 years or older[3] are asked by the SC to provide assent to participate in intervention 2 of the NCGENES study, the RA and SC must collect the developmental age of any child participant *chronologically* age 7 or older at the time of their first visit. Developmental age **must be collected** before the family is consented to study intervention 2 (i.e. genomic sequencing). It is up to the RA to collect the developmental age of relevant participants. When the RA completes the ~~Confirm Visit 1 Appointment Date and Provider~~ task, a ~~Collect Developmental Age~~ task will appear for any participant 7 years or older chronologically. This indicates that a developmental age should be collected for this participant. The RA will need to consult with

the provider after the visit to collect the developmental age of the child from them. The RA should record this developmental age by completing the ~~Collect Developmental Age~~ task **and** by making a note of the participant's developmental age in the participant's folder. If the participant is over 7 developmentally, the tracking system will automatically generate the required assent tasks for the SC/GC to review with the participant. The SC/GC should also verbally confirm the developmental age with the RA.

Developmental age not available? If the provider does not inform the RA of a child's developmental age, the RA should ask the counselor (for genetics patents) or nurse (for neurology patients) if the provider has given them this information. If not, the RA should ask the counselor/nurse if the doctor can be reached so that the developmental age can be obtained. The RA should inform the person obtaining consent for study intervention 2 of the above ASAP. The person obtaining consent for study intervention 2 will inform the parent of the following:

- a developmental age from the provider is required for continued participation
- unfortunately, this information is currently unavailable, so the study team is working to contact the provider
- once this information is obtained, they (i.e. the person who is obtaining consent) will contact the parent

After informing the parent of the situation, provide the family with snacks as appropriate and walk them to the phlebotomy area or exit as necessary.

If the developmental age is determined after the parent and child have concluded their visit and left the clinic, next steps will depend on the developmental age of the child. If the provider says the participant is developmentally age 7 or older, the SC should inform the family by phone that they are unable to participate in the second part of the study as both parental consent and their child assent are required for participation and the time period for obtaining this permission has passed. If the provider says the child is developmentally less than age 7, the SC will inform the family they will able to participate in the second part of the study, and that the necessary forms for this participation will be sent to them. Then follow the protocol for **Phone Consent to Intervention 2**.

Study Intervention 2

When the parent and child arrive in the consultation room, the study coordinator will thank the parent for participating in the study and remind them that they have spoken previously on the phone during the enrollment call (or state that they are the person mentioned during this call that would speak with them about the second part of the NCGENES study). Then the SC will ask that the family make themselves comfortable in the room and inform the parent of the next steps (i.e. discuss the second part of the study, escort them to check-

out/phlebotomy). The SC will ask the parent for permission to offer the child an iPad with pre-recorded videos and a snack. The SC should inform the parent of the types of snacks (in order to avoid providing something that the child is allergic to or the parent would not like for them to have). This will be done before the child sees the iPad and snacks. If the parent gives permission for the iPad/snacks, the SC should provide the child with these items. The coordinator will then begin reviewing consent form 1 with the parent.

> **Parent cannot extend visit to provide consent?** In some cases, a parent and child may not have the time and/or ability to extend their visit and complete the consenting process in person. While it is strongly preferred for consents to occur in person, such cases may necessitate a phone consent to intervention 2. If the parent cannot consent in person immediately following their clinic visit, but would still like to remain in the study, the SC/GC can offer them the option of a phone consent. The SC/GC should still attempt to complete as much of the study visit as possible, namely distribution of reimbursement.[4] If the option of a phone consent is requested by a parent, the SC/GC should note this in the tracking system and follow the **Phone Consent to Intervention 2** protocol to complete the consent.[5]

The SC will discuss consent form 1 (i.e. ~~Randomization to Genome Sequencing Consent~~) with the parent by reviewing this form screen-by-screen on the SC's laptop and in general conversation. The parent should be offered several opportunities to ask any questions and receive an answer from the SC. The SC should remind the parent of their ability to ask questions periodically during their discussion of the consent. The SC also informs the parent that (1) they will receive a paper copy of any consent form discussed with them (and their child) and (2) they may contact the SC via the study number and email address that is on these forms if they have any questions following the study visit.

> **Both parents present?** If both parents are present, the SC will inform the parents that for consistency the parent who provided consent via telephone must also sign the consent forms for the second part of the study should the family decides to continue with study participation. The non-consenting parent will be informed they can also ask any questions they have during this time and can look at the laptop or follow along via a paper version of the consent.

If the Parent Consents

If consent form 1 is signed, the SC will review the ~~Visit 1 Parent HIPAA~~ following the same procedure as consent form 1 (see above).

> **All participants who consent to the genomic sequencing randomization MUST also have a signed HIPAA document to continue participation in the study.** If a participant refuses to sign

the HIPAA document, they must be manually given the final status of **REFUSED** and a note detailing the reason for this change should be added to the participant's log.

After the HIPAA consent is signed, the parent/family will be informed of the intervention 2 assignment (i.e. genomic sequencing or non-genomic sequencing). This status will appear on the ~~**participant's individual page**~~.

If the participant is assigned to non-genomic sequencing, the parent/family will be informed that have not been assigned to be offered genomic sequencing. The SC should inform the parent/family that their remaining study participation will consist of completing follow-up surveys and having their child's information obtained until they are 18 years of age as discussed during the consent process. The SC should then thank the family for their time, provide **parent and child compensation**, and escort them to either phlebotomy (for provider bloodwork), check-out, or towards the appropriate hospital exit.

Mark Participant as REFUSED Manually[6]

In some cases, a participant status may need to be changed to **REFUSED** manually. This can happen if the parent refuses to sign the

- ~~Randomization to Genome Sequencing~~
- ~~Visit 1 Parent HIPAA~~

In either of these cases, study staff should close the task **without** clicking the "Finish and Finalize" button before marking the participant **REFUSED** . Detailed instructions for changing a participant's status manually can be found ~~**here**~~.

If the participant is assigned to genomic sequencing, the SC will inform the parent/family that they have been assigned to be offered genomic sequencing. Then the SC or Genetic Counselor will review consent form 2 (i.e. ~~Genome Sequencing Consent~~) following the same procedure as consent form 1 (see above). If the parent signs consent form 2, the SC/GC will proceed with **biospecimen** and **parent and child compensation**.

If the Parent Declines

If the parent declines to sign either consent form 1 or the HIPAA consent, the parent/family will be informed their study participation ends at the conclusion of the study visit. In the tracking system, the SC should exit whichever consent form they are viewing with the parent and mark the participant **REFUSED** manually with the reason "Declined at Visit 1 – Intervention 2" and a short explanation. The SC should thank the family for their time, provide **parent and child compensation**, and escort them to either phlebotomy (for provider bloodwork), check-out, or towards the appropriate hospital exit.

If the parent declines to sign consent form 2, the parent/family will be informed that their remaining study participation will consist of completing follow-up surveys and having their

child's information obtained until they are 18 years of age as discussed during the consent process. The SC should then thank the family for their time, provide **parent and child compensation**, and escort them to either phlebotomy (for provider bloodwork), check-out, or towards the appropriate hospital exit. These participants will have a status of **DECLINED TO GS** .

> **Tracking system down?** If the tracking system is down, all consents/assents should be administered using the paper versions in the participant's folder. After the visit, when the tracking system is working again, upload these paper versions to the ~~Participant Documents~~ tab. Then, complete the relevant consent tasks and, if the parent consented, write "Completed Document on Paper" in the signature field or mark the participant **REFUSED**

Obtaining assent

If the child's developmental age is 7 or greater (**see above**), the SC/GC must collect assent from that child for the parent and child to continue in the study.

~~Randomization to Genome Sequencing Assent~~ and ~~Genome Sequencing Assent~~ are obtained by the SC/GC in the same manner as outlined above for obtaining parental consent for intervention 2. Assent forms are typically discussed once the parent consent process is complete. In rare occasions, assent form 1 is discussed after the parent signs the HIPAA consent form, and then assent form 2 is discussed after the parent signs the parent consent form 2. These alternative time periods for obtaining assent are necessary because parents may be more interested in hearing about the second part of the study, while participants are tired and/or need time to become engaged in the process or are focused on the iPad/snacks. The SC should use their judgement as to when to begin the assent process. The SC should inform the parent of the timing of the assent process and check their agreement. If they agree, the SC can proceed with that timing. If there is disagreement, the SC should defer to the parents preferences. Regardless of the timing of the assent process, the SC starts the process by re-introducing themselves to the participant. Then, the SC asks the participant if they have any questions about why they are seeing the SC or what they heard the SC discuss with their parent(s). After questions are answered, the SC tells the participant what will happen next (i.e. they will talk about the study by looking at the laptop and talking) and that they can ask the SC questions, their parent(s) questions about their talk with the SC or ask their parent(s) to call the SC if they have questions later. Then, the SC begins the assent process.

> **Note:** The assent process should involve more discussion than a screen by screen review on the SC's laptop, especially with younger participants.

If the participant signs assent form 1, they are told if they are in the group of kids that are asked to give a little bit of their blood (about 1-2 teaspoons) or if they are in the group of kids that do not have to do anything extra then what the doctor has already talked to their parent(s) about during their doctor's visit. The participant is asked if they have any questions, and if so, the questions are answered. Then depending upon the intervention 2 assignment the SC proceeds with assent 2 or with providing **parent and child compensation**.

> **Note:** Parent(s) are given a copy of the assent forms that are discussed with their child.

If the participant declines signing assent form 1, the SC informs the parent(s) and participant that study participation for intervention 2 cannot proceed. In the tracking system, the SC should exit (without saving) the current task and mark the participant Refused manually with the reason "Declined at Visit 1 – Intervention 2" and a short explanation. Then the SC thanks the family for their time, provides parent and child compensation as described below, and escorts them to either phlebotomy (for provider bloodwork), check-out, or towards the appropriate hospital exit.

If the participant declines assent form 2, the SC informs the participant that no genetic sequencing will be done but the participant would continue to be in the NCGENES 2 study and the parent would be provided with follow-up surveys. Then the SC thanks the family for their time, provides parent and child compensation as described below, and escorts them to either phlebotomy (for provider bloodwork) or check-out, or towards the appropriate hospital exit. These participants will have a status of **DECLINED TO GS** .

> **Cases of discordant consent/assent.** If a child can assent to participate in Intervention 2, both the parent and child must agree to continue participation. Further, both parent and child must have concordant consent/assent for the check boxes related to the study's continued access to the child's medical records and for the disclosure of medically actionable secondary findings. If the child is 7 years or older chronologically and developmentally, the parent must consent AND the Child must assent for the participants (parent-child pair) to remain in NCGENES. If the consent and assent are discordant, a participant should be manually given the final status of Refused and a note detailing the reason for this change should be added to the participant's log in the study's tracking system.

Distribution of Parent and Child Compensation

At the completion of the consent/assent process parents will sign for compensation through the ~~Visit 1-Parent Reimbursement~~ task. If the tracking system does not work, the SC will use a receipt book to complete this task. The study coordinator fills in the amount provided to the parent according to what was completed before and during visit 1. Child participants in the study will be offered a nonmonetary gift at the end of visit 1. See here for more information on ~~**Tracking Participant Compensation**~~.

Biospecimen Collection

After the appropriate forms are signed (i.e. parental consent form 2 and if necessary, assent form 2) and the parent and child compensation have been distributed, the SC escorts the family to the phlebotomy area appropriate to that clinic. At UNC, the SC will direct the participants to UNC's Women's Hospital for phlebotomy check-in. If the patient is having provider bloodwork, the SC escorts the parent to the individual check-in area. If the patient is not having provider bloodwork, the SC escorts the family to the area where they can pull a number for general check-in. At Mission, the SC will direct the family to the phlebotomy area of the Mission Children's Hospital. When the participant is called for blood draw, the SC should escort the family to the blood draw area and inform the phlebotomist of the need to use the research blood tubes immediately after the provider's blood order is filled. The SC will pass the phlebotomist the labeled research blood tube either right before they are to be filled or places them next to the tubes for the provider's bloodwork, depending upon the level of SC assistance needed.

SC assistance

When necessary, the SC assists the phlebotomist/parent in holding the child for blood draw, as well as trying to keep them calm for this procedure. Assistance is typically needed, however the SC should take care not to obstruct the phlebotomist. See ~~**here**~~ for more information regarding biospecimen labeling, collection, lab distribution, processing, and reporting.

Study Withdrawal & No Show Protocol

This sections outlines a few different statuses set manually by the SC.

WITHDRAWN

When a participant expresses a desire to no longer participate in the study at any point, the should be marked **WITHDRAWN** with a type corresponding to the point in the study at which they withdraw. The only exception to this would be when a participant declines to continue with the study during consent 1 or 2, at which point they will (automatically or manually) be given a status of **REFUSED** . When a participant requests to remove themselves from the study, a **Withdrawal Form** must be completed by the study coordinator or RA to confirm what study data, if any should be scrubbed from the participant's record. Once this form has been completed, the SC/RA should complete a **Withdrawal Checklist** . Further instructions for changing a status manually can be found ~~**here**~~.

INVESTIGATOR WITHDRAWAL

In other circumstances, it may be necessary for study staff to withdraw a participant. Participants are subject to **INVESTIGATOR WITHDRAWAL** when:

1. A pediatric patient is found to have a confirmed genetic related diagnosis during Visit 1. This would be considered **INVESTIGATOR WITHDRAWAL** with a type of **"Diagnosis during Visit 1"**. These participants will/can complete the Baseline Intake, Pre-, and Post-Visit Surveys but are not considered for intervention 2. Parents can receive up to $70 in compensation, and the child will receive a nonmonetary gift.
2. NCGENES study staff unable to attend the research/clinic appointment (e.g. due to illness or other conflict). This should be an **INVESTIGATOR WITHDRAWAL** with the type of **"No Staffing for Clinic"**. Participants that attend their clinical appointments can receive up to $40 ($10 for parking and $30 if they submit a completed Baseline Intake).
3. A participant (child or adult) was ineligible at the time of enrollment BUT whose ineligiblity was only discovered after participant was already enrolled (e.g at Visit 1). For example, a participant has a confirmed genetic diagnosis prior to the enrollment call (i.e. this diagnosis does not occur at Visit 1), but this diagnosis was not disclosed during the enrollment call and was not found in the patient's medical record. In these cases, all the data associated with this participant will be removed for the analytic database. If the participant is found to be ineligible for reasons which preceded their enrollment, the participant should be marked **INVESTIGATOR WITHDRAWAL** with a type of **"Ineligiblity Identified Post-Enrollment,"** and the following phrase should be copied into the reason text box when changing the participant's status:

   > *Participant was ineligible at the time of enrollment BUT this was only discovered after participant was already enrolled, thus participant coded as* **INVESTIGATOR WITHDRAWAL** *and data removed from analytic database.*

Further instructions for changing a status manually can be found ~~**here**~~.

NO SHOWS

Participants are considered a **NO SHOW** if the study staff are unable to complete the research visit with a consented participant.

A participant should be considered a **NO SHOW** with a type of **"Research Visit ONLY"** if there is not enough time for the study staff to complete the research visit tasks (e.g. pre- and post- survey or consenting process) at the time of the clinic visit AND the participant must be assented and is thus ineligible for phone consent. This can happen

if a participant arrives to the clinic at or after their scheduled clinic appointment time or if the participant has multiple clinical visits that conflict with the research visit protocol. In this case, participants are censored from the study.

> A participant should also be marked **NO SHOW** with a type of **"Research Visit ONLY"** if they completed their clinic visit while research visits were suspended due to COVID-19. If this is the case, the corresponding note should begin with the following:
>
> > *Visit completed during suspension of research activities due to COVID-19 pandemic.*
>
> Additional explanations of the specific situation (e.g. telemedicine visit) should also be noted.

A participant should be considered a **NO SHOW** with a type of **"Research and Clinic Visit"** if they miss their clinical appointment completely. In this case, the participant is given 30 days to reschedule their appointment[7]. If they do reschedule their appointment in 30 days to some date in the future, they can still participate in the study. Participants may be rescheduled up to 3 times. If the participant is not rescheduled for an appointment within 30 days after their original appointment date, the participant is coded with a final status of **NO SHOW** . The SC will periodically monitor EPIC to determine if the participant has been rescheduled and work with the tracking system team and other study team members to complete necessary steps based upon the participant's reschedule status. The study biostatistician will generate regular reports to indicate participants whose statuses should be changed to a **NO SHOW** .
Further instructions for changing a status manually can be found ~~**here**~~.

Alert Protocol for NCGENES 2 Distressed Adult Participants

The purpose of the NCGENES 2 alert protocol is to ensure that participants reporting clinically elevated anxiety and depression symptoms have resources to cope. It is not designed to identify and intervene for imminent suicide risk. Even though the NCGENES 2 alert protocol is not designed to assess *imminent* risk, it is reasonable for the study clinical psychologist to screen study participants with elevated anxiety and/or depression symptom scores who are called and reached by study psychologist for suicidal ideation and behavior. If they happened to be at *imminent* risk on the call, then the study psychologist implements the suicide screening script referenced in this alert protocol.
The system will score the GAD7 (anxiety measure) and the PHQ8 (depression measure) as electronic data is collected and entered in the patient tracking system (the usual route of

survey administration). The measures appear on the questionnaires listed below that are a part of both the Pre-Visit Parent Survey, 2-week Post-Return of Results (RoR) and the 6-month Post-RoR Parent Surveys:

- Pre-clinic visit 1 parent survey: **Question 6, A-G** (GAD7, anxiety, 7 items)
- Pre-clinic visit 1 parent survey: **Question 6, H-O** (PHQ8, depression, 8 items)
- Post-Return of results (2 weeks after RoR) parent survey: **Question 21***, **A-G** (GAD7, anxiety, 7 items)
- Post-Return of results (2 weeks after RoR) parent survey: **Question 21***, **H-O** (PHQ8, depression, 8 items)
- Final Follow up (6 months after RoR) parent survey: **Question 14***, **A-G** (GAD7, anxiety, 7 items)
- Final Follow up (6 months after RoR) parent survey: **Question 14***, **H-O** (PHQ8, depression, 8 items)

*Questions numbers subject to change

Both the GAD7 and the PHQ8 should be scored (separately) as follows:

- Not at all=0, Several days=1, More than half the days=2, Nearly every day=3
- Sum the items to create measure score
- If a participant scores 15 to 21 on the GAD7 (indicating severe/clinically elevated symptoms) AND/OR scores 20 to 24 on the PHQ8 (indicating severe/clinically elevated symptoms), the system will create an alert.

> **IMPORTANT NOTE:** For any surveys *administered by paper or over the phone*, the data will be entered directly into the electronic data collection system within 24 hours of collection or first thing Monday morning if the data is collected late on Friday afternoon. Expedient data entry will allow for rapid distress score calculation, alert reporting, and appropriate follow-up action according to the protocol described above. (**NOTE:** The NCGENES 2 staff has also been trained regarding how to calculate manual scores in the rare case that the tracking system is not functioning). If this manual score calculation is required, the questionnaire responses and calculated scores are verified by a member of the Measures and Outcome (M&O) team. When meeting alert protocol requirements, the score(s) is reported to the Study Coordinator immediately who contacts both the Clinical Director and Study Clinical Psychologist within 24 hours of verification by the M&O team.

Immediately upon data entry, the system will score the measures (or scores will be manually calculated) and, when score(s) meet the specified cutoffs described above, an email alert will automatically be sent to the Clinical Director, notifying them of the participant's alert status and distress score(s). The Clinical Director will inform the study coordinator that an alert has been triggered and provide the score result(s). The study coordinator will complete the first section of the **Distress Call Form** and email it to the study clinical psychologist within 24 hours of receiving the alert message.

NOTE:

1. This email will include a receipt confirmation.
2. The study coordinator will indicate whether this alert score was generated from the Pre-Visit Parent Survey or the 6-mo Post-Return of Result (RoR) Parent Survey, or if this is a repeat alert for this patient – having had an alert of some type at both the time of the Pre-Visit Parent Survey and the 6-mo Return of Results (RoR) Parent Survey.

The study coordinator will also call the study psychologist to confirm that they have received the emailed form if receipt confirmation is not obtained. The purpose of this call will be to inform them of the participant who reported high distress and to provide the measure(s) (GAD7 and/or PHQ8) that triggered the alert for that participant. If the alert is received on a Friday afternoon, the study coordinator will contact the study psychologist by end of day on the following Monday. The study psychologist will then follow up with the participant (e.g. by phone or in-person) within two weeks, making a minimum of three call attempts, to assess the report of distress and provide any relevant support/resources. The study psychologist will complete the bottom section of the **Distress Call Form** (regardless of whether they were able to reach the participants) and return it to the study coordinator. The study psychologist will follow the NCGENES **Distress Screening Script** developed for this study to evaluate the participant.

NOTE: It is critical to note that this distress call reporting protocol is not meant to identify *imminent* risk for suicide. The NCGENES study does not include items about suicidality, and thus individuals flagged for high distress may or may not be experiencing suicidal ideation. The purpose of this alert protocol is to ensure that participants reporting clinically elevated anxiety and depression symptoms have resources to cope. It is not designed to identify and intervene for *imminent* suicide risk. A suicide screening instrument based off the Columbia Suicide Severity Screen is provided for use in case a participant signals possible suicidal ideation during the clinical psychologist's screening call.

After the study psychologist evaluates the participant, they will complete the NCGENES Participant Distress Call Form and return it via email to **Jeanette Bensen** and the study coordinator (**Tracey Grant**). The study coordinator will email the study PIs to inform them that the psychologist has been notified about a participant with an elevated anxiety and/or depression score (clinically elevated symptoms). The study coordinator will be responsible for recording all alert protocol actions taken in the patient tracking system. When relevant the study coordinator will also report on the status of action taken for severely distressed NCGENES 2 caregivers/adult participants at Steering Committee meetings.

Visit 1 Post-visit Physician Survey and PhenoTips

The physician will complete the MD survey on their own using their login in for the tracking system. They will receive an email notification the patient's physician survey is ready for completion with an email reminder every 24 hours after the clinic visit (due date).

NCGENES 2 Patient Tracking Instructions for Physicians/Providers

1. Login to **https://ncgenes2.sirs.unc.edu** by entering your email and password
2. You will land on a page automatically that is the MD Survey tab
    a. Click on the 'GO TO SURVEY' for the relevant patient
    b. Complete the Survey
        i. Click Save – this will return you to the MD Survey landing page. You will note that the patient whose survey you completed no longer appears on this screen
3. Click on the PhenoTips tab
    a. Click on the PhenoTips button for the relevant patient
    b. PhenoTips will open in a new window
    c. Login with your PhenoTips username and password
        i. NOTE: this is not necessarily the same as your login for the Patient Tracking Syste
    d. Complete PhenoTips entry of patients – save and logout
    e. **You must also logout of the patient tracking system which is still open in another window**
4. If you cannot access PhenoTips from the tab in the patient tracking system, try copying and pasting this link into a web browser: **https://phenotips.med.unc.edu/**

1. **Note:** Intake form must be for the age that the child was at the time of eligibility. Children 24 months old should get the toddler 2-3 year old survey and NOT the 12-24 months form. ↑
2. The envelope with parent compensation and assent should be pulled out immediately after flipping the yellow sheet over. These documents should be put out in the open where they can be seen and not missed when the visit ends. ↑
3. Pediatric participants in NCGENES 2 must be <16 years at eligibility determination. The age-specific study documents sent to parent participants are based on the age determined at eligibility. Pediatric participants may age-up while actively in the study, but age is treated as static in the study. Assent is based on the child's *developmental* age at Visit 1. ↑
4. Reimbursement may also be completed by mail if absolutely necessary and should not, in any circumstances, be withheld should a parent decline the offer of consent. Reimbursement is for study activities already completed (i.e. surveys, Visit 1) and is not contingent upon a parent hearing an explanation of consent. ↑

5. Only child participant's with a developmental age less than 7 are eligible for phone consent. Any participant requiring assent cannot give that assent by phone and must do so in person to continue in the study. ↑
6. All statuses entered manually are final statuses. Only tracking system administrators can change these statuses once they are set. ↑
7. The appointment does not need to occur within 30 days; it must be rescheduled within 30 days. ↑

Protected: Remote Research Visits

In some cases, a parent and child pair may not have the time and/or ability to extend their visit and complete the consenting process in person. This can happen if

1. NCGENES 2 staff plan to complete intervention 2 in person, but unforeseen circumstances prevent this from happening immediately following the participant's clinic visit, even though the participant would still like to remain in the study.
2. the clinic visit occurs at a UNC clinic while in-person research visits are suspended as a results of COVID protocols[1]. **Skip to this section**

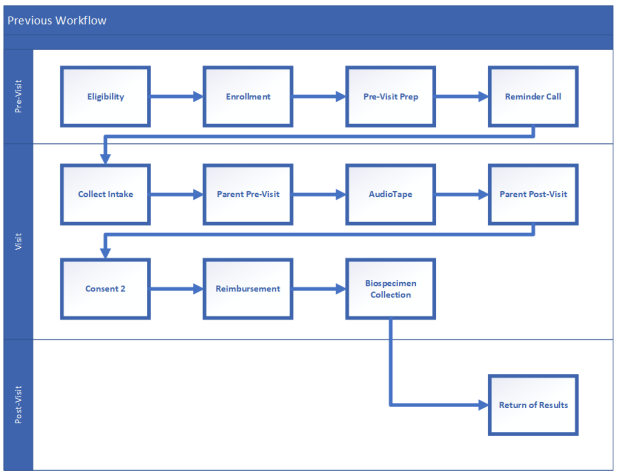
Non-COVID Remote Consent to Intervention 2

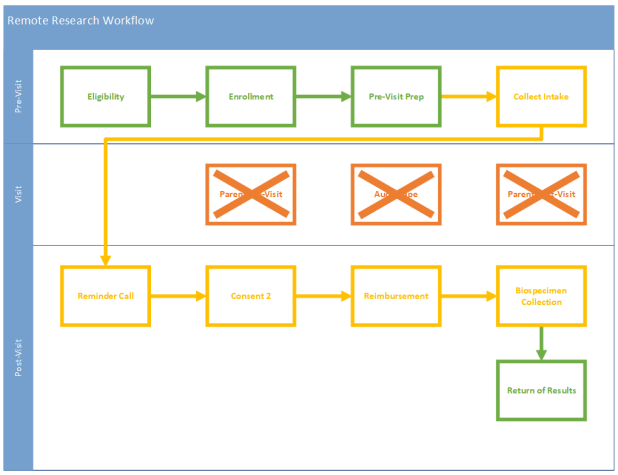
If a participant arrives to the clinic at or after their scheduled clinic appointment time or if the participant has multiple clinical visits that conflict with the research visit protocol, there may not be time to perform an in-person consent. While it is strongly preferred for consents to occur in person, such cases may necessitate a remote consent to intervention 2 and the SC/GC can offer them the option of a remote consent. The SC/GC should still attempt to complete as much of the study visit as possible, particularly distribution of reimbursement[2]. Within a week from the completion of Visit 1, the SC will call the parent participant to explain the process of phone consent. The SC will explain that certain forms will need to be reviewed, signed by the parent, and returned before the child and parent can continue with the study, and that reviewing these forms will require an additional phone call. The SC will ask whether that call can be scheduled and, if the participant agrees, attempt to schedule a follow-up call 1 to 2 we

eks from the current date. This call should be recorded in the ~~Communication Log~~ and the follow-up call entered into the NCGENES Outlook Calendar. The SC should also mail consent forms (**~~Mailing 4~~**) at the conclusion of the call and record this mailing in the communication log.

Remote Visits due to COVID

Due to restrictions on in-person research at all UNC clinics, NCGENES 2 implemented an entirely remote protocol for participants enrolled to the study after August 3, 2020[3]. As of that date, all UNC participants were designated to recceive a ~~remote research visit~~ in the tracking system. When a participant receives this designation, several steps of the study, starting with enrollment, are affected.





Pre-Visit Remote Changes

Once a participant is designated for a remote research visit and deemed eligible for enrollment, the tracking system will generate a ~~Enrollment Call (with Selection) – Remote~~ task will be generated for the participant. This task should be completed like the usual enrollment task (see **here**) with a few key differences:

1. Because the participant won't meet with a staff member immediately before and after their clinic visit, participants enrolled to a remote research visit do not complete the pre and post-visit parent surveys. In light of this, the possible compensation for remote participants drops from $170 to $120, and this change is reflected in the enrollment script.
2. All references to an in-person research or clinic visit are removed from the remote enrollment script.
3. The remote enrollment script includes a section for scheduling the remote research visit. This visit should be scheduled 7-10 days after the scheduled clinic visit. Once the remote research visit has been scheduled in the remote enrollment call, it can be viewed and edited from the ~~participant's individual page~~ .

In addition to changes in the enrollment call script, the contents of Visit 1 Appointment Packet (~~**Mailing 2**~~) are modified to reflect differences in study procedures for remote participants. Information on the number of surveys, possible reimbursment, and scheduled research visit is updated to reflect the remote nature of the research. Also, the Visit 1 Appointment Packet will include a return envelope for parents to mail back their Baseline Intakes. See ~~**Mailing 2**~~ for more information.

Visit Remote Changes

With the in-person research visit no longer occuring, the Study Coordinator should check the EMR to confirm that the clinic visit did occur the day after the visit. If the visit did not occur or was rescheduled, the Study Coordinator should ~~note~~ this in the participant's page and then update the appointment date (if posisble). If it is not possible to update the date of the participant's clinic visit, the SC should follow the **No Show** protocol for follow up to a missed visit.

Confirming the Clinic Visit

If the clinic visit has occurred, the SC should complete the ~~Confirm Visit 1 Appointment Date and Provider~~ task, which will generate several additional tasks. The pre and post-visit parent questionnaires and the permission to audiotape tasks will be canceled by site admin and can be disregarded. The SC should immediately complete the ~~Visit 1 – Collect Info about Intake Completion~~, ~~Questionnaires – Collection Method~~, and (if applicable) ~~Collect Development Age~~ tasks in order to trigger subsequent tasks.

Reminder Call

For remote research paritcipants, the reminder call occurs following confirmation of the *clinic* visit, rather than prior to that visit. Shortly after the clinic visit is confirmed, the SC should complete the ~~Reminder Call for Visit 1 – Remote~~. This call is meant to remind the parent of the remote research visit that was scheduled during the enrollment call, and to make them aware that NCGENES staff will be mailing them some paperwork that they should wait to review until that visit. Additionally, if a ~~Baseline Intake~~ survey has not been received, the reminder call script provides a prompt for reminding the parent about this survey and making sure they have a copy to complete. If the parent does not answer the call, the SC should leave a message as scripted.

*After the reminder call, the SC should mail consent forms (**~~Mailing 4~~**) and record this mailing in the ~~Communication Log~~.*

> Remote Consent to Intervention 2

In many ways, the flow of the remote consent process mimics that of the in-person consent. When the SC reaches the parent participant, they will first confirm that they have received hard copies of the consent and HIPAA forms.

> **Mailing not received?** Remote consent may not proceed without the parent possessing physical copies of the consent/HIPAA forms. If they have yet to receive the mailing or cannot locate the forms, schedule a future call with the parent or resend the forms as appropriate.

The SC will ask them to collect their forms so that they can review them and answer any questions they might have. The SC will discuss consent form 1 with the parent by reviewing the form and by general conversation. The parent will be offered several opportunities to ask and have answered any questions and during the discussion by the SC. The SC also informs the parent that

1. they should keep one copy of the consent form and
2. they can contact the SC via the study number and email address that is on these forms if there are any questions following the study visit

During the conversation, the ~~Randomization to Genome Sequencing Consent~~ task should be completed by the SC:

> The tracking system should be used to record the parents stated decision. If the parent consents, the SC should record "Remote Consent" in the parent's signature box and place their own signature in the box for witness. When the hard copy of the consent is received from the parent by mail, it should be scanned and uploaded to the participant's document page. If there are any discrepancies between the hard copy consent and the tracking system, the hard copy takes precedence. Should significant differences exist, the SC should consult the study director, ✉ **Jeanette Bensen**.

> **Both parents present?** If both parents are present, the SC will inform the parents that for consistency the parent who provided a remote consent must also sign the consent forms for the second part of the study should the family decides to continue with study participation. The non-consenting parent will be informed they can also ask any questions they have during this time and can look at the laptop or follow along via a paper version of the consent.

If the Parent Consents

If consent form 1 is signed, the SC will review the HIPAA consent by following the same procedure outlined above. After the HIPAA consent is signed, the parent/family will be informed of the intervention 2 assignment (i.e. genomic sequencing or non-genomic sequencing). This status will appear on the ~~participant's individual page~~ .

> All participants who consent to the genomic sequencing randomization MUST also have a signed HIPAA document to continue participation in the study. If a participant refused to sign the HIPAA document, they must be manually given the final status of **REFUSED** (see **here**) and a ~~Note~~ detailing the reason for this change should be added to the participant's notes.

If the participant is <u>not</u> assigned to receive genomic sequencing, the SC should inform the parent/family of that assignment, and let them know their remaining study participation will consist of completing follow-up surveys and having their child's information obtained until they are 18 years of age as discussed during the consent process. Next, the SC should

thank the family for their time and ask that they place one copy of the signed consent 1 and the signed HIPAA forms in the prepaid envelope they received and mail them as soon as possible.

If the participant is assigned to genomic sequencing, the SC should inform the parent/family of that assignment, and then the SC (or Genetic Counselor, depending on clinic) will review consent form 2 (i.e. ~~Genome Sequencing Consent~~) by following the same procedure outlined for consent form 1. **If the parent signs consent form 2,** the SC/GC will explain that the next step involves collecting a sample of the child's saliva for analysis. In order to do this, the SC will be mail a saliva kit to the parent as soon as they receive the signed consent forms from the parent. The SC should ask the parent to place one copy of each signed form (consents 1 & 2 and HIPAA) in the prepaid envelope they received and mail them as soon as possible. When the forms are received,

If the Parent Declines

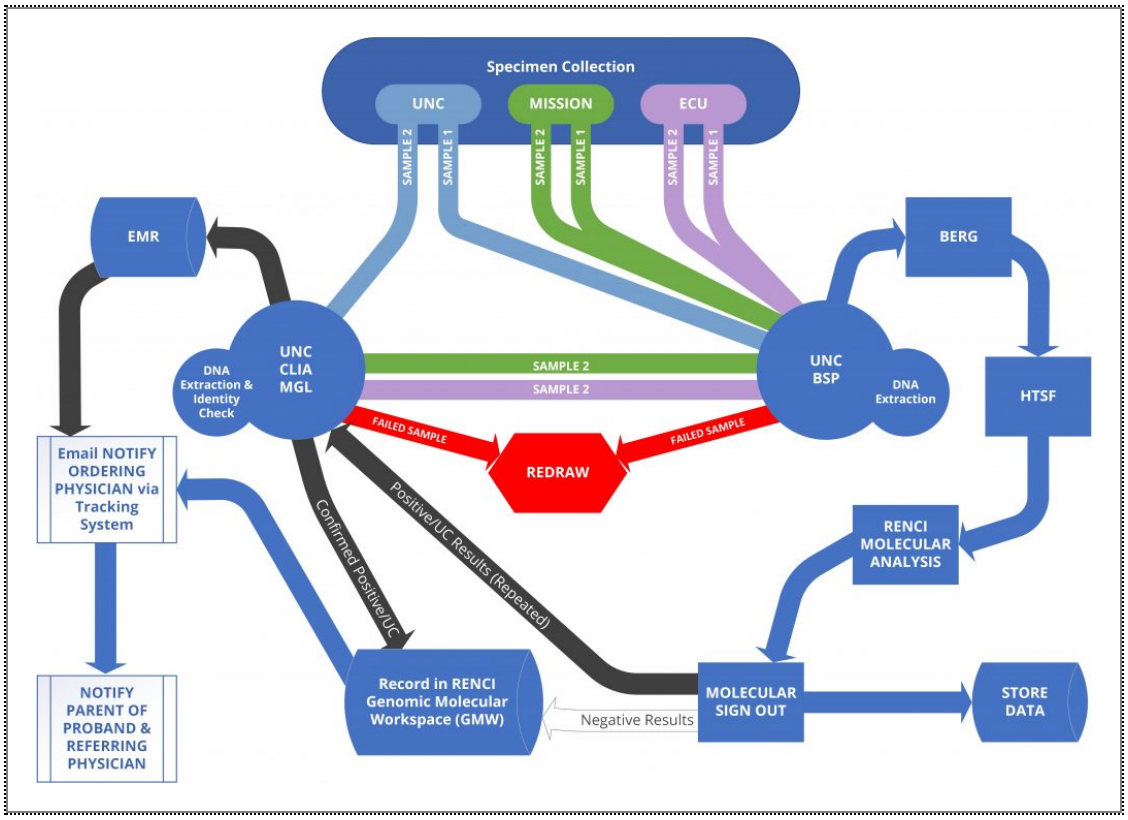
If the parent declines signing either consent form 1 or the HIPAA consent, the parent/family should be informed that they will no longer be participating in the study. In the tracking system, the SC should exit (without saving) the current task and mark the participant **REFUSED** manually with the reason "Declined at Visit 1 – Intervention 2" and a short explanation (see **here**). The SC should then thank the family for their time and ensure they have received proper reimbursement for their visit, either in person or by mail.

If the parent declines signing consent form 2, the parent/family should be informed that their remaining study participation will consist of completing follow-up phone interviews and having their child's information obtained until they are 18 years of age as discussed during the consent process. The SC should then thank the family for their time and ensure they have received proper reimbursement for their visit, either in person or by mail. These participants will have a status of **DECLINE TO GS**

1. NCGENES began enrolling participants at UNC clinics to remote visits as of August 2020 in order to account for restrictions implemented during the COVID-19 pandemic. For more information on the effects of COVID-19 on NCGENES 2, see **NCGENES 2 COVID Timeline** ↑
2. **Note:** Reimbursement may also be completed by mail if absolutely necessary and should not, in any circumstances, be withheld should a parent decline the offer of consent. Reimbursement is for study activities already completed (i.e. surveys, Visit 1) and is not contingent upon a parent hearing an explanation of consent. ↑
3. Participants enrolled prior to 8/3/20 but with clinic visits after that date, usually due to a reschedule, also participated in remote research visits. ↑

NCGenes

Protected: Handling Biospecimens



For participants randomized to genome sequencing as part of the NCGENES 2 study, blood is drawn at the first clinicalvisit (evaluation) for DNA extraction, library preparation, sequencing, identity check genotyping and clinicallysignificant genetic variant confirmation for positive or uncertain results (with respect to their association with thepatient's clinical phenotype). Specifically, one blood tube is sent to the Biospecimen Processing Facility (BSP) and one is sent to UNC Clinical Molecular Genetics Laboratory (CLIA labs) for processing. All laboratories initially extract the DNA. The CLIA lab will also genotype 8 Single Nucleotide Polymorphisms (SNPs) via Sanger sequencing in all participants, which will later be compared to genotypes obtained via research GS. This comparison is used as an identity check to identify any potential sample mix-ups. The CLIA lab additionally stores the remaining DNA for later confirmation ofclinically significant research results that may arise during the course of the study.The BSP sends a portion of the extracted DNA to the Berg Laboratory for library preparation. The sequencing librariesare then sent to the High Throughput Sequencing Facility (HTSF) for research GS. The genetic data is annotated,undergoes molecular analysis

and is reviewed in conjunction with clinical/phenotypic data at a molecular sign-outmeeting.If any clinically significant primary or secondary findings are identified, the CLIA Lab is notified to requestconfirmation and reporting. Confirmation is conducted via Sanger sequencing. CLIA confirmed results are placed in the patient's medical record which automatically notifies the onsite physician. If the CLIA confirmation is being conducted for an offsite institution, then the CLIA lab results will be sent via fax to the ordering physician. Negative research GS results cannot be confirmed in the clinical lab. All results (CLIA confirmed and negative) are reported by the research team to the ordering physician via email notification. Additionally, physicians are notified by CLIA confirmed results via the electronic medical records (EMR) system. The research email notification asks the physician to return results of testing and complete the NCGENES 2 post return of results (RoR) provider survey (the email subject line indicates "ACTION REQUIRED"). A patient friendly research report regarding the results of genomic sequencing is attached to the email notification to the physician. Additionally, the physician email notification includes a link to the patient tracking system (for participants in the GS arm). Once at the physician landing page in tracking, the MD clickson the ~~PhenoTips & Results~~ tab, where there is a link to the ~~Molecular Analysis~~ tab for each participant who is in the GS arm. Results on the molecular analysis tab may indicate that the test results are pending,negative or positive/uncertain (CLIA confirmed). There is also a link on this page to a patient's research result report (Word document that can be printed). Remaining DNA can be used for future research with parent consent and in rare cases with required concordant child assent (which is obtained at the time of GS randomization consent/assent). DNA will be stored indefinitely, but linked data will be destroyed on the patient's 18th birthday rendering all remaining samples anonymized. In some cases, the physician may determine that parent/relative DNA confirmatory testing is needed to interpret the genomic sequencing results of the child. In this case, the genetic counselor or nurse notifies the family and the research team of the need to collect parent/relative DNA. The research team contacts the patient's parent to let them know that parent/relative genetic testing consents and saliva kits are being mailed (one for each parent). The research study coordinator will wait approximately one week and phone the parents to consent them by phone, have them sign the consents and return them along with their saliva samples to the BSP lab in an addressed/postage paid envelope. Extra consentswill be provided so that the parents may keep copy for their records. In rare cases other adult relatives may need to be tested. This will be determined by the ordering physician. NCGENES 2 will pay for additional confirmatory testing in the CLIA of the physician determines that it is necessary for the interpretation of the results for the child.

Collecting Blood Samples at Visit 1

NCGENES 2 prioritizes collection of blood for research biospecimens. As often as possible, NCGENES 2 blood specimens will be collected immediately following Visit 1 from participants consented to exome sequencing. This section outlines the protocol for collecting blood samples at each NCGENES 2 site.

Pre-Visit 1: Preparation of the Blood Collection Kit

All sites will use a generally uniform procedure for preparing blood collection kits. A blood kit is created for each participant and clipped to that participant's folder for use in the clinic (see **Preparation for Visit 1**). In addition, a second blood kit (without forms) should always be brought to the clinic should a redraw become immediately necessary due to failed collection.\

Kit contents

Each blood collection kit will include:

- 2 biohazard bags
- 2 purple top 3ml EDTA vacutainers **(ALWAYS CHECK EXPIRATION DATE)**
- 5 ID barcode labels (includes 1-2 extra)
- 1 **CLIA Molecular Genetics Test Request Form** signed/provider-specific[1] – printed on white paper
- 1 **BSP Requisition Form** printed on blue paper[2]

Kit assembly before the visit

Place print patient-specific barcode ID labels, both blood tubes, one folded biohazard bag and a folded Molecular Genetics Test Request Form and/or BSP Requisition Form into the second biohazard bag. ALWAYS bring a pair of gloves should you need to handle the blood tubes. A biohazard-labeled cooler bag should also be brought to the clinic appointment for transporting/mailing blood tubes to the BSP post-Visit 1

After the Visit: Collection and Distribution

Each site will follow a slightly different protocol for collecting and distributing blood samples. This section describes the protocol for creating a phlebotomy order, assisting with blood collection, assembling the blood collectionkits, and distributing blood samples at each site.

University of North Carolina at Chapel Hill – UNC +

East Carolina University – ECU +

Mission Health – Asheville +

Saliva Collection for Child Participants

Overview

NCGENES 2 prioritizes collection of blood samples from child participants consented to exome sequencing. A family should be offered saliva collection only if one of the following scenarios occurs:

1. *No Blood* was collected at visit 1: Neither tube of blood was able to be collected
    a. Attempted blood collection was not successful[10]
    b. Parent refused blood collection for child
    c. Research visit was completed remotely, i.e. research staff were not physically present to collect blood during the first visit
2. *Insufficient blood* was collected at visit 1: One or both tubes have < 1ml of blood (1 ml is minimum volume for each lab) at collection
3. *Samples failed processing (FAILED RESULTS):* One or both labs (BSP & CLIA/MGL) notify NCGENES 2 Study Coordinator/Co-Investigator that completely or partially and saliva kit(s) are needed to obtain DNA for testing
    a. Sample tube(s) arrive broken
    b. A sample is dropped in the processing lab
    c. The volume is 1ml or more at collection but yields an insufficient amount of DNA

Scenarios 1 and 2 should be identified by the SC at the time of the blood draw. Scenario 3 will occur after the conclusion of Visit 1. The protocol in each scenario is described below.

Saliva Collection Initiated at Visit 1

Scenario 1: No Blood Drawn

The Study Coordinator may encounter a scenario in which blood collection fails entirely at phlebotomy or the parent declines blood draw for the child at Visit 1. In these cases, the parent is offered the option of saliva collection by mail. In the tracking system, this will be recorded in the ~~Visit 1 Biospecimen Collection~~ task with "Question 1. Blood collection Complete?" Answering this question "No" will trigger two tasks automatically: ~~V1 BSP Saliva Kit Due to No Blood Drawn~~ and ~~V1 CLIA Saliva Kit Due to No Blood Drawn~~. Because DNA will be needed for both labs, two saliva kits are mailed to the parent.

Scenario 2: Insufficient Blood Collection at Visit 1

The Study Coordinator may encounter a second scenario of insufficient sample collection (<1ml in either tube). If this occurs the Study Coordinator will ask the phlebotomist to attempt to draw an additional tube (or attempt a second stick if the parent agrees) to see if enough blood may be collected to satisfy each lab's requirements (at least 1 ml for each lab). If the phlebotomist is unable to obtain two 3ml tubes (or a set of >2 tubes that provides at least 1 ml for each lab), the Study Coordinator will inform the family that they will receive 1-2 saliva kits by mail depending on the need, e.g. if enough blood was collected (1 ml) to satisfy the needs of one of the labs, then only 1 kit would be needed. In the tracking system, this will be recorded in the ~~Visit 1 Biospecimen Collection~~ with Questions 2-3. Answering Question 2

"No" will automatically trigger the ~~V1 BSP Saliva Kit Due to No Insufficient Sample~~ task and answering Question 3 "No" will automatically trigger the ~~V1 CLIA Saliva Kit Due to Insufficient Sample~~ task.

Scenario 3: Saliva Collection Initiated by Lab (BSP/CLIA)

Failed Results

If insufficient specimen is received (either blood (<1ml) or saliva (<0.5ml)) by the lab(s) OR if DNA extraction fails to produce sufficient quantities of DNA for study needs at either lab, then the lab staff must notify Co-Investigator ✉ **Jeannette Bensen** and Study Coordinator ✉ **Tracey Grant** within 24 business hours of sample receipt/sample extraction failure to allow for recollection by saliva kit mailing. The UNC research team will (if necessary) notify the partner site and work together to ensure that the tracking system is updated and the saliva kit(s) are properly mailed (in most cases the UNC staff will be responsible for mailing saliva kit(s) to collect a pediatric patient's specimen).[11] If the need for saliva collection arises after the conclusion of Visit 1, the study coordinatoror other study staff under the direction of the study coordinator will notify the parent by phone of the need for saliva kit collection. This contact is recorded in the ~~communication log~~ . Additionally, the local Study Coordinator must record the failed results from blood collection (failed extraction/insufficient blood) reported by the lab(s) by creating ~~V1 BSP/CLIA Saliva Kit Due to Failed Results~~ task for one or both labs.

Sample Fails Identity Check

If the identity check genotypes assayed in the CLIA Lab do not match the identity genotypes assayed by the High Throughput Sequencing Facility (HTSF), a recollection of DNA via mailed saliva kit will be required. The Molecular Analysis group (✉ **Bradford Powell**) will notify the study coordinator if discordance in identity genotyping occurs. In the event of failed identity check, one or two DNA saliva kits will be mailed, one for DNA extraction in the UNC CLIA laboratory and possibly one for DNA extracted in the BSP (the need for one vs. two saliva kits will be determined by the molecular analysis team at the time ofidentify check discordance). Upon receipt, the CLIA laboratory will perform genotyping of the identity-check SNPs on their received sample, and the decision for additional processing of the BSP sample will depend on whether the new CLIA genotyping establishes sample identity.

Saliva Kit Mailing Preparation

A patient saliva kit[12] includes: one large bubble mailer with one or two saliva kit(s) (swab and case), one or two plastic bag(s), and one folded, pre-posted and addressed bubble mailer (this bubble mailer will be smaller than the larger one that the rest of the supplies are mailed in). One saliva kit is mailed if only one lab needs a sample, but 2 kits are mailed if both BSP and CLIA labs need samples.

Sample collection swabs/swab tubes are **removed** from the plastic kit box(es) and are **labeled** with patient-specific barcode labels (generated from tracking system and shown here →) and then replaced back into the plastic kit box(es) prior to mailing. Patient barcodes will always end with -00.

One plastic box/kit will go inside each provided plastic bag to prevent leakage during transport. The large bubble mailer will also include three sheets of paper:

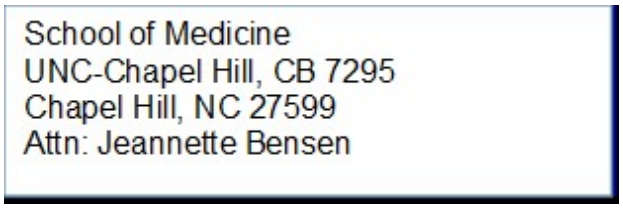
1. an NCGENES 2 participant saliva letter (see **here**)
2. an enlarged Oragene OG 575 saliva kit instructions printed on a yellow sheet of paper. (see **here**)
3. an NCGENES 2 saliva kit mailing instructions sheet that outlines how to return the saliva back to the BSP (see **here**). These instructions are the same as the ones inside the saliva kit, however this form additionally collects the data and time of saliva collection and is returned to UNC along with the saliva samples.

All relevant paperwork can be found on IRBIS.

Example return labels[13] and saliva mailing contents/package for 2 kits shown here.


NO POSTAGE STAMP NECESSARY
POSTAGE HAS BEEN PREPAID BY

BioSpecimen Processing Facility
Attn: Patricia Basta
Michael Hooker Research Center, Rm. 3213
135 Dauer Drive
Campus Box 7406
UNC-Chapel Hill
Chapel Hill, NC 27599-7406
919-966-7738

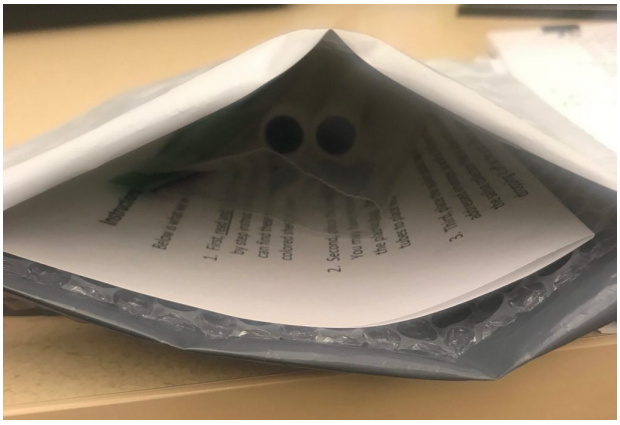

School of Medicine
UNC-Chapel Hill, CB 7295
Chapel Hill, NC 27599
Attn: Jeannette Bensen

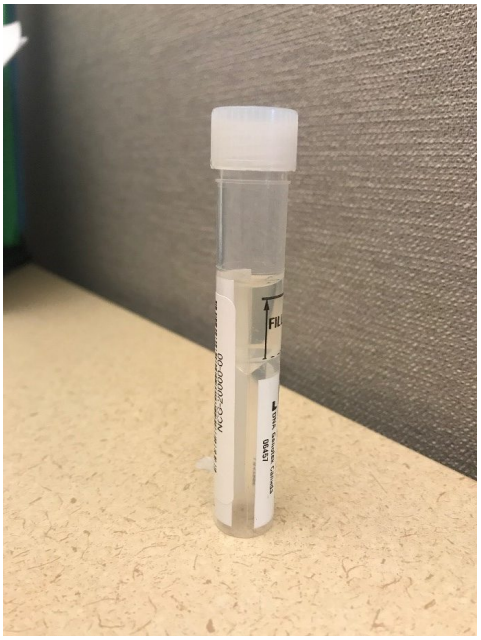
For Mission saliva samples, the Mission SC will address the return envelope to the UNC BSP.

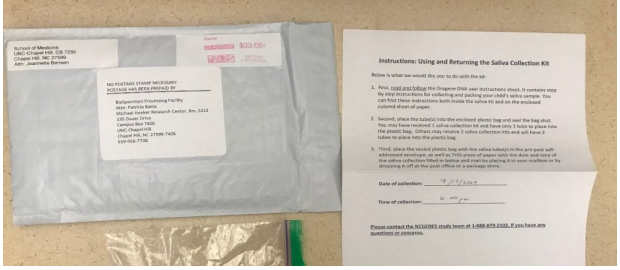
Mailing and receipt of saliva kits as well as distribution to relevant lab(s) is recorded in the patient tracking system by the Study Coordinator. Routine reports are run by the study analyst to ensure that the loop is closed from sample collection to receipt and processing. The participants will be instructed on the NCGENES 2 saliva kit collection process and how to return the completedsaliva kit(s) by mail to the UNC BSP. The parent will include the following in the returned pre-posted and addressedbubble mailer:

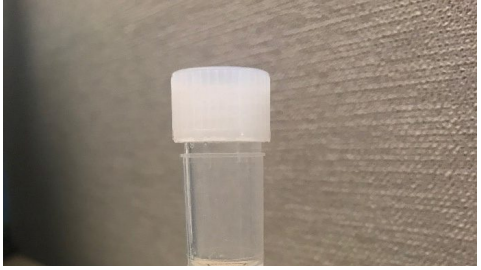
1. NCGENES 2 saliva kit mailing instructions with the date and time of the saliva collection completed by the parent,
2. the Ziploc bag with one or two saliva tube(s).

Example return mailings shown here.









Upon receipt of returned saliva kits to the lab, the BSP staff will notify ✉ **Jeannette Bensen** and ✉ **Tracey Grant**. Returned kits will follow the same sample distribution as outlined for blood specimens above and will depend on site (UNC, ECU, Mission Health) and the lab reporting the sample failure (UNC BSP lab, UNC CLIA/MGL lab). The UNC Study Coordinator/staff will go to the BSP when notified of saliva sample receipt andwill take the appropriate request forms and ensure distribution to the correct labs:

1. Blue BSP request form – be sure to indicate that saliva is the "TYPE" of sample on the form and place an appropriate label on the form
2. MGL/CLIA request form – be sure to complete the signed version (correct ordering physician) of the appropriate child/pediatric patient saliva request for exome sequencing form.

Saliva Collection For Parents/Relatives

Overview

To initiate the parent/relative saliva kit collection the clinical team (MD/GC) must contact the local SC, who must in turn notify the UNC SC (✉ **Tracey Grant**) and ✉ **Jeannette Bensen** of the need to collect a DNA sample from parents/relatives to resolve interpretation of the child's exome sequencing results. Confirmatory DNA tests will be paid for by NCGENES 2research funds, performed in the MGL/CLIA lab (UNC), and reported to the ***child's*** medical record. Any adult relatives (e.g. parents) must be consented in advance of saliva collection. The general procedure for this will be tomail the consents (2 copies of each for each parent so that one can be signed and returned to UNC/Mission and one keptby the parent).[14] This can be done in conjunction with the saliva kit mailing, i.e. each parent is mailed 1 saliva kit with an accompanying consent and other standard documents that are contained in the saliva kit (described below). The UNC Study Coordinator should call the parent to consent them to the parent/adult relative DNA testing. Following this phone consent, the parent or relative signs and dates the form and places it in the addressed/postage paid envelope provided.

> **DNA Sample needed from child relative?** Relatives under the age of 18 must provide assent and have a parent/legalguardian consent in advance of saliva collection. ***Assenting by phone is not***

approved. All assents to relative testing must be made in person for NCGENES 2 to cover family testing.

Saliva Kit Mailing Preparation

A parent/relative saliva kit[15] includes:

1. one large bubble mailer withone saliva kit (swab and case),
2. one Ziploc bag,
3. one folded, pre-posted and addressed bubble mailer (this bubble mailer will be smaller than the larger one that the rest of the supplies are mailed in).

The saliva tube is removed from the kit and the appropriate participant label is placed directly on the tube. Labels are generated from the tracking system. The labeled tube is then replaced back inside its plastic kit box. Examples of participant ID barcode labels for mom and dad are shown here:

Mom –01

Dad –02

Parent barcodes will always end with -01 for mom/parent 1 and -02 for dad/parent 2. The indication that the saliva kit is for -01 mom/parent 1 and -02 dad/parent 2 should be explicit, with a barcode on the saliva tube, a label that says “mom – 01” or “dad – 02” on the outside of the plastic casing holding the saliva kit, and a label that says “mom – 01” or “dad – 02” on the outside of the plastic Ziploc bag.[16]

The plastic box/kit will go inside the Ziploc bag to prevent leakage during transport. The saliva tube will be pre-labeled with a parent appropriate barcode with the correct participant ID ending in “-01” for mom/parent 1 and “-02"for dad/parent 2. The large bubble mailer will also include four sheets of paper:

1. an NCGENES 2 parent saliva letter (see **here**)
2. Parent/Relative DNA testing consent (two copies *per parent*, one to return and one to keep)
3. an NCGENES 2 saliva kit mailing instructions sheet that outlines how to return the saliva back to the BSP[17] (see **here**)
4. an enlarged Oragene OG 575 saliva kit instructions printed on a yellow sheet of paper. (see **here**)

All relevant paperwork can be found on IRBIS.

Parents/relatives will be instructed on the NCGENES 2 saliva kit collection process and how to return the completed saliva kit by mail to the UNC BSP. The parent will include the following in the returned pre-posted and addressed bubblemailer:

1. a signed copy of the saliva consent for each parent
2. NCGENES 2 saliva kit mailing instructions with the date and time of the saliva collection completed by the parent
3. the Ziploc bag with one or two saliva tube(s).

Upon receipt of returned saliva kits to the UNC lab, the BSP staff will notify **Jeannette Bensen** and **Tracey Grant**. Samples collected from Mission participants may be mailed to the UNC BSP and then brought to the UNC CLIA lab as necessary. The UNC RA will go to the BSP lab when notified of saliva sample receipt and will take the appropriate request forms OR actions (enter into an electronic system) and ensure logging of sample receipt and distribution (UNC MGL CLIA lab). Two forms for parent/relative collection are needed by the UNC MGL CLIA lab:

1. the signed version (with correct ordering physician) of the appropriate child/pediatric patient saliva request for exome sequencing form./p>
2. the Phenotypic information MGL request form with a parent-specific bar code This should be completed by the Genetic Counselor for each parent when the initial request for parent saliva kits is made, held until sample arrival, and paired with the MGL confirmatory testing request form and submitted with the sample to the MGL/CLIA lab.

Mailing and receipt of the saliva kit is tracked in the communication log of the tracking system by the SC or designee. Any consents should be uploaded to the appropriate participant's document tab. Receipt of the sample is also tracked in the RENCI molecular workspace and in the MGL/CLIA laboratory LIMs. Routine reports are run by the study analyst to ensure that the loop is closed from sample collection to receipt and processing.

Mailed Saliva Kit Tracking– for samples processed and logged into the BSP LIMs

The UNC BSP will notify a member of the NCGENES 2 team when saliva samples have arrived to the BSP. The NCGENES SC/RA will transport the saliva kit to the CLIA lab along with the appropriately completed MGL forms. For returned parent saliva kits, an additional MGL form titled, "NCGENES Request for Family Studies: Molecular Genetics Laboratory" will be completed by the participant's physician or (more likely) genetic counselor. The study team will request that this form be completed when the request is made for parent testing. The genetic counselor will return the completed form to the study team who will hold it until sample arrival in BSP. At that time the study team will complete the MGL request form(pre-signed by the relevant ordering physician) for parent saliva confirmatory testing and will combine that form withthe Family Studies form completed by the counselor. Both forms will be sent with the saliva sample to the MGL/ CLIA labby the hospital tube system. Each parent's

saliva sample will have their own set of 2 MGL forms. The MGL will log receipt of saliva kit in the RENCI workflow system, extract DNA from the saliva kit, and perform the requested confirmatory testing.

ECU and Mission Health– Saliva Sample Request/Need

The local Study Coordinator is responsible for coordinating saliva kit mailing for the UNC MGL Lab. The saliva kit is mailed from the UNC Study Team (including appropriate lab request forms) for ECU to the family and is/are returned to the UNC BSP. If two kits are mailed both are returned to the UNC BSP lab return address. The BSP will notify the study team upion receipt, who will be responsible for completing appropriate forms and distributing the saliva samples to the appropriate lab for processing. The UNC Study Coordinator records and logs the contact with the parent, as well asthe kit mailing/blood recollection and receipt and distribution of the sample in the patient tracking system.

Biospecimen Processing, Distribution and Reporting

All specimen processing protocols are documented **here**. This section provides an overview of the general process:

Samples processed and distributed by the UNC Biospecimen Processing Facility (BSP)

Blood or Saliva Specimen Processing

For pediatric participants enrolled at either UNC, ECU or Mission Health in the genomic sequencing arm of the clinicaltrial, either a 3ml blood specimen or saliva swab kit is sent to the UNC BSP laboratory where DNA is extracted and quantitated. The UNC BSP Lab sample flow overview and blood and saliva DNA extraction and quantitation protocols are available **here**. Following DNA extraction and quantitation, the sample is sent to the Berg Lab for library preparation prior to high-throughput sequencing.

Distribution of blood or saliva DNA to Berg Lab

After BSP processing (DNA extraction), quantitation and aliquoting the samples are placed into the protocol “BSP_TO_BERG”. The BSP lab staff will send the Berg lab (specifically Alicia Brandt) an email indicating that a set ofsamples is ready and provide the list of sample IDs in the batch. Batches are approximately 10 or more samples pertransfer. Berg lab staff (Alicia Brandt or technician TBD) pick up the samples in the BSP and sign a copy of the samplemanifest (hard copy of the BSP_TO_BERG worksheet). This signed copy goes into the BSP transfer log and the Berg labtakes a second copy. The BSP staff input the pickup information (courier, date, time) into the BSP LIMS and then closeout the worksheet. This then allows the Berg lab to perform a core transfer of the samples into their (Berg) LIMS.

Samples processed and POSITIVE OR UNCERTAIN RESULTS reported by the UNC Molecular Genetics CLIA Lab (UNC MGL)

Blood or Saliva Specimen Processing

For pediatric participants in the genomic sequencing arm of the clinical trial enrolled at UNC, Mission, or ECU either a 3ml blood specimen or saliva swab kit is sent to the UNC Molecular Genetics Lab (UNC MGL) where DNA is extracted, quantitated, and identity check genotype completed (used to resolve potential sample mix-ups). The UNC MGL blood and saliva DNA extraction, quantitation and identity check protocols are available **here**. Following DNA extraction and quantitation, the DNA sample undergoes genotyping for 8 single nucleotide polymorphisms to be used for comparison to data obtained through GS. The remaining DNA sample is held until notification at the molecular sign-out meeting that positive or uncertain research findings must be confirmed.

Confirmation of Positive or Uncertain Research Genomic Sequencing Findings

Research sequencing confirmation is conducted via Sanger sequencing in the UNC MGL CLIA lab (protocol available **here**). CLIA confirmed results are placed in the patient's medical record which automatically notifies the UNC ordering physician. If the CLIA confirmation is being conducted for an ECU or Mission study participant, then the CLIA lab results will be sent via fax to the ordering physician. Negative research GS results are NOT confirmed in the CLIA clinical lab. Negative results notification is done by the NCGENES 2 Patient Tracking System that generates an email notification to the ordering physician indicating results are available. This notification includes a patient friendly research result report and points the MD to the molecular analysis tab to see the negative result report and requests the physician to complete the physician post-RoR survey. All results (positive, negative or uncertain) are reported to the family by the clinical genetic counselor or ordering physician by phone or in-person.

Sample reporting of NEGATIVE RESULTS by UNC NON-CLIA RENCI System – All Sites

Return of NEGATIVE RESEARCH results to NCGENES 2 patients (All Sites)

Negative research results cannot be confirmed, thus negative results will not be confirmed by the UNC CLIA Molecular Genetics Labs. Instead, negative results notification is done by the NCGENES 2 Patient Tracking System that generates an email notification to the ordering physician indicating results are available. This notification includes a patient friendly research result report and points the MD to the molecular analysis tab to see the negative result report and requeststhe physician to complete the physician post-RoR survey. All results (positive, negative or uncertain) are reported tothe family by the clinical genetic counselor or ordering physician by phone or in-person.

Final Genomic Sequencing Report to Parent/Caregiver

At the end of the study, after the final survey, parents will be mailed a final thank you letter for their participation (a copy of the final genomic sequencing results for their records MAY accompany their thank you note).

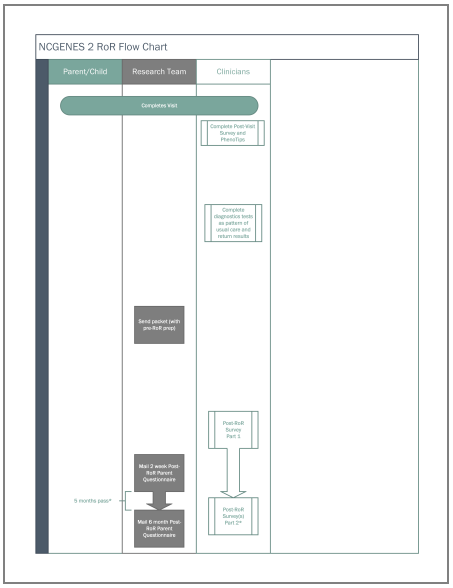
1. A UNC MGL form will need to be signed by each physician on the study team one time – then these can be photocopied for use throughout the study. The study coordinator will select the appropriate MGL/CLIA lab physician's form to include with the blood kit.↑
2. The **BSP Requisition Form** is printed on blue paper to easily distinguish which form is which when both are folded and placed in separate blood bags.↑
3. All staff placing orders must comply with Epic training and receive authorization for placing research phlebotomy orders (See ~~**here**~~)↑
4. Labeling of tubes and forms follows blood collection to avoid wasting pre-labeled tubes and forms if blood collection is declined or unsuccessful. ↑
5. The MGL staff enters sample receipt once/week (and other data as sample is processed) into the Genomic Molecular Workbench hosted by RENCI (see **here** for details of data entry process and content)↑
6. All staff placing orders must comply with Epic training and receive authorization for placing research phlebotomy orders (See ~~**here**~~)↑
7. Labeling of tubes and forms follows blood collection to avoid wasting pre-labeled tubes and forms if blood collection is declined or unsuccessful. ↑
8. The MGL staff enters sample receipt once/week (and other data as sample is processed) into the Genomic Molecular Workbench hosted by RENCI (see **here** for details of data entry process and content)↑
9. All staff placing orders must comply with Cerner training and receive authorization for placing research phlebotomy orders (See **here**).↑
10. In some cases an extra tube or second stick (after the clinical draw) may be necessary to acquire a sufficient volume of blood, so the SC should always have an extra set of tubes/labels should this be necessary at blood draw.↑
11. If insufficient sample is identified by one lab, the UNC Study Coordinator should email the other study lab to confirm that the other sample is sufficient prior to mailing the saliva collection kit in case 2 saliva kits are needed.↑
12. See **here** for information on ordering supplies.↑
13. Use the Dymo label maker to print the return address and the 5264 shipping labels to print the BSP address.↑
14. In some cases, consent and/or saliva collection can occur in the clinic should the family be returning for another reason. A clinic visit should not be scheduled solely for the purpose of parent or relative consent/collection.↑
15. See Appendix XXXII on page 268 forinformation on ordering supplies.↑
16. Note: -03will designate other relatives as needed – the relative type (mom, dad, maternal aunt, etc should be written on the MGLforms that go to the CLIA lab).↑
17. These instructions are the same as the ones inside the participant saliva kit outside of additionally recording the data and time of saliva collection. These should be returned to UNC along with the saliva samples.↑

Protected: Return of Results

Currently in NCGENES 2, the term "Return of Results" (RoR) is used in two senses: (1) to refer to the general time period following Visit 1/Biospecimen Collection and (2) to refer to the process/task of returning results to participants who were randomized and consented to the genomic sequencing group. The RoR process flow can be seen in the diagram below. This diagram is broken apart and explored in detail in the sections that follow.

After Visit 1: All Participant Groups

At Visit 1, NCGENES participants are randomized into two groups, Exome Sequencing (i.e. **EXOME**) and No Exome Sequencing (i.e. **NO EXOME**).



This group also includes participants who are randomized to genome sequencing, but decline to receive it and have a status of **DECLINE TO GS** , as well as those for whom specimen collection is not possible, who will be marked as **EXOME – NO BIOSPECIMEN** .

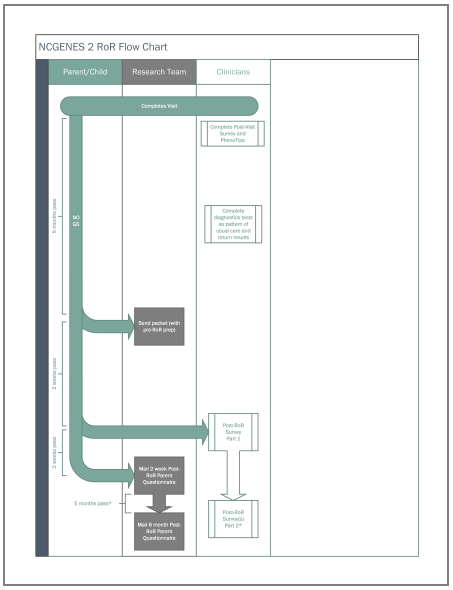
Much to the RoR process differs depending on the randomization arm of the participant. However, a few things can be generally stated about the process:

1. *Post-Visit Provider Activities* – Providers will be asked to completed a Post-Visit 1 Clinician Questionnaire and enter patient clinical data in the NCGENES2 PhenoTips Web Software regardless of the participant's randomization.

2. *Usual care* – Providers should *not* adjust their plan of care for a participant based on their participation in NCGENES 2 or their randomization. Providers should complete and return the results of any non-NCGENES 2 diagnostic tests according to their usual practices and timelines.
3. *Pre-RoR Mailing* – All participants will receive a "Pre-RoR" mailing of some type. The contents and timing of that mailing depend and the participant's randomization. See below for more detail.
4. *Post-RoR Provider Survey(s)* – Providers will be asked to complete a 2-part post-RoR questionnaire for each NCGENES 2 participant. The content and timing of these questionnaires depends upon the randomization and documented treatment of the participant.
    a. *Part 1* addresses the utility of diagnostic tests (including genome sequencing, if applicable) and plan for continued care of the patient. The participant's primary genetic/neurology provider, usually a physician, will always complete this part of the survey.
    b. *Part 2* addresses the actual process of returning results, i.e. the interaction with the participant's caregiver(s). Whoever completes part 1 of the survey for a participant will indicate all parties that took part in returning results, e.g. genetic counselors or nurses. Each of those participating providers will complete a copy of part 2 of the survey for that participant.
5. *Post-RoR Parent/Caregiver Survey(s)* – Parent participants will be asked to complete a post-RoR questionnaire 2 weeks and 6 months after results have been returned. The content and exact timing of these questionnaires depends upon the randomization, documented treatment, and age of the participant. Questionnaires will be mailed to participants, but may also be completed by phone on request.

RoR for **NO EXOME** Participants

The Return of Results process for **NO EXOME** participants is generally simpler than that for **EXOME** participants. That being said, certain limitations of this clinical trial do create quirks that may be confusing to staff, providers, and participants.



Defining Results for **NO EXOME**

Unlike their **EXOME** counterparts, **NO EXOME** participants have no standardized diagnostic test (i.e. exome sequencing performed by NCGENES 2) that might reliably produce results returned to the patient's

caregivers. Instead, "results" for **NO EXOME** participants should be understood as the results of all diagnostic tests ordered (if any[1]) by the participant's provider *during their first visit* .

Timing of RoR Tasks for **NO EXOME**

Because the actual timelines for return of results for **NO EXOME** participants will vary widely, the timelines surrounding RoR research tasks for these participants have been set chronologically to mimic, as best as possible, the timelines expected for participants in the other arm of the study. This means that the timing will rarely correspond to usual clinical practice in terms of returning results of diagnostic tests ordered at Visit 1. This is a necessary limitation of the study that should be understood by study staff should other stakeholders express confusion at the process.

Pre-RoR Mailings – NO EXOME

Pre-RoR Mailings (~~**Mailing 3**~~) for **NO EXOME** participants will always be sent exactly 5 months after the participant's Visit 1. Staff should complete the ~~Pre-RoR Packet – No GS without Pre-Visit Prep~~ task in the tracking system upon completion of this mailing.

RoR Date – NO EXOME

Functionally, the RoR Date for **NO EXOME** participants is always set at 6 months after Visit 1. This date determines the windows in which post-RoR Parent Surveys are sent and received. Providers may also indicate in their Post-RoR surveys a date when results from ***all*** diagnostic tests ordered at Visit 1 where returned to the participants (i.e. the date the final result from these tests was returned). While this information is important to the study, it does not determine timelines for **NO EXOME** participants.

Provider Post-RoR Surveys – NO EXOME

Providers of **NO EXOME** participants will receive an email notification exactly 5.5 months after visit one that informs them a ~~Post-RoR Clinician Questionnaire – Part 1~~ is due. Providers can access this survey using the link in the email or from the MD surveys tab in their tracking system account. Once Part 1 of the provider survey is complete, Part 2 will be triggered automatically based upon feedback offered in the first part of the survey. If the initial provider is completing a ~~Post-RoR Clinician Questionnaire – Part 2~~ , they will be automatically directed to it upon completion of Part 1. Any other provider designated to complete a ~~Post-RoR Genetic Counselor/Nurse Questionnaire – Part 2~~ will receive an email notification. Surveys should be completed as quickly as possible to minimize recall bias.

Parent Post-RoR Surveys – NO EXOME

Each parent will be sent two surveys after the RoR Date. These surveys will be mailed to the parents, filled out, and returned. Parent's also have the option of completing surveys by phone.

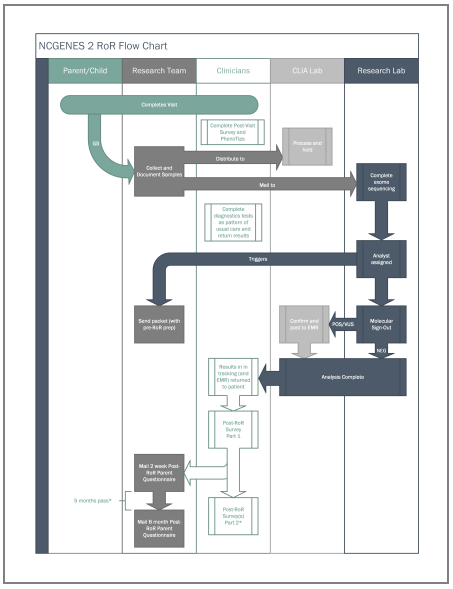
Post-RoR 2 Week Parent Survey

The first parent survey should be completed roughly two weeks after the RoR date. The window for completing the Post-RoR 2 week Parent survey is 0-6 weeks after return of results. For **NO EXOME** participants, this means the 2 week survey should be completed between 6-7.5 months after Visit 1. Exactly six months after Visit 1, study staff will mail a Post-RoR 2 Week Parent Questionnaire (~~**Mailing 4**~~) to parents of participants not randomized to GS. Staff should complete the ~~Post-RoR – Parent 2 Week Questionnaire Mailing~~ task in the tracking system upon completion of this mailing. When the parent returns a completed Post-RoR 2 week survey by mail, staff should complete the ~~Post-RoR – Parent 2 Week Questionnaire Mailing – Received~~ task in the tracking system, the paper copy of the survey should be scanned and uploaded in the participants ~~documents~~, and the data in the survey should be entered in the ~~Post-RoR – Parent 2 Week Questionnaire~~ task in the tracking system. This data entry should be done regardless of whether the survey was completed within the given window. Finally, staff should send a thank you note with gift card to the parent (~~**Mailing 5**~~).

Post-RoR 6 Month Parent Survey

The first parent survey should be completed roughly six months after the RoR date. The window for completing the Post-RoR 6 month Parent survey is 5-7 months after return of results. For **NO EXOME** participants, this means the 6 month survey should be completed between 11-13 months after Visit 1. Exactly eleven months after Visit 1, study staff will mail a survey to parents of **NO EXOME** participants (~~**Mailing 6**~~). Staff should complete the ~~Post-RoR – Parent 6 month Questionnaire Mailing~~ task in the tracking system upon completion of this mailing. When the parent returns a completed Post-RoR 6 month survey by mail, staff should complete the ~~Post-RoR – Parent 6 month Questionnaire Mailing – Received~~ task in the tracking system, the paper copy of the survey should be scanned and uploaded in the participants documents, and the data in the survey should be entered in the ~~Post-RoR – Parent 6 month Questionnaire~~ task in the tracking system. This data entry should be done regardless of whether the survey was completed within the given window. Finally, staff should send a thank you note with gift card to the parent (~~**Mailing 7**~~).

RoR for **EXOME** Participants



The Return of Results process for **EXOME** participants is complex and depends upon multiple teams contributing to perform tests, return results, and document the process.

Results for **EXOME**

"Results" for **EXOME** participants refers to the results of NCGENES 2 exome sequencing. NCGENES 2 staff will collect two biospecimens from each participant randomized to **EXOME** . One specimen will be sent to a CLIA lab to process and hold for potential confirmation. The other sample will be sent to UNC's Biospecimen Processing Facility. From there, DNA will be extracted and sent for sequencing. When data from sequencing returns, an analyst will be assigned to review any reported variants and perform a preliminary assessment of clinical significance. This report will be presented at regular Molecular Sign-Out committee meetings. If no variants are deemed clinically significant (i.e. results are negative), the results will be reported directly to the child's provider. If results are positive or uncertain, variants will be sent to the CLIA lab for confirmation. Confirmed positive/uncertain results will be posted in the patient's EMR. For more on specimen collection and lab procedures, see **Handling Biospecimens**.

Timing of RoR Tasks for **EXOME**

Unlike **NO EXOME** participants, the timelines for RoR tasks for **EXOME** participants are variable and depend on upon the completion of tasks by a variety of NCGENES 2 teams. Because of this, timely completion of tasks is critical, particularly to ensure Post-RoR parent surveys can be collected within an acceptable timeframe.

Pre-RoR Mailings – **EXOME**

Pre-RoR Mailings ~~**Mailing 3**~~ for **EXOME** participants will always be sent as soon as an analyst is assigned to interpret that participant's sequencing data. Staff should complete the ~~Pre-RoR Packet – GS without Pre-Visit Prep~~ or ~~Pre-RoR Packet – GS with Pre-Visit Prep~~ task in the tracking system upon completion of this mailing.

RoR Date – **EXOME**

The RoR Date for **EXOME** participants is set in one of two ways:

1. Prior to August 2020, the RoR Date was only set by the provider(s) during Part 2 of the Post-RoR Clinician Questionnaire. In that portion of the survey, the provider(s) are asked to indicate when all planned communications associated with returning the exome sequencing results for the participant were complete. This date determined the windows in which post-RoR Parent Surveys are sent and received. However, because there may be a delay between the provider completing their survey(s) and the actual RoR date, NCGENES also uses the date of completion of Part 1 of the Post-RoR survey as a temporary RoR date until Part 2 of the survey is complete. Since Part 1 of the survey can only be completed after results are returned, this allows study staff to quickly move forward on administering parent surveys without interfering with standard clinical practice.
2. As of August 2020, NCGENES staff will perform weekly checks of the EMR for any participant for whom results have been posted to the tracking system. If these checks reveal that NCGENES 2 results have been returned, the staff member will enter that RoR Date into the "Edit Info" page on the participant's page in tracking. This will trigger the post-RoR Parent survey tasks. The Post-RoR Provider Part 1 trigger will remain in place. However, if any Parent RoR tasks trigger on that basis, UNC staff will immediately review the patient's EMR, determine the RoR Date, and enter it into tracking to trigger the remaining Post-RoR parent tasks.

Provider Post-RoR Surveys – EXOME

Providers of **EXOME** participants will receive an email notification as soon as the molecular analysis for that participant is complete that informs them they have results and that a ~~Post-RoR Clinician Questionnaire – Part 1~~ is due. Providers can access this survey using the link in the email or from the MD surveys tab in their tracking system account. Once Part 1 of the provider survey is complete, Part 2 will be triggered automatically based upon feedback offered in the first part of the survey. If the initial provider is completing a ~~Post-RoR Clinician Questionnaire – Part 2~~, they will be automatically directed to it upon completion of Part 1. Any other provider designated to complete a ~~Post-RoR Genetic Counselor/Nurse Questionnaire – Part 2~~ will receive an email notification. Surveys should be completed as quickly as possible to minimize recall bias.

Parent Post-RoR Surveys – EXOME

Each parent will be sent two surveys after the RoR Date. These surveys will be mailed to the parents, filled out, and returned. Parent's also have the option of completing surveys by phone.

Post-RoR 2 Week Parent Survey

The first parent survey should be completed roughly two weeks after the RoR date. The window for completing the Post-RoR 2 week Parent survey is 0-6 weeks after return of results. As soon as an RoR Date is confirmed, study staff will mail a survey to participants randomized to the **EXOME** Group (~~**Mailing 4**~~). Staff should complete the ~~Post-RoR – Parent 2 Week Questionnaire Mailing~~ task in the tracking system upon completion of this mailing. When the parent returns a completed Post-RoR 2 week survey by mail, staff should complete the ~~Post-RoR – Parent 2 Week Questionnaire Mailing – Received~~ task in the tracking system, the paper copy of the survey should be scanned and uploaded in the participants documents, and the data in the survey should be entered in the ~~Post-RoR – Parent 2 Week Questionnaire~~ task in the tracking system. This data entry should be done regardless of whether the survey was completed within the given window. Finally, staff should send a thank you note with gift card to the parent (~~**Mailing 5**~~).

Post-RoR 6 Month Parent Survey

The first parent survey should be completed roughly six months after the RoR date. The window for completing the Post-RoR 6 month Parent survey is 5-7 months after return of results. Exactly 5 months after the RoR Date, study staff will mail a survey to parents of **EXOME** participants (~~**Mailing 6**~~). Staff should complete the ~~Post-RoR – Parent 6 month Questionnaire Mailing~~ task in the tracking system upon completion of this mailing. When the parent returns a completed Post-RoR 6 month survey by mail, staff should complete the ~~Post-RoR – Parent 6 month Questionnaire Mailing – Received~~ task in the tracking system, the paper copy of the survey should be scanned and uploaded in the participants documents, and the data in the survey should be entered in the ~~Post-RoR – Parent 6 month Questionnaire~~ task in the tracking system. This data entry should be done regardless of whether the survey was completed within the given window. Finally, staff should send a thank you note with gift card to the parent (~~**Mailing 7**~~).

1. In some cases, the provider may not have ordered any diagnostic tests during the first visit. Even in these situations, the participant (and their provider) will receive post-RoR questionnaires tailored to that specific case.↑