Human Subjects Protocol (HSP)

Form Version: February 1, 2017

- You are applying for IRB review of the research described in this form.
- To avoid delay, respond to all items in order and include all required approvals and documents. For more tips, see the UAB IRB website.
- To complete the form, click the underlined areas and type or paste in your text; double-click checkboxes to check/uncheck.
- All responses should be Times New Roman, Bold, and Underlined.
- Submit all materials to AB 470, 701 20th Street South, Birmingham, AL 35294-0104

Indicate the type of review you are applying for:

☒ Convened (Full) IRB ***-OR-***

☐ Expedited - See the Expedited Category Review Sheet, and indicate the category(ies) here:

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

1. IRB Protocol Title: South-seq: DNA sequencing for newborn nurseries in the South

2. Investigator and Contact Person

a. Name of Principal Investigator: **Bruce Korf MD, PhD**

Degree(s)/Title: **MD, PhD** BlazerID: **bkorf**

Dept/Div: **Genetics/Chair's Office** Mailing Address: **720 20th Street S** UAB ZIP: **35244**

Phone: **4-9411** Fax: **4-9488** E-mail: **bkorf@uabmc.edu**

b. Name of Contact Person: **Shaila Handattu PhD, MBA** Title: **Program Director III**

Phone: **205-934-9417**

E-mail: **hande@uabmc.edu** Fax: **4-9488**

INVESTIGATOR ASSURANCE STATEMENT & SIGNATURE

By my signature as Principal Investigator, I acknowledge my responsibilities for this Human Subjects Protocol, including:

- Certifying that I and all key personnel comply with reporting requirements of the UAB Conflict of Interest Review Board;
- Certifying that the information, data, and/or specimens collected for the research will be used, disclosed and maintained in accordance with this protocol and UAB policies;
- Following this protocol without modification unless (a) the IRB has approved changes prior to implementation or (b) it is necessary to eliminate an apparent, immediate hazard to a participant(s);
- Verifying that all key personnel listed on the protocol have completed initial IRB training and will complete continuing IRB training as required;
- Verifying that all personnel are licensed/credentialed for the procedures they will be performing, if applicable;
- Certifying that I and all key personnel have read the *UAB Policy/Procedure to Ensure Prompt Reporting of Unanticipated Problems Involving Risks to Subjects or Others to the IRB, Institutional Officials, and Regulatory Agencies* and understand the procedures for reporting;
- Applying for continuing review of the protocol at least annually unless directed by the IRB to apply more frequently;
- Conducting the protocol as represented here and in compliance with IRB determinations and all applicable local, state, and federal law and regulations; providing the IRB with all information necessary to review the protocol; refraining from protocol activities until receipt of initial and continuing formal IRB approval.

Signature of Investigator: _____ **Date: 05/14/2019**

3. Protocol Personnel

Including the PI, list all key personnel (each individual involved in the design and conduct of this protocol). See the Key Personnel Flowchart.

Complete the UAB (3.a.) and non-UAB (3.b) tables, as applicable. Use the checkboxes to show each individual's role, whether the individual has financial interests as defined by the UAB CIRB, and briefly describe the individual's protocol responsibilities and qualifications to perform those responsibilities. **Insert additional rows as needed.**

FDA: For studies involving investigational drugs, list all investigators who will be listed on FDA Form 1572 and include a copy of the 1572. Send the IRB a copy of Form 1572 any time you update the form with the FDA.

a. UAB Personnel (includes UAB affiliates and Children's of Alabama personnel)

Name, Degree, and Dept.	Blazer ID	Role	Financial Interest?*	Protocol Responsibilities and Qualifications (indicate if this person obtains consent)
Name: **Bruce Korf** Degree: **MD, PhD** Department: **Genetics**	**bkorf**	Principal Investigator	☒No ☐Yes	**Recruitment/enrollment of participants, consent, counseling and explanation of results, medical management and follow-up for patients/ Principal Investigator and Chairman of the UAB Dept. of Genetics and practicing medical geneticist**
Name: **Kenneth G. Saag** Degree: **MD, MSc** Department: **Medicine**	**ksaag**	☒Sub-Investigator ☐Other	☒No ☐Yes	**Dr. Saag is Jane Knight Lowe Professor in the Division of Clinical Immunology and Rheumatology at UAB, Professor of Epidemiology at the UAB School of Public Health, and Vice Chair for Faculty Development in the Department of Medicine. Dr. Saag will assist with the design of the clinical trial (Aim3).**
Name: **Maria Danila** Degree: **MD, MSc, MSPH** Department: **Medicine**	**mdanila**	☒Sub-Investigator ☐Other	☒No ☐Yes	**Dr. Danila is an associate professor in the Division of clinical Immunology and Rheumatology. Dr. Danila will oversee the design and manage the clinical trial (Aim3).**
Name: **Shaila Handattu** Degree: **PhD. MBA** Department**: Genetics**	**hande**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Dr. Handattu is the Program Director in the Dept. of Genetics. She will be assisting Dr. Korf with the study and will serve as the contact person for IRB correspondence.**
Name: **Jeff Foster** Degree**: MPH** Department: **Medicine**	**fosterau**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Mr. Foster will assist the study team with development of education materials and contribute to the design of the clinical trial (Aim3).**
Name**: Gabriella Oates** Degree: **PhD** Department: **Medicine**	**goates**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Dr. Oates is an instructor in the Division of Preventive Medicine and serves as the Director of Research of the UAB Minority Health and Health Disparities Research Center. She will be assist with the design of the study and help with the development of the educational materials.**

Name: **Elizabeth Rahn** Degree: **PhD** Department: **Medicine**	**rahneli**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Dr. Rahn is a scientist in the Division of Clinical Immunology and Rheumatology and will assist in the development of the educational materials and design of the clinical trial (Aim3).**
Name: **Josh Melnick** Degree: **MPH** Department: **Medicine**	**jmelnick**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Mr. Melnick will assist the study team with the development of educational materials and contribute to all aspects of the clinical trial (Aim3).**
Name: **Eve Markovitz** Degree: **BA** Department: **Medicine**	**esm**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Ms. Markovitz will assist the study team with the development of the educational materials and contribute to all aspects of the study.**
Name: **Anna C.E. Hurst** Degree: **MD, MS** Department: **Genetics**	**acehurst**	☒Sub-Investigator ☐Other	☒No ☐Yes	**Recruitment/enrollment of participants, consent, counseling and explanation of results, medical management and follow-up for patients.**
Name: **Edward Lose** Degree: **MD** Department: **Genetics**	**elose**	☒Sub-Investigator ☐Other	☒No ☐Yes	**Recruitment/enrollment of participants, consent, counseling and explanation of results, medical management and follow-up for patients.**
Name: **Waldemar Carlo** Degree: **MD** Department: **Pediatrics/Neonatology**	**wacarlo**	☒Sub-Investigator ☐Other	☒No ☒Yes	**Experienced neonatologist and researcher; Recruitment/enrollment of participants, consent, medical management and follow-up for patients.**
Name: **Brian Sims** Degree: **MD** Department: **Pediatrics/Neonatology**	**bsimsmd**	☒Sub-Investigator ☐Other	☒No ☐Yes	**Experienced neonatologist and researcher; Recruitment/enrollment of participants, consent, medical management and follow-up for patients.**
Name: **Hannah Hightower** Degree: **MD** Department: **Pediatrics/Neonatology**	**hannahlb**	☒Sub-Investigator ☐Other	☒No ☐Yes	**Experienced neonatologist; Return of results to participants randomized to the experimental arm of the proposed clinical trial. She may also assist with consent, medical management and follow-up for patients.**
Name: **Carl H. Coghill** Degree: **MD** Department: **Pediatrics/Neonatology**	**ccoghill**	☒Sub-Investigator ☐Other	☒No ☐Yes	**Experienced neonatologist; Return of results to participants randomized to the experimental arm of the proposed clinical trial. He may also assist with consent, medical management and follow-up for patients.**

Name: **Allison Black** Degree: **MD** Department: **Pediatrics/Neonatology**	**acblack**	☒Sub-Investigator ☐Other	☒No ☐Yes	**Experienced neonatologist; Return of results to participants randomized to the experimental arm of the proposed clinical trial. She may also assist with consent, medical management and follow-up for patients.**
Name: **Shirley Cosby, RN** Degree: **BSN** Department: **Pediatrics/Neonatology**	**scosby**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Experienced neonatal study coordinator; identify participants; obtain consent**
Name: **Tara McNair, RN** Degree: **BSN** Department: **Pediatrics/Neonatology**	**temcnair**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Experienced neonatal study coordinator; identify participants; obtain consent**
Name**: Deborah Laney, RN** Degree: **BSN, MSN** Department: **Pediatrics/Neonatology**	**dlaney22**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Experienced neonatal study coordinator; identify participants; obtain consent**
Name: **Lee Ann Merin, RN** Degree: **ADN** Department: **Pediatrics/Neonatology**	**lamerin**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Experienced neonatal study coordinator; identify participants; obtain consent**
Name: **Ashley Moellinger** Degree: **RN, CPNP-AC** Department**: CV Services**	**amoe**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Will assist with the conduct of Aims 1 and 3 including identification of participants, obtain consent, and scheduling visits.**
Name: **Katelyn Staley, RN** Degree: **ADN** Department**: Obstetrics & Gynecology and Maternal Fetal Medicine**	**Katelyn.Staley@childrensal.org**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Experienced care coordinator; identify participants; obtain consent**
Name: **Rebecca L. T. Heaven** Degree: **MSN, PhD** Department**: CVICU, Children's of Alabama**	**Rebecca.Heaven@childrensal.org**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Experienced care coordinator; identify participants; obtain consent. Over 10 years of genetics experience prior to becoming a nurse practitioner.**
Name: **Akila Subramaniam, MD, MPH** Degree: **MD, MPH** Department**: Obstetrics & Gynecology, Division of Maternal Fetal Medicine**	**asubra**	☒Sub-Investigator ☐Other	☒No ☐Yes	**Assistant professor and Assistant director of OBGYN Diagnostic and Research Lab who will assist with SouthSeq recruitment/enrollment of participants, consent, medical management and follow-up for patients.**
Name: **Brian Casey, MD** Degree: **MD** Department**: Obstetrics & Gynecology, Division of Maternal Fetal Medicine**	**bcasey**	☒Sub-Investigator ☐Other	☒No ☐Yes	**Professor and Director of MFM who will assist with SouthSeq recruitment/enrollment of participants, consent, medical management and follow-up for patients.**
Name: **Cindie Buie, RN** Degree: **ADN** Department: **Pediatrics/Neonatology**	**cbuie**	☐Sub-Investigator ☐Other	☒No ☐Yes	**Experienced neonatal nurse; identify participants; obtain consent**

Name: **Zechen Chong** Degree: **PhD** Department: **Genetics**	**zchong**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Conduct of protocol including data analysis/Assistant professor of genetics and member of the informatics institute.**
Name: **Nicole Lewdon** Degree: **BS** Department: **Clinical Immunology and Rheumatology**	**nlewdon**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Nicole will help with administrative tasks including payment and participant tracking for the clinical trial.**
Name: **Brittany Langner** Degree: **BS** Department: **Clinical Immunology and Rheumatology**	**blangner**	☐Sub-Investigator ☒Other	☒No ☐Yes	**Brittany will help with administrative tasks including payment and participant tracking for the clinical trial.**

b. Non-UAB Personnel Relying on UAB IRB - If you are requesting that the UAB IRB serve as the IRB of record for anyone not affiliated with UAB, list these individuals below.

Name and Degree	From Institution with or without own IRB?	Financial Interest?*	Protocol Responsibilities and Qualifications (indicate if this person obtains consent)
Name: **Gregory Cooper** Degree: **PhD** Institution: **HudsonAlpha Institute for Biotechnology** Email: **gcooper@hudsonalpha.org**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Manages sequencing, data analysis, and return of results at HudsonAlpha Institute for Biotechnology/Principal Investigator and Faculty Investigator.**
Name: **Greg Barsh** Degree: **MD, PhD** Institution: **HudsonAlpha Institute for Biotechnology** Email: **gbarsh@hudsonalpha.org**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Design and conduct of this protocol including participation in the variant review committee and outline of data return/ Principal Investigator and Faculty Investigator.**
Name: **Kevin Bowling** Degree: **PhD** Institution: **Hudson Alpha Institute for Biotechnology** Email: **kbowling@hudsonalpha.org**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Design and conduct of protocol including data analysis/Senior Scientist and genomic analyst. This investigator has a critical Role in Aim 1.**
Name: **Kelly East** Degree: **CGC** Institution: **HudsonAlpha Institute for Biotechnology** Email: **keast@hudsonalpha.org**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Design and conduct of protocol including genetic counseling, educational tools for participants and providers/Certified Genetic Counselor. This investigator has a critical role in Aim 1. She will also be providing guidance to the genetic counseling student named in section 3c. of this HSP.**
Name: **Candice Finnila** Degree: **PhD** Institution: **HudsonAlpha Institute for Biotechnology** Email: **cfinnila@hudsonalpha.org**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Design and conduct of protocol including data analysis/clinical project manager and genomic analyst. This investigator has a critical role in Aim 1.**

Name: **Kyle Brothers** Degree: **MD, PhD** Institution: **University of Louisville School of Medicine; Division of Clinical & Translational Research, Dept of Pediatrics** Email: **kyle.brothers@louisville.edu**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Dr. Brothers is bioethicist, pediatrician, and qualitative researcher with >10 years of experience conducting pediatric translational research. He will help design the survey administered to parents, lead interviews with parents, and advise the project on addressing ethical challenges that arise in the course of the study, including managing secondary findings (Aim 1). He will also serve as the UofL Site PI, provide oversite and leadership for all study activities at this site.**
Name: **Susan Hiatt** Degree: **PhD** Institution: **HudsonAlpha Institute for Biotechnology** Email: **shiatt@hudsonalpha.org**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Design and conduct of protocol including data analysis/Senior scientist and genomic analyst. This investigator has a critical role in Aim 1.**
Name: **Michelle Thompson** Degree: **PhD** Institution: **HudsonAlpha Institute for Biotechnology** Email: **mthompson@hudsonalpha.org**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Design and conduct of protocol including data analysis/Senior scientist and genomic analyst. This investigator has a critical role in Aim 1.**
Name: **Michelle Amaral** Degree: **PhD** Institution: **HudsonAlpha Institute for Biotechnology** Email: **mamaral@hudsonalpha.org**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Design and conduct of protocol including data analysis/Senior scientist and genomic analyst. This investigator has a critical role in Aim 1.**
Name: **Renate Savich** Degree: **MD, FAAP** Institution: **University of Mississippi Medical Center** Email: **rsavich@umc.edu**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Chief of Neonatology and Newborn Services and director of pediatrics at the University of Mississippi Medical Center (UMMC). Dr. Savich will be overseeing the CSER2 study at UMMC including recruitment/enrollment of participants, consent, medical management and follow-up for Patients (Aim 1).**
Name: **Laura Godfrey Hendon** Degree: **CGC** Institution: **University of Mississippi Medical** Email: **lhendon@umc.edu**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Design and conduct of protocol including genetic counseling, educational tools for participants and providers/Certified Genetic Counselor. This investigator has a critical role in Aim 1.**
Name: **Whitley Kelley** Degree: **CGC** Institution: **HudsonAlpha Institute for Biotechnology** Email: **wkelley@hudsonalpha.org**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Design and conduct of protocol including genetic counseling, educational tools for participants and providers/Certified Genetic Counselor. This investigator has a critical role in Aim 1.**

Name: **Meagan Cochran** Degree: **CGC** Institution: **HudsonAlpha Institute for Biotechnology** Email: **mcochran@hudsonalpha.org**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Design and conduct of protocol including genetic counseling, educational tools for participants and providers/Certified Genetic Counselor. This investigator has a critical role in Aim 1.**
Name: **Veronica Greve** Degree: **CGC** Institution: **HudsonAlpha Institute for Biotechnology** Email: **vgreve@hudsonalpha.org**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Design and conduct of protocol including genetic counseling, educational tools for participants and providers/Certified Genetic Counselor. This investigator has a critical role in Aim 1.**
Name: **Adam Hott** Degree: **PhD** Institution: **HudsonAlpha Institute for Biotechnology** Email: **ahott@hudsonalpha.org**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Design and conduct of protocol including managing Genome Gateway/Digital Applications Lead. This investigator has a critical role in Aim 1.**
Name: **Heather Williams** Degree: **RN** Institution: **University of Mississippi Medical Center** Email: **hbarth@umc.edu**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Neonatal nurse with experience in research. In this project, she will identify participants and obtain consent**
Name: **Carly Tuura** Degree: **RN** Institution: **University of Mississippi Medical Center** Email: **ctuura@umc.edu**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Neonatal nurse with experience in research. In this project, she will identify participants and obtain consent**
Name: **Bronwyn Briseno** Degree: **RN** Institution: **University of Mississippi Medical Center** Email: **bwelsh@umc.edu**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Neonatal nurse with experience in research. In this project, she will identify participants and obtain consent**
Name: **Steven Spedale** Degree: **MD** Institution: **Woman's Hospital** Email: **steve.spedale@infamedics.com**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Neonatologist who will serve as the site PI at Woman's Hospital. Dr. Spedale will oversee enrollment/recruitment, consent, and medical management for this study at Woman's Hospital**
Name: **Duane Superneau** Degree: **MD** Institution: **Woman's Hospital** Email: **duane.superneau@ololrmc.com**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Geneticist who will assist with the enrollment/recruitment, consent and medical management for this study at Woman's Hospital.**
Name: **Hillary Wienpahl** Degree: **CGC** Institution: **Woman's Hospital** Email: **Hillary.Wienpahl@womans.org**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Conduct of protocol including genetic counseling, explanation of results and assisting with referrals for follow-up/ medical management if necessary.**

Name: **Sara Knight** Degree: **PhD** Institution: **University of Utah** Email**:** **sara.knight@hsc.utah.edu**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Dr. Knight is Professor in the Division of Epidemiology at the University of Utah. She will manage the ELSI work and assist with the design of the study.**
Name: **Kelly Jackson** Degree: **MS, CGC** Institution: **University of Louisville School of Medicine; Division of Clinical & Translational Research, Dept of Pediatrics** Email: **kelly.jackson@louisville.edu**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Certified Genetic Counselor with over 20 years of experience who will return study findings to participants enrolled in Louisville. This investigator has a critical role in Aims 1 and 3.**
Name: **Sarah Deans** Degree: **RN, BSN** Institution: **University of Louisville School of Medicine; Division of Clinical & Translational Research, Dept of Pediatrics** Email: **sarah.deans@louisville.edu**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Sarah Deans is a nurse with experience in research. In this project, she will identify participants and obtain consent, lead recruitment, manage enrollment, sample collection, data collection and scheduling of study visits in for Louisville participants. She will be the primary nurse coordinator at the site (Aims 1 and 3).**
Name: **Alexander Asamoah** Degree: **MD, PhD** Institution: **University of Louisville School of Medicine; Dept of Pediatrics; Weisskopf Center** Email: **alexander.asamoah@louisville.edu**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Over 20 years of experience as a medical geneticist in pediatric clinical settings. Dr. Asamoah will support identification of potential study participants, assist with reviewing results (Aims 1 and 3) assist with oversight of study.**
Name: **Kristen Lee** Degree: **BS, CCRC** Institution: **University of Louisville School of Medicine; Division of Clinical & Translational Research, Dept of Pediatrics, KCPCRU** Email: **kristen.lee@louisville.edu**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Inpatient clinical trial team leader who helps to run an oversee multiple studies in the NICU. Kristen Lee will oversee the research nurses and clinical research activities in Louisville and will serve as a resource for the nurses.**
Name: **Jennifer Nason** Degree: **RN, BSN** Institution: **University of Louisville School of Medicine; Division of Clinical & Translational Research, Dept of Pediatrics, KCPCRU**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Previously worked in the PICU and has taken part in several NICU studies. Jennifer Nason will serve as a backup/support to the Louisville nurse coordinator for all study related activities (Aims 1 and 3).**

Email: **Jennifer.nason@louisville.edu**			
Name: **Stephanie Houston** Degree: **BSN, RCN-NIC** Institution: **University of Louisville School of Medicine; Division of Clinical & Translational Research, Dept of Pediatrics, KCPCRU** Email: **stephanie.houston@louisville.edu**	☒Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☒No ☐Yes	**Previously worked in the PICU and has taken part in several NICU studies. Stephanie Houston will serve as a backup/support to the Louisville nurse coordinator for all study related activities (Aims 1 and 3).**

***Financial Interest** – for each individual listed above, answer **Yes** or **No** as to whether the individual or an immediate family member has any of the following:

- An ownership interest, stock options, or other equity interest related to the investigator's institutional responsibilities of any value.
- Compensation greater than $5,000 in the previous two years when aggregated for the immediate family
- Proprietary interest including, but not limited to, a patent, trademark, copyright, or licensing agreement.
- Board of executive relationship, regardless of compensation.
- Any other Financial Interest as defined by the UAB CIRB.

UAB Personnel: If the individual or his/her spouse or dependent child has a Financial Interest, a disclosure has to be made to the UAB CIRB. A completed CIRB evaluation has to be available before the IRB can complete its review.

Non-UAB Personnel: If the individual has a Financial Interest, ***include a copy of the report from his/her own institution's conflict of interest review with this submission to the UAB IRB.***

c. Do the investigators listed above include any students using this research for their thesis or dissertation?

☐ No, continue with Item 3.d.
☒ Yes, complete the following

Student Name	Thesis/Dissertation Title
Brittany Griffin, PhD	**Do counseling/communication strategies differ by provider type (genetic counselor vs trained non-genetics provider) or result type? (advisor: Tricia Page)**

d. Is the principal investigator a student, fellow, or resident? ☐Yes ☒ No

If Yes, complete items below and obtain signature of faculty advisor or supervisor:

Supervisor's Name: _____
Degree(s) / Job Title: _____
Additional Qualifications pertinent to the protocol: _____
Telephone: _____
E-Mail: _____
Signature: _____

e. Describe the principal investigator's activities related to this protocol and provisions made by the PI to devote sufficient time to conduct the protocol: **Drs. Greg Cooper, Greg Barsh, and Bruce Korf will serve as principal investigators for this grant-funded project and assume primary responsibility for the design and conduction of this study. Brief descriptions of each PI are provided below. Dr. Bruce Korf has been named PI of this IRB-approved protocol and will oversee the project as outlined in this document.**

Dr. Korf (PI) is a practicing medical geneticist and Chairman of the Department of Genetics at UAB. He will dedicate 20% of his time to this project focusing on the identification of genetic variation that might contribute the phenotypes exhibited by participants recruited from the UAB Hospital nursery. Specifically, Dr. Korf will devote 1 day/week to recruitment for this study

(clinical examination, participation in the variant review committee, and returning results) in addition to participating in routine administrative meetings required to coordinate with teams from the other sites involved in the project.

Dr. Greg Cooper (PI) at HudsonAlpha Institute for Biotechnology who will manage the analysis of the genomic data generated from the study outlined in this protocol. Dr. Cooper will dedicate 25% of his time to this project, focusing on organization and supervision of the genomic and analysis pipelines. He will also participate in the variant review committee and in administrative meetings required to coordinate with teams from the other sites involved in the project.

Dr. Greg Barsh (PI), a faculty investigator at HudsonAlpha Institute for Biotechnology will serve as the liaison for external clinical sites, contribute to the design and implementation of the protocol, and act as a member of the variant review committee. Dr. Barsh will dedicate 20% of his time to this project and will participate in regular administrative meetings required to coordinate with teams from the other sites involved in the project.

f. Is medical supervision required for this research? ☐Yes ☒ No

If Yes, who will provide the medical supervision?

☐ PI will provide ***-OR-***

☐ Other:

Name: _____ Telephone: _____

If other than PI, obtain signature of person providing medical supervision:

Signature _____

g. Describe your process for ensuring all key personnel are adequately informed about the protocol and their research-related duties and functions:

All persons assisting with the research have been included in the discussion about the design of this project and each specific aim, and all will be given copies of the protocol outlining their research-related duties. Key clinical and research personnel involved in this protocol will meet on a regular basis via in-person and phone meetings including but not limited to variant review committee meetings, consortium meetings, and administrative meetings. Relevant information from those meeting will be relayed to others members of the study team.

4. Funding

Is this protocol funded? ☒ Yes ☐No

If No, specify that costs of the protocol will be covered by funds from the UAB department or other source named: _____

If Yes, attach one copy of completed application or request for funding sent to sponsor, and complete a-d.

a. Title of Grant, Contract, or Agreement: **South-seq: DNA sequencing for newborn nurseries in the South**

b. UAB PI of Grant, Contract, or Agreement: **Bruce Korf MD, PhD**

c. Office of Sponsored Programs (OSP) Assigned Number: **000514101**
(If not yet available, enter "Pending" and provide upon receipt from OSP.)

d. Sponsor, Funding Route:
(Check and describe all that apply)
(If subaward, list both the funding source and the institution receiving the direct award)

☒ Gov't Agency or Agencies—Agency name(s): **NIH/NHGRI (NIH Grant Number 2U01HG007301-05)**

☐ Department of Defense (DoD): Identify DoD component: _____

☐ Department of Energy (DOE)

☐ Department of Justice (DOJ)
☐ Department of Education
☐ NIH Cooperative Group Trial - Group name: _____
☐ Private Nonprofit (e.g., Foundation) - Name: _____
☐ Industry, investigator-initiated - Name: _____
Describe the funding arrangement: _____
NOTE: The UAB IRB typically only reviews industry-sponsored protocols that are investigator initiated or when the protocol qualifies for expedited review or involves gene therapy.
☐ UAB Departmental/Division Funds—Specify: _____

5. Locations Involved

a. Indicate all performance sites that will provide space, services, or facilities for the conduct of this protocol.

☒ UAB Hospital
☐ UAB Hospital - Highlands
☐ The Kirklin Clinic of UAB Hospital
☐ The Kirklin Clinic at Acton Road
☐ UAB Callahan Eye Hospital
☐ UAB Clinical Research Unit
☒ Children's of Alabama
☐ Birmingham Veterans Affairs Medical Center
☐ Jefferson County Department of Health
☒ Other (i.e., any performance site not listed above, including those covered by subawards related to this protocol) - Describe:

Specific Aim 1: Conduct whole genome sequencing (WGS) testing on 1,500 newborns with signs suggestive of a genetic disorder being treated at hospitals in which African-American and rural populations are highly represented. UAB Hospital and Children's of Alabama (UAB), HudsonAlpha Institute for Biotechnology (HudsonAlpha), HudsonAlpha Clinical Services, Laboratory, LLC., HudsonAlpha Genome Services Laboratory, the University of Mississippi Medical Center (UMMC), Woman's Hospital in Baton Rouge, and the University of Louisville (UofL). Each of the participating institutions will rely on UAB IRB using a reliance agreement.

Specific Aim 3: Compare technology-assisted community-based WGS result delivery by non-genetics providers to formal genetic counseling by genetic counselors.
Conduct a clinical trial on 800 parents or caregivers of the newborns enrolled in Specific Aim 1 being treated at hospitals in which African-American and rural populations are highly represented. UAB Hospital and Children's of Alabama (UAB), the University of Mississippi Medical Center (UMMC), Woman's Hospital and the University of Louisville (UofL).

Cardiovascular intensive care, maternal fetal medicine, and palliative care units at UMMC, Woman's Hospital, UAB, and UofL will also be performance sites for specific aims 1 and 3. Study participants may be enrolled in these units as well as in the neonatal intensive care units at each hospital.

NOTE: Documentation of IRB approvals from sites receiving subawards must be received by the UAB OIRB before funding will be released for that subaward.

b. Describe the space, service, or facilities available for the conduct of the research in the performance sites listed in Item 5.a (For research on UAB campus, include building names):

Specific Aim 1:
Participant families (proband child and both biological parents, if available) will be recruited in

the neonatal intensive care units (NICUs), step down or intermediate level care nursery (including palliative care, maternal fetal medicine and cardiovascular intensive care units) under the supervision of the neonatology faculty at UAB Hospital, UMMC, Woman's Hospital, and UofL. From this point on, we will refer to these locations as "the nursery" or "the nurseries". Face to face participant interactions will only occur in these 4 medical centers. Clinicians (medical geneticists, neonatologists, nurses, etc.) and genetic counselors, will interact with the participants in these spaces to recruit, enroll, consent and return findings. These study personnel will have access to private spaces to meet with families as well as access to computers/ tablets and internet services in order to assist participants in the online consent and onboarding processes.

Blood samples collected from the study participants will be sent to the HudsonAlpha Clinical Services Laboratory (CSL) for CAP/CLIA DNA isolation. An aliquot of DNA from this sample will be sent to the HudsonAlpha Genomic Services Laboratory (GSL) for whole-genome sequencing (WGS) and analysis as part of a research protocol. Variants found by the research team at HudsonAlpha, led by Dr. Greg Cooper, to be potentially clinically relevant and the data generated will be analyzed by the research team at HudsonAlpha.

Collaborators at UofL will use their office space to help with the design of this study and the analysis of de-identified data collected from research participants centered about the ethical, legal, and social implications (ELSI) of participating in a study of this nature.

Specific Aim 3:

Participant families (biological parents or caregiver if available) will be recruited in the neonatal intensive care units (NICUs), step down or intermediate level care nursery under the supervision of the neonatology faculty, or other inpatient setting at UAB Hospital (including Children's of AL, COA), UMMC, Woman's Hospital, and UofL (including Norton Hospital). Face to face participant interactions will only occur in these 4 medical centers. Clinicians (medical geneticists, neonatologists, nurses, etc.) and genetic counselors will interact with the participants in these spaces to recruit, enroll, consent and return findings. These study personnel will have access to private spaces to meet with families as well as access to computers/tablets and internet services in order to assist participants in the consent and return of results (ROR) sessions.

c. Is this protocol a clinical trial requiring clinical services at one of the performance sites listed in Item 5.a above? ☐Yes ☒No

If Yes, will any of the services be billed to either participants/their insurance or to the study account through the Hospital Billing Office (PFS) or the HSF Billing Office (MSO)? ☐Yes ☐No

If Yes, submit a Full Fiscal Approval Process (FAP)-designated unit submission to s complete a FAP submission and send to fap@uab.edu. For more on the UAB FAP requirements, go to FAP - SiteMinder Processes.

d. Is this a field study? ☐Yes ☒No

If Yes, describe the community and include information about how the community will be involved in the design, implementation and analysis of the research. This would include focus groups, training local facilitators/community health advisors: _____

e. Has this protocol been rejected or disapproved by another review board (another IRB, similar review board, or departmental review committee(s)) that authorizes the use of its patient populations? ☐Yes ☒No

If Yes, provide name(s) of the review board(s) and reason(s) not approved: _____
Attach copies of the disapprovals.

NOTE: If this protocol is subsequently rejected or disapproved by another review board, promptly notify UAB IRB.

f. Will the protocol be conducted at or recruit participants from the Birmingham Veterans Affairs Medical Center (BVAMC)? ☐Yes ☒No
If Yes, describe the involvement of the BVAMC: _____
Attach the VA IRB approval and VA IRB-stamped consent form(s), if applicable.
NOTE: See the BVAMC section of the IRB Guidebook for more information.

g. Will the protocol be conducted at or recruit participants from the Jefferson County Department of Health (JCDH)? ☐Yes ☒No
If Yes, describe the involvement of the JCDH and list the JCDH clinics being used: _____
Attach the JCDH Research Review Panel approval, if applicable.
NOTE: Human subjects research conducted at certain JCDH clinics requires review by the JCDH Research Review Panel. See the JCDH section of the IRB Guidebook for more information.

6. Clinical Trial

Does this protocol meet the following definition of a clinical trial? ☒Yes ☐No
**A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. For more information, see the full definition of clinical trial here.*
If Yes, you will need to fulfill the following requirements (regardless of funding):

a. All key personnel must complete the Good Clinical Practices (GCP) training. For information on this requirement, visit the IRB website here.

b. This protocol must be registered on ClinicalTrials.gov. Provide the National Clinical Trial (NCT) identifier number: **NCT03842995**
If you have any questions regarding registering a study on ClinicalTrials.gov, email the UAB Center for Clinical and Translational Science at ccts@uab.edu.

7. Multi-Site Studies

a. Is this a multi-site study with the UAB investigator as the lead investigator? ☒Yes ☐No

b. Is this a multi-site study with UAB as a coordinating site? ☒Yes ☐No

c. If Yes to a or b, describe the management of information obtained in multi-site research that might be relevant to the protection of participants. Include, at a minimum, how the following items are managed:

- IRB approvals from other sites
- Unanticipated problems involving risks to participants or others. (For example, if there is an unanticipated problem involving risks to participants or others, which site is responsible for reporting it?)
- Interim results
- Protocol modifications

Specific Aim 1 and Specific Aim 3:

The IRBs representing the collaborators/investigators at each site involved in the proposed project (UMMC, Woman's Hospital, UofL and HudsonAlpha) will agree that UAB will be the IRB of record. Any documents necessary to facilitate this collaboration will be submitted to the UAB IRB upon request. We will follow this same process for the additional recruitment site to be determined and added to the protocol at a later date.

Should there be unanticipated problems, the issues will be reported to the UAB IRB. Protocol modifications are anticipated and amendments will be drafted and discussed by

the research teams from each of the sites involved with this protocol then submitted to the UAB IRB for approval. Interim results will be supplied as part of the annual continual review process.

8. Drugs

Will any drugs or supplements be *used or studied* in this protocol? ☐Yes ☒No

If Yes, attach the completed Drug Review Sheet.

9. Devices

a. Will any devices be *studied* in this protocol? ☐ Yes ☒ No

b. Will any *not FDA-approved* devices be *used or studied* in this protocol? ☐ Yes ☒ No

If Yes to a or b, attach the completed Device Review Sheet.

10. Special Approvals

a. Does this protocol involve the use of radioisotopes? ☐Yes ☒No

If Yes, attach documentation of approval from the Radiation Safety Division.

b. Does this protocol include patients with contagious infections (e.g., mumps, measles, chickenpox, TB, meningitis)? ☐Yes ☒No

If Yes, attach documentation of approval from the Infection Control Committee of the appropriate facilities.

c. Does this protocol involve obtaining remnant biopsy or surgical material from the Department of Pathology or any other source? ☐Yes ☒No

If Yes, attach documentation of approval from the entity or individual providing the materials (e.g., the UAB Division of Anatomic Pathology Release of Pathologic Materials).

d. Does this protocol require obtaining any remnant clinical laboratory specimens, body fluids, or microbiological isolates from the Department of Pathology or any other source? ☐Yes ☒No

If Yes, attach documentation of approval from the entity or individual providing the materials (e.g., the UAB Division of Laboratory Medicine Release of Pathologic Materials).

e. Does this protocol use stored (existing) specimens from a repository? ☐Yes ☒No

If Yes, attach documentation of approval for use of specimens, and describe how existing specimens are labeled: _____

11. Use of Specimens

Does this protocol involve the collection of specimens? ☒Yes ☐No

If Yes, complete 11.a-11.h.

If No, skip to Item 12.

a. How will specimens be obtained, processed, distributed, and stored?

Specimens will only be collected and stored to address Specific Aim 1 of this project. Details about this process are included below.

Specific Aim 1:

Enrolled infants (probands) will have a one-time blood draw, no more than the maximum allowable volume will be drawn. Specific volumes will be determined based on the proband's weight at the time of sample collection. Please see Section 17a of this protocol for specific amounts. For the biological parents, if available, a one-time blood draw of 4ml of whole blood will be collected for DNA analysis and 2.5ml may be collected for RNA and/or protein analysis. These samples will be sent to a CAP-accredited and CLIA-certified laboratory at the HudsonAlpha Clinical Services Laboratory, LLC (CSL) for CLIA DNA isolation and then to the Genome Services Laboratory at HudsonAlpha (GSL) for whole genome sequencing in the research laboratory. The probands' samples will be subjected to DNA isolation and whole genome sequencing, standardized processes performed routinely by the CSL and GSL,

respectively. RNA and/or protein analysis may also be completed on the probands' samples should validation of transcript-level effects of a variant be necessary. Parental samples will be stored for future DNA sequence analysis and/or validation if indicated to confirm a variant.

Alternative samples may be collected, for example cord blood, DNA, etc., with assistance of the laboratory or pathology staff, in cases where collection from the proband is not possible or if the proband has expired.

Unused samples will be stored in the HudsonAlpha GSL in a de-identified manner, and coded with unique study identifiers, for future research.

b. How will specimens be labeled (e.g., unique identifier, medical record number, Social Security number, name, date of birth)?

Biological specimens will only be collected and stored to address Specific Aim 1 of this project. details about this process are included below.

Specific Aim 1:

Samples will be labeled with unique study identifiers that will not include the participants' names, date of birth, medical record numbers or any other PHI. These identifiers will be utilized to code the samples for all members of the research team outside of those in the clinic where the families will be recruited. A key linking the participant's name and study ID will be maintained by the clinic staff and will only be accessible by the clinical team involved with this study. No PHI will be shared with the research team at HudsonAlpha.

c. How will clinical data associated with the specimens be collected and stored?

Clinical data will only be collected to address Aim 1. Please see notes below.

Specific Aim 1:

Clinical data will be coded and entered into a database accessible by the research team using the study identifier correlating to that participant's sample. This information may include the participant's clinical phenotype/presentation, family history, and any other information relevant to the analysis of the participant's sample.

d. What participant-identifying information will be collected and linked to the specimens?

Participant -identifying information will only be collected to address Aims 1 and 3.

Specific Aim 1:

Participants will be consented into the study at one of the 4 clinical sites (nurseries at UAB, UMMC, UofL, and Woman's Hospital) and all participant-identifying information will be visible only to the clinical team, no researchers will have access to PHI. Identifiable information will not be shared with members of the research team outside of those at the site where the participants were enrolled in the study. All communication about a particular sample outside of the clinical setting will be done in a coded manner using the unique study identifier.

Specific Aim 3:

Participants will be asked to complete a W9 form so that they can be compensated for their participation in study-related survey measures. Members of the clinical trials team (names on this HSP) will have access to this information so that they can send payment to the study participants.

Contact information for participants who are asked to take part in outcomes and utility interviews (previously approved by this IRB) will be made available to the appropriate study personnel.

e. What steps will be taken to maximize the confidentiality of linked identifiers? For example, procedures could include using a password-protected computer database to link identifiers, with limited personnel knowledgeable of the password, or coded identifiers released without the ability to link to clinical data (also called "stripped" or "anonymized" specimens).

Linking the participant's PHI and sample ID is only required to address Aims 1 and 3 due to the need to contact families to return study findings and compensate them for participation in the clinical trial surveys. The steps we plan to take to maintain confidentiality are addressed below.

Specific Aims 1 and 3:

The link between the research study sample identifier and participant/family's PHI will be maintained in a database at the clinic that is backed up and secured with other medical information, accessible only by enrolled participants, clinic personnel, clinical trial personnel and genetic counselors involved with the study (each noted in section 3). No other individuals will be able to identify individual participants, with the technicians, analysts, and key research personnel only given access to the study identifier and genomic sequence information as needed. All genomic data or sample-related information, regardless of its location or identifiability, will be kept in secured file systems. Additionally, all the key personnel on this proposal have completed, and will update and repeat as required, both Human Subjects Assurance Training from the Office for Human Research Protection and the Protecting Human Research Participants training from the NIH Office of Extramural Research.

f. Is genetic testing planned as part of this protocol? ☒Yes ☐No

If Yes, describe the planned genetic testing here.

Specific Aim 1:

Whole genome sequencing will be carried out the HudsonAlpha GSL for the purpose of identifying rare DNA sequence differences (mutations) that may be causally related to the observed clinical abnormalities. Parental samples will be collected, if available, for confirmation of variants deemed (see below for a description of this process) to be significant and relevant to patient care.

The research team at HudsonAlpha will analyze the WGS data generated by the GSL to identify sequence variants that they believe to be pathogenic, likely pathogenic, or variants of uncertain significance in genes associated or potentially associated with the proband participant's phenotype. Rationale for scoring these variants will be based on many criteria, including utilizing databases of genomic data in unaffected controls and disease-specific databases to which the team has access. Variants of interest will be brought before the variant review committee (VRC) for discussion. The VRC will then determine which variants should be returned to the enrolled participants and assign a pathogenicity score using criteria defined by the American College of Medical Genetics. The variants deemed to be returnable will be clinically validated (i.e Sanger confirmation with variant interpretation) using the DNA specimen stored in the CSL and confirmation of inheritance or lack of inheritance will be determined using the parental samples, if available. These Sanger tests will be CAP/CLIA certified and produce results that may be placed into patients' medical records. If the participant families decide to share any variants identified via this process with their healthcare providers, the clinical Sanger reports can be shared with the medical professional of their choice and identifiers can be reassigned at that time.

Individual variants found to be medically relevant along with de-identifed phenotype information will be shared via ClinVar (http://www.ncbi.nlm.nih.gov/clinvar). In the event that a variant is identified in a gene where there is limited information about functional or

clinical relevance, de-identified clinical phenotypes or other health information along with select variant information may be shared with collaborators via resources such as GeneMatcher (www.genematcher.org), or other genotype and phenotype connecting outlets for clinicians and researchers. Participants will be allowed to decide whether or not we share the entire collection of WGS data along with de-identified phenotype data via dbGAP (http://www.ncbi.nlm.nih.gov/gap**), AnVIL (**https://anvilproject.org/**) or any other NIH-designated data repository. We will ask for parental permission if opportunities for functional follow-up are identified that would require DNA and/or RNA to be shared with researchers at other institutions. This may provide the opportunity to connect with researchers pursuing functional studies, but in a de-identified way. Should there be a request for identifiable information, participants will be contacted and consented appropriately.**

g. Will specimens be stored for future use? ☒Yes ☐No

If Yes, indicate whether they will be used for the disease under study in this protocol or research on other diseases.

Specific Aim 1:

Coded samples will be stored in the HudsonAlpha GSL and may be used in the future for research on variants of uncertain significance, other genetic conditions or rare phenotypes.

h. Will specimens be shared with other investigators in the future? ☒Yes ☐No

If Yes, answer i. and ii.

i. What identifiers, clinical information and demographic information will be shared; or will the specimens be stripped of identifiers (i.e., anonymized)?

Specific Aim 1:

Any specimens or clinical phenotypes will be shared in an anonymized fashion. No PHI will be shared with other clinicians or researchers to protect the privacy of study participants

ii. Outline your procedure for assuring IRB approval for release and use prior to release of specimens.

Specific Aim 1:

Specimens shared with other collaborators at HudsonAlpha, UAB, or other institutions that are outside of the scope of this project, will require IRB approval.

NOTE: Investigators who receive and/or use these specimens must document approval from the appropriate IRB(s) before the specimens may be released.

12. Gene Therapy

Does this protocol involve gene therapy or administering recombinant materials to humans? ☐Yes ☒No

If Yes, submit the Gene Therapy Project Review Panel Report ***-OR-*** the Protocol Oversight Review Form For Clinical Vaccine Trials, as applicable.

13. HIPAA Privacy and Security

Will the PI or others obtain, review, or make other use of participants' "protected health information" (i.e., information, whether oral or recorded in any form or medium that (a) is created or received by a health care provider and (b) relates to past, present, or future physical or mental health or condition of an individual; or provision of health care; or payment for provision of heath care)? ☒Yes ☐No

If Yes, complete Items 13.a-13.**f.**

If No, skip to 14.

a. Will the data/information be stored or managed electronically (on a computer)?

☒Yes ☐No

b. Is the principal investigator requesting that the UAB IRB waive patient HIPAA authorization from another institution or entity (e.g., insurance company, collaborating institution)? ☐Yes ☒No

If Yes, attach copies of the privacy notices from each institution/entity, and provide the name of each institution/entity: _____

c. Indicate which of the entities would provide health information for this protocol, maintain health information as it was collected for this protocol, and/or store health information after it has been collected for this protocol.

☒ UAB Hospital or UAB Hospital - Highlands
☐ The Kirklin Clinic of UAB Hospital or Acton Road (and/or associated clinics)
☐ UAB Callahan Eye Hospital
☒ Children's of Alabama
☐ Jefferson County Department of Health
☐ School of Dentistry
☐ School of Health Professions
☒ School of Medicine
☐ School of Nursing
☐ School of Optometry
☐ University of Alabama Health Services Foundation
☐ UAB Health Centers
☐ Viva Health
☐ Ophthalmology Services Foundation
☐ Valley Foundation
☐ Medical West - UAB Health System Affiliate
☐ None - **If None, skip to Item 14.**

d. Indicate any information systems that will be the sources of information used for the protocol.

☒ A system maintained centrally by UAB Health System (these include the following: HealthQuest for registration, billing, and patient administration; PowerInsight (clinical data warehouse); Cerner IMPACT for PowerNotes for meds, Lab, Radiology, UED, Surgery

NOTE: If a researcher needs information in a specified format or a specified time, the researcher must confirm with the unit who can supply the information/service that the request can be met before writing the information/service into the research protocol. In addition, the researcher must be aware that these services may have a cost attached that should be considered in the research budget.

To request access to clinical systems for research purposes, visit https://www.oneuabmedicine.org/web/hsis/technical-support, click "Accounts Request" and complete the form indicating access for research purposed.

☐ Another system on a UAB server - Describe: _____

e. Indicate which of the listed identifiers will be accessed, associated and/or linked with the protected health information (PHI) used for this protocol.

☒ Names
☒ Geographic subdivisions smaller than a state
☒ Elements of dates (except year) related to an individual
☒ Telephone numbers
☐ Fax numbers
☒ Email addresses
☒ Social security numbers
☒ Medical record numbers
☐ Health plan beneficiary numbers
☒ Account numbers
☐ Certificate/license numbers
☐ Vehicle identifiers and serial numbers

☐ Device identifiers and serial numbers
☒ Biometric identifiers
☐ Web universal resource locators (URLs)
☐ Internet protocol address numbers
☒ Full-face photographic images
☐ Any other unique identifying number - Describe: _____
NOTE: Codes are not identifying as long as the researcher cannot link the data to an individual
☐ None - **If None, skip to Item 14.**

Specific Aim 1:
These identifiers will be collected to clarify the phenotype of the enrolled proband, determine if the participant family is from the rural region from which we plan to recruit, and to contact families for return of genetic results.

Specific Aim 3:
Identifiers will be collected to clarify the demographics of the enrolled parent or caregiver, determine if the participant is from the rural region from which we plan to recruit, and to contact for return of genetic results and the subsequent clinical trial surveys (enrollment, ROR, 1-month post-ROR, 4-months post-ROR, and 4.5-months ROR). Participants will complete a W9 (blank form submitted to IRB as an example; othermisc(W9form).190312) that will be accessed by members of the clinical trial team who will assist with the dispersement of study-related compensation.

f. Choose one plan to describe your use of the personal health information:
☐ The data collected meet the specifications for a "limited data set" (LDS)
-If the LDS will leave the covered entity or will be received from another covered entity you will need a Data Use Agreement

☒ Research staff will obtain authorization from each participant to use the information
-Include the HIPAA Authorization form, complete except for participant name and IRB protocol number, as the final page of the consent form

☐ PI requests waiver of authorization to use the information
-Attach Waiver of Authorization and Informed Consent form

PROPOSED RESEARCH
- The IRB will not accept grant applications and/or sponsor's protocols in lieu of the items as outlined below.
- Do not separate responses from items. Instead, insert your response to each item below the item, keeping the information in the order of this form.

14. Purpose - in nontechnical, lay language
a. Summarize the purpose and objectives of this protocol in one short paragraph.
Specific Aim 1:
The overall goal of the research and clinical teams participating in this project is to use whole genome sequencing (WGS) to identify genetic variants that could be contributing to the phenotype/symptoms of newborn patients presenting with conditions that are suspected to be genetic. For Specific Aim 1, we plan to enroll individuals from diverse ancestral/cultural and rural populations that are currently underrepresented in clinical and genomic research. We plan to structure our recruitment strategies to optimize enrollment of these groups and achieve at least ~60% overall study participation from minority or underserved populations. Our project has both clinical and basic biological aspects. With respect to basic biology, we are interested in better understanding of how genes associated with disease, especially rare pediatric disease.

Specific Aim 3:

Due to the limited number of genetic counselors available to support patients that may benefit from WGS, we will be comparing two results delivery methods: genetic counselors or genetics providers (standard of care), and healthcare providers (e.g. neonatologists, neonatology nurse practitioners, etc.) who undergo specific genetics results delivery training. In this clinical trial, we aim to demonstrate that both delivery methods are equivalent (i.e. there is no difference between the two methods). In order to so this, we plan to record the return of results conversations that you will have as part of this study.

b. Describe how outcomes will be measured for this protocol.

Specific Aim 1:

Identification of pathogenic/likely pathogenic variation and successful return of results will be the primary outcomes measured for the proposed project. One of our major goals is to identify pathogenic/likely pathogenic variation using WGS within newborns with symptoms suggestive of a genetic disorder. We also aim in this study to improve representation of minority and underserved populations and thereby more comprehensively understand the factors that relate to broad, successful application of WGS to identify pathogenic/likely pathogenic variation contributing to rare disease in children.

Specific Aim 3:

In order to compare technology-assisted WGS result delivery by trained healthcare providers to formal genetic counseling by genetic counselors or genetics providers (standard of care), a series of surveys have been developed and will be completed online using Genome Gateway. The survey time points are enrollment, return of results (ROR) (roughly 2-3 months post-enrollment), 1-month post-ROR counseling, 4-months post-ROR counseling, and 4.5 months post-ROR counseling.

15. Background - in nontechnical, lay language

Summarize in 2-3 paragraphs past experimental and/or clinical findings leading to the design of this protocol. Include any relevant past or current research by the PI. For drug and device studies, summarize the previous results (i.e., Phase I/II or III studies).

Specific Aim 1:

Rare undiagnosed phenotypes inflict considerable, life-long suffering on both affected children and their families. This suffering manifests in both physical and mental health difficulties, emotional distress, and financial strain. Further, as these conditions are diverse in both clinical presentation and origin, and in many cases are unique, standard diagnostic tools often fail to determine the origin of the problem, the prognosis for the child, or the optimal treatment or educational choices. In our previous Clinical Sequencing Exploratory Research (CSER) study, we focused on using WGS to identify pathogenic/likely pathogenic variation in children with intellectual disability/developmental delay. We enrolled children seen at a pediatric specialty clinic in Huntsville, AL who had unexplained developmental and intellectual disabilities, performed WGS on them and their parents, analyzed the data to identify variants that contribute or may contribute to at least some of the symptoms present in their child (the proband), and returned variants deemed medically relevant to affected children and their families. We have to date enrolled 1,309 individuals from 464 families. We found that ~28% of probands carried a pathogenic or likely pathogenic genetic variant relevant to their phenotypes, and an additional ~15% carried a variant of uncertain significance that may be relevant. Assessments based on surveys, questionnaires, and follow-up interviews indicate that families generally believe such genetic information to be of considerable value, especially for parents of younger affected children.

We have also conducted, and continue to conduct, a variety of other similar projects. For example, one such project is to use WGS to test children with developmental disabilities that are

seen at a clinic associated with Children's Rehabilitative Services (CRS), an Alabama state government agency that serves families of children with special needs. We have thus far enrolled 68 individuals from 26 families, and have found 4 pathogenic or likely pathogenic variants and an additional 5 variants of uncertain significance. Also, the leaders of this project are also leading the Alabama Genomic Health Initiative (AGHI). AGHI seeks to enroll ~10,000 participants over the next 4-5 years, subject their DNA to genome-wide SNP genotyping or WGS, identify and return medically relevant variants, and better understand the clinical and population health effects of genetic testing. While this project is in its early stages, we have already enrolled more than 270 individuals, and genotyping and WGS are currently in progress.

In general, these studies have produced and are producing considerable value to both basic and clinical research. This includes, for example, identification of pathogenic/likely pathogenic variation for numerous families affected by rare disorders, improvements to the process by which we collect and analyze data, evidence as to the personal and clinical utility of genetic testing, and the discovery of novel genetic disorders. The study we pursue in this protocol will build upon and expand the basic foundation and infrastructure built by our previous work.

Specific Aim 3:

Barriers to widespread and routine implementation of WGS-enabled clinical care exist at several levels. Surveys of clinicians indicate discomfort in their understanding of genomics and ability to communicate results to patients, and also concern about the time required to do so. Medical geneticists and genetic counselors are disproportionately concentrated in large academic centers, and their numbers are inadequate to support the number of patients that may benefit from WGS. This limitation will have a disproportionate effect on patients in rural and/or medically underserved areas. For example, currently all but one of the genetic counselors in Alabama are based in Birmingham or Huntsville (lone exception is in Mobile), which means that the southern 2/3 of the state, including major rural underserved areas, have little to no local access to genetic counseling services.

These barriers are especially apparent in neonatal care. For parents of sick neonates, their first interactions with the healthcare system take place in the NICU. Neonatology training traditionally emphasizes critical care and can neglect communication, with one study reporting that 93% of fellows stated that their training in this area should be improved. There is a particular lack of training in genomic neonatal medicine, with few didactic lectures, role-play sessions, simulated experiences, or hands on training in clinically relevant scenarios. When infants are diagnosed with congenital anomalies in utero, prenatal consultation with subspecialists can be confusing for genetic conditions with a spectrum of causes and outcomes, and inconsistent information given by different providers, e.g., the neonatologist and the pediatric surgeon.

A central premise underlying our proposal is that non-genetics health care providers, including those outside of academic medical centers, can be empowered to use WGS-testing in their practices. There is ample precedent for implementation of complex technology in primary care: pediatricians, internists, and family practitioners routinely use advanced imaging technologies without a deep understanding of the underlying technology. Bringing WGS-enabled genomic medicine to community health care providers requires, at the least, straightforward criteria to identify patients who may benefit, a user-friendly consent process, clearly worded laboratory reports, easily accessible patient education materials, ready access to support from medical geneticists and genetic counselors, and basic training in how WGS can be applied routinely. We seek to demonstrate that, if these factors are provided, WGS can be carried out and relevant results returned by newborn medicine providers, and that the patient experience will be at least equal to that achieved with the traditional approach of face-to-face counseling by a geneticist or genetic counselor.

16. Participants (Screening and Selection)

a. How many participants are to be enrolled at UAB (if other sites relying on UAB IRB, list the number for each site)?

If multi-site study, total number at all sites/institutions:

Specific Aim 1:

For Specific Aim 1 we anticipate enrolling 500 participants at UAB. There will be 4 recruitment sites (UAB, UMMC, UofL, and Woman's Hospital) targeting enrollment of an additional 1,000 participants. We estimate ~2,250 total parents will be recruited from all participating sites.

Specific Aim 3:

For specific Aim 3 we anticipate enrolling 800 parents and caregivers across all participating sites (UAB, UMMC, UofL, and Woman's Hospital) from the newborns enrolled in Specific Aim 1. To determine whether there is a difference in participant satisfaction among those who received results from genetics providers (i.e. genetic counselors) and those who receive results from non-genetics providers (i.e. neonatologists), we will train non-genetics providers to return results. Due to their participation in the training, these providers will be considered participants in the research. This group will include approximately 5 providers from each clinical site.

b. Describe the characteristics of anticipated or planned participants (if multiple groups, repeat list for each group).

Sex: **male and female**

Race/Ethnicity: **Any, with ~60% of the total enrollment from underserved populations including rural and underrepresented minorities. Alabama and Mississippi have the highest proportion of African Americans in the US at 37% and 27%, respectively. Based on the populations served by each of the 4 recruitment sites, we anticipate equal recruitment totals with the following proportions of African Americans recruited from each site: UAB-47%, UMMC-41%, >40% from Woman's Hospital, and >30% at UofL/Norton Hospital .**

Age: **newborns (up to 12 months of age), providers (18yrs or older) or biological mothers contributing samples for analysis may be under 18years or older to consent for themselves and their children since they are considered to be emancipated adults. Biological fathers must be at least 18yo to participate in the research study.**

Specific Aim 3:

Parents and caregivers (18 yrs or older) can participate in the clinical trial-related surveys.
Healthcare providers (18 yrs or older)

Health status: **Probands will be enrolled in this study if they are admitted to the nursery at UAB, UMMC, or Woman's Hospital and exhibit rare phenotypes suspected to be genetic in origin. Probands who are born deceased or who expire shortly after birth may also be enrolled. Antenatal consent is allowable; however, a child and guardian/parents are not considered to be enrolled participants until biological samples have also been collected for this study.**
Biological parents of the probands may be enrolled regardless of their health status.
Non-genetics providers who are interested in returning results to participants enrolled in this study may be enrolled regardless of their health status.

Specific Aim 3:

There are no restrictions on health status for providers, parents or caregivers enrolled in the clinical trial.

c. From what population(s) will the participants be derived?

Pertaining to Specific Aim 1, patients admitted to the nursery at UAB, UMMC, and Woman's Hospital along with their biological parents, if available and willing to participate, will be recruited for this study. These patients are expected to be newborns exhibiting symptoms suggestive of a genetic disease.

Specific Aim 3:
Parents and caregivers will be derived from the newborns enrolled in Specific Aim 1.
Providers will be clinicians caring for patients at one of the enrollment sites named on this study.

Describe your ability to obtain access to the proposed population that will allow recruitment of the necessary number of participants:

To address Specific Aim 1, parents of patients admitted to the nursery at each recruitment site who meet enrollment criteria will be offered participation in the research study. Nursery staff will determine eligibility during their normal clinical activities or after screening the participating units for eligible patients. Patients can be enrolled into the study antenatally, after delivery and nursery admittance and up until time of discharge from the nursery. Because the nursery staff and clinicians(s) caring for the children in the unit will be familiar with the study and the clinical information/phenotype of the potential probands, we do not anticipate that access to these populations will be a problem. As members of the study team, these personnel will be able to recruit the nursery patients that they care for who meet criteria for this study. To facilitate identification and recruitment of appropriate patients, the research team will provide information about the study to nursery staff, neonatologist, and other physicians at and near to each clinical site to help build awareness of the study among clinicians who might recruit potential participants upon identification of physical anomalies. Education for nursery staff and physicians about the study, the use of WGS in the clinic, elements of informed consent, and common patient questions and concerns will be developed and provided to each site. This information will be delivered both in-person and online, and printed materials about the study as well as the enrollment criteria and process will be displayed in a visible area as a reminder and just-in-time resource for staff.

Specific Aim 3: Parents and caregivers will be selected from the population of newborns and their families recruited in Specific Aim 1.
Providers will be clinicians caring for patients at one of the enrollment sites named on this study.

d. Describe the inclusion/exclusion criteria:

For inclusion in this study as a proband, an infant must be receiving care in the nursery or inpatient setting, e.g. surgical and/or cardiac intensive care unit during their first hospital admission, or first 12 months of life, AND meeting one of the following criteria:

A. **A pattern of congenital anomalies consistent with a genetic, i.e, syndromic cause, and for which the primary care team does not know of an obvious etiology. "Obvious etiology" refers to a genetic, infectious, or environmental cause that has been or can be rapidly confirmed by history and/or laboratory testing, e.g. Trisomy 21, TORCH infection, fetal hydantoin exposure.**

B. **A major medical condition such as seizures, metabolic abnormality, or conjugated hyperbilirubinemia for which the primary care team does not know of an obvious etiology. Again, "obvious etiology" refers to a genetic, infectious, or environmental cause that has been or can be rapidly confirmed by history and/or laboratory testing, e.g. intraventricular hemorrhage associated with significant prematurity, seizures associated with an inborn error of metabolism for which a molecular diagnosis can be confirmed.**

Acceptable anomalies may include those described in the table below. Please note that this list is not exhaustive.

Infants born deceased or those who expire soon after birth may also be enrolled as long as they meet the criteria outlined above. Infants who otherwise would have met inclusion criteria, but passed away during the time that SouthSeq has been actively enrolling participants (Feb 2018 to present) may also be enrolled if blood samples are available and parents are willing to consent.

Individuals will be excluded from the study if they have:

A. **A pattern of findings and/or abnormalities consistent with known or strong suspicion for a chromosomal aneuploidy (Ts13, 18, 21, Monosomy X);**
B. **Isolated anomalies known to have a low diagnostic yield for Mendelian causes, e.g. gastroschisis, hydronephrosis;**
C. **A pattern of findings and/or abnormalities consistent with confirmed teratogenic exposures, e.g. hydantoin, valproate.**
D. **A pattern of findings and/or abnormalities consistent with confirmed congenital infection, e.g. TORCH.**

Additional Comments:

1. **Patients with suspected Down syndrome or life-threatening whole chromosome aneuploidies in which acute clinical care depends on a diagnosis, e.g. Ts13 or Ts18, will not be enrolled, but patients with congenital anomalies for which a clinical chromosomal microarray would otherwise be obtained may be enrolled.**
2. **Patients with a history of potential teratogenic exposures or congenital infection may be eligible for inclusion if there are congenital anomalies and/or conditions that are not explained by the potential teratogen or infection. In this situation, one of the study investigators should be consulted.**
3. **"Pattern of findings and/or abnormalities" refers to established principles for medical genetics, in which general guidelines are "2 or major congenital anomalies", "1 major and 2 or more minor anomalies", "1 major anomaly and an unexplained major medical condition", or "1 major anomaly and a first degree relative with the same anomaly", with examples (not intended to be exhaustive) indicated below.**

As this is a research study, it is not intended to replace routine clinical care. Patients will also be provided standard of care clinical genetics consultation, which may include microarray/array CGH. Should the array result be abnormal, the research team can decide if sequencing should proceed. We intend to keep these criteria broad to allow for the enrollment of individuals with rare symptoms and avoid exclusion of those who might benefit from whole genome sequencing.

Biological parents of the proband (infant admitted into the nursery) may also be enrolled in the study, whether they are affected or unaffected with a rare disease, for the purpose of confirming inheritance of variants of interest.

Major *Structural malformations likely to require surgical intervention or be of significant functional effect*	**Minor** *Physical variants that are a departure from normal development but only have a cosmetic effect*	**Medical Conditions** *Medical conditions not explained by prematurity (such as NEC, ROP, IVH)*
Structural brain malformations (holoprosencephaly,	Abnormal hair whorls (position or	Seizures

schizencephaly)	number -- absent, triple, multiple)	
Cleft lip and palate	Abnormal fontanelles (third sagittal, metopic)	Cataracts
Severe micrognathia	Preauricular pits or tags	Unexplained Hypoglycemia
Macroglossia	Atypical ear formation or placement (microtia, cupped, crumpled, low-set)	Conjugated (direct) hyperbilirubinemia
Structural heart defect	Epicanthal folds	Hearing Loss (confirmed)
Congenital diaphragmatic hernia	Cleft/bifid uvula	Ichthyosis
Structural renal anomaly	Neck webbing	Hypotonia
Coloboma – iris or retina	Supernummary nipple	Myopathy
Trachoesophageal fistula	Sacral dimple	Arthrogryposis
Symmetric IUGR	Syndactyly	Hepatic dysfunction
Anotia	Single transverse palmar crease	Apnea (central or obstructive)
Omphalocele	Clinodactyly	
Vertebral anomalies	Hypospadias	
Limb deficiency or shortening	Abnormal pigmentation	
Ambiguous genitalia	Dysmorphic findings not otherwise mentioned	
Biliary atresia		
Imperforate anus		
Heterotaxy		

Specific Aim 3:
Inclusion Criteria:
- **Newborn (proband) meets the inclusion criteria in Specific Aim 1**
- **Parent or caregiver is willing to participate and answer surveys**

Exclusion Criteria:
- **Proband has secondary findings from WGS**
- **Parent or caregiver is not available to participate and answer surveys**
- **Parent or caregiver requires language interpreter services/translated materials**

f. If participants will comprise more than one group or stratification, describe each group (e.g., treatment/intervention, placebo, controls, sham treatment) **and** provide the number of participants anticipated in each group.

Specific Aim 1:
N/A

Specific Aim 3:
Parents or caregivers of the newborns in Specific Aim 1 will be randomized based on site location and type of WGS results (positive, inconclusive, and no finding) to one of two study arms. Both groups will receive customized support through a web platform, Genome Gateway.

Intervention Group: Return of results will be delivered by a trained healthcare provider. Anticipate 550 participants.

Control (Standard of Care): Return of results will be delivered by a genetics provider (genetic counselor or medical geneticist). Anticipate 550 participants.

f. Indicate which, if any, of the special populations listed below will be involved in the protocol. Include the Special Populations Review Form (SPRF) if indicated.

☒ Pregnant Women: Attach SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
☐ Fetuses: Attach SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
☒ Neonates/Nonviable Neonates: SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
☐ Prisoners: Attach SPRF—Prisoners
☐ Minors (<18 years old): Attach SPRF—Minors
☒ Employees or students at institution where research conducted
☐ Persons who are temporarily decisionally impaired
☐ Persons who are permanently decisionally impaired
☐ Non-English Speakers

For each box checked, describe why the group is included **and** the additional protections provided to protect the rights and welfare of these participants who are vulnerable to coercion:

The goal of this project is to utilize WGS technologies to identify the genetic cause for the enrolled newborn probands with rare compilation of symptoms and their parents. It is expected that this will identify a genetic cause soon after symptoms appear in the hope that earlier identification of a genetic cause for symptoms will improve patient care/management and decrease costs associated with unnecessary, futile testing performed in a quest to identify the cause of the neonate's symptoms/condition. In order to accomplish the study goals, we will enroll neonates and adults. Employees and students of participating institutions are not excluded from participating in this study if they have a child in the nursery who meets the criteria for inclusion in the study. If any UAB employees take part in this research our consent form will make it clear that this not part of their work or duties. Whether or not they take part in this activity is their choice and that there is no penalty for those that do not participate. In order to minimize discomfort, parents may provide consent for themselves and their child to participate in the study antenatally/prior to delivery so that the specimen can be collected during a time that is less hectic for enrolled families.

g. List any persons other than those directly involved in the protocol who will be at risk. If none, enter "None":

Due to the nature of this study, we will be examining inheritance of variants. Therefore, enrolled parents may learn that they are carriers for a recessive condition. Such information may be relevant to their affected child and future children, may also have implications for their relatives. We may also generate secondary or incidental findings, such as genetic variants that relate to heart disease or cancer risk, and this may have clinical, social, or psychological implications to the participants and their family members. Genetic counselors and physicians associated with this study will provide education and help facilitate understanding and comprehension of both the types and possible implications of findings that might be generated (at time of consent) and details about the implications of each returned variant, if any (at time of return of results). This is most pertinent to Aim 1.

h. Describe the recruitment process (e.g., medical record review, referrals, letter of invitation, existing patients) that will be used to seek potential participants (e.g., individuals, records, specimens). Research recruitment by non-treating physicians/staff may require completion of Partial Waiver of Authorization for Recruitment/Screening.

For Specific Aim 1.
Participants will be under the care of physicians/staff at each of the 3 recruitment sites. Nursery staff, neonatologists, medical geneticists and genetic counselors at each of the 3 recruitment sites will determine the patients that might qualify for participation in the study using the inclusion and exclusion criteria outlined in this protocol. Once the research nurses and/or clinicians have identified

patients who are eligible, the physicians and/or nurses will approach the families and obtain consent for participation in the study. During enrollment, clinicians and nursery staff overseeing the participant's clinical care will provide information about the proband's phenotype to the research team in a de-identified manner.

Trained research nurses will be used at each of the three recruitment sites to assist with identification and enrollment of appropriate families.

After the physician or research nurse has discussed the study with eligible participants, the physician or nurse will meet with the parents to introduce the study and describe the study's goals, process, potential benefits, and limitations. Parents who are interested in enrolling will then have an in-depth informed consent conversation with a study-dedicated nursery staff member where consent documents will be signed. At this time, information about the child's phenotype and relevant family history will be collected and shared with the research team in the a de-identified format. The staff member responsible for informed consent will elicit and address any patient questions or concerns. At the end of the consent discussion, the staff member will review the next steps in the study including sample collection, sequencing and analysis, and result return. The participant will be provided with contact information for questions that arise in the interim. After enrollment, a baseline survey will be administered to participants via Genome Gateway. The survey to be administered was submitted by amendment. Any changes to the survey will be submitted to the IRB for review and approval.

Those who declined participation in the study will be given the option to complete a decliners survey which will be administered in paper format. This information will be collected to inform the research team of barriers to participation in the research study. The survey for decliners has been submitted for IRB review and approval.

Specific Aim 3: After probands are identified and approached via methods described above, the parents/caregivers will be asked to participate in the clinical trial surveys and they will be randomized into the experimental or control arm for return of results once analysis of WGS data is complete.

Study personnel at each of the enrollment sites will tell other clinicians at their hospitals about the SouthSeq study. Many of these providers may be aware of the study as results are returned to patients that they care for. Non-genetics providers who are interested in disclosing results to participant families will have to undergo training providing them with example cases and education on how to handle participant responses, questions, etc. Materials that will be used at these trainings have been submitted to the UAB IRB for review.

i. If you will use recruitment materials (e.g., advertisements, flyers, letters) to reach potential participants, attach a copy of each item. If not, identify the source (e.g., IRB Protocol Number for approved databases) from which you will recruit participants.

We have created flyers for each of the enrollment sites to be distributed to interested parties (participants and providers serving patients who might qualify for participation in the study – both as participant families and as providers disclosing study results) and they have been submitted to the IRB for approval. We have also placed this information on a website (hudsonalpha.org/southseq).

j. Describe the screening process/procedures for potential participants.

Members of the research staff will train clinical staff members assisting with recruitment to identify potential participants. After the training, potential patients will be screened by clinicians and/or nursing staff managing their clinical care. The nursery staff is knowledgeable about the infants and will review study criteria and enroll the participants

in the research study. Information about the proband's clinical presentation and family history will be collected and documented in a coded format and linked to the participant's study ID by the nursery staff working on this project.
Clinicians interested in participating in SouthSeq as "non-genetics providers" disclosing study findings will tell the study coordinator or department lead at their hospital who will let the study coordinator know that they would like to participate in the mandatory training. The study coordinator will ensure that they are trained prior to meeting with any participant families.

17. Protocol Procedures, Methods, and Duration - in nontechnical, lay language

a. Describe the procedures for all aspects of your protocol. Tell us what you are doing.

Procedures to address Aims 1 and 3 are detailed below. Amendments will be submitted to address other aims of the projects in the future.

Specific Aim 1: Conduct WGS testing on 1,500 newborns with signs suggestive of a genetic disorder being treated at hospitals in which African-American and rural populations are highly represented.

Throughout the duration of the study, ~1500 children with rare undiagnosed phenotypes suspected to be genetic in origin and their biological parents, if willing, will be enrolled and consented. Blood samples will be collected in an environment commonly used by the physicians' participants. Blood draws will occur via the method traditionally used at the nursery at each institution. The study coordinator will work with the coordinator at each of the three sites to ensure that all employees working on the study demonstrate an understanding of HIPAA policy, the study, and their responsibilities.

After enrollment, blood samples will be collected from the proband and biological parents and submitted to the CSL and GSL at HudsonAlpha. The required blood draw (the volume collected from newborns will be within the Children's of Alabama guidelines (Maximum Blood Draw Volumes, version 12/01/14) for blood draws and up to 8mL will be drawn from adults as outlined above) presents minimal discomfort and the process used to collect this research specimen is furthermore a normal, routine part of care. Blood will be collected from the arm of enrolled parents and from the most accessible, safe location for newborns.

DNA will be extracted from the blood samples at the HudsonAlpha CSL, a CAP/CLIA-accredited laboratory. Thereafter, a sample of DNA will be given to the HudsonAlpha GSL, which uses similar infrastructure and personnel at the CSL but which is not CAP/CLIA. The GSL will perform the genomic data generation; we anticipate that most proband samples will be subject to whole-genome sequencing and analysis, although other types of experiments (e.g., exome-sequencing, RNA-sequencing, SNP array genotyping, etc.) may be considered depending on costs, feasibility, relevance, and other factors. DNA will also be isolated from parental samples and stored within the CSL, with the expectation that it will be used to differentiate de novo variants from inherited variants via Sanger confirmation (see below). The goal for these experiments and analysis is to discover genetic variants that are relevant to the child's condition and/or other medical conditions. We will identify and evaluate various types of genetic variants, including large-scale copy-number variants (CNVs), small insertion-deletion events (indels), and single-nucleotide variants (SNVs) among other possible categories of variation.

Variants of interest will be evaluated by the research analysts or "Genomic Analysis Team" (GAT) with a combination of both automated and manual procedures to identify candidate causal variants. The GAT will be led by Dr. Greg Cooper, and will also include other faculty and supporting HudsonAlpha staff as needed. The GAT will consider many types of information, including genomic annotations, patterns and frequencies of variants observed in other populations sequenced at HudsonAlpha or elsewhere, scientific literature regarding individual variants, genes,

or phenotypes, and other resources. All strong disease or clinically relevant candidates identified by the GAT will be summarized in a report that will include any evidence, both supporting and not supporting, relevant to the likelihood that the variant(s) is causal. These reports will be shared with the "Variant Review Committee" (VRC) composed of clinicians and researchers involved with the project and together the VRC will determine which variants might be relevant to the proband's phenotype and are appropriate for return.

Once the GAT makes a determination about the pathogenicity of any given variant and its suitability for return, variants will be confirmed in the proband and parents, if available, using Sanger sequencing. Sanger sequencing will be conducted in a CAP/CLIA laboratory using the original CAP/CLIA DNA that was extracted and stored by the CSL. This testing step will serve to determine the presence of the variant and provide a clinical interpretation. This information will be captured in a clinical report that can be provided to clinicians and the patient's medical record. Genetics providers (including medical geneticists and/or genetic counselors) will communicate the findings of the VRC to the enrolled families and when necessary, make referrals to aid in clinical follow up in response to the genetic finding(s). These providers will also communicate the implications of negative findings to those participants who the research team was unable to identify a genetic cause for disease. For those with relevant findings, the results will be placed in the child's medical record for other physicians to access.

This communication will be in person, via phone or certified letter. If we are unable to schedule the family for a clinic visit, we will then try to contact them by phone twice to disclose the result over the phone. If that is not successful, we will mail a certified letter disclosing their results. These findings will only be placed in the medical record after they have been disclosed to the family in-person, by phone, or via a certified letter.

Educational materials will be administered to families upon enrollment and after results are returned. These materials were submitted in an amendment. Any changes to the survey will be submitted to the IRB for review and approval.

Table - Blood Draw Volumes

Children's of Alabama

Maximum Blood Draw Volumes

Patient's Weight		Patient's Total Blood Volume	Daily Maximum Blood Draw Volume	Suggested Maximum Blood Draw Volume Every 30 Days
kg	lbs	mL (TBV)	2.5 mL/kg/24 hrs	5% of Patient's TBV
1	2.2	100	2.5	5
2	4.4	200	5.0	10
3	6.6	240	7.5	12
4	8.8	320	10.0	16
5	11.0	400	12.5	20
6	13.2	480	15.0	24
7	15.4	560	17.5	28
8	17.6	640	20.0	32
9	19.8	720	22.5	36
10	22.0	800	25.0	40
11	24.2	880	27.5	44
12	26.4	960	30.0	48
13	28.6	1040	32.5	52
14	30.8	1120	35.0	56
15	33.0	1200	37.5	60
16	35.2	1280	40.0	64
17	37.4	1360	42.5	68
18	39.6	1440	45.0	72
19	41.8	1520	47.5	76
20	44.0	1600	50.0	80
21	46.2	1680	52.5	84
22	48.4	1760	55.0	88
23	50.6	1840	57.5	92
24	52.8	1920	60.0	96
25	55.0	2000	62.5	100
26	57.2	2080	65.0	104
27	59.4	2160	67.5	108
28	61.6	2240	70.0	112
29	63.8	2320	72.5	116
30	66.0	2400	75.0	120
31	68.2	2480	77.5	124
32	70.4	2560	80.0	128
33	72.6	2640	82.5	132
34	74.8	2720	85.0	136
35	77.0	2800	87.5	140
36	79.2	2880	90.0	144
37	81.4	2960	92.5	148
38	83.6	3040	95.0	152
39	85.8	3120	97.5	156
40	88.0	3200	100.0	160
41	90.2	3280	102.5	164
42	92.4	3360	105.0	168
43	94.6	3440	107.5	172
44	96.8	3520	110.0	176
45	99.0	3600	112.5	180
46	101.2	3680	115.0	184
47	103.4	3760	117.5	188
48	105.6	3840	120.0	192
49	107.8	3920	122.5	196
50	110.0	4000	125.0	200

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Specific Aim 3: Compare technology-assisted community-based WGS result delivery by non-genetics providers to formal genetic counseling by genetic counselors.

After enrollment in the study and completion of enrollment materials required to generate an account in Genome Gateway, participants will asked to complete a survey at enrollment. This survey is the first step of the clinical trial. Once the VRC meets and determines which findings are to be returned to the enrolled participants, each family will be randomized into an experimental (trained non-genetics healthcare providers) or control (standard of care; genetic counselors or

medical geneticists) arm for return of results. Families with secondary findings will automatically be placed in the control arm. During the return of results (ROR) appointment, parents/caregivers will be asked to complete the ROR survey. At 1 month, 4 months, and 4.5 months post-ROR additional surveys will be administered to enrolled families via Genome Gateway. Those who complete the surveys will be given $25 for each completed survey via check for their participation in the clinical trial.

Healthcare providers who will participate in the clinical trial will take part in a training session that has been outlined and described in a document submitted with this amendment to add the clinical trial to the approved SouthSeq study. ROR disclosures will be recorded and reviewed by genetic counselors at HudsonAlpha who will track major and minor errors. The person who disclosed the result will recontact participant families in cases where major errors occur in order to correct the error. We expect that these cases will occur very rarely, if at all. More information about the planned trial has been submitted along with this amendment and a detailed outline of the surveys to be administered are outlined below.

Enrollment Visit

- **After the consent form is signed, families are supplied with an iPad to complete Genome Gateway registration, the enrollment survey, and family history questionnaire/pedigree in Genome Gateway.**
- **Forms/survey measures completed at enrollment:**
    - **Informed Consent Form (ICF)**
    - **Baseline Survey**
    - **Sociodemographic information**
    - **Genetic Counseling Outcome Scale (GCOS)**
    - **Genetic Knowledge Assessment (GKA)**
    - **Visual Analog Scale (VAS)- Child's Health**
    - **Parental Perceptions of Uncertainties in Genomic Sequencing (PUGS)**
    - **Health Literacy**
    - **Subjective Numeracy Scale (SNS)**
    - **12-item Short Form Survey (SF-12)**
    - **Medical Outcomes Survey (MOS)**

3-month Visit: Return of Results (ROR)

- **After samples have been sequenced, analyzed the enrolled families will be scheduled for a return of results (ROR) appointment by the site research RN/study coordinator (preferably in-person) where a genetic counselor/healthcare provider will return the finding(s)**
    - **The ROR appointment can be given over the phone if necessary, as a last resort. Reasons for offering a phone ROR include families who are unwilling to return to clinic because of distance or psychosocial distress. Caution should be made to not let the type of result dictate the ROR setting (i.e. do not preferentially offer negative results phone disclosures and positive results in-person consultations).**
    - **If a phone ROR is to be completed, the same provider should do the disclosure who would have been expected to do an in-person meeting. The phone experience should be made to feel as similar to the in-person experience as possible (length, content, staff, flow).**

- **It is important that the parent/caregiver who completes the enrollment surveys continue to be the person attending and completing the ROR visit and surveys.**

- **Genome Gateway will automatically administer surveys to participant families at enrollment. The ROR survey is administered by the research nurse or GC immediately following the ROR visit. After completion of the ROR visit, subsequent surveys can be programmed for automatic administration.**
- **Forms/survey measures completed at ROR visit:**
  - **Sociodemographic information (if status has changed)**
  - **Genetic Counseling Outcome Scale (GCOS)**
    - **This survey needs to be administered by the RN or coordinator after ROR. This is the primary outcome and needs to be completed directly after ROR.**
  - **The Feelings About genomic Testing Results (FACToR)**
    - **This survey needs to be administered by the RN or coordinator after ROR. This needs to be completed directly after ROR.**
  - **Patient Assessment of Communication (Adapted from PACE**
  - **Visual Analog Scale (VAS)- Child's Health**
  - **Parental Perceptions of Uncertainties in Genomic Sequencing (PUGS)**
  - **Parental Personal Utility Scale (PrU)**
  - **12-item Short Form Survey (SF-12)**
  - **Medical Outcomes Survey (MOS)**
  - **Understanding (Novel Measure)**

1-month post-ROR

- **Forms/survey measures completed at 1-month post-ROR visit:**
  - **Sociodemographic information (if status has changed)**
  - **The Feelings About Genomic Testing Results (FACToR)**
  - **Patient Assessment of Communication (Adpated from PACE**
  - **Visual Analog Scale (VAS)- Child's Health**
  - **12-item Short Form Survey (SF-12)**
  - **Medical Outcomes Survey (MOS)**
  - **Understanding (Novel Measure)**

4-month post-ROR

- **Forms/survey measures completed at 4-month post-ROR visit:**
  - **Sociodemographic information (if status has changed)**
  - **The Feelings About Genomic Testing Results (FACToR)**
  - **Patient Assessment of Communication (Adpated from PACE**
  - **Visual Analog Scale (VAS)- Child's Health**
  - **Parental Personal Utility Scale (PrU)**
  - **12-item Short Form Survey (SF-12)**
  - **Medical Outcomes Survey (MOS)**
  - **Understanding (Novel Measure)**
  - **Family Communication****

****Family Communication survey will be completed at the 4.5-month post-ROR time point. This is done to break up the survey burden on the parents/caregivers.**

For Specific Aims 2 and 4 we are still developing the protocols and methods to accomplish these aims. Once these are finalized they will be submitted to the IRB as an amendment for review/approval.

b. What is the probable length of time required for the entire protocol (i.e., recruitment through data analysis to study closure)?

Specific Aim 1:

This study will be ongoing as long as funding allows (expected 4 year grant term). During this time, we plan to enroll ~1500 probands along with their biological parents (when available) for whole genome sequencing. We expect turnaround time from participant enrollment to return of results to be approximately 2-3 months. This time may vary due to the need for participants to schedule an in-clinic return of results appointment that may take 2-4 weeks to arrange. We plan to allow for medical records review for up to 5 years.

Specific Aim 3:

From enrollment to participant completion, we anticipate the entire clinical trial process to take roughly 8 months to complete

c. What is the total amount of time each participant will be involved?

We anticipate approximately 3-3.5 hours (see breakdown below in part e) for participants to participate via the intended process. Additional time may be required for the collection of family history information (i.e. family pedigree information, pregnancy and birth history, symptoms of the child, etc.). This estimate includes two in-person visits, one to enroll and consent while obtaining samples, and the second to discuss the results. The first visit will take place while the proband is being treated as an in-patient in the neonatal intensive care unit (1.5 hours), and the second visit for return of results can be completed in the neonatal intensive care unit if the patient is still admitted or in outpatient clinic (1.5-2 hours). Should new information become available, participants may be contacted by phone or asked to come in for third visit in the NICU if they are still admitted or in an outpatient clinic (30mins-1 hour). The clinical trial surveys will take parents and caregivers about 20-35 minutes to complete at the various time points, for an estimated total of 80-140 minutes.

Training for non-genetics providers will take approximately 4 hours. A detailed breakdown of the time is included in the Information Sheet for Providers which was submitted by amendment and below in section 17.e.

d. If different phases are involved, what is the duration of each phase in which the participants will be involved? If no phases are involved, enter "None." **None**

e. List the procedures, the length of time the procedure takes, the total # of times the procedure is performed, and indicate whether each is performed solely for research or would already be performed for treatment or diagnostic purposes (routine care) for the population.

-Insert additional table rows as needed.

-If procedure is sometimes research and sometimes routine care, include on separate lines with number of times as each.

Procedures to address Aim 1 are detailed below.

Procedure	Length of Time Required of Participants	Total # of Times the Procedure is Performed	Research (Res) –OR- Routine Care
Medical chart review, physical examination (if new patient), family history review	**30 minutes**	**once**	☐Res ☒Routine

Explanation of study and WGS	**20 minutes**	**once**	☒Res ☐Routine
Completion of study consent form	**30 minutes**	**once**	☒Res ☐Routine
Specimen collection (blood)	**10 minutes**	**once**	☒Res ☐Routine
Return of Results	**60 minutes**	**once**	☒Res ☐Routine
Discussion of clinical management (if changes are required)	**30-60 minutes**	**once**	☐Res ☒Routine
Baseline Survey	**20-35 minutes**	**once**	☒Res ☐Routine
Return of Results Survey	**20-35 minutes**	**once**	☒Res ☐Routine
1-month post- ROR Survey	**20-35 minutes**	**once**	☒Res ☐Routine
4-months post-ROR Survey	**20-35 minutes**	**once**	☒Res ☐Routine
4.5-months post-ROR Survey	**20-35 minutes**	**once**	☒Res ☐Routine

Procedures to address Aim 3 are detailed below.

Tentative Schedule for Training Session

Procedure	Length of Time Required of Participants	Total # of Times the Procedure is Performed	Research (Res) –OR- Routine Care
Meet and greet; pre- training survey	15 minutes	once	☒Res ☐Routine
Introductions; Overview of the SouthSeq study *Didactic*	15 minutes	once	☒Res ☐Routine
Whole genome sequencing (WGS) *Didactic*	15 minutes	once	☒Res ☐Routine
Logistics of return of results in SouthSeq *Didactic*	15 minutes	once	☒Res ☐Routine
Q/A	10 minutes	once	☒Res ☐Routine
Logistics of the trial *Didactic*	15 minutes	once	☒Res ☐Routine
Genome Gateway training *Hands-on*	45 minutes	once	☒Res ☐Routine
Returning WGS results *Didactic; Hands-on; Small group discussion*	60 minutes	once	☒Res ☐Routine
Anticipating impact *Didactic; Simulation*	60 minutes	once	☒Res ☐Routine
Wrap up; Q/A: post-training survey	30 minutes	once	☒Res ☐Routine

f. Will an interview script or questionnaire be used? ☒Yes ☐No
If Yes, attach a copy.

g. Will participants incur any costs as a result of their participation? ☐Yes ☒No
If Yes, describe the reason for and amount of each foreseeable cost. _____

h. Will participants be compensated? ☒Yes ☐No
If Yes, complete i-v.
i. Type: (e.g., cash, check, gift card, merchandise): **Check (providers and participant families)**
ii. Amount or Value: $**25 (surveys), $50 (outcome and utility interviews)- participant families; $200 – providers participation in the training session; $30- key informant interviews**
iii. Method (e.g., mail, at visit): **Checks will be mailed; Checks will be distributed with paycheck**
iv. Timing of Payments: (e.g., every visit, each month): **Monthly**
v. Maximum Amount of Compensation per Participant: $255 (surveys and interviews)-participant families. Please note that we do not intend to ask any one family to complete all 3 interview types, however the estimate above includes the maximum possible compensation for a participant family.; $200-providers

18. Benefits
Describe the potential benefits of the research.
Many rare diseases are genetic in origin, however, and, as such, new DNA sequencing strategies, such as WGS, may be of use in identifying pathogenic/likely pathogenic variation that might contribute to disease. By employing such strategies, we may be able to find genetic factors that are causally related the phenotypes observed in probands enrolled in this study. We also plan to offer participation in the study to populations who are historically underrepresented in rare disease and genomic research. Additional benefits will be outlined in future amendments.

Medical benefits
A major goal of the work proposed here is to generate benefits for the enrolled individuals, both the affected children and their parents. By identifying the root cause of the child's condition, we expect to provide genetic information about pathogenic/likely pathogenic variation to aid physicians as they determine the child's clinical diagnosis. Outcomes of receiving a clinical diagnosis from a physician could fall into one of four categories:

A genetic diagnosis may end, or at least circumscribe, the costly, burdensome, and lengthy diagnostic odyssey that might otherwise occur for many affected families. By reducing the number of tests and procedures that may otherwise be performed, along with their concomitant side effects, risks, and costs, a concrete diagnosis is of considerable value.

A genetic diagnosis for a child can provide psychological benefits to the parent(s) or guardian(s). There is ample evidence that parents informed of a diagnosis feel less anxiety and have a greater sense of control over their child's health. Feelings of guilt may furthermore be alleviated by a diagnosis that makes clear that no decisions, actions, or inactions of the parents are at fault for their child's illness.

Finally, given the extent to which communities already exist for many rare diseases and that such community building is made increasingly easier with the internet and social media, we expect that many families will use information about pathogenic/likely pathogenic variation in their child's genome to establish connections with other families with similar phenotypes. Such communities may provide both the psychological benefits of belonging to a larger group and help identify educational or interventional procedures that may be particularly useful or effective in helping the affected children.

Clinical sequencing benefits
Another major goal of the work proposed here is to enable improvements to the practice of

clinical sequencing more broadly, such as:

We hope that by enrolling a diverse cohort, we may and generate data that is more representative of the general population and provide access to testing to individuals who may not have had access to it before, thus benefits of WGS may translate to a broader audience.
We expect this work to result in continued development of and improvement to the experimental, computational, and analytical pipelines required to go from DNA in a tube to a clinically relevant genetic finding. In particular, better defining the annotations and evidentiary standards that should be used to evaluate the disease-relevance of genomic variation is likely to be of considerable value.

We regard the interpretive restriction that limits most large-scale sequencing efforts to exome analyses to be a large impediment to unlocking the full potential for genomics to impact clinical decision making. The evidence that many variants missed by exome sequencing, such as structural variation and regulatory variants is overwhelming. By more comprehensively discovering clinically relevant variants, we believe that WGS will improve the efficiency and yield of clinical sequencing.

While many such discoveries may be of limited or no use to change therapies for individual families in the near future, we regard the discovery of disease-causal variants and genes as tremendously valuable to long-term improvements in clinical care. While a full characterization of the clinical benefits of basic genetic research is well outside the scope of this proposal, we wish to underscore that we anticipate making genetic discoveries in this project, unearthing novel causal variants and describing the specific phenotypes with which they associate

19. Risks - in nontechnical, lay language

a. List the known risks for participants as a result of participation in the research. This should not include the minimal risk of loss of confidentiality. However, it should include any physical, psychological, social, economic, and/or legal risks. If there is a greater than minimal risk of loss of confidentiality describe why this is so. Do not list risks associated with the standard-of-care procedures.
NOTE: Risks included here should be included in the consent form or information sheet, as applicable.
Risks associated with Aim 1 are detailed below and additional risks associated with other study aims will be submitted with future amendments.

Blood Draw: All participants will have blood drawn for genetic testing. The risks associated with blood draws are pain and distress as well as a small risk of infection.

Privacy and Risk for Discrimination: Data collected from participant families will include personal health information and information that could potentially be stigmatizing or embarrassing. In addition, genetic results generated through this project could potentially be stigmatizing or support discrimination against the proband child or parents.

Voluntary Research Participation and Vulnerable Research Participants: Parents pursuing a diagnosis for their newborn child with a rare undiagnosed disease could be viewed as vulnerable to participate in research without adequate consideration of risks and benefits, since the desire to obtain a diagnosis can be quite strong and parental willingness to sacrifice can be significant. Some proband children, such as those affected with DD/ID, regardless of age, will never reach a developmental stage consistent with the ability to assent or consent to research. Their participation in research will likely depend, therefore, on their parent(s) or guardian(s) assessment of their best interests.

Return of Genetic Results: When receiving certain genetic results, some individuals may become distressed or anxious. However, routine care for children with suspected genetic conditions often involves CMA or targeted genetic tests; many of the risks associated with receiving genetic

results in this study would therefore be encountered in routine care in other clinical settings as well (examples include prenatal carrier testing, cancer diagnosis and treatment, and others).

Misattributed Paternity: The genetic technologies utilized in this study are capable of discerning genetic relationships, including parent-child relationships. For this reason, misattributed genetic paternity could be identified through this study if the proband's father is available and willing to participate, and is relevant to the clinical findings that can be generated through these technologies. The revelation of misattributed paternity can create discord within families and could place the child at risk by creating estrangement between caregivers. Of note, parental samples will not be utilized for WGS; they will be used for Sanger validation of variants of interest in the proband.

Administered Surveys for the Clinical Trial: Participants may experience some anxiety in completing the surveys related to their health, their understanding of the genetics results returned, and how the results influence future life planning.

Disgruntled parents: Non-genetics providers may have to address both positive and negative reactions, displayed by participant families, to the study results. (Aim 3)

b. Estimate the frequency, severity, and reversibility of each risk listed.

Each of the risks associated with Aim 1, are expected to occur only one time, in the enrollment or return of results appointments. These risks are anticipated to be mild and we anticipate the potential benefits to outweigh the potential risks. These potential risks are irreversible in the sense that once genetic information has been provided it cannot be taken away. However we plan to equip each member of the research team with the tools and resources to adequately address any questions or concerns posed by enrolled participants. Clinicians involved with the study will also follow up with probands in need of clinical referrals to coordinate medical care for genetic results related to primary findings. In cases where genetic findings elicit an extremely negative response, referral to a mental health provider will be made by the genetic counselor or clinician. The genetic counselors and PIs will be available to answer any questions about the state laws regarding GINA. We hope that these resources will help provide support for non-genetics providers concerned about returning study findings.

The minimal risks associated with specific aim 3 (anxiety) are expected to only occur at the time of survey administration (5 times).

c. Is this a therapeutic study or intervention? ☐Yes ☒No

If Yes, complete i.-iii.

i. Describe the standard of care in the setting where the research will be conducted: _____

ii. Describe any other alternative treatments or interventions: _____

iii. Describe any withholding of, delay in, or washout period for standard of care or alternative treatment that participants may be currently using: _____

d. Do you foresee that participants might need additional medical or psychological resources as a result of the research procedures/interventions? ☒Yes ☐No

If Yes, describe the provisions that have been made to make these resources available.

In the event that a pathogenic/likely pathogenic variant is identified through this study, clinicians involved with the project will make the necessary referrals to facilitate proper clinical follow-up for the proband with the consent of the parent/guardian.

e. Do the benefits or knowledge to be gained outweigh the risks to participants?

☒Yes ☐No

If No, provide justification for performing the research: _____

20. Precautions/Minimization of Risks

a. Describe precautions that will be taken to avoid risks and the means for monitoring to detect risks.

Risk Mitigation Plan for Blood Draw:
Sample collection (blood draw) will be conducted by certified phlebotomists that routinely work with newborns in the nursery. Phlebotomists at each location will follow standard operating procedures intended to minimize risks of sample collection including pain, distress, bruising, redness and swelling, a rare risk of fainting, and risk for infection.

Risk Mitigation Plan for Privacy and Risk for Discrimination:
1. All electronic data will be stored on a password-protected encrypted server, and all computers used to access the server will meet national and local encryption requirements. Any paper copies of data and/or identifying information collected in person from participants (e.g., consent forms) and demographic information will be identified using an anonymous descriptor and stored in the appropriate physician's office in a locked file cabinet. All PHI will remain at the clinic where the participants are enrolled and where the clinicians associated with the research project will protect participant confidentiality. Only the clinicians, nursery staff, and genetic counselors working on the study will have access to identifiable private information on participating human subjects. In compliance with Common Rule requirements and local IRB policies, team members will participate in training for the responsible conduct of research with human subjects.
2. Consent procedures, described below, will include information for parents on genetic results and issues of privacy. Research participants will be provided with information on their right to privacy under the Health Insurance Portability and Accountability Act of 1996 and other applicable laws, as well as their protection from discrimination under the Genetic Information Nondiscrimination Act of 2008.
3. Genetic variants generated through this study, for which the sequence has been validated, and deemed returnable will be reported to the proband's parent/guardian to determine if they would like to include the finding(s) in his/her medical record. The participating clinic will store these results using paper and/or electronic systems that comply with all applicable regulations for personal health information.

Risk Mitigation Plan for Voluntary Research Participation and Vulnerable Research Participants:
1. During the research screening and informed consent process, parents will be informed that they need not participate in this research study to pursue a genetic diagnosis for their child. Alternatives such as Clinical Chromosomal MicroArray (CMA) and panels are established clinical tests for individuals with suspected genetic conditions and are not considered experimental. This test, along with other clinically-established diagnostic tests, may be available in the same clinic consistent with the national standard of care. Parents will be informed that a refusal to participate in this research study will have no effect on their child's care in the nursery.
2. The consent process will include an explicit statement on the experimental nature of whole genome sequencing (WGS) and the other genomic technologies used in order to minimize any therapeutic misconception.
3. Consistent with 45 CFR 46, all research procedures will be approved, monitored, and reviewed by UAB IRB in order to ensure an appropriate balance of risks and benefits with respect to the research participation of proband children, given that they represent a vulnerable population.

Risk Mitigation Plan for the Return of Genetic Results:
1. The Variant Review Committee (VRC) will develop criteria for pathogenic/likely pathogenic genetic results and secondary findings to be returned to participant families (likely only returning variants inherited by an affected child in a recessive manner that are believed to be causal for the child's phenotype as carrier status in enrolled parents). The VRC will include most of the key personnel of this proposal and at least one individual with expertise in each of medical genetics, genomics, genetic counseling, and bioethics.

2. The VRC will include individuals that work with scientists and clinicians from other laboratories and medical centers to evaluate the impacts of returning genetic information to individuals and families, including ongoing separate projects such as the HudsonAlpha Clinical Sequencing Exploratory Research (CSER) project and the UAB Undiagnosed Disease Program (UDP). Knowledge and experience from these efforts and from other groups performing similar research will be accounted for in this project and used to minimize risk and maximize benefit as appropriate.
3. All genetic results will be returned in person or by phone and will be delivered by a genetics provider. The meeting with the enrolled family may include the child's physician, nursery staff member, and/or a certified genetic counselor. The genetics providers will use appropriate clinical techniques to help proband's parent(s) process genetic results, and will screen for adverse affective responses to results to both anticipated and unanticipated results.

Risk Mitigation Plan for Misattributed Paternity:
1. To protect the proband child from adverse effects introduced by the revelation of misattributed paternity, we currently plan not to reveal the discovery of misattributed paternity to either of the enrolled parents.
2. If a variant found to be relevant to the child's condition is identified in a family in which the genomic analysis reveals misattributed paternity, the parents may be informed of the child's variant but told that the mode of inheritance could not be determined. The child's physician can then proceed with any targeted genetic tests deemed necessary in the clinical setting.

Risk Mitigation Plan for Administered Surveys for the Clinical Trial:
1. If a parent/caregiver decide that completion of the surveys caused too much anxiety, they may opt to not complete the surveys without penalty.

Voluntary Research Participation and Vulnerable Research Participants:
Parents pursuing a diagnosis for their newborn child with a rare undiagnosed disease could be viewed as vulnerable to participate in research without adequate consideration of risks and benefits, since the desire to obtain a diagnosis can be quite strong and parental willingness to sacrifice can be significant. Some proband children, such as those affected with DD/ID, regardless of age, will never reach a developmental stage consistent with the ability to assent or consent to research. Their participation in research will likely depend, therefore, on their parent(s) or guardian(s) assessment of their best interests.

Risk mitigation plan for handling disgruntled parents: In cases where genetic findings elicit an extremely negative response, non-genetics providers will be trained to contact a genetic counselor who can help with a referral to a mental health provider or speak with the participant family.

If the protocol involves drugs or devices skip Items 20.b. and 20.c. and go to Item 21. Instead include this information in the Drug Review Sheet or Device Review Sheet, as applicable.

b. If hazards occur to an individual participant, describe (i) the criteria that will be used to decide whether that participant should be removed from the protocol; (ii) the procedure for removing such participants when necessary to protect their rights and welfare; and (iii) any special procedures, precautions, or follow-up that will be used to ensure the safety of other currently enrolled participants. **N/A**

c. If hazards occur that might make the risks of participation outweigh the benefits for all participants, describe (i) the criteria that will be used to stop or end the entire protocol and (ii) any special procedures, precautions, or follow-up that will be used to ensure the safety of currently enrolled participants. **N/A**

21. Informed Consent

a. Do you plan to obtain informed consent for this protocol? ☒Yes ☐No

If Yes, complete the items below.

If No, complete and include the Waiver of Informed Consent or Waiver of Authorization and Informed Consent, as applicable.

b. Do you plan to document informed consent (obtain signatures) for this protocol? ☒Yes ☐No

If Yes, complete the items below.

If No, complete the items below **and** include the Waiver of Informed Consent Documentation.

c. How will consent be obtained?

For Aims 1 and 3, potential participants will meet with a member of the research team (clinician, genetic counselor, or nursery staff member) who will explain the study and obtain informed consent from parent/legal guardian for their child's participation. Biological parents must also provide consent for their participation should they elect to do so and provide a blood sample. The software platform Genome Gateway will be used to obtain informed consent electronically or scanned copies will be stored within Genome Gateway if the documents were signed in the paper format. Genome Gateway is a HIPAA-compliant platform used for clinic research and patient communication. Upon the parent/legal guardian verbally agreeing to undergo the informed consent process, a Genome Gateway account for the patient will be established. The entire informed consent document will be reviewed on a tablet or computer with the parent/legal guardian prior to signing the consent document. Potential participants will be provided with access to this consent document and given the opportunity to consider the study for up to 24 hours prior to enrollment. The parent/legal guardian may sign the informed consent document at anytime within that window. Following enrollment participants can login review/download the consent document in Genome Gateway at any time. Notification of signature will be sent to the research team. In this amendment, we have proposed that providers be given an Information sheet and a waiver of consent for their participation in the study (submitted for review).

d. Who will conduct the consent interview?

For Aims 1 and 3, clinicians, genetic counselors, and/or nursery staff named on this protocol will administer consent. We are proposing to use a waiver of consent for non-genetics providers participating in the study.

e. Who are the persons who will provide consent, permission, and/or assent?

Participants will provide consent for themselves and their child. Providers will waiver consent for their participation in the study.

f. What steps will be taken to minimize the possibility of coercion or undue influence?

For Aims 1 and 3, consent appointments will take place in a private room and participation will be explained as voluntary and will not affect the participant's relationship with the nursery or medical staff attending to their child at UAB, UMMC, or Woman's Hospital. Providers will be informed that their participation in the study is voluntary.

g. What language will the prospective participant and the legally authorized representative understand?

English

h. What language will be used to obtain consent?

English

i. If any potential participants will be, or will have been, in a stressful, painful, or drugged condition before or during the consent process, describe the precautions proposed to overcome the effect of the condition on the consent process. If not, enter "None." **None**

j. If any protocol-specific instruments will be used in the consenting process, such as supplemental handouts, videos, or websites, describe these here and provide a copy of each. If not, enter "None."
None

k. How long will participants have between the time they are told about the protocol and the time they must decide whether to enroll? If not 24 hours or more, describe the proposed time interval and why the 24-hour minimum is neither feasible nor practical.
The consent and enrollment process must occur within the first 90 days of the child's life. Since many of these children will be referred upon initial presentation of symptoms, the study will be introduced at that time and families will be given time to consider participation. This time may vary based on the severity of the child's medical condition, impending discharge form the nursery, parental availability, etc. If a family does not enroll after initial introduction of the study, our research team plans to approach each eligible family at least twice during the child's time in the nursery, giving the family to consider enrollment in the study.
Providers will be notified about the opportunity to participate in the study and then a training time will be scheduled. They will have at least 24hrs to decide if they would like to participate.

22. Procedures to Protect Privacy

Describe how you will protect the privacy interest of the participants. Include how you will make sure others cannot overhear your conversation with potential participants and that individuals will not be publicly identified or embarrassed.
Private rooms will be utilized for participant contact, both in-person and related phone conversations (Aim 1 and 3). Results will only be disclosed to those enrolled in the study.

23. Procedures to Maintain Confidentiality

a. Describe how you will store research data to maintain confidentiality (both paper records and electronic data), including how access is limited. If data will be stored electronically anywhere other than a server maintained centrally by UAB, identify the department and all computer systems used to store protocol-related data

Specific Aim 1 and 3:
Genome Gateway is hosted on a HIPAA secure cloud server contracted by HudsonAlpha through Datica Health, Inc. Both physical and software security measures are taken to encrypt and protect data hosted through Datica platforms (https://hipaa.datica.com/). Access is controlled by unique username and password for each user on the front end, while back end access is defaulted to no access unless overridden manually. UAB IT has reviewed and approved Genome Gateway to be used within the AGHI project. The use of Genome Gateway in this study will be a separate, but equally secure instance. Administrators of Genome Gateway will have access to all data entered into the software, including PHI of study participants.

If a participant family chooses not to use the electronic platform for consent, paper consent forms will be made available. These paper forms will be stored in the locked office of the study personnel at each site who will coordinate with those recruiting and enrolling participants. These forms will only be accessible to those who have access to PHI at each site and who will interact with the participants directly.

Any information (including the key linking patient names and study IDs) stored electronically will be maintained on a password/network protected computers available only to study personnel. Only de-identified info will be accessible to the laboratory performing the sequencing and analysis of the samples.

b. Will any data from this protocol be given to any person, including the subject, or any group, including coordinating centers and sponsors? ☒Yes ☐No

If Yes, complete i-iii.

i. Who will receive the data?

Specific Aims 1 and 3:
Parent participants of probands, the research team, and those monitoring the project (funding agency, IRB, etc.) will have access to the data generated. Parents will receive the results of the WGS conducted. We also plan to contribute to the scientific knowledge-base in the form of publications in scientific journals, contribution to databases such as ClinVar, etc.

ii. What data will be shared?

Specific Aims 1 and 3 - Coded information about the clinical phenotype and determined genotype will be shared with the scientific community (scientific literature) and the general public (news articles, etc.).

iii. How will the data be identified, coded, etc.?

Specific Aims 1 and 3- Anonymous, unique study identifiers will be used to code the samples and data in order to protect the identity of enrolled participants in the research project.

24. Genomic Data Sharing (GDS)

Researchers who collect genomic data as part of a NIH grant funded after January 25, 2008 may be required to submit those data to a NIH database for broad scientific sharing. See Genomic Data Sharing in the IRB Guidebook for more information.

a. Does this protocol involve the proposed submission of genetic data into genomic repositories created to share genetic information for research purposes? ☒Yes ☐No

b. Will UAB be uploading the final genomic data to the central repository (e.g., dbGaP)? ☐Yes ☒No

If Yes to both a and b, submit a Detailed Data Sharing Plan to the IRB for review. This plan should include any known data use limitations and indicate whether aggregate-level data are appropriate for general research use. For guidance see the NIH Genomic Data Sharing Policy.

c. Submit a copy of the NIH Institutional Certification Form.

To determine which certification form to include, answer i-ii.

i. Was this protocol funded prior to January 25, 2015? ☐Yes ☒No

- **If yes,** and consent will be obtained, submit the Extramural Institutional Certification - Before January 25 - With Consent.
- **If yes,** and consent will not be obtained, submit the Extramural Institutional Certification - Before January 25 - Without Consent.

ii. Was this protocol funded after January 25, 2015? ☒Yes ☐No

- **If yes,** submit the Extramural Institutional Certification - After January 25.

25. Additional Information

In the space below, provide any additional information that you believe may help the IRB review the proposed research, or enter "None." **None**