**UCSD Human Research Protections Program**
**New Biomedical Application**
**RESEARCH PLAN**

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Form Version date: 9/30/2013

## 1. PROJECT TITLE

Study #: 161983
Perinatal Precision Medicine (NSIGHT2): A randomized, blinded, prospective study of the clinical utility of rapid genomic sequencing for infants in the acute-care setting

## 2. PRINCIPAL INVESTIGATOR

Stephen F. Kingsmore, MD, DSc
CEO and President of Rady Children's Institute for Genomic Medicine (RCIGM)

## 3. FACILITIES

Rady Children's Institute for Genomic Medicine
Rady Children's Hospital (RCHSD) – All locations
Rady Children's Clinical Genomics Laboratory
University of California at San Diego

## 4. ESTIMATED DURATION OF THE STUDY

Enrollment in Rady Children's Hospital acute care settings to begin in 2017 and to continue through 2019, with follow-up including chart review of outcomes through 2025.

## 5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

This study will seek to determine if rapid genomic sequencing improves outcomes for acutely ill infants. We will enroll up to 1,000 acutely ill infants in a prospective, randomized, blinded study to either rapid Whole Genome Sequencing (WGS) or rapid Whole Exome Sequencing (WES, which is 2% of the genome and ~2-fold less expensive). Outcomes will be measured both by objective clinical measures and family perceptions (patient/family centered outcomes). Primary analysis of WGS or WES will be in infants alone. Secondary analysis, in infants who do not receive a diagnosis, will be of families – ideally trios (mother, father and affected infant), which is ~2-fold more expensive. Trios will be analyzed within the same randomization arm (WGS or WES). This study is designed to quantify which acutely ill infants benefit from rapid genomic sequencing, by how much they benefit, how they benefit, which rapid genomic sequencing method is superior, and the cost effectiveness of such testing.

## 6. SPECIFIC AIMS

**Specific Aim 1.** Determine if, and by how, much rapid WGS is associated with better outcomes than rapid WES in acutely ill infants. The null hypothesis is that both tests are equivalent. This may occur, for example, if the diagnosis rate is similar or the additional diagnoses from WGS do not alter clinical management.

**Specific Aim 2.** Determine if and by how much rapid WGS is associated with better perceived outcomes in parents of acutely ill infants than rapid WES in acutely ill infants. The null hypothesis is that both tests are

equivalent. In addition, this will be the first study to examine the family-centered outcomes of rapid genomic sequencing, and particularly in Hispanic/Latino families.

**Specific Aim 3.** To compare diagnostic rates, time to diagnosis, and outcomes of rapid genome-wide sequencing compared with historical matched cases who received standard care before genome-wide sequencing was available. The null hypothesis is that genome wide sequencing does not increase diagnosis rate, time to diagnosis or outcomes.

**Specific Aim 4.** To compare diagnostic rates of singleton analysis versus familial analysis (ideally trio) and the cost-effectiveness of each testing method (rapid singleton WGS, rapid singleton WES, rapid trio WGS and rapid trio WES). The null hypothesis is that adding familial sequencing data does not significantly increase diagnostic yield.

## 7. BACKGROUND AND SIGNIFICANCE

15% of the 4 million infants born in the US each year are admitted to a Neonatal Intensive Care Unit (NICU) or Pediatric Intensive Care Unit (PICU) for diagnosis and treatment of an acute illness. Approximately 6% of infants born in San Diego county are admitted to the RCHSD Level IV NICU or regional PICU. Genetic diseases are common among infants in ICUs, although precise prevalence data does not exist. There are more than 8,000 defined genetic diseases. Malformations and genetic disorders are the leading cause of infant mortality, NICU mortality and PICU mortality in the US. One study in a large children's hospital reported that 51% of infant deaths were from a malformation and/or a genetic disorder. 19% of deaths in the PICU of a large children's hospital were due to genetic diseases. Our experience suggests that up to 40% of level IV NICU infants may benefit from rapid WGS for genetic disease diagnosis. However, studies to date have been limited to a small proportion of NICU admissions, and may therefore be subject to ascertainment bias.

Newborn Screening (NBS), although variable by state, identifies 44 diseases within several weeks of birth, primarily inborn errors of metabolism (IEM) that collectively affect 0.3% of newborns. Typically, these diseases are asymptomatic at birth. NBS is not designed to diagnose genetic conditions in acutely ill infants, but rather to screen the population. However, IEMs are detected in 1.5% of NICU infants, and are associated with ~20% mortality. Rapid diagnosis of IEMs by NBS allows timely institution of treatment that saves thousands of Quality Adjusted Life Years (QALY) and Disability Adjusted Life Years (DALY) per year. The QALY is a generic measure of disease burden, including both the quality and the quantity of life lived. It is used in economic evaluation to assess the value of medical interventions. One QALY equates to one year in perfect health. Likewise, the DALY is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death. IEMs represent the tip of the genetic disease iceberg in NICU and PICU infants, but it is not known whether broad use of genomic sequencing in such infants would save additional QALYs and DALYs.

Other than IEMs and common chromosomal diseases (e.g. Down syndrome and 22q11 microdeletion syndrome), ascertainment rates of genetic diseases in NICUs and PICUs are low. Serial, single gene sequencing is the current standard for molecular diagnosis of genetic diseases for acutely ill infants. However, it is usually too slow for clinical utility in these sick infants as time-to-result for each test is >4 weeks, and more typically 6 - 26 weeks. Sequential testing may take years. Rapid WGS and WES allow simultaneous testing of most of the 8,000 known genetic disorders within 1 week.

Due to lack of methods for rapid molecular diagnosis, NICU and PICU treatment of genetic diseases is usually empiric. We recently invented WGS with time-to-result of ~26 hours, providing a method for timely diagnosis in acutely ill infants. In the only published study of rapid WGS (with our prior 2-day protocol), we found that

20 (57%) of 35 enrolled infants received a diagnosis by rapid trio WGS, in contrast to 9% using all conventional testing methods. Acute clinical usefulness was noted in 13 (65%) of 20 infants with a rapid WGS diagnosis, four (20%) had diagnoses with strongly favorable effects on management, and six (30%) started palliative care. However, ascertainment of eligible infants was delayed, and the median diagnosis was at day of life ~50. This impacted the effect of diagnosis on outcomes since 100-day mortality was 57% (12 of 21) in infants with a genetic diagnosis. This was not a randomized controlled study, infants were selected based on likelihood of having an actionable genetic diagnosis, and all infants received both WGS and conventional tests. Thus, this study was not designed to determine the maximum improvement in outcomes achievable nor the proportion of NICU infants who benefit. The diagnostic variants affected coding regions of genes, and therefore would potentially have been detected by WES (rather than WGS). The most common mechanism was de novo mutation causing dominant disorders, which are much more difficult to identify by singleton than trio testing.

Recently we implemented rapid (3 days) trio WGS at RCIGM. For 4 months we have enrolled acutely ill infants at RCHSD in the protocol "Genomic Biorepository: Protocol for the Collection, Storage, Analysis, and Distribution of Biological Samples, Genomic and Clinical Data (IRB #160468)". Among 35 families with acutely infants nominated, 29 (83%) were enrolled. The fastest time to diagnosis was 41 hours from blood draw to communication of provisional diagnosis. On average, diagnosis occurred within one week. At time of submission, WGS had been interpreted in 29 families with 30 symptomatic infants, yielding informative data in 28. 15 (53%) of infants received diagnoses. In 14 (50%), the initial diagnosis was by rapid trio WGS. 13 patients had single nucleotide variants and two had structural variants. The leading mechanism of disease was de novo mutations causing dominant genetic disorders. Only two patients received diagnoses prior to completion of rapid trio WGS. Following diagnosis by rapid trio WGS, clinical management changed in 12 (43% of infants tested). Of these, medications were changed in 9 (32%) infants; One infant avoided needless major surgery; Palliative care was initiated in two infants with > $6M potential healthcare savings. This data replicated our published previous experience at Children's Mercy Hospital in Kansas City, but was remarkable since enrollment was much broader at RCHSD (namely, the 4 or 5 infants with greatest need of a definitive diagnosis each week).

Additionally, we recently concluded the first randomized, controlled, partially blinded, prospective trial of the 28-day diagnostic yield of rapid trio WGS plus conventional testing versus conventional testing in acutely ill NICU infants (the NIH-funded "NSIGHT" study). While the results are still being evaluated, we found that patients in the control arm of the study also received genetic diagnoses through next-generation sequencing, including WES and WGS, upon unblinding of neonatologists. Similarly, we observed a cross-over rate for compassionate use of WGS of 10%. Nevertheless, we found that the 28-day rate of diagnosis was 5 of 33 (15%) in the control arm and 14 of 32 in the rapid trio WGS arm (44%, $p<0.01$). Thus, provisionally, we conclude that rapid trio WGS has greater 28-day diagnostic yield than conventional testing. This study was not designed to evaluate clinical utility.

Finally, a group that we are collaborating with in Melbourne Australia published a study of 80 children <2 years of age with likely genetic diseases. Singleton WES yielded a 58% rate of diagnosis. WES is four-fold less expensive than WGS, and singleton testing is 2-fold less expensive than trios. Their enrollment criteria favored children with a positive family history, which enriched for infants with recessive diseases (which are readily identified by singleton testing). While de novo mutations were the leading cause of diagnosis in their study, recessive diseases were much more common in their cohort than other studies. They utilized WES at standard speed (~6 month time to diagnosis), and thus their study was not well designed to assess clinical utility.

These studies, which comprise the literature to date, demonstrate that rapid WGS significantly increases the rate of diagnosis and time to diagnosis compared with traditional testing. As yet, however, no randomized

controlled study has compared the rate of diagnosis of WGS and less costly WES, nor of trio versus less costly singleton testing. It is no longer acceptable to have randomization to a control arm that delays reporting of results up to 12 weeks (such as routine speed WGS or WES). Furthermore, although data from studies to date shows clinical utility of WGS or WES, it is not yet clear what the specific indications for such testing should be in acutely ill infants, nor whether WGS or WES are associated with improved outcomes. Furthermore, both the cost of WGS and WES, and their clinical utility, increase as time to result decreases. The optimal match of timeliness and cost effectiveness are not yet known. Finally, it not clear whether patient and family perceptions of improved outcomes match those of physicians. Therefore, we propose to examine standard and family-centered outcomes in acutely ill infants receiving rapid WGS or rapid WES as a first-line test.

Little data exists on the clinical utility of rapid genomic sequencing for cost-effectiveness modeling of interventions initiated in the early days to weeks of life. Studies have shown that NBS decreases morbidity and mortality because it provides rapid screening at birth for diseases that benefit from early treatment. Additionally, rapid genomic diagnosis of critically ill babies may diagnose lethal disorders, enabling initiation of palliative care, potentially decreasing physical suffering to the infant, and prioritizing bonding with family members rather than futile heroic interventions. Studying the clinical impact of WGS or WES for acutely ill infants compared with historic controls will provide information on the incidence of genetic disease in this population and help determine how WGS and WES benefit acutely ill infants, their families and their clinical care providers. Likewise, we will attempt to aggregate data for QALYs and DALYs to analyze the clinical utility of genomic sequencing, in addition to clinician surveys of utility, and to assess economic impact of testing over the lifetime of each patient.

Rapid WES is ~2-fold less expensive than rapid WGS but has at least one additional day of time to results. There is no data comparing the diagnostic or clinical utility of WES and WGS. WES is the only genome wide sequencing test routinely covered by insurers. In addition, as noted above, all of our rapid WGS cases could theoretically have been detected by WES. Conversely, although WES can analyze the coding regions of nearly all potentially disease causing genes, we believe that WGS is superior, despite its higher costs, due to its ability to detect de novo variants, structural variants (SV), and to interrogate regions of extreme GC content. WGS provides coverage of non-coding variants that can be clinically identified as definitely disease causing. As such, we believe an analysis of diagnostic rates between the two types of tests will show that WGS does in fact provide more diagnoses than WES. However, such increases in diagnoses may not lead to an increase in changes in care as the variants that can be detected only by WGS may be less amenable to specific therapeutic interventions. The primary goal of this study is to evaluate which method provides the optimal outcomes in acutely ill infants with likely genetic diseases. However, we anticipate that we may also – in subsequent amendments – retrospectively re-analyze these samples to determine if WGS or WES has superior ability to yield pharmacogenomic and secondary findings related to childhood-onset conditions. In subsequent amendments, families may potentially be asked for their opinions on receiving such additional testing results, if available, following the discharge of their child. As pharmacogenomics knowledge grows, the need for informed drug choice and dose will be crucial in effectively managing critically ill patients and preventing secondary harm. In particular, we anticipate a future amendment to examine the prevalence of the genetic predisposition to hearing loss following the administration of aminoglycosides, an antibiotic very commonly used in NICUs.

The incidence of genetic diseases in acutely ill infants receiving NICU and PICU care is unknown since no large scale genomic sequencing study has been performed in this population. While genetic diseases are known to be a leading cause of death among infants, the impact of timely diagnosis in acutely ill infants on clinical care of these diseases is unknown. We propose a prospective, randomized study to compare outcomes in up to 1,000 acutely ill babies, all of whom will receive some form of genomic sequencing. We will use genomic

sequencing to prospectively test the hypothesis that rapid WGS confers significantly better outcomes to a subset of ill neonates/infants and their families than rapid WES or current clinical practice (clinical diagnosis and standard diagnostic tests). Molecular diagnostic yield, time to diagnosis and changes in management will be secondary outcomes.

## 8. PROGRESS REPORT

This study has resulted in 23 publications to date:


1. Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases. Clark MM, Stark Z, Farnaes L, Tan TY, White SM, Dimmock D, Kingsmore SF. NPJ Genom Med. 2018 Jul 9;3:16.
2. Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization. Farnaes L, Hildreth A, Sweeney NM, Clark MM, Chowdhury S, Nahas S, Cakici JA, Benson W, Kaplan RH, Kronick R, Bainbridge MN, Friedman J, Gold JJ, Ding Y, Veeraraghavan N, Dimmock D, Kingsmore SF. NPJ Genom Med. 2018 Apr 4;3:10.
3. The case for early use of rapid whole-genome sequencing in management of critically ill infants: late diagnosis of Coffin-Siris syndrome in an infant with left congenital diaphragmatic hernia, congenital heart disease, and recurrent infections. Sweeney NM, Nahas SA, Chowdhury S, Campo MD, Jones MC, Dimmock DP, Kingsmore SF; RCIGM Investigators. Cold Spring Harb Mol Case Stud. 2018 Jun 1;4(3).
4. The NSIGHT1-randomized controlled trial: rapid whole-genome sequencing for accelerated etiologic diagnosis in critically ill infants. Petrikin JE, Cakici JA, Clark MM, Willig LK, Sweeney NM, Farrow EG, Saunders CJ, Thiffault I, Miller NA, Zellmer L, Herd SM, Holmes AM, Batalov S, Veeraraghavan N, Smith LD, Dimmock DP, Leeder JS, Kingsmore SF. NPJ Genom Med. 2018 Feb 9;3:6.
5. Rapid whole-genome sequencing identifies a novel AIRE variant associated with autoimmune polyendocrine syndrome type 1. Sanford E, Watkins K, Nahas S, Gottschalk M, Coufal NG, Farnaes L, Dimmock D, Kingsmore SF; RCIGM Investigators. Cold Spring Harb Mol Case Stud. 2018 Jun 1;4(3).
6. Rapid whole-genome sequencing identifies a novel GABRA1 variant associated with West syndrome. Farnaes L, Nahas SA, Chowdhury S, Nelson J, Batalov S, Dimmock DM, Kingsmore SF; RCIGM Investigators. Cold Spring Harb Mol Case Stud. 2017 Sep 1;3(5).
7. Rapid whole-genome sequencing identifies a novel homozygous NPC1 variant associated with Niemann-Pick type C1 disease in a 7-week-old male with cholestasis. Hildreth A, Wigby K, Chowdhury S, Nahas S, Barea J, Ordonez P, Batalov S, Dimmock D, Kingsmore S; RCIGM Investigators. Cold Spring Harb Mol Case Stud. 2017 Sep 1;3(5).
8. Bedside Back to Bench: Building Bridges between Basic and Clinical Genomic Research. Manolio TA, Fowler DM, Starita LM, Haendel MA, MacArthur DG, Biesecker LG, Worthey E, Chisholm RL, Green ED, Jacob HJ, McLeod HL, Roden D, Rodriguez LL, Williams MS, Cooper GM, Cox NJ, Herman GE, Kingsmore S, Lo C, Lutz C, MacRae CA, Nussbaum RL, Ordovas JM, Ramos EM, Robinson PN, Rubinstein WS, Seidman C, Stranger BE, Wang H, Westerfield M, Bult C. Cell. 2017 Mar 23;169(1):6-12.
9. Genomic newborn screening: public health policy considerations and recommendations. Friedman JM, Cornel MC, Goldenberg AJ, Lister KJ, Sénécal K, Vears DF; Global Alliance for Genomics and Health Regulatory and Ethics Working Group Paediatric Task Team. BMC Med Genomics. 2017 Feb 21;10(1):9.
10. Newborn Sequencing in Genomic Medicine and Public Health. Berg JS, Agrawal PB, Bailey DB Jr, Beggs AH, Brenner SE, Brower AM, Cakici JA, Ceyhan-Birsoy O, Chan K, Chen F, Currier RJ, Dukhovny D, Green RC, Harris-Wai J, Holm IA, Iglesias B, Joseph G, Kingsmore SF, Koenig BA, Kwok PY, Lantos J, Leeder SJ, Lewis MA, McGuire AL, Milko LV, Mooney SD, Parad RB, Pereira S, Petrikin J, Powell BC, Powell CM, Puck JM, Rehm HL, Risch N, Roche M, Shieh JT, Veeraraghavan N, Watson MS, Willig L, Yu TW, Urv T, Wise AL. Pediatrics. 2017 Feb;139(2). pii: e20162252.
11. Clinical detection of deletion structural variants in whole-genome sequences. Noll AC, Miller NA, Smith LD, Yoo B, Fiedler S, Cooley LD, Willig LK, Petrikin JE, Cakici J, Lesko J, Newton A, Detherage K, Thiffault I, Saunders CJ, Farrow EG, Kingsmore SF. NPJ Genom Med. 2016 Aug 3;1:16026.
12. USE OF GENOME DATA IN NEWBORNS AS A STARTING POINT FOR LIFE-LONG PRECISION MEDICINE. Brenner SE, Kingsmore S, Mooney SD, Nussbaum R, Puck J. Pac Symp Biocomput. 2016;21:568-75.
13. Whole-Exome Sequencing and Whole-Genome Sequencing in Critically Ill Neonates Suspected to Have Single-Gene Disorders. Smith LD, Willig LK, Kingsmore SF. Cold Spring Harb Perspect Med. 2015 Dec 18;6(2):a023168.
14. Newborn testing and screening by whole-genome sequencing. Kingsmore SF. Genet Med. 2016 Mar;18(3):214-6.
15. Rapid whole genome sequencing and precision neonatology. Petrikin JE, Willig LK, Smith LD, Kingsmore SF. Semin Perinatol. 2015 Dec;39(8):623-31.
16. A novel epileptic encephalopathy mutation in KCNB1 disrupts Kv2.1 ion selectivity, expression, and localization. Thiffault I, Speca DJ, Austin DC, Cobb MM, Eum KS, Safina NP, Grote L, Farrow EG, Miller N, Soden S, Kingsmore SF, Trimmer JS, Saunders CJ, Sack JT. J Gen Physiol. 2015 Nov;146(5):399-410.
17. MMP21 is mutated in human heterotaxy and is required for normal left-right asymmetry in vertebrates. Guimier A, Gabriel GC, Bajolle F, Tsang M, Liu H, Noll A, Schwartz M, El Malti R, Smith LD, Klena NT, Jimenez G, Miller NA, Oufadem M, Moreau de Bellaing A, Yagi H, Saunders CJ, Baker CN, Di Filippo S, Peterson KA, Thiffault I, Bole-Feysot C, Cooley LD, Farrow EG,

Masson C, Schoen P, Deleuze JF, Nitschké P, Lyonnet S, de Pontual L, Murray SA, Bonnet D, Kingsmore SF, Amiel J, Bouvagnet P, Lo CW, Gordon CT. Nat Genet. 2015 Nov;47(11):1260-3.
18. A 26-hour system of highly sensitive whole genome sequencing for emergency management of genetic diseases. Miller NA, Farrow EG, Gibson M, Willig LK, Twist G, Yoo B, Marrs T, Corder S, Krivohlavek L, Walter A, Petrikin JE, Saunders CJ, Thiffault I, Soden SE, Smith LD, Dinwiddie DL, Herd S, Cakici JA, Catreux S, Ruehle M, Kingsmore SF. Genome Med. 2015 Sep 30;7:100.
19. Emergency medical genomes: a breakthrough application of precision medicine. Kingsmore SF, Petrikin J, Willig LK, Guest E. Genome Med. 2015 Jul 30;7(1):82.
20. Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings. Willig LK, Petrikin JE, Smith LD, Saunders CJ, Thiffault I, Miller NA, Soden SE, Cakici JA, Herd SM, Twist G, Noll A, Creed M, Alba PM, Carpenter SL, Clements MA, Fischer RT, Hays JA, Kilbride H, McDonough RJ, Rosterman JL, Tsai SL, Zellmer L, Farrow EG, Kingsmore SF. Lancet Respir Med. 2015 May;3(5):377-87.
21. CLPB variants associated with autosomal-recessive mitochondrial disorder with cataract, neutropenia, epilepsy, and methylglutaconic aciduria. Saunders C, Smith L, Wibrand F, Ravn K, Bross P, Thiffault I, Christensen M, Atherton A, Farrow E, Miller N, Kingsmore SF, Ostergaard E. Am J Hum Genet. 2015 Feb 5;96(2):258-65.
22. Loss of function variants in human PNPLA8 encoding calcium-independent phospholipase A2 γ recapitulate the mitochondriopathy of the homologous null mouse. Saunders CJ, Moon SH, Liu X, Thiffault I, Coffman K, LePichon JB, Taboada E, Smith LD, Farrow EG, Miller N, Gibson M, Patterson M, Kingsmore SF, Gross RW. Hum Mutat. 2015 Mar;36(3):301-6.
23. Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. Soden SE, Saunders CJ, Willig LK, Farrow EG, Smith LD, Petrikin JE, LePichon JB, Miller NA, Thiffault I, Dinwiddie DL, Twist G, Noll A, Heese BA, Zellmer L, Atherton AM, Abdelmoity AT, Safina N, Nyp SS, Zuccarelli B, Larson IA, Modrcin A, Herd S, Creed M, Ye Z, Yuan X, Brodsky RA, Kingsmore SF. Sci Transl Med. 2014 Dec 3;6(265):265ra168.

## 9. RESEARCH DESIGN AND METHODS

**Summary of design**

A prospective, randomized, controlled, blinded trial to evaluate the comparative outcomes and effectiveness (clinical utility, perceived family utility, and cost effectiveness) of two methods of rapid genomic sequencing (WGS and WES) and two methods of analysis (singleton probands and familial trios) in acutely ill infants. Enrollment in this study includes enrollment into a Newborn/Infant biorepository and co-enrollment into the Genomic Biorepository: Protocol for the Collection, Storage, Analysis, and Distribution of Biological Samples, Genomic and Clinical Data (IRB #160468). Historic controls will be obtained from a separate retrospective chart review study following IRB approval.

Acutely ill infant inpatients who have an undiagnosed illness, and their families, will be eligible to participate in the study. We will enroll up to 1,000 infants. Locally, the study population will be recruited from Rady Children's Hospital (RCH) inpatient population, primarily the NICU, PICU and cardiovascular intensive care unit (CVICU), with a smaller population presenting to other hospital in-patient services. Recruitment will be targeted at the RCH main campus, but it may include referrals from satellite locations in the RCH network (particularly the RCH NICU network throughout San Diego County). All patients will continue to receive routine care as clinically indicated, including the state NBS and other genetic testing as determined by their treating providers. Half of the affected study participants will be randomized to receive rapid WGS and the other half will receive rapid WES. Each arm will initially be analyzed using the patient's (proband's) sample only. If a proband-only analysis fails to yield a diagnosis, genomic data from the biological family members (typically parents), when available, will be used to supplement analysis (trio analysis). Occasionally, a second affected sibling may be available for family analysis. Not infrequently, the father is not available for study. Similarly, we anticipate the need for targeted genetic analysis of biological parents, and possibly other family members, to confirm diagnostic results and/or provide additional information regarding inheritance.

**Recruitment, Enrollment and Sample Collection:**

Enrollment will be sought within the first 96 hours following admission to RCH or an RCH network ICU or within 96 hours of meeting eligibility criteria for the study if the infant was not previously eligible. The clinicians will typically confirm study eligibility and make a referral to the research staff. The research staff

will approach the families and provide them with a brief summary of the study, including a study brochure (see appendix), research team contact information, and consent documents if requested. Families may also receive additional study information and potentially consent at the initial time or the study staff will leave the materials and follow up the next day. Families will be given the option to opt-out as a part of the study brochure, which may be given to the clinical staff or the research staff at any time. A decision to opt-out will require families to re-contact the research team directly should they change their minds.

Informed consent and permission will be sought for the patients and biological parents. Other family members, affected or unaffected, may be asked to enroll as well to assist with analysis. Other family members may include children or adults. Blood will be collected from patients and family members following informed consent. An order for "RCIGM Research Testing", at no charge, will be placed in the medical record of each participant for sample collection and tracking purposes. The order will be marked as "Completed" at the conclusion of the analysis. A second clinical order will be entered, at no charge, for clinical confirmation of the research results. The results of the clinical confirmation will be entered into the affected child (or children if there are multiple affected individuals in one family) medical record(s) (see Return of Results below).

Following informed consent, subjects will have blood drawn for nucleic acid (DNA and possibly RNA) isolation at the time of enrollment in the study. All maximum blood sample volumes will be determined by the patient's weight in a volume per kg calculation. A minimum of 0.5 ml (up to 3 ml) will be collected from the admitted patients by their clinical nursing staff when scavenged blood/DNA is not available. Volume will depend on the size of the patient and other clinical lab draw volumes at the time of collection. Up to 6 ml of blood will be collected from adult participants by trained research staff. Priority will be given to clinical lab samples over research samples. Buccal smears and saliva may be collected in addition to blood or in lieu of blood; heel-prick blood spots, additional blood, urine and left over fluid and tissue samples, if available, may also be collected and stored in the Rady Children's Clinical Genome Center as part of the Genomic Biorepository (Study 160468). The latter samples will not involve invasive sampling, and are helpful for diagnosis in cases, for example, of mitochondrial diseases and somatic mutations. Samples scavenged from other clinical testing and/or other research studies (such as the RUB) will be determined based on the participant's clinical presentation and symptoms. It is impossible to say at this time what amounts and sample types will be collected due to the large number of genetic diseases being studied.

We may collect additional samples for functional studies needed to confirm genetic results. The sample amounts, types and additional family members who may be requested to provide additional samples will be determined on a case-by-case basis. Whenever possible, previously obtained clinical samples and/or samples stored in the Genomic Biorepository and/or RUB will be scavenged to avoid unnecessary patient blood draws. If additional samples are required that are not available from other studies or left-over clinical samples, families will be contacted regarding these research-only additional samples. The specific sample type and amount will be discussed with each family and permission will be requested prior to any additional research-only sample collection. Additional samples that may be collected for research-only purposes include blood, buccal swabs, saliva, non-invasive stool collection, and/or a clean-catch urine specimen. The study team will coordinate collection of such samples, and whenever possible, will coordinate these collections to overlap with routine clinical care. No charges will be applied for research-only sample collection. We may also use non-invasive methods of DNA collection to test the sample accuracy against whole blood.

**Randomization and DNA Analysis**

Patients and their family members who consent to participate will be randomized to receive either rapid Whole Genome Sequencing (WGS) or rapid Whole Exome Sequencing (WES). DNA will be extracted and rapid genomic sequencing will occur per Standard Operating Procedures within the Rady Children's Clinical

Genome Center and in accordance with the Genomic Biorepository (Study 160468). Genomic data will be analyzed using the clinical features and symptoms as extracted from the patient's medical record, reported by clinicians, and/or by physical exam by research staff.

Stage One Analysis:

The initial symptom-driven analysis will be conducted on the patient's sample only (singleton analysis).

Stage Two Analysis:

If a diagnosis is not found promptly (within 24 hours) via a singleton analysis, the family (or any combination of parents and/or other family members) will be analyzed using the same technology that the patient was randomized to receive. Dependent upon logistics and the acuity of the patient's illness, we may generate trio genomic sequences simultaneously or in stages (singleton then parental duo).

Other Analysis:

Some family members may have targeted sequencing and analysis done to confirm results and/or provide additional inheritance information of singleton analysis results.

Data analysis will follow the standards set by the clinical diagnostic laboratory and in line with recommendations from the American College of Medical Genetics (ACMG). Currently, a minimum of two expert data analysts will be responsible for analyzing the DNA variants following genomic sequencing. Analysts will be rotated among qualified RCIGM staff, including but not limited to laboratory directors, genetic counseling staff, trained medical and research staff. One of the analysts will then compile a report to be reviewed by the Molecular Pathology Laboratory Directors, Shareef Nahas or Shimul Chowdhury, or the Medical Director, David Dimmock.

We anticipate that in rare cases a newborn may be so ill that the team lacks equipoise that the child can wait for the estimated ten day turnaround time of our send-out exome testing. In these rare cases, the PI, or his delegate, will decide if the child is not eligible for randomization. These children will remain in the research study throughout the entirety of the study, but they will receive in-house ultra-rapid whole genome sequencing by the RCIGM laboratory in lieu of either a rapid genome or rapid exome (both anticipated to be 10 day turn-arounds). For the purpose of study analysis, these subjects will be treated as excluded from randomization and analyzed as a separate category.

**Return of Results**

All findings: Follow up with the patient's family of testing results will be guided by the clinical care team. All subjects who receive results as a part of this study may be offered the opportunity to follow-up with licensed genetic counselors and/or medical staff from the genome institute to discuss the return of results in-person. This post-test genetic counseling will be available to all subjects as a part of this study and may be done in the in-patient setting, over the telephone or other telecommunication device, or in an out-patient setting. These post-test counseling visits will be documented in the subject's RCHSD EHR, but there will not be any billing or charges associated with these visits. All genetic counseling sessions (including any pre-test counseling, generation of a pedigree, or post-test follow-up contact) with our licensed research team will be documented in the patient's EHR to facilitate communication amongst clinical teams. Such sessions are in addition to any clinically indicated counselling or testing which will be performed and billed as appropriate by the clinical genetics team and other clinical providers. If the findings pertain to someone who is not a patient in the hospital system, in addition to our counselling, we will ask the subject to identify a provider to whom the results can be

returned.

Primary findings: Pathogenic and likely pathogenic variants (as determined by ACMG guidelines) that relate in part or in whole to the patient's current phenotype will be reported into the patients' medical record. In the case of positive study findings that may be diagnostic, confirmatory clinical diagnostic testing will be performed on the proband and, when warranted, segregation analysis on other family members. Following this confirmation, a standard clinical diagnostic report will be placed in the patient's medical record, and the nominating physician will be contacted. In the event that an affected family member, such as a sibling, is also a patient of the enrolling hospital system, clinical results will also be returned to that patient's medical record. In the event that clinical genomic sequencing is done by a CLIA accredited laboratory these negative results will be treated as clinical-grade and will be placed in the affected subject's medical record indicating the symptoms used for analysis, the testing done, and the limitations of the results at this time.

Negative findings: Although the intention of the study is to return symptom-driven results to the medical record, the clinical report for confirmation of symptom-driven findings may include negative findings of testing. We believe this negative clinical testing result is clinically relevant and should not be withheld as it may be pertinent to patient care and future testing. This testing will preferentially use FDA approved in vitro diagnostics tests where available. In this situation the entirety of the approved test, not just the target variant information will be returned. Similarly, clinical confirmation may be required by an outside laboratory; results reported by this outside laboratory may include variants of unknown significance, genome-wide negative results and/or secondary findings per the clinical lab's testing protocol. These results will be placed in the patient's medical record to reflect the clinical testing ordered. Clinical tests required for confirmation of research results will be charged to this research study.

Secondary findings: Whenever possible, this study will not report secondary findings. That is, the laboratory will not intentionally seek to evaluate disease status or predisposition beyond attempting to identify the cause of the child's current health issues. Similarly, other information, identified as a result of the testing but not relevant to the clinical question, such as family relations not being as stated and adult onset conditions will not be returned. In accordance with standard care for clinical laboratories, we will report clinically that no pathogenic results were found related to the patient's specific symptoms. This report will include a list of the symptoms used, the type of testing, and the limitations of the testing. Parents and family members of the affected patient may also be enrolled in this study for the purpose of comparing genetic variants with the affected patient. Similarly to the proband the data will not be evaluated to specifically find carrier information, disease status or predisposition beyond that required to identify the cause of disease in the proband. Only in the event that an immediately life-threatening illness is inadvertently found, such as familial hypercholesterolemia, will results be returned to family members. In this rare event, the family member will be asked to identify a clinician to whom our team may return these results. Genetic inheritance patterns and reoccurrence risks will be included in the patient's results and genetic counsellors will be available to all families enrolled in this study as well as to support their physicians.

As noted above it is the intention of the team to not evaluate the genome for "secondary findings". However it is possible that federal or local rules change more strongly recommending analysis of the genome for other such findings or there is s future research interest in such analysis. The team will therefore seek to identify families that would not want to be contacted in the future to specifically enroll in a study evaluating the return of such secondary findings. If families opt out of such contact, they still may be contacted in the future about primary study questions but will not be approached to consent for future studies about secondary findings return.

Preliminary Reports – In instances where a diagnosis suggests an intervention that needs to be implemented

prior to the time required for orthogonal confirmation to potentially avoid morbidity or mortality, the diagnosis will be communicated to the clinical team verbally and a preliminary clinical report will be placed into the medical record. This will be amended or updated when orthologous testing is completed. A preliminary clinical report allows greater access and better adoption of the genomic test information for physicians in EMRs. Additionally, evidence in the literature and internally at RCIGM have shown that data generated from whole genome sequencing (WGS) is equivalent, or even superior in certain instances, to orthogonal methods in terms of sensitivity and specificity. In over 150 diagnoses at RCIGM since inception in 2016, all clinically significant variants have undergone successful orthogonal confirmation. All results are generated in the CAP-accredited, CLIA-certified RCIGM-Clinical Genome Center or collaborating clinically accredited laboratories under the guidance and oversight of the laboratory director. Thus, the preliminary report can be viewed as a preliminary clinical report.

Incidental - During the course of the phenotype-driven analysis, if a pathogenic variant is identified that is medically actionable and does not overlap with the patient's reported phenotype, the variant will be reported. Consensus by at least one laboratory director and one RCIGM staff physician must be obtained and documented that the possible benefits of reporting the incidental finding of interest exceeds the potential harms. Clinically significant variants incidentally ascertained in genes associated with a medically actionable condition will be reported as incidental findings if appropriate consent for return of incidental findings has been obtained. Reporting of incidental findings will be reported as stated in the RCIGM clinical laboratory guidelines. Criteria for consideration include, but are not limited to: available evidence of pathogenicity of the variant, medical actionability of the condition of interest, and the benefit:risk ratio of potential medical interventions.

VUS - A "variant of uncertain significance" is one for which there is insufficient current evidence to determine if the variant is disease causing (i.e. clinically significant). This may be due to a lack of available evidence supporting pathogenicity or conflicting evidence currently exists. Universally, diagnostic reference laboratories performing whole genome sequencing and whole exome sequencing as commercial diagnostic tests report variants that are classified by the American College of Medical Genetics as "variants of uncertain significance" in genes that are implicated in human disease. Per RCIGM clinical laboratory standard operating procedures, selected VUS's will be placed in a separate table in the report and verbiage will state that additional testing and clinical correlation will be required to re-classify the variant as clinically significant. Consensus by at least one laboratory director and one RCIGM staff physician must be obtained and documented that the possible benefits of reporting the VUS of interest exceeds the potential harms. This type of reporting is necessary as often the physicians treating the patients are best positioned to conduct follow up testing and further examinations to provide adequate and timely follow-up for a VUS result.

**Surveys:**

**Family Surveys:**

After enrollment into the research study, families will have a brief survey administered assessing their trust in medical providers (see appendix). In-person surveys will be given the option to take the survey on paper independently or administered by research staff verbally. Families for whom a translated survey is not available will have the survey administered using an interpreter. Families will receive two follow-up surveys (see appendix) assessing decisional regret and perceived benefits or harm of testing. The first follow-up survey will be administered within one week of the return of results (including the return of no results), and the second follow-up survey will be administered approximately one year after enrollment. If families are still in the hospital at the time of follow-up, research staff will attempt to meet the families bedside to conduct the survey. For families that are no longer in-patient at the time of follow-up, research staff will attempt to contact families by phone prior to administration of follow-up surveys and families will be offered the choice to decline further

surveys at that time. Barring a verbal decline for further surveys, families will have the choice to take the survey electronically e.g. via a REDCap survey or by phone. Families who chose the electronic survey will be told that if the survey is not completed within 72 hours, the research staff will contact them to conduct the survey by phone, with a possible second contact at a scheduled time.

**Clinician Surveys:**

Within one week of the return of results (including the return of no results), clinicians caring for the patient will be asked to complete a brief survey (see appendix) regarding the clinical utility of genomic testing. The surveys may be administered in-person on paper or independently completed on paper or via email messaging to the providers' secured RCHSD or UCSD electronic mail account. Surveys will contain the minimum information required to identify the child in which the testing focuses on. It aims to identify what, if any, changes were made to the immediate management of the patient as a result of testing as well as general utility from the diagnosis. As these surveys are directed at obtaining clinical information about the patients and not assessing the clinicians as research subjects, the clinicians will not be enrolled as a part of this study. A second study of clinicians may be performed under a separate protocol in the future.

**Data Sharing and Privacy:**

Samples that undergo clinical confirmation will be labeled as such and stored with identifiers for future confirmation and tracking. Following return of results, all other samples will have patient identifiers removed and be labeled with a research study ID and a second unique sample identifier. These unique identifiers will be linked with a Master List within the Rady Children's Institute for Genomic Research. The Master List will be password protected with access limited to research staff only. The Master List may take the form of an Excel file housed on an internal secure shared drive, with limited access, and/or a password protected, limited access REDCap database administered by RCH. Samples will also be tracked using the Rady Children's Clinical Genome Center's Laboratory Information Management System (LIMS) system.

Patient data will be stored securely in this HIPAA compliant sample tracking system separate from the electronic medical record. RCIGM is collaborating with researchers at UCSD; therefore data will be stored on the UCSD servers as well as the RCIGM servers. Researchers at UCSD will contribute expertise relevant to all aims of the study, especially to the ethical, social, and behavioral impacts and implications of newborn sequencing research. They will contribute expertise from previous studies of patient and physician response to genome sequencing for disease diagnosis, as well as attitudes and preferences about the personal genomic information for research. Researchers will analyze data collected from surveys of patients and physicians, draft manuscripts that report on findings from those data, and contribute to the design of future empirical studies focused on the ethical, social, and behavioral impacts of newborn genome sequencing.

Biorepositories:

Sample testing, storage and analysis will adhere to the RCIGM Genomic Biorepository protocol, IRB# 160468. Following the clinical storage of samples in accordance with RCIGM CLIA laboratory requirements, all data and samples from participants in this study will be stored for future research. Coded and/or de-identified data will be shared with the RCIGM Genomic Biorepository (IRB# 160468).

Participants in this study will also be included in the Genomic Biorepository (IRB# 164068). Under this

protocol nucleic acids may be isolated and prepared for genomic sequencing with Standard Operating Procedures (SOP) at the Genomic Institute. Familial samples (for example, mother, father, affected or unaffected siblings) will also be obtained, and nucleic acids will also be sequenced per the Genomic Biorepository's SOP, as indicated, to assist in diagnosis of the acute medical condition in the infant. All sequencing and sample data will be stored by the Genomic Biorepository (IRB #160468). Clinical information will be shared with the Genomic Biorepository including referring clinician details, testing, symptoms, age of symptom onset and relevant medical and family history. All future research and data sharing will be regulated through the Genomic Biorepository protocol.

Similarly, this study will operate as a Newborn/Infant Biorepository. De-identified data collected from this study will be shared and aggregated with other sites participating in this or similar future research studies administered by the Rady Children's Institute for Genomic Research collecting genotypic and phenotypic data from infants. It is anticipated that a protocol mirroring this study will be made available as a multi-site research study hosted by Rady Children's Institute for Genomic Research subject to RCHSD/UCSD and Local IRB approval in the near future.

Data and sample sharing among researchers is key to enhancing the scientific community's understanding of genomics. De-identified data from this Newborn Biorepository will also be shared with public databases such as Clinvar and dbGAP as well as other research databases like the Longitudinal Pediatric Data Resource (LPDR) hosted by the Newborn Screening Translational Research Network (NBSTRN). Samples and data will be stored in the Rady Children's Institute for Genomic Research and Rady Children's Clinical Genome Center laboratory. The research team will review all cases to ensure that the phenotypic data and genotypic data being shared with other researchers as well as in publications and public databases are not individually identifiable. In rare cases where this information is determined to be identifiable, the research team will seek out specific permission from the family to release this information for the advancement of scientific understanding.

**Optional Questions:**

Participants will also be offered the optional question to allow for the use of photographs as a part of this study. The RCH policy regarding the use of photography will be followed and the release form will be signed at the time photographs are taken. Photography may be used for publications. Whenever possible, the identifying features will be blocked. Names and other personal health identifiers will not be released as a part of publications. If, in the future, photographs are to be used for research purposes to test new technologies, including algorithms designed to identify phenotypic features, the PI will submit a separate protocol and obtain approval from the IRB for such research activity. Phenotypic features identified with this technology, as well as other phenotypic data collected from the medical record and patient assessments, may be shared with both public databases as well as in publications.

**Opt-Out for Incidental Findings**

Families will be given the opportunity to opt-out of receiving actionable incidental results. In the event that our analysis incidentally finds a pathogenic variant for which a treatment or intervention exists to improve morbidity and/or mortality, families may choose to receive this additional information. We will not be intentionally looking for results unrelated to the primary cause of disease (secondary findings). All findings will be confirmed using an appropriate standard clinical testing method prior to the return of such results. Affected adult individuals will also be given the option to have their symptom-driven diagnosis reported clinically. All adults who are not patients at Rady Children's Hospital will be provided copies of their clinical results and advised to follow-up with their primary care provider. Results will be returned by, or on the instruction of, a

licensed clinical geneticist or genetic counsellor. These results will be discussed with both clinicians and the affected individual or their legal guardian following confirmation.

Unaffected subjects enrolled in this study will only receive results if they do not opt-out for incidental results. In the event that results are returned to unaffected participants who are not patients at Rady Children's Hospital, the participants will be provided with their results directly and advised to follow-up with their primary care provider. DNA from unaffected individuals and family members enrolled will be used primarily for comparison to the proband. Return of results will include inheritance patterns and risk for reoccurrence with Genetic Counsellors and/or Board Certified Clinical Geneticists available for families enrolled in this study.

**Clinical Information Collection**

**Patient clinical information**
We will collect patient identifiers (name, date of birth, family contact information, names, dates of birth, medical record numbers), demographic information (race, ethnicity, zip code at birth), birth information (birth history, APGAR score, interventions at birth, newborn screening results, pregnancy complications), clinical and phenotypic information (clinical symptoms, clinical presentations, lab values, imaging results, clinician notes, family histories and pedigrees), genetic testing information (types of tests ordered, test order and result dates, results of testing), and billing information (diagnostic codes, billing data, DRG data). After consent, information will be collected for this study at the following time points: at birth, at enrollment, at (or following) return of results, at time of significant clinical events and post significant clinical events (if any), at hospital discharge, at death if it occurs, at one year, and annually throughout the duration of this study. Additional data may be collected for long-term follow-up through the Genomic Biorepository to assess changes in the patient's medical condition and to possibly re-analyze sequences for symptom-driven diagnoses. This is often necessary to track disease progression, changes to clinical presentation and to correlate symptoms with genomic findings in light of new knowledge of genetic diseases.

**Sequencing information**
All specific sequencing information will be kept in the Genome Biorepository per their protocol. We will collect quality metrics for each study run, run time length, total amount of data generated, and average coverage.

**Data Analysis:**

Aggregate demographic and clinical information will be characterized and analyzed. Measures of outcomes and clinical utility will be determined for both arms of the study. Outcome measures will include Quality Adjusted Life Years saved, Disability Adjusted Life Years, mortality and severe morbidity. Clinical utility measures will include changes in medications, surgeries, diets, and other interventions, including institution of palliative care. Measures of diagnostic utility will also be collected (rate of diagnosis, type of diagnosis, time to diagnosis, completeness of diagnosis). Family perceptions of benefit and/or harm will be measured and results will be correlated to diagnoses and clinical reports of testing utility. Singleton versus family analysis diagnostic rates will be analyzed. Cost-effectiveness modelling will be developed. Utilization of genetic counseling and/or clinical genetics will be measured. The time spent consenting families will be measured as a baseline for future research.

This study will monitor parental feedback annually. In the event that a family states that this testing caused harm, additional information will be sought. Whenever possible, trends will be identified and changes to the research protocol will be submitted for IRB approval if harm can be mitigated. The study team will contact the

IRB in the event that 25% or more of the families enrolled perceived the testing to be harmful.

## 10. HUMAN SUBJECTS

Up to 1000 acutely ill infants and their families will be randomized to receive rapid whole genome sequence versus rapid whole exome sequencing. We anticipate that we will enroll up to 2500 family members related to the 1000 acutely ill neonates and infants.

Multi-site enrollment:

- RCH will enroll ~1000 infants per year for an estimated total enrollment of ~250 to be enrolled and analyzed by the end of the NIH administrative supplement period ending September 2019.
- Additional funding will be provided by Rady Children's Institute for Genomic Medicine.

CMH will consult on Ethical, Legal and Social Implications of genomic testing in infants through their Pediatric Bioethics Center.

- Additional sites may be recruited to ensure enrollment goals are being met.

**Sample size determination**

Preliminary results indicate that rapid trio WGS will result in a change in clinical utility index (CUI) ~50% of cases (a key secondary outcome). We propose that WES must yield a CUI of 40% or lower to justify the cost differential between WGS and WES. Using $\alpha$=0.05, we can achieve a power of 80% with 325 patient per arm, well below our proposed 500 patients per arm. Preliminary results indicate that rapid trio WGS is associated with 2.9 QALYs saved per infant tested (a key primary outcome). No similar analysis has been performed for WES. Additional patients, therefore, increase our power to assess differences in outcomes, and also compensates for technical or other issues that may cause some sample to be unanalyzable. Notably, we have proposed multiple measures of outcomes and clinical utility in addition to QALYs and CUI, respectively, and our power calculations do not correct for multiple testing. We feel this is acceptable for two reasons: First, these outcome variables are not completely independent making a Bonferroni correction overly conservative. Second, as there is little preexisting data on this subject, we felt a less conservative approach often utilized in preliminary studies is appropriate.

**Affected Participant Inclusion Criteria**

Individual in whom one of the following criteria is met:

1. Acutely ill inpatient of less than 4 months of age and within 96 hours of admission
2. Acutely ill inpatient of less than 4 months of age and within 96 hours of development of an abnormal response to standard therapy for an underlying condition
3. Acutely ill inpatient of less than 4 months of age and within 96 hours of development of clinical feature or laboratory test value suggestive of a genetic condition
4. Biological relative of an infant enrolled in this study

**Affected Participant Exclusion Criteria**

Inpatients of greater than 4 months of age, or who do not meet any of the inclusion criteria, or with:

1. Neonatal infection or sepsis with normal response to therapy
2. Isolated prematurity
3. Isolated unconjugated hyperbilirubinemia
4. Hypoxic Ischemic Encephalopathy with clear precipitating event
5. Previously confirmed genetic diagnosis that explains their clinical condition (i.e. have a positive genetic test)
6. Isolated Transient Neonatal Tachypnea
7. Permission is unable to be obtained by a legal guardian or court-appointed representative within 96

hours of becoming eligible for enrollment.

8. Nonviable neonates- newborns less than 28 days of life with a modified code status (only full code patients may be enrolled).

**Family Members of Affected Participants Inclusion Criteria**

Family members are eligible for participation in this study if the following criterion is met:

1. Presumed genetically related to a patient participant eligible for the study under section Affected Participant.

For participants over the age 18, they must be able to provide consent or have a legal guardian able to provide consent. For participants under age 18 who have not achieved emancipation, a legal guardian must be available to provide permission, and children who are 7 to 17 years of age will also be required to assent for this research unless not required per IRB SOP regarding child assent.

**Family Members of Affected Participants Exclusion Criteria**

Family members are ineligible for participation in this study if:

1. They are known to not be genetically related to the patient participant
2. They are a member of a protected research population unless they are a neonate and meet criteria for enrollment as a patient participant under section Affected Participant.

**Clinicians**

As the clinicians caring for enrolled patients are being surveyed to return clinical feedback regarding their patients only, we request a waiver of consent as the clinicians themselves are not the subject of our research.

**Vulnerable Populations**

Enrollment will include the following vulnerable populations: neonates, those with cognitive disabilities, pediatric patients, minorities, and employees. Vulnerable populations, specifically pediatric patients, those with cognitive disabilities, newborns, and pediatric patients are being included so that they may benefit by receiving to a diagnosis and/or better understanding of their medical condition. Sample collection will be coordinated with clinical care whenever possible. All information will be stored de-identified. Only clinically-confirmed diagnoses will be reported to the medical record. As such, we believe this study to be of minimal risk to the participants.

Minorities will be sought to aid in the diversification of study population. Consents will be translated to accommodate the most common foreign language(s), and UCSD approved and translated short-forms will be used in lieu of full translations to allow for the inclusion of the most diverse population possible. If no short forms are available for the family's preferred language, consent will be obtained through a certified interpreter and documented on the English consent form. In the event a short form is used, UCSD informed consent policy will be followed regarding the documentation and consenting process. The full consent form will be translated and after approval from the IRB of record will be sent to the participant within 30 days. Interpreters may serve as a witness to the short form consent process per OHRP guidelines; their signature as an interpreter will serve as a witness signature.

Pregnant women and fetuses will only be included in this study in the rare circumstances that an associated family member is incidentally pregnant. Fetal testing is not a part of this study at this time.

Newborns will be included in this study as well for the purposes of enhancing early detection and diagnosis. It is believed that early diagnoses will prevent disease progression and co-morbidities from developing with early interventions. As such, permission will only be required from one parent, although both parents' permission

and participation will be sought.

Employees may be included in this study if they are genetically related to a patient referred to this study. Employees will not be specifically recruited to participate in this study. Inclusion of employees will be done only for the benefit of the affected patient. Study related information will not be released to the employer. Similarly, employment status will not be affected by participation or refusal to participate. Informed consent will not be obtained by a direct supervisor of the employee.

For participants less than 18 years of age and participants aged 18 or older who are not able to consent on their own behalf, informed consent must be obtained from legally authorized representatives. For those participants 7 to 17 years of age, the participant must assent if developmentally capable of doing so (cognitive age of 7 years). Those for whom consent was provided by a guardian when they were under the age of 18 will be asked to consent for continued participation in this study after they become 18 years old. Those who are unable to be located or re-consented into the study will be removed from the study, see section 12 for process of withdrawing a patient from the study.

Enrollment for all vulnerable populations will follow 45 CFR 46 as outlined in the code and section 12.

## 11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

**Identification of Study Participants**:

Investigators will query the RCH NICU, PICU and CVICU census list daily and identify potential candidates based on primary diagnosis and symptoms. Alerts may be created in Epic to either generate a list, or notifications will be sent of potential candidates based on whether genetic tests or genetic consults were ordered on the patient. Potential candidates may be discussed with the clinical team regarding eligibility. Alternatively, clinicians, including those from other hospital services, may nominate patients who they feel meet inclusion/exclusion criteria.

Those patients identified through the screening process will have the following data recorded in the prescreening log.

- Identifiable Information: Patient- name, date of birth, medical record number, location in the hospital, date of admission. Parents- names, dates of birth if available (or ages), and contact information.
- Clinical Information: clinical symptoms, positive genetic testing results, list of genetic tests pending, sex of patient, date eligible/identified for potential enrollment,
- Study tracking date: date of enrollment if enrolled, enrollment status. Documentation of interactions with the families will be captured- such as contact attempts, parental feedback, and anticipated future meetings with families.
- Other Information: We will also collect demographic information of if available in medical record (child's race and ethnicity and family's primary language spoken) and reasons for declining this research study, if voluntarily given.

The identifiable data collected from the pre-screening log will be used strictly for study management to avoid unnecessary contacting of families. This log is necessary to track referrals, avoid duplications, unnecessary contacting of families who have previously declined participation, and to ensure that all eligible referrals are approached for the study. All identifying information from the prescreening log will be destroyed at the conclusion of the study. These recruitment procedures are considered minimal risk to the potential subjects.

We request that enrollment rates, demographics, and reasons given for declining enrollment be allowed to be

retained and aggregated for analysis; all data will be de-identified. Published studies of genomic medicine report enrollment of only 3% minorities and as low as 6% of all families approached for genomic testing of newborns. We wish to collect such information to allow potential future amendments to this protocol should minority enrollment lag relative to the demographics of RCH NICU populations. This other data will be de-identified and aggregated for the purpose of researching reasons families' reasons for not enrolling in genomic research studies, racial or ethnic disparities, and disparities possibly related to the primary language spoken. It is anticipated that this data may be used for future presentations and/or publication and the creation or modifications of future genomic research studies.

This latter analysis of potential subjects who decline to participate in research cannot be conducted by other methods requiring consent as often these subjects have already indicated they do not wish to participate in research at this time. We believe this data will help guide future studies aimed at minimizing disparities and better understanding reasons families decline research in general, genomic research, research on newborns, and/or research in an intensive care setting. No identifying information will be used and only aggregate data will be reported. The rights and welfare of potential subjects should not be negatively affected by this analysis; furthermore, the welfare of collective subpopulations may be improved if enrollment disparities can be identified and future research undertaken. Therefore, we believe this additional information and analysis is a minimal risk to these potential subjects that could not otherwise be conducted. In the event that this additional research conducted with a waiver of consent is determined to be harmful or has risks unforeseen at this time, such pertinent information will be communicated to the families affected whenever possible by the research team either in-person if possible, via a telephone call, or by mail (any letters that will be sent to families will be submitted for IRB approval prior to mailing). The research team will make every effort to contact these potential subjects based on the most recent contact information recorded in the medical record at the time such pertinent information is identified.

A waiver of consent and a partial waiver of HIPAA authorization is requested for the prescreening process stated herein.

## 12. INFORMED CONSENT

**Institutional Review Board (IRB) Review and Informed Consent**

This protocol, and any subsequent modifications, will be reviewed and approved by the IRB at UCSD. Research activities and protocol changes for other locations will be reviewed and approved by their local IRB.

Potential subjects will be determined by study personnel by reviewing the daily neonatal intensive care census and identifying potential affected candidates. Medical Information Technology (MIT) will also provide a list of potential subjects. We request a partial waiver of HIPAA Authorization for this pre-screening review of charts. Once general eligibility is determined, the parents or guardians of potential subjects will be approached by study staff. Subjects will be approached at the hospital bedside of the affected subject or if parents not directly available via phone. Prior to drawing any blood or performing any other procedures related to this study, the permission/assent form or consent form will be reviewed carefully with the participant (and parent) in person or by telephone in extenuating circumstances (for example, lives over 50 miles away from hospital, and not able to be physically present, currently admitted following delivery of their child, with acknowledged parental rights). In the event that the child's mother is still admitted to another hospital due to the labor and delivery, all efforts will be made to include the mother in the consent conversation with the father.

Telephone consenting would be rare and only utilized in case the custodial parent cannot physically attend the visit due to the circumstances mentioned above. It is the intention of the study team to obtain consent from both parents in-person whenever possible to facilitate their enrollment and blood collection. It is anticipated that in

rare cases, we will need a mother to enroll and have blood or saliva collected prior to her discharge from the birthing hospital. In those extreme cases, we will attempt consent via phone and work with the other hospital to collect the sample and return the consent documentation.

Whenever possible, all efforts will be made to conduct the consent process in-person. Should a participant be unable to be consented in-person, telephone consents may be used when appropriate. Telephone consent policies will be followed in such circumstances. In the event that a telephone consent be necessary the following will happen:

1) The absent party will be contacted by phone. The research team will explain the research study in general and the process required for telephone consent. If the other party does not object, an email address or fax number will be obtained to send the consent form electronically. A mailing address may be obtained in lieu of the above. A time will be scheduled for a full informed consent when both parties will be able to have the consent physically in front of them to sign.
2) The consent will be sent to the absent party. The absent party will be advised that they are welcome to read this document, but they will be asked not to sign the document until the time of the scheduled consent.
3) At the time of the scheduled consent, the research staff will have a witness present to confirm the validity of the telephone consent. All study information will be discussed. All questions will be answered. Should the consent be in another language, an interpreter will be used whenever necessary. The signature of the interpreter may be used in lieu of a separate witness.
4) Following the explanation of the study, the absent party will be asked to sign and date the document. The research staff and witness will also sign and date their copy.
5) The participant will be asked to return the signed document to the research team, either electronically or by mail. The participant will not be considered enrolled until such time as the signed document is received.
6) Copies of both signed documents will be made and returned to the participant.
7) If necessary, the research team will attempt to arrange for a blood collection or send a saliva collection kit to the participant.
8) The consent will be documented per hospital and IRB policies.

All questions will be answered and signatures will be obtained by study staff form the parent before procedures begin on the child. The PI will ensure the procedures for securing telephone consent are followed.

Study personnel will obtain informed permission, assent, and consent from eligible participants. All study personnel will have completed CITI training. Referring clinicians may be asked to speak with families prior to their approach by the research team depending on the family and clinical circumstances. Researchers will contact the family either in-person or by telephone if the family is unavailable. Following the informed permission/assent/consent process, copies of the signed consents along with the HIPAA authorization will be given to the family member. Participants will also be given contact information for study personnel. In the event of telephone consent, copies will be mailed or sent electronically (fax or email) per the choice of the participant. The signed consent will be scanned into the medical records along with a consent note. Original copies will be maintained in a locked file cabinet or secure storage facility.

All efforts will be made to conduct the consent process at times where emotional distress is minimal. The consent process will be done in privacy to the greatest extent possible. Families will be given as much time to consider the study and read the consent documents as they deem necessary. Emphasis will be made that their decision not to participate will in no way affect their child's or their own medical care. The consent process will not include any

use of exculpatory language regarding rights or liability. Employees will be notified that participation or refusal to participate will in no way affect their employment status.

Samples and clinical data collection will not be done prior to consent into the study.

**Waiver of Consent for Clinician Participation:**

As a part of this research study, clinicians will be administered a brief questionnaire regarding changes in care as a result of this research study's result. Multiple clinicians may be surveyed for any one subject depending on what clinicians and subspecialties were involved in clinical care at the time results were returned. No identifying information will be collected about the clinicians. General information such as years of experience and credential information will be collected. The remaining data collected will be regarding the child's clinical care and perceived utility of testing.

The analysis of clinician surveys will include correlating credentials and/or years of experience with perceived clinical utility. The rights and welfare of clinicians should not be negatively affected by this analysis. No identifying information will be used and only aggregate data will be reported. As each patient may have any number of providers caring for the child at the time results are returned, it is not feasible to obtain informed consent from each clinician prior to administering the surveys. Similarly, only publicly available data such as years of experience and credentials are being collected about the clinician themselves. Therefore, we believe this to be a minimal risk to clinicians that could not otherwise be conducted. A waiver of consent is requested for the surveying of clinicians as a part of this study.

In the event that this research conducted with a waiver of consent is determined to be harmful or has risks unforeseen at this time, such pertinent information will be communicated to the clinicians whenever possible by the research team either in-person if possible, via a telephone call, by mail, or most likely by email (any letters that will be sent to families will be submitted for IRB approval prior to mailing. Any emails sent will not show identifying information of other participants.). The research team will make every effort to contact clinicians based on the employee directory and department records at the time such pertinent information is identified.

**Vulnerable Populations:**

This research is believed to hold the prospect of enhancing the chance of survival of affected individuals with minimal risk to participants.

In accordance with 45 CFR 46 subpart D, pediatric patients will require one parent or legal guardian to provide permission for the child to participate. Participants over the age of seven or who show cognitive capabilities to assent for this research study will be required to assent for participation. Those participants enrolled under the age of 18 will be asked to re-consent after turning 18 years old in order to remain in the study. Those who are not re-consented after turning 18 years old will be removed from the study, no additional data will be collected, and all identifying information will be removed.

Pregnant women may be included as a part of this study. As fetal testing is not the purpose of this research, the fetus would not be a subject of this research. Therefore, we will not seek permission from the father. This study will have no role in determining viability or decisions regarding pregnancy termination.

In accordance with 45 CFR 46 subpart B, as this study is a minimal risk study and may improve morbidity and mortality of neonates less than 29 days, permission to enroll will be sought from both parents but only required

from one parent.

Employees will be notified that participation or refusal to participate will in no way affect their employment status.

Fully translated consents will be made available in Spanish. A qualified interpreter will be used for all non-English speaking families. When an interpreter is not available for an in-person consent, a professional phone interpreter service may be used. Family members will not serve as interpreters due to the nature of genetic testing.

Consents will be translated to accommodate the most common foreign language(s), and UCSD approved and translated short-forms will be used in lieu of full translations to allow for the inclusion of the most diverse population possible. If no short forms are available for the family's preferred language, consent will be obtained through a certified interpreter and documented on the English consent form. In the event a short form is used, UCSD informed consent policy will be followed regarding the documentation and consenting process. The full consent form will be translated and after approval from the IRB of record will be sent to the participant within 30 days. Interpreters may serve as a witness to the short form consent process per OHRP guidelines; their signature as an interpreter will serve as a witness signature.

If the participant is unable to consent for themselves due to either age or cognitive disability, a parent or legally authorized representative may sign permission. Assent will be sought when appropriate. See section 30 for additional details.

**Post-consent Process:**

Following the informed permission/assent/consent process, copies of the signed consents along with the HIPAA authorization will be given to the family member. The study personnel will:

- Review the Permission/assent/consent form and ensure that is properly completed
- Provide the participant or legal representative with a copy of the signed form
- File original signed form securely in the research file
- Scan a copy of the form into the patient medical record
- Record that consent was obtained in the medical record
- Schedule or perform blood collection from the participant, if a sample is not available in the clinical laboratory
- Add the participant to the Master List in the secure Institute's folder on the internal shared drive and/or secure REDCap database.

If the patient or legal representative refuses to participate in the study:

- Communicate refusal to relevant study or clinical personnel.

Original copies will be maintained in a locked file cabinet or secure storage facility.

**Optional Questions:**

The consent document will ask about the use of photographs. Subjects who agree to the use of photographs who have clinical features that would aid the scientific community by publishing a photograph of such features will have their picture taken. In the event that the subject agrees to the use of photographs, this would be the only

identifying information released for publication. The research team may also request the use of these photographs for new technologies to ascertain physical features through the use of programmatic algorithms. The photographs themselves would not be shared outside of the research team. The RCHSD policy regarding the use of photographs will be followed.

**Withdrawal of consent:**

Participation in this study is completely voluntary. As part of the parental permission/assent/consent process, participants are informed that they can withdraw consent at any time, for any reason. If at any time, a patient decides to withdraw consent, personnel at the bio bank will take appropriate steps to respect the will of the participant and ensure that the participant is able to withdraw without reprisal.

**Follow-up action after receiving a request to withdrawal:**

Upon receipt of request to withdrawal, the study staff will notify the Rady Children's Clinical Genome Center of the subject's withdrawal. In accordance with this protocol and the Genomics Institute Biorepository study protocol (IRB #160468), the following actions will be taken by both studies:

1. Ensure that unused blood from the participant is destroyed. Permanently break any link between personal identifying information and purified DNA and/or RNA from the participant. Isolated DNA and RNA that has not been sequenced will be destroyed in the event of withdrawal of a study subject.

2. Permanently break any link between personal identifying information and the anonymized records in the bioinformatic database by replacing PHI in the Master List with a note that the subject has withdrawn.

3. Not collect any additional clinical information about the individual from any source.

4. Only anonymized data may be used for future research after consent has been revoked.

5. Should a back-up of the inventory database/informatics system ever be restored, then the director should ensure that identifying records stored on the discarded samples log (that are relevant to the samples) are again deleted from the records.

6. Shred any hard copies of associated identifying information not required to be maintained for regulatory purposes.

7. Retain the executed consent form and request to withdrawal in a separate, secured file of discontinued subjects and redact any identifiers that link the subject to the data (such as subject number).

8. The Repository Director will certify that identifying links have been broken, that unused and unprocessed biological material has been destroyed.

**Proprietary Interest Disclosure/ Moore Clause:**

Consent into this study requires participants to agree to giving blood or tissue specimens, these specimens will become the property of the Genomic Institute. Dr. Kingsmore or designee will be responsible for deciding how samples and collected data will be used. Dr. Kingsmore and his associates or his successors in these studies will keep specimen, DNA, clinical data and/or the information derived from the specimens indefinitely. If as a result

of participation in this study, the study team obtains information that could significantly affect a participant's health and well-being, we will attempt to inform the participant of the existence of this information. The information obtained from this testing will be kept completely confidential to the extent permitted by law.

The specimens, the DNA they contain, and the clinical data collected may be used in this research and in other research, and may be shared with other organizations. In addition, de-identified data will also be shared with public databases sponsored by the National Institutes of Health and other agencies, and possibly with future scientists that are not known at this time. The specimens could lead to discoveries or inventions that may be of value to RCIGM or to other organizations. These discoveries or inventions may have significant commercial value. Under state law, participants do not have any right to money or other compensation stemming from products that may be developed from the specimens.

## 13. ALTERNATIVES TO STUDY PARTICIPATION

The alternative to this study is to not participate in this study.

## 14. POTENTIAL RISKS

Risks associated with blood draws include pain, anxiety, bleeding, bruising, or possibility of fainting or infection.

Slight risk of loss of confidentiality.

Risk of discrimination associated with genetic testing.

Genetic testing may cause anxiety or emotional distress due to feelings of responsibility for carrying genetic components passed on to children.

Risk of secondary or incidental findings being determined.

## 15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Whenever possible, samples for this study will be obtained from clinical samples to minimize risk and invasive procedures. All sample collection will be obtained by qualified staff following the hospital guidelines and standard precautions.

All study related material will be stored securely. All identifying information will be kept in a separate database with access limited to study personnel. All data will be maintained in password protected, secure databases and or internal servers with access limited to study personnel and approved investigators.

Information regarding the protections and limitations of the Genetic Information Nondiscrimination Act (GINA) will be included in the consent.

Genetic counselors will be a part of the study team and will be available to all participants at all times while enrolled in the study to answer questions or concerns related to testing or results.

This study does not intend to report matters of paternity, carrier statuses or other secondary findings.

As the inclusion of pregnant women is for the purpose of improving clinical outcomes for the living affected infant, study participation is considered minimal risk. Blood draws and sample collection from the mother may be done independently for research or with routine clinical care.

Study auditing and monitoring will be conducted internally. The PI will periodically review the collection, storage, and distribution practices associated with this data bank and determine whether changes to enhance

confidentiality and privacy are required. Annual progress reports will be conducted and available to the IRB. All protocol deviations will be reported to the PI and the IRB as soon as identified. In the unlikely event of a serious adverse event or breach in confidentiality, the event will be reported to the IRB within 48 hours of it becoming known to the PI.

External auditing and monitoring by members of the NIH and/or FDA will be conducted per agency request. DSMB will monitor study through NIH consortium.

Any employees of the hospital who are eligible to participate will be consented by a study team member who is not their direct supervisor and, whenever possible, not a coworker or acquaintance of the staff member. Employees will be notified that participation or refusal to participate will in no way affect their employment status.

All clinical testing and therapy appropriate to the study participant's care will be continued without disruption during the study. The clinicians are initially blinded to the randomization and will continue all clinical testing regardless of whether rapid genomic sequencing is performed.

## 16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

**Subject Confidentiality-**

Research personnel will identify patients meeting inclusion criteria via daily census review as well as through recommendations of clinicians and a list from MIT. Upon enrollment, each medical record will be reviewed by research staff and data entered into the research record. All genomic sequencing and biospecimens will be performed and maintained under the Genomic Institute Biorepository protocol (IRB #160468).

All research records and genomic sequencing data will be electronically stored in a password protected database accessible only to research personnel. HIPAA identifiers of all study subjects will be kept in a password protected database and will be linked only with a study identification number for this research. All computer entry and networking programs will be done using study identification numbers only. All data will be entered into a computer that is password protected. All sequencing data and biospecimens will be stored securely under the Genomic Institute Biorepository protocol (Study #160468). Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the OHRP, the Sponsor, or the Sponsor's designee. Data will be stored in a locked office of the investigators and maintained for a minimum of three years after the completion of the study.

**Records to be kept**

Information will be collected on a data collection sheet for each patient participant (Appendix) and stored in a password protected relational database. A master linking list will be maintained that links the subject's medical record number with their study number (Appendix). De-identified genomic sequencing data will be stored in a password protected relational database.

**Secure Storage of Data**

The research record generated will consist of an excel sheet and/or secured REDCap database. Only the data points listed will be entered into the data collection sheet (Appendix ). Security measures include: storage of the password protected excel sheet on a password protected computer in a restricted access departmental folder limited to only listed study personnel and/or in a secured, password protected REDCap database with access limited to research study members.

All study related material will be stored securely. Access to research records, pre-screening logs, and the master

list will be limited to study personnel and maintained securely with password protection on a secure internal server.

Surveys may be sent via email by REDCap to clinicians and family members. Study information, personal identifiers, such as name, MRN, and contact information will be stored in REDCap. The survey functionality of REDCap does not allow survey participants access to any other REDCap data or forms.

Participant and clinician survey data will be collected by researchers at RCIGM/RCHSD. The data will be stored in a secure, HIPAA compliant, password protected database such as REDCap, within the RCIGM server. The IT department from RCIGM will send de-identified data to UCSD to be stored and analyzed on the UCSD secured server.
All samples and data will be stored de-identified in the Genomic Institute Biorepository (IRB #160468).

All transfer of study related information between sites will be done securely without identifying information whenever possible.

## 17. POTENTIAL BENEFITS

Study may or may not have any benefit to participants. Affected participants may receive a diagnosis or additional information regarding their medical condition. This information may improve their clinical care and outcomes. There will be no direct benefit to participation for unaffected family members except where a diagnosis provides information regarding reproductive decisions and future recurrences.

## 18. RISK/BENEFIT RATIO

This study does not intend to report secondary findings, non-actionable findings on healthy subjects, nor will it affect decisions of pregnancy termination. The direct benefits to the affected participants may improve clinical care, morbidity, and mortality. As such, we believe the potential benefits far outweigh the slight risks.

## 19. EXPENSE TO PARTICIPANT

No expense to participate.

## 20. COMPENSATION FOR PARTICIPATION

No compensation for participation.

## 21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

All study personnel, unless otherwise indicated, will have completed CITI training.

Research Team:

| | |
|---|---|
| Stephen Kingsmore, MD, DSc | Principal Investigator. Research scientist and CEO and President of Rady Children's Institute for Genomic Medicine. Dr. Kingsmore has research privileges at RCHSD. |
| David Dimmock, MD | Co-Investigator. Medical Director, Pediatrician, Medical Geneticist, Biochemical Geneticist, licensed to practice medicine within the state of California. |
| Lauge Farnaes, MD | Co-Investigator. Asst. Medical Director, licensed to practice medicine within the state of California and has privileges at RCHSD |
| James Perry, MD | Scientific Investigator. Cardiologist licensed to practice medicine within the state of California. |

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| Joe Gleeson, MD | Scientific Investigator. Neurologist licensed to practice medicine within the state of California. |
| Jennifer Freidman, MD | Scientific Investigator. Neurologist licensed to practice medicine within the state of California. |
| Julie Ryu, MD | Scientific Investigator. Pulmonologist licensed to practice medicine within the state of California. |
| George Chiang, MD | Scientific Investigator. Urologist licensed to practice medicine within the state of California. |
| Jeanne Carroll, MD | Scientific Investigator. Neonatologist licensed to practice medicine within the state of California. |
| Kristen Wigby, MD | Sub-Investigator. Genetics Fellow licensed to practice medicine within the state of California and has privileges at RCHSD. CITI Biomedical Training, HIPAA. |
| Erica Sanford Kobayashi, MD | Sub-Investigator. PICU Fellow licensed to practice medicine within the state of California and has privileges at RCHSD |
| Amelia Lindgren, MD | Sub-Investigator. Orthopedic Fellow licensed to practice medicine within the state of California and has privileges at RCHSD |
| Chelsea Gatcliffe, MD | Sub- Investigator. Pulmonology Fellow licensed to practice medicine within the state of California. |
| Benjamin Briggs, MD | Sub-Investigator. Oncology &Hematology Fellow licensed to practice medicine within the state of California. |
| Nathaly Sweeney, MD | Sub-Investigator. Neonatologist Fellow licensed to practice medicine within the state of California and has privileges at RCHSD |
| Serena Galosi, MD | Sub-Investigator. Intern. Neurologist licensed to practice medicine within the state of California |
| Shareef Nahas, PhD FACMG | Co-Investigator. Lab Director and Molecular Geneticist licensed (or pending) to practice within the state of California. |
| Shimul Chowdhury, PhD, DABMGG | Co-Investigator. Lab Director and Molecular Geneticist licensed (or pending) to practice within the state of California. |
| Kasia Ellsworth, PhD | Co-Investigator. Associate lab director and molecular geneticist with license (or pending) to practice within the state of California. |
| Mari Tokita, MD | Co-Investigator. Associate lab director and molecular geneticist with license (or pending) to practice within the state of California. |
| Yan Ding, MD, MS, MB, ASCP | Director of Sequencing Operations not practicing medicine at this time. MB, ASCP national licensure is active. |
| Luca Van Der Kraan | Clinical Lab Staff licensed to practice in California |
| Laura Puckett | Clinical Lab Staff licensed to practice in California |
| Cathy Yamada | Clinical Lab Staff licensed to practice in California |
| Zaira Bezares Orin | Clinical Lab Staff licensed to practice in California |
| Jennie Le | Clinical Lab Staff licensed to practice in California |
| Meredith Wright, PhD | Research staff. Clinical genomics analyst. |
| Terence Wong, Ph.D. | Research staff. Clinical genomics analyst. |
| Kiely James, Ph.D. | Research staff. Clinical genomics analyst. |
| Sylvia Breeding | Quality Assurance |

| | |
|---|---|
| Lisa Salz, MS, LCGC | Genetic counselor. Board certified, licensed to practice within the state of California. |
| Kelly Watkins, MS, LCGC | Genetic counselor. Board certified, licensed to practice within the state of California. |
| Jerica Lenberg, MS, LGCG | Genetic counselor. Board certified, licensed to practice within the state of California. |
| Cheyenne Camp, BS | Genetics Intern |
| Michelle Clark, PhD | Scientific Investigator. |
| Matthew Bainbridge, PhD | Co-Investigator. Research PI at RCIGM |
| Narayanan Veeraraghavan, PhD | IT & Bioinformatics Director |
| Sergey Batalov | Bioinformatics Staff |
| Ray Hovey | Bioinformatics Staff |
| Dorjee Tamang | Bioinformatics Staff |
| Katherine Nguyen, MPH | Research Staff |
| Caryn Rubanovich, MS | Sub-Investigator |
| Cinnamon Bloss, PhD | Sub-Investigator. Psychologist and Statistical Geneticist. |
| Julie Cakici, BA, BSN, RN | Co-Investigator/Data Analyst with Cinnamon Bloss; |
| Sara Caylor, BS, BSN, RN | Research Coordinator. Licensed nurse in the state of California. |
| Christina Clark, BSN, RN | Research Coordinator. Licensed nurse in the state of California. |
| Mary Gaughran, BSN, RN | Research Coordinator. Licensed nurse in the state of California. |
| Iris Reyes, MPH | Program Specialist. |
| Michele Feddock, BS, CCRP | Program Specialist. |
| Maria Ortiz-Arechiga | Lab Accessioner |
| Nanda Ramchander, MD | Co-Investigator |
| Kee Chan, PhD | Consultant |
| | |
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Co-Investigators and Sub-Investigators may consent, collect samples, collect data, analyze data, manage regulatory matters, and follow up with participants. Staff includes David Dimmock, Luage Farnaes, Amelia Lindgren, Erica Sanford, Nathaly Sweeney, Kristen Wigby, Chelsea Gatcliffe, Benjamin Briggs, Serena Galosi, Caryn Rubanovich, Cinnamon Bloss, Julie Cakici, Nanda Ramchander, and Mathew Bainbridge. Staff not actively licensed in the state of California will not collect samples until they have obtained their licensure.

Scientific investigators may collect data, analyze data, and follow up with participants. Staff includes Jeanne Carroll, George Chiang, Jennifer Friedman, Joseph Gleeson, Julie Ryu, James Perry, and Michelle Clark.

Research staff and Genetic Counselors may collect data, analyze data, and follow up with participants. Staff includes Kasia Ellsworth, Mari Tokita, Kiely James, Terence Wong, Meredith Wright, Katherine Nguyen, Lisa Salz, Kelly Watkins, Jerica Lenberg and Cheyenne Camp.

Molecular Geneticists will review and report clinical results into the medical record. Staff may also collect, analyze data, manage regulatory matters and follow up with clinicians and participants. Staff includes Shareef Nahas and Shimul Chowdhury.

Laboratory staff will have access to the master list and EMR to verify participation and consent prior to Biorepository Study activities. Staff includes Yan Ding, Sylvia Breeding, Zaira Bezarek Orin, Laura Puckett, Luca Van Der Kraan, Jennie Le, Catherine Yamada, and Maria Ortiz-Arechiga .

Clinical Research Coordinators and Project Managers/Specialists may consent, collect samples, collect data, analyze data, manage regulatory matters, and follow up with participants. Staff includes Sara Caylor, Christina Clark, Mary Gaughran, Michele Feddock, and Iris Reyes.

Bioinformatics staff will have access to genomic and sample data as well as the entire research record. Staff may collect and analyze data. Staff includes: the Genomic Institute's Bioinformatics Director, Narayanan Veeraraghavan, PhD, Serge Batalov, Raymond Hovey, and Dorjee Tamang.

**Outside investigators:**

Outside collaborators able to request de-identified data for secondary analysis.

Kee Chan, PhD, will be consulting on the Health Economics Analysis.

## 22. BIBLIOGRAPHY


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## 23. FUNDING SUPPORT FOR THIS STUDY


A 5-year NIH U19 grant entitled Genomic Sequencing and Newborn Screening Disorders

**NIH Full Grant Number:** 5 U19 HD 77693-3
**Project Title:** **N**ewborn **S**equencing **I**n **G**enomic medicine and public **H**eal**T**h (NSIGHT).


## 24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable, biological samples to be transferred within Rady Children's Hospital San Diego. BMTA for sequencing related material transfers regulated through Genomic Institute's Biorepository (IRB Study #160468)

## 25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

**Study Modification/Discontinuation**

This study has been reviewed by the FDA and granted non-significant risk (NSR) status. Thus, this study does not require an investigational device exemption from the FDA. However, the study may be modified or discontinued at any time by the IRB, the Sponsor, the OHRP, or other Government agencies as part of their duties to ensure that research subjects are protected.

## 26. IMPACT ON STAFF

Nursing and clinical lab staff may be involved in sample collection and transfer.

| 27. CONFLICT OF INTEREST |
| --- |
| N/A |
| **28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES** |
| N/A |
| **29. OTHER APPROVALS/REGULATED MATERIALS** |
| RCIGM Genomic Biorepository Protocol, IRB# 160468 |
| **30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT** |
| Due to the nature of this study, any individual, adult or child, suffering from cognitive or developmental disability will be secondary to a suspected underlying genetic disorder. As such, these individuals will have been suffering chronically from this disability for which a parent or legal guardian is anticipated to be available to provide informed consent. If an individual having chronic compromised cognitive function such that they function at delayed levels yet are capable of providing assent, such assent will be sought. The assessment will follow the requirements of the UCSD HRPP Decision Making Capacity Guidelines. We do not anticipate acute changes in cognitive function, such as would require an acute transfer of decisional capacity. |