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Implementation of rapid genomic sequencing in safety-net neonatal intensive care units: protocol for the VIrtual GenOme CenteR (VIGOR) proof-of-concept study

Alissa M D'Gama,[1,2] Sonia Hills ,[3] Jessica Douglas,[3] Vanessa Young,[1] Casie A Genetti,[3,4] Monica H Wojcik,[5,6] Henry A Feldman,[1] Timothy W Yu,[2,3] Margaret G Parker,[7] Pankaj B Agrawal,[8,9] VIGOR Network

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MGP and PBA contributed equally.
AMD and SH contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Dr Pankaj B Agrawal;
pagrawal@miami.edu

ABSTRACT

Introduction Rapid genomic sequencing (rGS) in critically ill infants with suspected genetic disorders has high diagnostic and clinical utility. However, rGS has primarily been available at large referral centres with the resources and expertise to offer state-of-the-art genomic care. Critically ill infants from racial and ethnic minority and/or low-income populations disproportionately receive care in safety-net and/or community settings lacking access to state-of-the-art genomic care, contributing to unacceptable health equity gaps. VIrtual GenOme CenteR is a 'proof-of-concept' implementation science study of an innovative delivery model for genomic care in safety-net neonatal intensive care units (NICUs).

Methods and analysis We developed a virtual genome centre at a referral centre to remotely support safety-net NICU sites predominantly serving racial and ethnic minority and/or low-income populations and have limited to no access to rGS. Neonatal providers at each site receive basic education about genomic medicine from the study team and identify eligible infants. The study team enrols eligible infants (goal n of 250) and their parents and follows families for 12 months. Enrolled infants receive rGS, the study team creates clinical interpretive reports to guide neonatal providers on interpreting results, and neonatal providers return results to families. Data is collected via (1) medical record abstraction, (2) surveys, interviews and focus groups with neonatal providers and (3) surveys and interviews with families. We aim to examine comprehensive implementation outcomes based on the Proctor Implementation Framework using a mixed methods approach.

Ethics and dissemination This study is approved by the institutional review board of Boston Children's Hospital (IRB-P00040496) and participating sites. Participating families are required to provide electronic written informed consent and neonatal provider consent is implied through the completion of surveys. The results will be disseminated via peer-reviewed publications and data will be made accessible per National Institutes of Health (NIH) policies.

Trial registration number NCT05205356/clinicaltrials.gov.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A key strength of our study is the application of implementation science methods to neonatal genomic medicine.
⇒ The findings from this proof-of-concept study will inform equitable delivery of genomic medicine in neonatal intensive care units (NICUs) that serve predominately racial/ethnic minority and low-income populations without access to state-of-the-art genomic care.
⇒ Potential limitations of our study include a limited number of NICUs that are part of the VIrtual GenOme CenteR project, which may limit generalisability of the study findings.

INTRODUCTION

Genomic medicine, as defined by the National Human Genome Research Institute, is 'a medical discipline that involves using a person's genomic information as part of their clinical care'.[1] Over the past decade, there have been significant advances in genomic medicine in the diagnostic and therapeutic realms. Rapid genomic sequencing (rGS) technologies, namely exome and genome sequencing, have enabled earlier diagnoses for patients with suspected underlying genetic conditions.[2] Early identification of genetic diagnoses is important for guiding precision care and has enabled development of groundbreaking precision therapies.[3 4]

Genomic medicine arguably has the greatest potential impact in neonates, particularly those admitted to neonatal intensive care units (NICUs) soon after birth.[2] This population has high rates of underlying genetic conditions with significant associated morbidity and mortality.[5–8] Studies from our

group and others have demonstrated that rGS among critically ill infants has high diagnostic yield (diagnostic utility), impacts clinical care (clinical utility), has patient-reported benefits (personal utility) and reduces healthcare costs.[2 9–24]

Currently in the USA, rGS is primarily available at large referral centres that have the expertise and resources needed to implement genomic medicine in neonatal intensive care.[25–27] Critically ill infants from racial and ethnic minority and/or low-income populations disproportionately receive care in safety-net and/or community centres and do not have access to the same advances in genomic medicine as critically ill infants from non-Hispanic white and/or higher income populations. Neonatal providers in these settings may have limited or no access to clinical geneticists or genetic counsellors (GCs), limited knowledge of and comfort with genomic medicine, and/or limited or no access to rGS tests.[28–30] This contributes to an unacceptable health equity gap and suboptimal care compared with infants who receive care in large referral centres. In some circumstances, infants are transferred to large referral centres for full genetic workup, often hours away from their birth hospitals, imposing significant financial and psychosocial burdens on their families.[31] Further, this scenario does not leverage existing trusting relationships between families and neonatal providers, or other community supports within their local environment, which is particularly notable in the setting of mistrust of the medical system among families of colour.[32]

To address these important service gaps in providing high quality, equitable genomic care to critically ill neonates, we launched the VIrtual GenOme CenteR in Infant Health (VIGOR) study in September 2021 funded by the National Institutes of Health. We developed and implemented an innovative virtual genome centre at a regional referral centre to remotely support safety-net NICUs predominantly serving racial and ethnic minority and/or low-income populations who currently do not have access to state-of-the-art genomic care.

Our study approach is grounded in implementation science methods. The widespread inability and/or delay of medical systems to implement evidenced-based interventions, also known as the 'research–practice gap' is well recognised.[33] We therefore designed our study to address known implementation gaps in the provision of genomic medicine to NICUs primarily serving racial/ethnic minority and/or low-income families and to examine relevant implementation outcomes—from the perspective of providers, the health system and families—that will inform future large-scale dissemination of our genomic care model. The aims of our proof-of-concept implementation study are to (1) develop the VIGOR network, including educating neonatal providers about genomic medicine and enrolling 250 eligible infants and their parents, (2) facilitate rGS and return of results via delivery of timely clinical interpretive reports (CIRs) and (3) examine comprehensive implementation outcomes. Here, we present our detailed protocol.

METHODS AND ANALYSIS

Study setting and overview

The VIGOR study is run out of Boston Children's Hospital (BCH), and the study team includes a diverse group of investigators with expertise in neonatology, genetics and genomics, genetic counselling, bioinformatics, health services research, implementation science and social disparities. Currently, there are five participating NICU sites (Baystate Medical Center, Boston Medical Center, The Children's Regional Hospital at Cooper, UMass Chan Medical Center and The Women's Hospital at Renaissance) and three additional sites are in the process of joining. Together, these sites comprise the VIGOR network (figure 1). To reach enrolment goals (n=250) and improve the diversity of our study sites, the VIGOR network is actively recruiting additional sites across the USA.

Neonatal providers at each site receive basic education about genomic medicine and identify eligible infants; the BCH-based VIGOR team enrols those eligible infants and their parents (Aim 1). Enrolled infants receive clinically accredited rGS, the VIGOR team creates CIRs based on the genomic sequencing results and local providers return the results to families. Additionally, the VIGOR team performs reanalysis of the sequencing data for infants with initially non-diagnostic results (Aim 2). Families are followed for 12 months after NICU discharge. Data is collected from infant medical records, families and providers and used to examine comprehensive implementation outcomes (Aim 3).

The VIGOR study is registered on clinicaltrials.gov (as of 25 January 2022) and is actively recruiting as of October 2022. The projected end date of recruitment is November 2025.

Aim 1 procedures

NICU site eligibility criteria

Safety-net NICUs are invited to participate in this study. Generally, safety-net centres predominately serve socially disadvantaged families.[34] For this study, we defined safety-net centres as those serving >40% non-Hispanic black or Hispanic patients and thus also likely serving a high percentage of low-income families. These demographic groups have historically not been reached in genetic studies. Participating NICU sites are also required to meet the following criteria: (1) level 3 NICUs, as these NICUs often serve as the first site of evaluation for newborns with suspected genetic conditions, (2) NICUs with a minimum of 20 beds and 250 admissions per year, to enable goal enrolment and (3) NICUs not routinely able to offer rGS. A diverse group of sites meeting these criteria have been selected so far varying in unit size, area served (rural vs urban) and proportions of non-Hispanic black and Hispanic patients served.

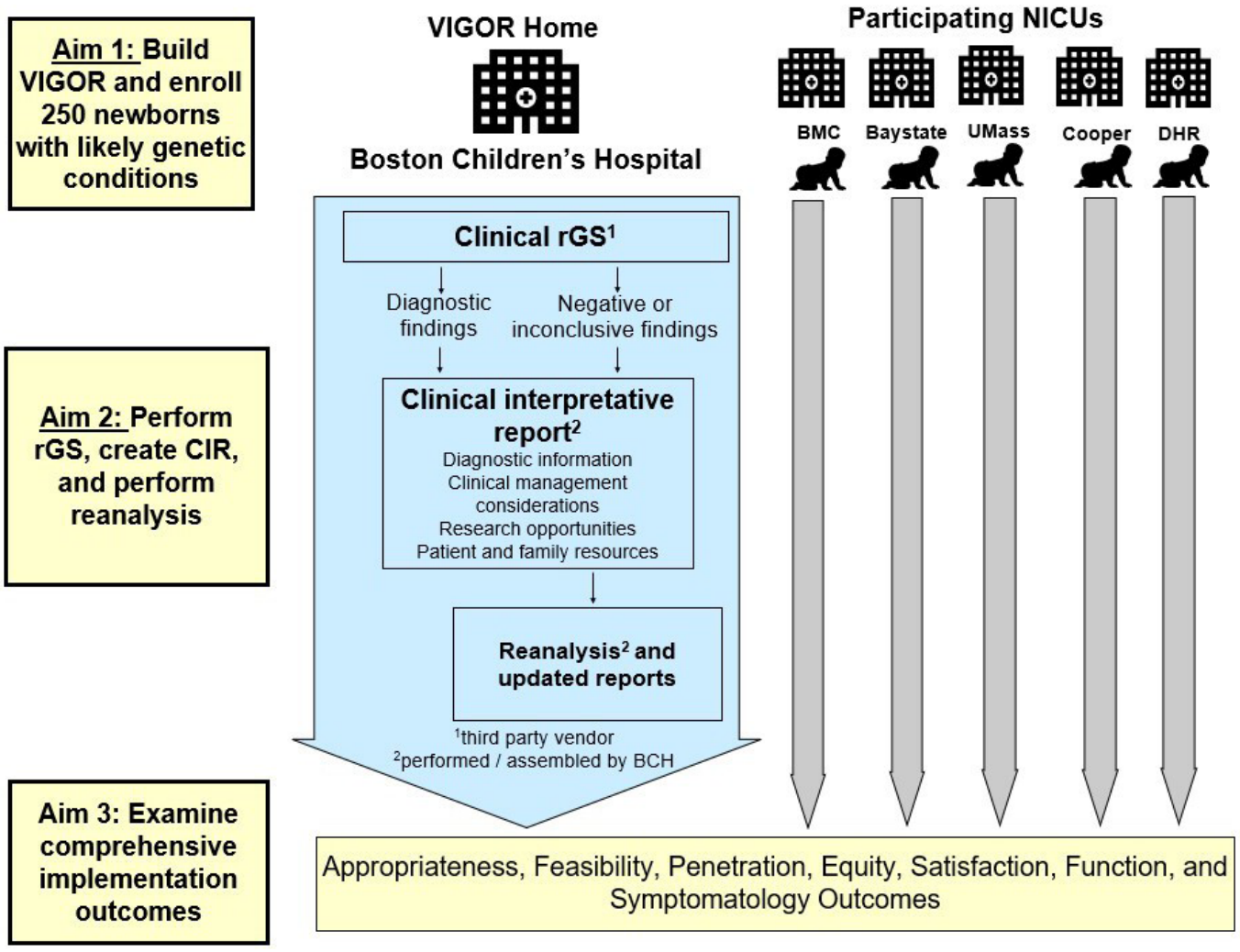

Figure 1 VIGOR study overview. The VIGOR study is run out of BCH and recruits subjects from five participating NICU sites. Enrolled infants receive clinically accredited rGS, the VIGOR team creates clinical interpretive reports, and local providers return results to families. Comprehensive implementation outcomes are examined using data collected from families, providers, and infant medical records. BCH, Boston Children's Hospital; BMC, Boston Medical Center; CIR, clinical interpretive report; DHR, Doctor's Hospital at Renaissance; NICUs, neonatal intensive care units; rGS, rapid genomic sequencing; VIGOR, VIrtual GenOme CenteR.

Subject eligibility criteria

In this study, neonatal providers, infants and their families (parents and/or other caregivers) are study subjects. We provide details on eligibility, recruitment, consenting and retention below.

Neonatal providers: All neonatal providers at participating sites who are involved in the care of critically ill infants with probable genetic conditions are invited to participate in the study. This includes all neonatologists, and, at the discretion of the site principal investigator (PI), neonatal nurse practitioners and physician assistants.

Families: Infant inclusion and exclusion criteria are designed to be primarily phenotype driven (box 1) and are based on our previous phenotype-based study of rapid exome sequencing (ES) in the BCH NICU.[17]

Biological parents of the infant are eligible to participate in the rGS portion of the study. Primary caregivers are eligible to participate in follow-up surveys regardless of biological relationship to the infant, to accommodate diverse family structures (eg, same sex caregivers, use of donor egg or sperm, etc)

For this pilot study, we are limited to approaching English-speaking and Spanish-speaking families only. Additionally, due to the complexities of enrolling infants in state custody and the varying state laws which would have to be considered due to the locations of participating sites, we are not enrolling infants in state custody or who are intended to be placed in state custody.

Notably, the study team encourages local providers to pursue any typical clinical care procedures that exist at their site for work up of infants with suspected genetic conditions, such as consultation with clinical genetics and/or other available genetic testing (ie, the VIGOR study is not meant to change existing clinical care).

Box 1 Infant inclusion and exclusion criteria

Inclusion criteria:

⇒ Infant is admitted to the neonatal intensive care unit (NICU) at a participating site

⇒ Infant is suspected to have a genetic condition, including, but not limited to:
- Unexplained seizures
- Unexplained hypotonia
- Multiple congenital malformations
- Metabolic disorders
- Disorders of sex development
- Interstitial lung disease
- Immunodeficiency

⇒ At least one biological parent is available for consent and participation

⇒ Caregiver(s) intend to care for the infant in the USA for 12 months following NICU discharge

Exclusion criteria:

⇒ Infant has a prenatally known genetic diagnosis

⇒ Infant has clinical features pathognomonic for a recognisable chromosomal abnormality (eg, Trisomy 21)

⇒ Infant has an association of symptoms known to have a low genetic diagnostic yield (eg, vertebral defects, anal atresia, cardiac defects, trachea-oesophageal fistula, renal anomalies and limb abnormalities association)

⇒ Infant's presentation is likely due to an environmental or other non-genetic cause (eg, fetal alcohol syndrome)

⇒ Infant has a known family history of genetic disease that is plausibly the cause of the infant's phenotype

⇒ Infant is deceased, transferred or discharged from the NICU prior to enrolment

⇒ One or more parents object to the infant's enrolment

Subject recruitment

Neonatal providers: Providers at each site are recruited through introduction by the site PI. Prior to approaching families regarding the study, neonatal providers are required to watch an orientation video explaining infant eligibility criteria and general study procedures and complete an attestation statement that orientation has been completed.

Families: Eligible infants are identified by neonatal providers at participating sites. The BCH VIGOR team is available for any questions regarding eligibility. Once an eligible infant is identified, a neonatal provider at the site approaches the family and introduces the study. If the family is interested, the NICU site team fills out a referral form and sends it securely to the VIGOR team. A VIGOR team member then reaches out to the family to set up a consent session via video conferencing or phone call.

Subject consent

Neonatal providers: Provider consent is implied through the completion of provider surveys (see survey details in Aim 3 procedures below).

Families: Interested families complete a preenrolment information session with a BCH VIGOR team GC or research assistant (RA) via video conferencing or phone call. During this session, the BCH VIGOR team member reviews study logistics, including possible risks and benefits of enrolling, provides an overview of the utility of rGS for critically ill infants and explains potential types of results. The consent form inquires about contacting the family about future research studies and reporting of American College of Medical Genetics and Genomics secondary findings.[35] Consent is obtained electronically, and the study team uses certified Spanish interpreters for sessions with Spanish-speaking families.

Neonatal provider education

As part of the VIGOR study, neonatal providers at participating sites receive virtual education in genomic medicine. The BCH VIGOR team created a series of eight training modules available on the publicly accessible VIGOR web platform (https://www.virtualgenomecenter.org/education). VIGOR investigators with expertise in neonatal genomic medicine deliver the training modules with content geared towards neonatal providers with basic training in genetics and genomics. The sessions include: (1) VIGOR orientation, (2) 'Genetics 101', (3) recognising a patient with a potential genetic diagnosis, (4) current genetic diagnostic tools, (5) genomic sequencing results, reports and variant interpretation, (6) breadth of genomics in the neonatal period, (7) mock consent and disclosure sessions and (8) summary. The VIGOR team also provides one on one or group site training tailored to site needs for the duration of the study as needed.

Subject retention

Neonatal providers: Providers at participating sites can receive continuing medical education credits for watching the genomic medicine education modules and receive Amazon gift cards on completion of surveys and interviews.

Families: Families receive gift cards of graduating amounts on completion of follow-up surveys. The subset of families selected for qualitative interviews receive an additional gift card incentive.

Aim 2 procedures

Rapid genomic sequencing

A commercial clinically accredited vendor (GeneDx, Gaithersburg, Maryland, USA) performs the rGS (we used ES for the first year and then switched to genome sequencing as sequencing costs decreased over the study period).[36] Local NICU staff collect a blood sample from the infant and buccal samples from enrolled biological parents using kits provided by the vendor. The site PI or RA orders the rGS test through the vendor portal as a clinically accredited test and samples are shipped from the study site to the vendor. To inform rGS analysis, the site provides relevant clinical information to the vendor. Additionally, the study site provides an infant medical history form to the VIGOR team and parents are sent a baseline survey regarding pregnancy and other medical history by the VIGOR team. After receiving all samples,

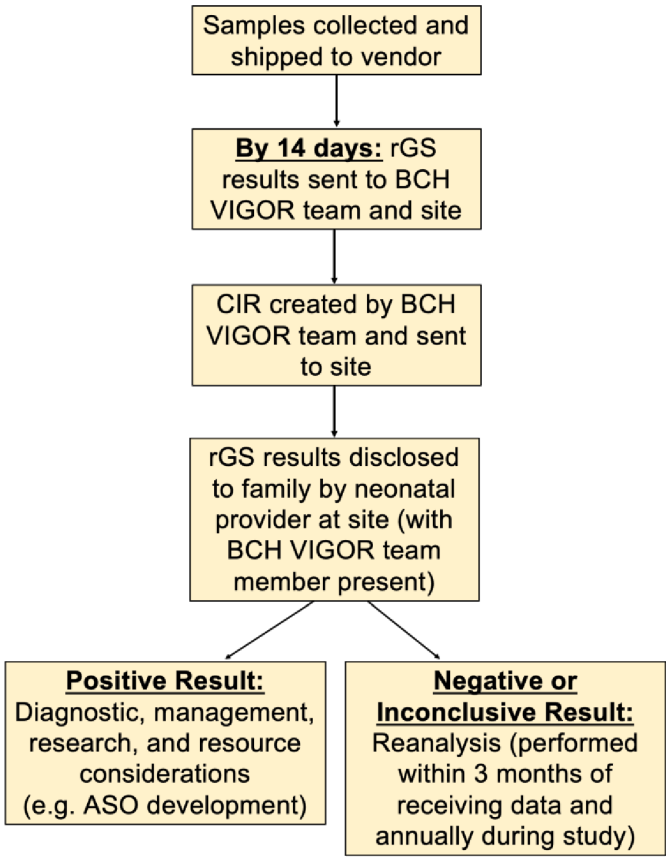

Figure 2 rGS workflow. Clinically accredited rapid genomic sequencing is performed using samples collected by local neonatal intensive care unit staff from the infant and biological parents when available. The vendor provides a written report within 14 days and the BCH VIGOR team creates a comprehensive interpretive report to provide guidance to neonatal providers. Both reports are sent to the site and local providers disclose results to families. Negative or inconclusive results are reanalysed over the course of the study and positive results may be used to direct future care and resource management. ASO, antisense oligonucleotide; BCH, Boston Children's Hospital; rGS, rapid genomic sequencing; VIGOR, VIrtual GenOme CenteR.

the vendor provides a verbal preliminary rGS result within 7 days and a written rGS report within 14 days to the VIGOR team and the ordering provider at each site (figure 2). The rGS report from the vendor provides the result (eg, positive, negative, inconclusive) and limited information regarding potential next clinical steps.

Clinical interpretive report (CIR)

Thus, the BCH VIGOR team creates a second report, a CIR, to provide guidance to the neonatal provider based on the rGS results. The VIGOR team uses available clinical information for the patient and genomic resources to create the CIR. The CIR interprets diagnostically relevant findings from the vendor report and links those findings to clinical management considerations, research opportunities and family resources. For a non-diagnostic or inconclusive finding, the CIR provides additional variant interpretation as relevant and describes plans for reanalysis. For example, for a variant of uncertain significance, the VIGOR team interprets the findings as likely, indeterminate or less likely of clinical relevance. The VIGOR team's goal is to complete the CIR within three business days of receiving the vendor report. The CIR is sent to the study staff at the site via secure email and is then internally sent to the disclosing provider at the site. The VIGOR team is available to answer any questions about the information in the CIR. Notably, while the VIGOR team members are not clinical providers for enrolled infants, clinical providers at the sites may use the CIR in the context of an infant's current clinical presentation.

Disclosure

If the preliminary rGS result indicates an urgent, life-threatening or immediately actionable condition, a BCH VIGOR team member immediately discloses results to the study site neonatal provider and family. Otherwise, a neonatal provider at the study site discloses the rGS results to the family, even if the infant has been discharged or transferred from the NICU prior to the results return. We planned for this method of disclosure for two reasons: first, disclosure from a trusted provider in a familiar environment may be the best approach for families; and second, experience with disclosure of genetic testing results may increase neonatal providers' comfort with genomic medicine in the NICU. It is at the discretion of the neonatal provider caring for the infant and family to choose when to disclose the rGS results (after receiving the preliminary result, final vendor report and/or CIR), with whom to disclose results (clinical geneticist or GC at their site, if available or any other member(s) of the care team at their site (nurse, social worker, additional subspecialist, etc)) and how to disclose results (in person, by phone call, or by video conferencing). A VIGOR team member is available to answer questions and provide support to the neonatal provider through the disclosure process and is present during the primary disclosure session, but does not communicate directly with families about the results.

Reanalysis

The vendor sends the sequencing data to BCH where it is securely stored. For cases with initially negative or inconclusive rGS results, the BCH VIGOR team reanalyses the data within 3 months of obtaining it and annually thereafter for the duration of the study. Reanalysis can reveal new diagnostic findings as we learn new information about the patient's clinical features, genomic analyses methods and gene–disease associations over time. The sequencing data is reanalysed by the VIGOR team using a custom in-house bioinformatics pipeline, Variant Explorer.[37] If clinically relevant results are identified by reanalysis, the results are clinically confirmed by the vendor and updated reports are created by the vendor and VIGOR team. The VIGOR team communicates the updated results to the original ordering provider at the site and/or to the infant's primary care physician.

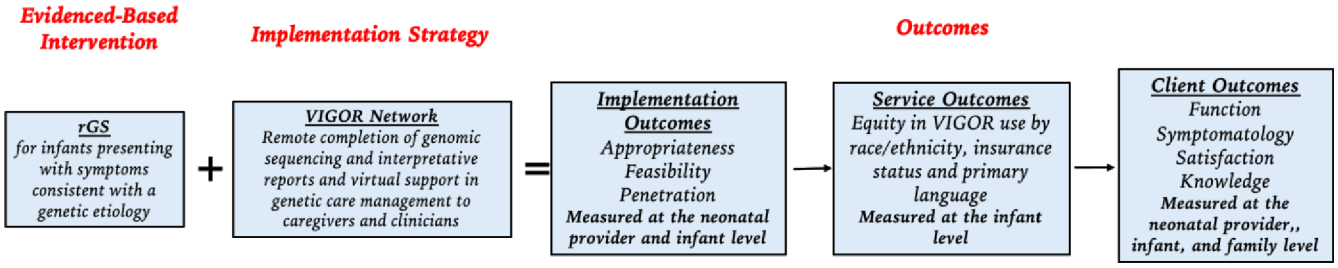

Figure 3 Adapted Proctor Implementation Framework. Evaluation of implementation outcomes will be based upon the Proctor Implementation Framework. The framework posits that both the evidence-based intervention and the strategies used to implement the intervention are required to improve health outcomes. Three levels of outcomes are incorporated: implementation, service and client. rGS, rapid genomic sequencing; VIGOR, VIrtual GenOme CenteR.

Aim 3 procedures

Implementation framework

This study uses the Proctor Implementation Framework to guide comprehensive evaluation of implementation outcomes (figure 3).[38] The Proctor Framework is based on the principle that both the evidence-based intervention and the strategies used to implement the intervention are needed to improve health outcomes. The framework incorporates three levels of outcomes: implementation, service and client. Using a mixed methods approach, we assess the implementation outcomes of appropriateness, feasibility and penetration, the service outcome of equity, and the client outcomes of function, symptomatology and satisfaction described in table 1.

Data measures

This study collects data through qualitative and quantitative methods to assess outcomes at the neonatal provider, infant and family levels (table 1).

Data collection procedures

Qualitative component

Virtual focus groups: A study PI conducts focus groups of neonatal providers at participating sites via video conferencing before and after implementation of VIGOR at each site. These focus groups are approximately 60 min in length.

Qualitative interviews: A study PI or BCH VIGOR team member trained in qualitative analysis conducts qualitative interviews for neonatal providers and families via video conferencing. These interviews are approximately 30–60 min in length. Interviews with neonatal providers are conducted after a provider has completed 3–5 results disclosures. Interviews with families are conducted within 2 months of results disclosure. We are using purposive sampling to select a subset of approximately 60 families to ensure breadth of perspectives, including English-speaking and Spanish-speaking families, families across study sites and families with infants with positive, negative and inconclusive genomic sequencing results.

The study investigators create open-ended question guides to assess constructs of interest in focus groups and interviews and revise them as needed as part of the iterative analytic approach. Focus groups and interviews are conducted by study team members trained in qualitative interviewing and are transcribed verbatim.

Quantitative component

Chart abstraction: Chart abstraction is performed at the time of infant enrolment, at the time of infant transfer/discharge from the NICU and 12 months after results disclosure. A study team member at each site completes chart abstraction forms which the BCH VIGOR team enters into a centralised REDCap database.

Surveys: All neonatal provider and caregiver surveys are administered by email or text message by REDCap. We send caregivers surveys at enrolment, within 2 weeks of results disclosure and 3, 6 and 12 months after results disclosure. After delivery of the initial survey at each time point, we send reminder surveys weekly for a maximum of 3 weeks. We send neonatal providers surveys before and after completion of virtual genomic medicine training and after each results disclosure.

Outcome definitions

Implementation outcomes

The implementation outcomes include: (1) penetration, which is the primary outcome and is defined as the percentage of eligible infants that are enrolled, have rGS sent (on the infant with or without biological parents), have vendor rGS report delivered, have CIR delivered and have a family disclosure session; (2) appropriateness, which is defined as neonatal providers' perception of the value of rGS and use of VIGOR in optimising NICU clinical care and (3) feasibility, which is defined as neonatal providers' perception of the ability of VIGOR to be implemented as designed in their NICUs.

Service outcome

Equity is defined as equal penetration by infant race/ethnicity, infant insurance status (public/private/uninsured) and language preferred by family for study communication (English/Spanish).

Client outcomes

Client outcomes include function, symptomatology and satisfaction. We examine function at the neonatal provider level, as comfort with caring for infants with likely genetic

Table 1 Outcomes and measurements

Outcome	Level	Mode of data collection	Timing of data collection
Implementation outcomes			
Appropriateness	Neonatal providers	Virtual focus groups	Preimplementation and postimplementation of VIGOR at participating sites
Feasibility	Neonatal providers	Virtual focus groups	Preimplementation and postimplementation of VIGOR at participating sites
Penetration	Infant	Tracking rapid ES report, CIR and disclosure	Throughout enrolment period
Service outcomes			
Equity	Infant	Tracking rapid ES report, CIR and disclosure, as well as chart abstraction	Throughout enrolment period
Client outcomes			
Function (provider) *Comfort with genomic medicine*	Neonatal providers	Survey	Pregenomic and postgenomic education survey
Function (family) *Mental health*	Family	Survey	At enrolment and 3, 6 and 12 months after results disclosure
Symptomatology *Neonatal clinical outcomes*	Infant	Chart abstraction	At NICU discharge/transfer and 12 months after results disclosure
		Survey	3, 6 and 12 months after results disclosure
Satisfaction (provider) *With disclosure process and the VIGOR study*	Neonatal provider	Survey	After each results disclosure
		Qualitative interviews	After 3–5 disclosure events
		Virtual focus groups	Postimplementation of VIGOR at participating sites
Satisfaction (family) *With disclosure process and participation in VIGOR*	Family	Survey	Within 2 weeks of results disclosure
		Qualitative interviews (with subset)	Within 2 months of results disclosure

CIR, clinical interpretive report; ES, exome sequencing; NICU, neonatal intensive care unit; VIGOR, VIrtual GenOme CenteR.

disorders, including identification, testing, disclosing results and management. We also examine function at the family level as two common mental health outcomes: stress measured according to the Perceived Stress Scale[39] and depression measured according to the Edinburgh Postnatal Depression Scale.[40] We measure symptomatology at the infant level over the first year post-NICU discharge. We will assess postdischarge healthcare utilisation with measures adapted from the National Survey of Children with Special Health Care Needs[41] and other clinical outcomes, including genetic diagnosis, management changes (eg, referrals, lab tests, imaging, treatment changes, procedures, surgeries), palliative care decisions and/or death, and family planning decisions. At the neonatal provider level, satisfaction including perceived comfort with the process of results disclosure, the level of VIGOR team support and perceived barriers and facilitators to implementation of VIGOR is measured. At the caregiver level, we measure satisfaction with the decision to enrol in the study and receipt of genomic sequencing results by neonatal providers.

Data analysis and power considerations

Qualitative component

The qualitative analysis uses a grounded theory iterative approach.[42] Study investigators with broad expertise in genomic medicine, neonatal care, social disparities, experience working in safety-net NICU settings and qualitative research, independently review transcripts and meet to develop and revise a uniform codebook. Investigators then code transcripts and convene to assure uniform coding and resolve any discrepancies through group discussion. Themes are developed and revised from coded manuscripts iteratively until no new themes emerge (thematic saturation). Investigator triangulation is used to assess reliability, whereby investigators

read transcripts independently and subsequently reach consensus through group discussion, and by member checking, whereby findings are communicated to participants to confirm results.[43]

Quantitative component

As the goal of this 'proof of concept' study is to assess implementation of a novel delivery system for genomic care, we do not have a control group, and therefore the quantitative analysis will be primarily descriptive. We will estimate penetration, the primary implementation outcome, by calculating the percentage of enrolled subjects completing the genomic sequencing and disclosure process as described above. To assess equity, we will use contingency-table statistics to compare penetration among subgroups (infant race/ethnicity, infant insurance status, language preferred by family for study communication). Measures to be collected at multiple time points include clinical outcome, family mental health and family and provider satisfaction (table 1), with most family surveys administered to both parents. We will analyse the longitudinal outcomes with repeated-measures linear regression for continuous outcomes and logistic regression for discrete outcomes. Each model will include random effects to account for serial correlation, within-family correlation and within-site clustering as well as fixed effects by time, subgroup and parent. We will construct contrasts from the fitted model parameters to describe the time course of each outcome and to test hypotheses comparing the mean response and the time course among subgroups.

In the planned sample of 250 enrolled infants and their families (N), we anticipate 80%–90% penetration (P). The estimate of achieved penetration rate will therefore carry precision of 1.9%–2.5%. For assessing equity, the detectable difference in penetration between subgroups (eg, by insurance status) depends on the subgroup sizes; however, we anticipate that with subgroup sizes between 0.2 and 0.4, the difference in penetration detectable with 80% power and 5% type I error will lie between 11% and 18%. The above estimates give us confidence that the planned sample size will provide ample precision for its descriptive aims and sufficient power to demonstrate relatively subtle subgroup differences and changes with statistical significance.

Patient and public involvement

Families of infants with suspected genetic disorders admitted to NICUs were not involved in the design of the study, but family participants are intimately involved in assessing the implementation of VIGOR. We intend to disseminate the main results of the study via publicly accessible platforms.

ETHICS AND DISSEMINATION

Ethics approval and informed consent

The institutional review board (IRB) of BCH (IRB-P00040496) and the participating sites approved this study with a 'no greater than minimal risk' risk determination. BCH is the central IRB of record, with active reliance agreements at partnering institutions.

Participating families are required to provide electronic written informed consent and neonatal provider consent is implied through the completion of surveys.

Data safety monitoring plan and adverse events

The BCH VIGOR team meets weekly to discuss any adverse events. The administrative PI evaluates all adverse events within 24 hours of notification by study staff, with all serious events immediately reported to the IRB and NIH.

Given the study population, we anticipate maternal/caregiver depression to be a potential adverse event. We use the Edinburgh Postnatal Depression Scale to assess maternal/caregiver depression.[40] If a mother/caregiver scores above 9, the survey presents links to resources, and if a mother/caregiver positively responds to the question 'the thought of harming myself has occurred to me', the survey immediately presents a message about hope and reaching out for help. Additionally, if a mother/caregiver scores above 19 or positively responds to the above question, the system notifies the VIGOR team automatically. The VIGOR team will notify the site PI, who will engage local resources including social work services.

While we exclude infants in state custody from VIGOR during initial screening, in the event that VIGOR becomes aware the state has become involved in the custody of the infant once enrolled, and prior to, the end of the study, we will follow the individual site's state laws as they pertain to wards of state and participation in research. In each state, it is required the state agency be made aware that the infant is enrolled in a research study.

Data sharing and dissemination

We will disseminate results via presentation at research conferences and publication in peer-reviewed journals. We will make data accessible per NIH policies, including submission of genomic sequencing data to appropriate repositories.

Author affiliations
[1]Division of Newborn Medicine, Department of Pediatrics, Boston Children's Hospital, Boston, Massachusetts, USA
[2]Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA
[3]Division of Genetics and Genomics, Department of Pediatrics, Boston Children's Hospital, Boston, Massachusetts, USA
[4]The Manton Center for Orphan Disease Research, Boston Children's Hospital, Boston, Massachusetts, USA
[5]Division of Newborn Medicine, Department of Pediatrics, Harvard Medical School, Boston Children's Hospital, Boston, Massachusetts, USA
[6]Division of Genetics and Genomics, Department of Pediatrics, Harvard Medical School, Boston Children's Hospital, Boston, Massachusetts, USA
[7]UMass Chan Medical School, Worcester, Massachusetts, USA
[8]Division of Neonatology, Department of Pediatrics, University of Miami Miller School of Medicine, Miami, Florida, USA

[9]Jackson Health System, Holtz Children's Hospital, Miami, Florida, USA

Collaborators VIGOR Network: Pankaj Agrawal (Division of Neonatology, Department of Pediatrics, University of Miami Miller School of Medicine and Holtz Children's Hospital, Jackson Health System, Miami, FL, USA), Tyler Allcroft (Division of Neonatology, Department of Pediatrics, UMass Chan Medical School, Worcester, MA, USA), Vineet Bhandari (Division of Neonatology, Department of Pediatrics, The Children's Regional Hospital at Cooper; Departments of Pediatrics, Obstetrics and Gynecology, and Biomedical Sciences, Cooper Medical School of Rowan University, Camden, NJ, USA), Luis Cantu Jr (DHR Health Institute for Research and Development, Edinburg, TX, USA), Alissa M D'Gama (Division of Newborn Medicine, Division of Genetics and Genomics, Department of Pediatrics, Boston Children's Hospital; Department of Pediatrics, Harvard Medical School, Boston, MA, USA), Jessica Douglas (Division of Genetics and Genomics, Department of Pediatrics, Boston Children's Hospital, Boston, MA, USA), Henry A Feldman (Division of Newborn Medicine, Department of Pediatrics, Boston Children's Hospital, Boston, MA, USA), Casie A Genetti (Division of Genetics and Genomics, Department of Pediatrics; The Manton Center for Orphan Disease Research, Boston Children's Hospital, Boston, MA, USA), Sonia Hills (Division of Genetics and Genomics, Department of Pediatrics, Boston Children's Hospital, Boston, MA, USA), Dynio Honrubia (DHR Health, Driscoll Children's Hospital RGV, UTRGV School of Medicine), Amy Kritzer (Division of Genetics and Genomics, Department of Pediatrics, BCH; Department of Pediatrics, Harvard Medical School, Boston, MA, USA), Qifei Li (Division of Neonatology, Department of Pediatrics, University of Miami Miller School of Medicine and Jackson Health System, Miami, FL, USA), Margaret Parker (Child Health Equity Center, Department of Pediatrics, UMass Chan Medical School, UMass Memorial Children's Medical Center, Worcester, MA), Lawrence Rhein (Division of Neonatology, Department of Pediatrics, UMass Chan Medical School, UMass Memorial Children's Medical Center, Worcester, MA, USA), Robert Rothstein (Division of Neonatology, Baystate Health, Department of Pediatrics, UMass Chan Medical School – Baystate, Springfield, MA, USA), Odalys Salinas (DHR Health Institute for Research and Development, Edinburg, TX, USA), Andres Santana (Baystate Health Clinical Trials Office, Springfield, MA, USA), Klaus Schmitz-Abe (Division of Neonatology, Department of Pediatrics, University of Miami Miller School of Medicine and Jackson Health System, Miami, FL, USA), Anyssa Serna (DHR Health Institute for Research and Development, Edinburg, TX, USA), Faye Shapiro (Department of Pediatrics, Division of Genetics, Cooper University HealthCare, Camden, NJ, USA), Anjana Bhami Shenoy (Division of Neonatology, Department of Pediatrics, UMass Chan Medical School, Worcester, MA, USA), Lindsey Simoncini (Division of Neonatology, Department of Pediatrics, UMass Chan Medical School, Worcester, MA, USA), Bharati Sinha (Department of Pediatrics, Boston Medical Center; Department of Pediatrics, Boston University Chobanian and Avedisian School of Medicine, Boston, MA, USA), Aubrie Soucy Verran (Division of Genetics and Genomics, Department of Pediatrics, Boston Children's Hospital, Boston, MA, USA), Anéya Sousa (Department of Pediatrics, Boston Medical Center, Boston, MA, USA), Marione Tamase Newsam (Division of Neonatology, Department of Pediatrics, University of Miami Miller School of Medicine/Holtz Children's Hospital, Jackson Health System, Miami, FL, USA), Monica H Wojcik (Division of Newborn Medicine, Division of Genetics and Genomics, Department of Pediatrics, The Manton Center for Orphan Disease Research, Boston Children's Hospital; Department of Pediatrics, Harvard Medical School, Boston, MA, USA), Vanessa Young (Division of Newborn Medicine, Department of Pediatrics, Boston Children's Hospital, Boston, MA, USA), Timothy Yu (Division of Genetics and Genomics, Department of Pediatrics, Boston Children's Hospital; Department of Pediatrics, Harvard Medical School, Boston, MA, USA)

Contributors PBA, MGP and TWY conceived the study. PBA, MGP and TWY developed the study protocol with consultation from JD, VY, CAG, and MHW. HAF was responsible for statistical analysis plans. AMD and SH wrote the initial manuscript draft. All authors critically reviewed and edited the manuscript. Figures were developed by PBA, MGP, TWY, AMD and SH. The VIGOR Network consists of investigators serving as scientific and medical advisors and investigators and study coordinators at participating sites responsible for patient care and subject recruitment.

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ORCID iD

Sonia Hills http://orcid.org/0000-0002-5302-3236

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