Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants

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Reviewer	Significance	Investigators	Innovation	Approach	Environment
R1	3	1	5	4	1
R2	3	1	3	3	1
R3	2	1	3	4	1

Introduction to Resubmission: We were pleased that reviewers described our proposal as "a highly significant topic that addresses an important problem" (R1), us as "exceptional investigators who are experienced in conducting high-quality clinical and translational research" (R3) and felt we were "very well positioned to recruit from traditionally underserved populations" (R2). We have made significant revisions in the proposal to address the thoughtful critiques of the reviewers, as shown below.

Significance: All 3 reviewers praised the importance of the topic and need for research in this area. In this section, R1 encouraged greater attention to historical community concerns, mistrust and fears (see revised Approach and Human Subjects). R2 and R3 noted concerns about sample size and representativeness (see revised Approach).

Innovation: R1 and R3 noted no weaknesses under innovation. R2 noted the limited sample size (see revised Approach). This research meets the criteria for innovative solutions as described in PAR-19-099 to "disseminate a solution to a translational science problem developed at one hub to other hubs, in so doing testing its robustness to different hub environments and structures...".

Approach: R1 noted that statistical measures are appropriate for the hypotheses we posed, but all reviewers were concerned about the modest sample size, and the relatively small number of participant families who would receive monogenic disease risks (MDRs). Our sample size was limited by the study budget and powered for psychosocial outcomes, but we are pleased to report that for this revised submission we have received commitments for institutional co-funding that will permit us to expand the sample size from 300 families to 500 families (see new Letters of Institutional Support)! This will enhance our ability to explore short-term clinical utility in those receiving MDRs, but the primary focus of this grant continues to be enrolling families that are more representative of "early adopters" of infant sequencing in outpatient clinics and exploring the acceptability and impact of doing so among more diverse populations.

R1 and R3 questioned the ethics of having health care providers (HCPs) communicate directly to parents without more training or support. We agree and have removed the prior Aim 2d (observing HCPs without additional education/support) and added new sub-aims, amending the workflow in three critical ways: (1) all HCPs will be required to undergo a brief structured curriculum built upon prior work in SouthSeq by HudsonAlpha co-investigators (Dr. Lamb and Ms. East) who have been newly added to this proposal, (2) all disclosures of positive genetic results will be carried out by the genetic counselor at each site, (3) a Genetics Resource Center will be created and available to respond to any HCP or patient queries.

R2 and R3 requested more details around calling of copy number variants and the use of VUS/non-coding variants, respectively, and these details have been added to the revised Approach.

Ethics Concerns and Protection of Human Subjects: In addition to concerns about HCP disclosure of genomic information (see above), all 3 reviewers highlighted the potential for exacerbating mistrust and fear among underrepresented minorities (URMs) around recruitment and disclosure. In the revised Aims (see new Aim 1a), revised Approach and in the revised Human Subjects section of the proposal, we now propose to conduct focus groups in order to pilot our recruitment and disclosure materials. We have also recruited a Stakeholder Board of diverse experts and research participants/advocates (see new letters from 12 individuals) to provide early and ongoing feedback as we develop each stage of the protocol in partnership with minority communities, and manage the disclosure to HCPs and families with greater input from experts and with greater sensitivity to historical injustices and cultural diversity.

With regard to the potential distress of disclosure, we present published and preliminary data from all 3 sites around our prior recruitment and outcomes experiences in genetic disclosure studies among diverse populations that we neglected to include in the first submission of this proposal and that we believe the reviewers will find reassuring. Importantly, if critical issues around fear and distrust emerge from underserved diverse communities around sequencing of infants, a rigorously controlled study like this will be able to document, mitigate and better understand these, and with oversight and input from our new Stakeholder Board, provide a roadmap to adjust our approach. In this manner we hope to minimize the possibility that unexamined dissemination of this technology will worsen health disparities in the coming era of genomic medicine.

Substantive revisions in this resubmitted proposal are italicized for reviewers to find more easily.

SPECIFIC AIMS

There is growing societal interest in using genomic sequencing (GS) to identify genetic predispositions for disease early in life but there is insufficient evidence of its' acceptability, psychosocial impact, and clinical utility. In order to begin to gather such evidence, over the past 5 years, our multi-disciplinary team launched the first randomized controlled trial (RCT) of GS in newborns: the BabySeq Project. We implemented a workflow for whole exome sequencing (WES), and curated 1514 disease-associated genes with favorable validity, age of onset, and penetrance. We randomized 325 families to a family history (FH) arm or a FH+GS arm, disclosed results and placed reports in each infant's medical record. Medically, we discovered and disclosed unanticipated monogenic disease risks (MDRs) in 11% of the infants randomized to GS, and we discovered previously unrecognized signs of underlying disease and relevant family history in over half of these. Behaviorally, we found no increased distress among parents or disruption to the parent-child relationship in response to receiving GS results. Economically, we found only modest increases in downstream health costs. The majority of healthcare providers (HCPs) felt there were health benefits associated with newborn GS.

The BabySeq Project demonstrated the feasibility of newborn GS, but the generalizability of our results was limited as participant families were recruited as inpatients from one geographic region, predominantly White, and socio-economically privileged. We now propose an entirely new RCT in ethnically/racially diverse communities from CTSA sites in Boston, New York City, and Birmingham, AL to study how GS in infants can be implemented in diverse, resource-limited, "real-world" outpatient primary care settings. We will also improve the technical aspects of the GS offering by moving from WES to whole genome sequencing (WGS) and adding interpretation of copy number variants (CNVs). *Through this research we will develop, pilot, implement, and evaluate a practical, sustainable approach to GS early in childhood that leverages underserved community engagement to minimize distrust and maximize benefit.*

Aim 1: *With input from a diverse stakeholder board and focus groups of parents from the 3 CTSA sites*, we will develop a recruitment and retention strategy to enroll 500 apparently healthy, ethnically and racially diverse infants (1-6 months) into an RCT of GS. *Support will be provided for the HCPs though a structured genomics curriculum, and results will be returned to families and their HCP.*

Aim 1a: *In light of distrust of research among underrepresented minorities (URMs), we will (a) establish a Stakeholder Board with community representation from all 3 sites, and (b) solicit parental input from the communities to understand the concerns, especially within URM populations, towards GS research and how we can address those concerns as we develop our protocol, recruitment strategies, and disclosure methods.*

Aim 1b: *We will modify a successful HudsonAlpha SouthSeq genomics education program utilizing brief didactic videos and live training sessions for the outpatient pediatric HCPs.*

Aim 1c: We will enroll and randomize a cohort of families with infants 1-6 months of age, over half of whom will be of self-reported African or Hispanic ancestry, from 3 CTSA sites with established expertise in engagement, diversity, and genomic clinical trials. Participants will be randomized into FH or GS+FH arms, *and results will be communicated by genetic counselors to the families and the participating HCPs.*

Aim 2: To evaluate the impact of GS on a diverse group of infants, their families and their HCPs.

Aim 2a: To assess the psychosocial impact of infant GS on parents from varying ethnic and racial backgrounds, we will conduct longitudinal surveys and compare validated scales between arms of the RCT.

Aim 2b: To assess the medical impact of GS on infants and their families, we will review medical records and survey parents to track symptoms, laboratory or diagnostic results, new diagnoses, and medical actions attributed to the GS findings. Among infants with an MDR, we will determine whether the MDR: (a) reveals an unsuspected phenotype in the infant or family, (b) explains a family history of a condition, and/or (c) prompts surveillance in the infant or family.

Aim 2c: *To assess the impact of GS in infants on clinical care, we will collect feedback from HCPs throughout the study by monitoring use of the "Genome Resource Center" and conducting interviews with HCPs towards the end of the study.*

Aim 3: Exploratory Aim: To evaluate healthcare utilization and associated costs of GS. Using novel approaches, we will identify healthcare services motivated by the study in the two study arms and examine attributable healthcare costs accrued for the infants and other family members.

SIGNIFICANCE

The era of genomic sequencing (GS) in medicine has arrived,[1-3] and numerous laboratories are offering CLIA-certified whole exome (WES) or genome sequencing (WGS) as a clinical service for characterization of rare disorders[4-6] and for individualized cancer treatments.[7-10] But many who envision a future of personalized and precision medicine have long considered GS to be equally or even more valuable for its potential to reveal predispositions to disease that would allow preventive measures,[11-13] and to have utility throughout the lifespan,[14] especially if performed early in life. Indeed, NIH director Francis Collins has said: "…whether you like it or not, a complete sequencing of newborns is not far away"[15] and former NICHD director, Alan Guttmacher, echoed this by stating: "One can imagine the day that 99% of newborns will have their genomes sequenced immediately at birth."[16] GS in the newborn period could reveal monogenic disease risks (MDR) that conventional newborn screening would miss, such as a pathogenic variant in *RB1* predisposing an infant to develop a retinoblastoma. As infants grow into their reproductive years, they would have access to the variants they carry for recessive conditions to use for family planning.[17-19] In adult life, sequenced individuals could benefit from knowing if they carry MDR variants in cancer predisposition genes like *BRCA1,*[20] or had pharmacogenomic (PGx) variants that could guide selection or dosing of certain medications.[21; 22] Some of the arguments against GS early in life arise from our understanding of population-based screening tests, where screening large numbers of individuals for rare conditions with poorly understood penetrance could identify more individuals at risk than would actually develop the condition. There are also cost considerations, with some questioning whether genomic information will lead to increased healthcare expenditures.[23; 24] Finally, there is concern that the provider workforce may not be prepared to interpret and manage genomic results in their patients.[25-31]

<u>One of the major impediments to understanding the ultimate value of GS early in life is the absence of methodologically rigorous data on psychosocial impact and clinical utility</u>. While there are large-scale attempts to match genomic information to phenotype data such as the **E**lectronic **Me**dical **R**ecords and **Ge**nomics (eMERGE) Network, the Geisinger *MyCode* Program, the Alabama Genomic Health Initiative, and the Mount Sinai *BioMe* Program, these programs are principally oriented toward adults and lack control populations against which to measure the clinical utility of GS. Over the past 5 years our team has taken a rigorous approach to start to explore the psychosocial impact and clinical utility of GS in newborns as part of the **N**ewborn **S**equencing **I**n **G**enomic medicine and public **H**eal**T**h (NSIGHT) Consortium by conducting the "*BabySeq Project*," the first pilot RCT of newborn GS.[32-35] The BabySeq Project demonstrated the feasibility of enrolling parents and their newborns in an RCT of GS, analyzing GS data to identify genetic findings that indicate risk of a disease, and returning results to parents and health care providers (HCPs). Importantly, there was no evidence for harm from returning the results (see Approach).[36; 37]

However, there were limitations to the BabySeq Project: parents were recruited in an inpatient setting immediately after giving birth, there was only a single site, and those who enrolled were overwhelmingly White and of higher socioeconomic status. *We now propose a new RCT to explore the implementation of GS in 3 diverse, resource-limited, "real-world" outpatient primary care settings across the country enriched for underrepresented minorities (URMs) focusing upon African-American (AA) and Hispanic (HA) families. AA and HA communities have not benefited from genomics research to the degree that White populations have,[38-41] in part because they tend not to participate in research. In the AA population, issues include mistrust, privacy concerns, fear of pain, and confusion around compensation,[42-45] which are reinforced by historical abuses, including the Tuskegee syphilis experiment and the development of the HeLa cell line from Henrietta Lacks.[46] Among HAs, lack of knowledge about research, lack of dissemination of results, fear of pain or harm, and distrust of the healthcare system are primary barriers to research participation.[47-50] It is critical to earn the trust of communities with robust engagement that involves welcoming patients/participants as essential and equal research partners before asking them to enroll in research studies.[51-53] The 3 CTSA sites in this project, in Boston, New York City, and Birmingham, AL, all have years of extensive experience in community engagement and in enrolling and retaining URMs in genomics research (see Approach - Prior Work and Data). We will leverage this experience and take a systematic approach to community engagement to address the concerns of URMs towards research and GS by involving parents, HCPs, and a Stakeholder Board in a substantial way as we develop and implement our study.* ***Our proposal is significant in that it asks how GS of healthy infants from ethnically and racially diverse populations can be ethically implemented.***

CTSA COLLABORATION

This project involves the formation of new collaborations with our colleagues at 3 CTSA Program hub institutions: Harvard Catalyst Clinical and Translational Science Center, the Icahn School of Medicine at Mount Sinai, and the University of Alabama at Birmingham. Our research team combines clinical and research experience and expertise in genetics, bioinformatics, molecular science, clinical trial design, engagement of ethnically and racially diverse populations in genetic studies, ethics, clinical education, and psychosocial, behavioral, and health outcomes measurement. Under a single shared protocol, each site will recruit and enroll participants, collect data and specimens for genetic analysis, and return results. The data will be stored in one repository, and the sites will work together on data analysis, publications, and dissemination of results to the CTSAs and beyond. There will be a Central IRB and the other sites will cede review (see IRB letters).

INNOVATION

This research proposal explores the extremely novel area of sequencing of infants as screening, and meets criteria for innovative solutions as described in the NCATS PAR-19-099 to "disseminate a solution to a translational science problem developed at one hub to other hubs, in so doing testing its robustness to different hub environments and structures...". While this proposal benefits from the infrastructure developed and feasibility demonstrated in our prior BabySeq Project, it is not a follow-up study to that; we have taken this work in several new directions. (1) We will implement GS in early childhood within the context of ongoing outpatient care. (2) *We will perform whole genome sequencing (not whole exome sequencing) in those in the GS arm, including analysis of copy number variants (CNVs). (3) We will evaluate and address concerns of URM populations towards research and GS through our Stakeholder Board, community engagement activities, and parent focus groups. (4) We will position the GS data as a longitudinal resource for families and HCPs for reanalysis if new medical issues arise where a genetic etiology is suspected.*

APPROACH - *Prior Work and Preliminary Data*

Here we demonstrate that (1) we have the infrastructure and experience to feasibly carry out the proposed research project *and* <u>*new to this revised proposal*</u>*, that (2) we have expertise in engaging diverse populations in genetic research, and (3) we have experience in safely returning genetic results to HCPs.*

Prior Work and Data: The BabySeq Project

<u>Study Design</u>**:** The BabySeq Project was a pilot RCT of two newborn cohorts, one healthy and one from neonatal and cardiac intensive care units (NICUs and CICUs). For all newborns, we obtained the state-mandated newborn screening (NBS) report, a 3- to 4-generation pedigree by a genetic counselor (GC), and DNA samples. Within each cohort, half were randomized for their parents to receive family history and NBS reports only (FH arm) and half to additionally receive their WES report (FH+WES arm). Families in both arms returned for an in-person disclosure with a study GC and a final report was sent to the parents and to the infant's HCPs and placed in the medical record. Parental surveys were conducted at enrollment (baseline), disclosure, and at 3- and 10-months post-disclosure, and HCP surveys were conducted at baseline and after they received a report on an enrollee.[32; 33; 54] <u>Recruitment and enrollment:</u> Our study staff approached 5,022 inpatient families and about 90% declined *prior to hearing the details of the study*, primarily due to lack of interest in "any research" during in the stressful postnatal period. *Of the families who agreed to hear about the study, 67% enrolled*, for a total of 325 families (257 healthy and 68 from the ICUs).[55] <u>Molecular Analysis and Reporting</u> (Figure 1): We curated 1,514 genes associated with monogenic disease risk (MDR) based upon the ClinGen clinical validity classification framework criteria, age of disease onset, estimated penetrance, and mode of inheritance, through evaluation of published evidence.[33] Of these, 954 genes met our criteria for reporting; additional genes were included in the analysis as they arose through the pipeline comparisons with known and

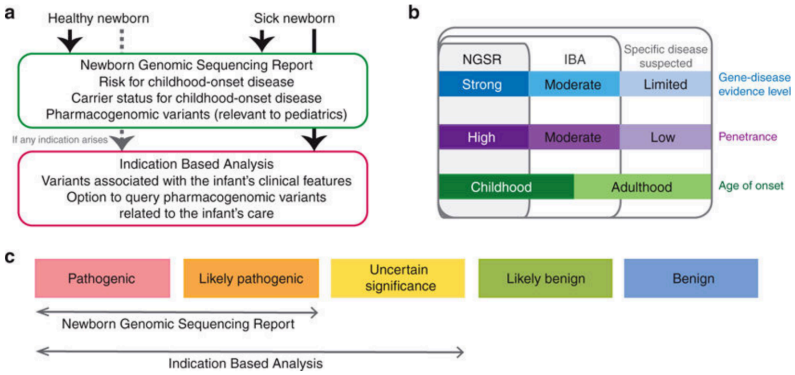


Figure 1. Return of results criteria in the BabySeq project

suspected genes and variants.[33; 34] Variant interpretation followed the American College of Medical Genetics and Genomics/ Association of Molecular Pathology (ACMG/AMP) guidelines for assessment of pathogenicity.[56] The *Newborn Genomic Sequencing Report (NGSR)*[32; 33] documented MDR, defined as pathogenic or likely pathogenic (P/LP) variants in the genes that met reporting criteria, recessive carrier variants, and pharmacogenomic (PGx) variants associated with medications used in pediatrics. The inheritance of the MDR allele/s (but not carrier status) were assessed by analysis of parental DNA. For infants with a condition suspected to have a genetic contribution, an additional Indication Based Analysis (IBA) was generated, which additionally included variants of uncertain significance (VUSs) for the gene/s suggested by clinical features. This strategy was an attempt to maximize the lifelong value of GS for each infant by routinely searching for MDR in a large set of genes and also conducting an IBA for any illness where a genetic etiology was suspected and there were candidate genes.

Medical Outcomes: Among the 159 infants who underwent GS, 18 (11%) had a MDR. As shown in Table 1, the findings in 3 cases prompted discovery of a related disease phenotype not previously recognized, in 2 cases identified vulnerability to future exposure, and in 1 case explained a previously unrecognized genetic etiology.[34] The remaining 12 cases offered future disease risk assessment for the infant and the parent carrying the variant. While surprisingly high, this is consistent with findings from an earlier GS study that we conducted in adults and is probably explained by the fact that few prior studies have comprehensively sequenced healthy individuals.[57] Carrier status was identified in 140 of the 159 (88%), with an average of 2 variants per infant (range 0-7).[58] Of the 7 genes identified most frequently, only *CFTR* is captured in conventional carrier screening, and most genes are not on expanded carrier screening panels.[59] Some parents used recessive carrier results to inform their reproductive planning, including one family that pursued preimplantation genetic testing after follow-up clinical carrier testing revealed that both parents carried pathogenic variants in the same gene.[60]

Table 1. BabySeq1 Monogenic Disease Risk Genes

ANKRD11^	ELN*	BTD*
G6PD+	GLMN*#	TTN$#
TTN$#	TTN$#	TTN$#
BRCA2$#	BRCA2$#	SLC7A9$#
KCNQ4$#	VCL$	CD46+
MYBPC3$	MSH2$#	CYP21A2$

^ Explains recognized clinical phenotype
* Prompted discovery of a clinical or laboratory phenotype
+ Identified vulnerability to future exposure
$ Predicts future disease risk
# Presence of associated family history

Behavioral Outcomes: We measured the impact of receiving GS information on the parent-child relationship using a modified version of the Vulnerable Baby Scale (VBS),[61] Mother-Infant Bonding Scale (MIBS),[62] and Parenting Stress Index (PSI-4-SF).[63] We assessed parents' risk for depression and anxiety using validated scales. We found no parental distress that could be directly linked to study participation, and for all domains of parental distress and family impact we observed no effect between randomization arms, nor between parents whose infant did vs. did not have MDR findings in the GS arm (Figure 2). These findings suggest that providing the parents with GS information about their newborn, including MDR, does not cause psychosocial distress or familial disruption.

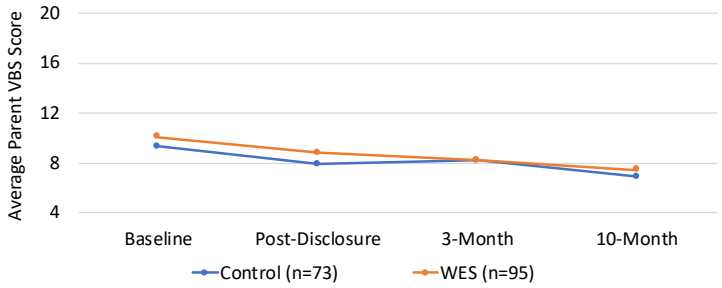


Figure 2. BabySeq1 average parent Vulnerable Baby Scale (VBS) score by study arm over time, showing no disruption to parent-child relationship

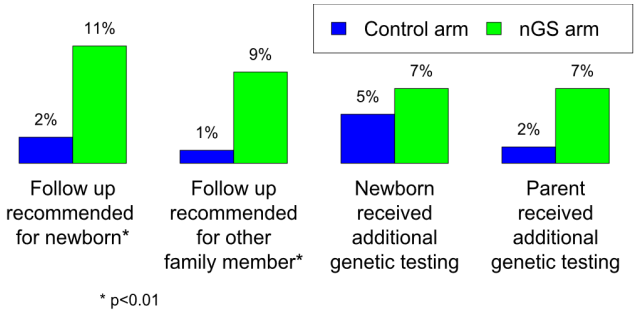


Figure 3. Percentage of BabySeq1 families who received recommendations for clinical follow-up at disclosure or genetic testing in the 10 months following disclosure

Healthcare Utilization/Cost Outcomes: We explored healthcare utilization and costs using techniques developed and piloted in our prior projects.[23; 35; 64; 65] Data collected through the parental surveys and medical record reviews captured medical costs and parental time lost from work, and we reviewed the notes

from the disclosure sessions. For those in the GS arm recommendations were frequently made for follow-up and testing for the newborn and a family member (Figure 3). Preliminary analyses of total healthcare spending in the 3-months following disclosure (Figure 4) showed that total costs per newborn were higher in the GS ($567) compared to control arm ($352).[66]

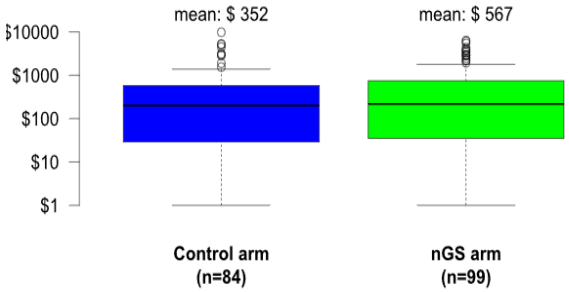


Figure 4. BabySeq1 total health sector expenditures in the 3 months following disclosure sessions.

Prior Work and Data: Engaging Diverse Populations in Genetic Research

We neglected to emphasize in the original application that all 3 of the sites bring extensive experience in engaging URMs in genomic research and in addressing mistrust, fear, stigma, and distress within URM communities, including through the All of Us Research Program (AoURP), the Clinical Sequencing Evidence-Generating Research (CSER) Consortium, and the Implementing GeNomics In pracTicE (IGNITE) Network. In Boston, Dr. Green has led NIH-funded collaborations that have explored URM issues related to genetic testing,[67-74] and consistently recruited 15-24% URM participants in some of the earliest trials disclosing genetic risk information.[75-78] Dr. Green also leads an NIH grant that is the first to systematically return genomic results to AA participants in the Jackson Heart Study, as presaged by these early data.[79] In New York, Dr. Horowitz and her team have successfully recruited and retained thousands of AA and HA individuals in genomic clinical trials via robust community engagement.[80] Her local "genomic stakeholder board" of largely Black and Latinx members is nationally known for community engagement and working with researchers on genomic discovery and translational research,[81] and has led engagement with URM groups in several ways, including the incorporation of novel tools for digital engagement and navigation.[82-84] Dr. Horowitz co-chaired the diversity-focused CSER II Consortium,[85] and chaired the IGNITE Consortium, forming and leading its Diversity Workgroup and engagement strategy.[86; 87] She has conducted mixed methods research to build, pilot, and revise a trial, similar to what we propose here,[88] testing over 2000 hypertensive AA patients at 16 clinical sites for APOL1 variants that increase risk of kidney failure, retaining 93% at 3- and 88% at 12-months follow-up,[80] and demonstrating positive outcomes. In Birmingham, University of Alabama (UAB) investigators are leading the Alabama Genomic Health Initiative and SouthSeq (part of the CSER II Consortium), and staff the leading recruitment site for the entire national AoURP with an overall recruitment of 88.5% participants designated as URMs in biomedical research, including 67.0% based on race/ethnicity. Each of these studies includes a highly functional community advisory board and conducts outreach to community groups to learn about concerns of the community regarding the research.[89; 90]

Prior Work and Data: Returning Unanticipated Genetic Results to HCPs

We neglected to emphasize in the original application our prior work in returning unanticipated genomic results to HCPs and managing the potential for distress and confusion. In addition to our experience in the BabySeq Project,[32-34; 36; 91] our group has extensive experience in the return of unanticipated genomic results to participants and HCPs and in studying the impact on both, which will inform our approach to return of results to HCPs. The NIH-funded MedSeq Project led by Dr. Green was the first to sequence healthy adults and report results directly to primary care HCPs,[57; 92; 93] demonstrating that after a minimal amount of education, HCPs returned the results to their patients without undue errors or distortion of the information.[57; 94] Dr. Holm is leading an NHGRI-funded study of the impact on HCPs of receiving unanticipated GS results in the eMERGE III Network. Interviews of HCPs prior to receiving GS showed concerns about workflow and lack of guidance on handling unanticipated genomic results.[95] The UAB group led by Dr. Korf is conducting a clinical trial of return of WGS results to parents of newborns in the special care nursery. In addition, Dr. Korf's colleagues at HudsonAlpha, now added to this revised proposal, developed a curriculum of didactic lectures and simulation exercises to train non-genetics HCPs in the return of

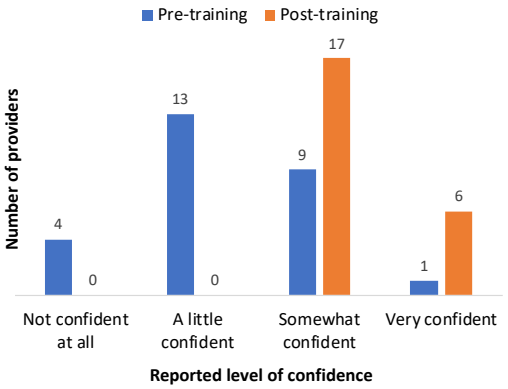


Figure 5. Healthcare provider confidence managing patient care based on WGS results after HudsonAlpha genomics curriculum

WGS results, demonstrating clear improvement in provider confidence (see Figure 5 showing number of providers endorsing each category pre and post curriculum).[96]

APPROACH - *Research Aims and Methods*

Aim 1. *With input from a diverse stakeholder board and focus groups of parents from the 3 CTSA sites,* we will develop a recruitment and retention strategy to enroll 500 apparently healthy, ethnically and racially diverse infants (1-6 months) into an RCT of GS. *Support will be provided for the HCPs though a structured genomics curriculum, and results will be returned to families and their HCP.*

Aim 1a: In light of distrust of research among underrepresented minorities (URMs), we will (a) establish a Stakeholder Board with community representation from all 3 sites, and (b) solicit parental input from the communities to understand the concerns, especially within URM populations, towards GS research and how we can address those concerns as we develop our protocol, recruitment strategies, and disclosure methods.

Methods Aim 1a

The Stakeholder Board: Building upon our prior experience,[97-100] *our Stakeholder Board of parents, community leaders, and clinicians, with representatives from each site, will consist of 12 members, all of whom are themselves AA or HA and a mix of academic experts and patient-participants (see Stakeholder Board letters). The Stakeholder Board will meet in person at the start of the study, then monthly via Zoom video conference for year 1 and quarterly for years 2-4. We will use community-based participatory research (CBPR) approaches described by co-I Dr. Horowitz to choose leaders and rules of engagement.*[80; 101-103] *In year 1, our Stakeholder Board will advise us on: (1) the perspectives of URMs and their HCPs towards genetics and research; (2) issues to address in parent focus groups, who to include, and how best to structure them; and (3) integration of what we learn through the parent focus groups to develop our protocol and materials. In years 2-4, our Stakeholder Board will review and suggest edits to study materials, discuss implementation challenges, and advise on all aspects of the study. Stakeholder Board members will receive a yearly stipend as compensation for their time.*

Parent/caregiver focus groups (Y1, m2-5): We will conduct 2 focus groups, 8-12 parents each, at each site (including 1 in Spanish at BCH and at Mt. Sinai). We will recruit parents who have a child 0-5 years of age through HCPs for 1.5 hour meetings at convenient times for participants. Participants will be compensated for their time. We will ask parents about their own perspectives and then ask them to shift from "I' to "we" by thinking about the community they feel they represent and provide feedback based on what they imagine different members of their community might say. We will develop a focus group guide that includes the following domains (in addition to those identified by our Stakeholder board): (1) how parents prefer to be approached in person and digitally; (2) beliefs about genetics, prior experiences with genetic testing; (3) barriers to participation; (5) concerns about the study; (5) types of genetic information to disclose e.g. monogenic, carrier status, adult-onset conditions, (6) how should genetic information be disclosed (in-person, phone, online); (7) what form results should be presented in, e.g. written, verbal, pictures, digitally; and (8) what outcomes and study results would be of interest. Focus groups will be conducted at each site by an investigator experienced with leading focus groups (and one who speaks Spanish for the Spanish focus groups) and a GC; there will be cross-site training to ensure the approach is similar at each site. Focus groups will be audio-recorded, transcribed, translated if in Spanish, and uploaded to Dedoose (https://www.dedoose.com/). Dr. Holm has experience with focus groups[104] *and she will work with Dr. Pereira (a trained anthropologist) and the BWH project coordinator to develop the focus group guides, code the transcripts, and identify and catalog themes.*

Development of study procedures and materials (Y1, m6-9) will be shaped by what we learn through the focus groups and our Stakeholder Board, our prior experiences in genomics research with diverse populations, and a literature review. The materials will include recruitment strategies, informed consent scripts, and results disclosure templates, and will accommodate low-literacy (<8th grade level) and non-English speaking participants. Stakeholder Board feedback will inform revisions.[84; 102; 105; 106]

Piloting of enrollment materials and procedures (Y1, m10-12): At the end of the enrollment session for the first 2-4 participants at each site we will elicit feedback on the approach, materials, and process using a set of specific questions, and will take notes. What we learn will inform changes in our materials and process.

Piloting of disclosure processes and materials (Y2, m1-3): In order to determine if we are successful in providing parents with genetic information that is comprehensible and informative, we will elicit feedback on process and content from the first 2-4 participants at each site at the end of the disclosure visit. Key questions: (1) understanding and perceived value of the reports; (2) modifications suggested to facilitate comprehension; (3) understanding of MDR (if there is one) and carrier status; and (4) communication strategies to accommodate participants' circumstances. What we learn will inform changes in our materials and process.

Aim 1b: We will modify a successful HudsonAlpha SouthSeq genomics education program utilizing brief didactic videos and live training sessions for the outpatient pediatric HCPs.

Methods Aim 1b

Although the study staff, not the HCPs, will be returning the results to the families, the HCPs will receive the results and follow the families, as in BabySeq. In order to provide education to the HCPs on WGS and the results they may receive, an HCP education program and assessments will be developed by collaborators at the HudsonAlpha Institute for Biotechnology, built upon a similar curriculum they developed and used to train neonatology providers in the SouthSeq project. ***Only the patients of HCPs who participate in the training will be recruited for the RCT (see below).*** *Intervention: The training will focus on helping HCPs understand WGS, the contents of the Genomic Sequencing Report (GSR – see below), what to do next with the results, how to counsel parents about results, resources, etc. The HCP curriculum will include brief, didactic videos as well as a live training at each site for facilitated small group discussion and simulation. Fact sheets and other just-in-time resources will also be provided. Enrollment: Prior to initiating recruitment of families into the RCT, we will invite all HCPs who care for infants at each site to sign a consent form and participate in the education intervention. HCPs will be given a small monetary incentive after completing training and for providing annual feedback. We expect 40% of HCPs at each site to participate at each site, for a total of 28 HCPs enrolled (Table 2). Assessments: (1) Brief, anonymous, pre- and post-training online surveys will be developed by HudsonAlpha to assess HCPs' genetics background and perceived confidence reading and using WGS results. (2) In years 2-4, structured feedback will be collected from HCPs through annual phone/video calls with a member of the HudsonAlpha education team. Topics discussed will include their experiences receiving WGS results, how often they engage in conversations with families about study results (all types), common patient questions, topics they feel more or less confident addressing, and whether gaps in education/training exist. Data analysis: Data from the assessments will used to develop additional clinical decision support resources, as well as to provide data about HCP educational needs.*

Table 2. Number of HCPs and expected enrollment at each CTSA site

Site	Clinic (see Aim 1c below)	# HCPs	Expected # enrolled
BCH	Primary Care Center (CHPCC)	30	12
	Martha Eliot Health Center (MEHC)	13	5
UAB	Children's of Alabama Primary Care Clinic	10	4
	Children's of Alabama Over the Mountain Pediatrics	7	3
Mt. Sinai	Mt. Sinai Pediatric Associated Practice	11	4
TOTAL		71	28

Aim 1c: We will enroll and randomize a cohort of families with infants 1-6 months of age, over half of whom will be of self-reported African or Hispanic ancestry, from 3 CTSA sites with established expertise in engagement, diversity, and genomic clinical trials. Participants will be randomized into FH or GS+FH arms, ***and results will be communicated by genetic counselors to the families and the participating HCPs.*** **(See Figure 6 for study design).**

Enrollment sites Aim 1c:

In Boston, the ***Boston Children's Hospital (BCH) Primary Care Center (CHPCC)*** is the largest pediatric practice in Boston and serves about 16,000 children, most of whom live in low-income neighborhoods of Boston. Forty-five percent of patients are AA and 35% are Latinx; 15% of families are exclusively non-English speaking. The ***Martha Eliot Health Center (MEHC)*** is owned and operated by BCH and is the second oldest community health center in the country. It cares for over 6,000 children, most living in local Boston

neighborhoods. The patient population is diverse with 20% AA, 70% Latinx. *In Birmingham,* the ***Children's of Alabama Primary Care Clinic*** is part of the UAB Department of Pediatrics providing primary care for about 4,200 pediatric patients, with 8000-9000 clinical encounters per year. The clinic accepts 25 new infants each month, most of whom will have at least 5 visits in the first 6 months of life. The clinic population is 80% AA and 8% Hispanic. ***Children's of Alabama Over the Mountain Pediatrics*** provides comprehensive medical care to approximately 11,000 patients, from birth through adolescence, with over 29,500 visits per year, seeing over 80 infants per week who are 21% AA, 3% Hispanic/Latinx. *In New York City,* the ***Mount Sinai Pediatric Associated Practice*** provides comprehensive pediatric care to approximately 10,000 patients with over 23,000 visits per year with a patient population that is 40% Hispanic and 34% AA.

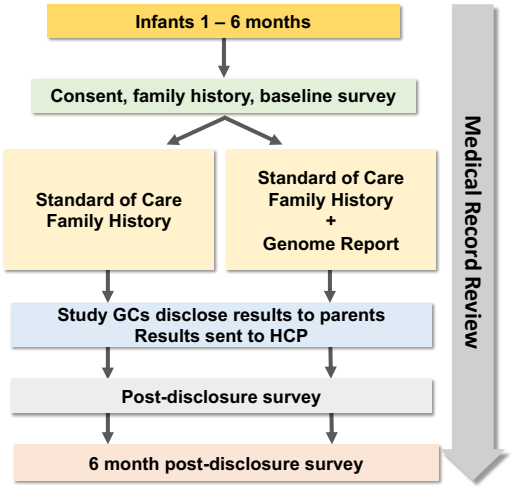


Figure 6. Project Overview

Recruitment, Enrollment, and Retention Aim 1c: Prior to initiating the study we will meet with the staff at each site (nurses, medical assistants, etc.) to review the recruitment, enrollment, and retention plans, as we did in BabySeq and MedSeq.

Recruitment: **Infant inclusion criteria**: (1) apparently healthy; (2) 1-6 months of age; (3) seen for pediatric care at the site; (*4) the primary HCP completed the WGS education program*; and (5) at least one biological parent with the **parent inclusion criteria:** (a) is 18 years of age or older, (b) has unimpaired decisional capacity, (c) is English or Spanish speaking, and (d) is physically available to have genetic counseling and provide consent for testing the infant. We will embed an RA in each clinic and will take advantage of the frequent well baby visits, at 1-, 2-, and 4-months. The RA will approach families to assess interest and provide parents with study materials, in English and Spanish, to take home (available in the clinic). The RA will be Spanish-speaking in clinics with a large Spanish-speaking population. We will strive to hire RAs from the same communities as our participants. They will be trained using techniques proven effective in recruiting URM patients, interviewing mock patients, and receiving feedback.[107-114]

Enrollment will take place in a secluded area to provide privacy and avoid interfering with clinical workflow. Parents will undergo consent with the RA supervised by the GC, ideally before/after an appointment. The staff will read the consent for those with low literacy, if necessary. We plan to enroll 500 infants and their parent(s) into the study (250 in each arm), roughly divided equally between the 3 sites.

Retention: We will leverage methods implemented in the AoURP at UAB and BWH to encourage relationship-building and retention of participants: 1) RAs will be paired with families to coordinate participation and follow-up. 2) We will collect multiple contact methods at enrollment. 3) We will keep track of when our participants return for a clinic visit, using that as an opportunity to connect with them, answer questions, and encourage continued involvement. 4) We will mail birthday cards to the child. 5) Quarterly newsletters, reviewed by the Stakeholder Board, will be shared via email and regular mail, and be available in print at follow-up visits, so families can stay updated on study progress and findings.

Sex and biological variables: We will enroll infants, parents, and HCPs regardless of sex or health status.

Data collection and randomization Aim 1c

At enrollment: After signing the consent form, the RA will collect information from the parent/s, including demographic data and a 3- to 4-generation family history. The parent(s) will complete the baseline survey and the infants will be randomized in a 1:1 ratio to the FH or FH+GS arm within the site. A sample for DNA will be obtained from the infants; although drawing blood is the preferred method, we recognize that this may be a deterrent for some parents to enroll their infant and will explore alternatives, such as heel sticks, with input from our Stakeholder Board. Samples for DNA will be collected from infants in both study arms in order to avoid unblinding the parents, but only samples of those randomized to the GS arm will be sent for analysis. A medical release form will be obtained from parent(s) to collect medical record data.

Genomic sequencing and reporting: For infants randomized to the GS arm, the Laboratory of Molecular Medicine (LMM) will extract DNA and send it to the Broad Institute for CLIA-compliant WGS. Using the same

criteria and reporting procedures as in BabySeq,[32; 34] the LMM will create a Genomic Sequencing Report (GSR) of P/LP variants (not VUSs) in genes known to confer (1) MDR for disorders of childhood-onset or where management may begin in childhood, (2) MDR for highly actionable adult-onset disorders for which parents may be at risk (as per the ACMG SF v2.0 list),[115] (3) carrier status for recessive conditions, and (4) PGx relevant to drugs used in children. A sample for DNA will not be routinely obtained from the parent(s). However, for MDRs found in the infant, saliva for DNA will be collected from the parent(s) at the disclosure visit, DNA extracted at the LMM, and Sanger sequencing of the variant performed in the parent(s) to determine if the finding was *de novo* or inherited; we recognize that if only 1 parent is available our ability to assess inheritance may be limited.

We will also employ GATK-SV to analyze the WGS to identify CNVs known to be associated with disease. P/LP SNPs (single nucleotide polymorphisms), indels (insertions or deletions), and CNVs known to confer risk for childhood-onset disorders will be reported on the GSR. *The LMM and the Broad Institute will collaborate in the validation of the CNV data, making use of on-going projects, including ongoing validation efforts on behalf of sample sequencing for the AoURP. The LMM and Broad have numerous known samples spanning a range of CNV sizes on which GS has been or will be conducted. Novel CNVs will be confirmed via an orthogonal technology (e.g., digital droplet PCR, arrays). We will make use of deeply analyzed benchmark datasets generated by the Genome in a Bottle Consortium and the Human Genome Structural Variation Consortium. We will only return P/LP variants (not VUSs). Regulatory (noncoding) variants will not be returned unless previously classified as disease-causing (e.g., in ClinVar or HGMD), in which case they will be evaluated according to the ACMG guidelines for prediciting pathogenicity. CNVs will not be confirmed in the parent(s).*

Indication-Based Analysis (IBA): If a child in the GS arm develops a phenotype that may have a genetic component, the HCP will be able to ask the LMM to query the genomic data for variants related to the phenotype. An IBA that includes P/LP variants and VUSs for the specific gene/s suggested by the clinical features will be generated and provided by the GC to the family and the HCP, as we did in BabySeq.

Surveys: Parents will complete web-based surveys at baseline (enrollment), and immediately and 6-months post-disclosure. We will develop alternative modes for administration to suit the needs of participants (e.g., phone versions). Surveys will be available in English and Spanish. For those of low literacy, the surveys can be completed verbally with the RA at a clinic visit or over the phone. Recognizing that retention and completion of follow-up surveys may be a challenge, we will have a robust Retention plan in place (see above).

Family history report (FHR): The multi-generation family history taken at enrollment will be interpreted and placed in an FHR, which will be returned to the parent/s and HCPs in both study arms.

Medical record data will be collected by the RA at enrollment and yearly, including diagnoses, visits, tests, procedures, prescription and over-the-counter medications, hospitalizations, and surgeries.

Database: Data will be collected and stored using a data platform created by *Clinical Research IO* (https://www.clinicalresearch.io), which supports electronic data capture for multi-center trials and includes modules for (1) tracking regulatory aspects of clinical trials, (2) participant screening and management, and (3) online, real-time data collection. Surveys will be implemented using the *Clinical Research IO* platform.

Return of Results (RoR) and Follow-up Aim 1c

Genetics Resource Center (GRC) Oversight of the return of reports to HCPs will be supported through the GRC, which will be available to the HCPs and families throughout the study. The GRC will be managed by the GCs and genetics specialists from each site: Dr. Holm (BCH) and Dr. Korf (UAB), both pediatricians and medical geneticists; Dr. Green (BWH), a medical geneticist; and Dr. Gelb (Mount Sinai), a pediatric cardiologist and Professor of Genetics and Genomic Sciences. The GCs and genetics specialists will be available to discuss the reports and other issues with HCPs, and to answer questions for families throughout the study.

Return of Genomic Reports to Parents: The disclosure session for both arms will be done at the 6-, 9-, or 12-month well-baby visit, depending on age at enrollment. We will return and discuss the FHR (FH arm) or the FHR and GSR (FH+GS arm). Prior to the session the GC will review the findings and plan the disclosure visit with the genetics specialist at the site. The GC will conduct the session with the RA (as we did in BabySeq) and the site study physician will be available by phone/ video chat during the session. For Spanish-speaking families, the session will be completed in Spanish with a professional interpreter and the reports will be in Spanish. In addition to a discussion of the FHR in both arms, the GSR discussion for the FH+GS arm will include an explanation of the results, the limitations of WGS, and any recommended actions. We expect the

session to take 30–60 minutes, based on our experience in BabySeq. *Families can contact the GRC throughout the study if they have any questions.*

Providing Genomic Reports to HCPs: The FHR +/- the GSR will be provided to the HCP via fax or secure email after disclosure to the parents. Given that we expect to enroll 500 infants (250 into the FH+GS arm), we anticipate that all of the 28 enrolled HCPs will receive a FHR+GS on at least one of their patients. *If there is a MDR finding on the GSR, the GRC geneticist specialist at the site will contact the HCP by phone or in person, discuss the report, and provide advice, if needed, on interpretation and clinical management. HCPs can use the results to guide care, make needed referrals, etc., informed by the educational activities (Aim 1b). In addition, the GRC geneticist and GC will be available at all times for any HCP with a question about the study, a FHR, or a GSR.*

Aim 2: To evaluate the impact of GS on a diverse group of infants, their families and their HCPs.

Aim 2a: To assess the psychosocial impact of infant GS on parents from varying ethnic and racial backgrounds, we will conduct longitudinal surveys and compare validated scales between arms of the RCT.

Rationale Aim 2a: Although we did not observe negative psychosocial impacts of GS on families in BabySeq, it is critical to determine the impact in more diverse populations and we will do so in 3 realms: 1) parent-child relationship, 2) partner relationship, and 3) personal impact (see Table 3).

Table 3. Aim 2a Variable Domains by Hypothesis

Domain	Construct	Measure
H1. Parent-child relationship	Parenting stress, relationship dysfunction	†Parenting Stress Index, 4th Edition Short Form
	Child vulnerability	Child Vulnerability Scale
H2. Partner relationship	Relationship satisfaction	†Kansas Marital Satisfaction Scale
	Partner blame	Novel, developed for BabySeq
H3. Personal distress	Anxiety	†GAD-7
	Depression	PHQ-9
	Self blame	Novel, developed for BabySeq
†denotes primary outcome for hypothesis		

Methods Aim 2a:

Hypothesis 1: Parents of infants in the FH+GS arm will report no greater disruption to parent-child relationship than those in the FH arm. The literature exploring parents' psychosocial response to expanded NBS has yielded mixed conclusions, with some finding increased parent-child relationship dysfunction,[116-118] and others not.[119] Research on parents' responses to NBS for genetic susceptibility has also found varying results.[120-124] In order to thoroughly assess the impact of GS on families, we will use the Parenting Stress Index Short Form (PSI-4-SF),[125] a well-accepted measure of parent-child relationships that has been previously used to examine the impact of expanded NBS,[116; 117; 119] as our primary outcome, and the Child Vulnerability Scale[126] as a secondary outcome.

Hypothesis 2: Parents of infants in the FH+GS arm will report no greater disruption to the parents' partner relationship than those in the FH arm. Existing research and recommendations raise the issue of parents placing blame on themselves or each other for passing on disease-causative genetic variants after receiving GS results.[127-129] To study relationship conflict and satisfaction, and partner blame, we will measure marital satisfaction with the Kansas Marital Satisfaction scale[116; 117; 119; 130] as our primary outcome, and partner blame using a novel measure developed for BabySeq as a secondary outcome. Given that a significant proportion of our parents may be single, relationship status will be important to factor into the analyses.

Hypothesis 3: Parents of infants in the FH+GS arm will report no greater personal distress than those in the FH arm. Though genetic testing in adults rarely results in long-term distress,[131-135] studies of returning genetic information to parents of children have had mixed results, with some finding increased short-term distress associated with positive results,[136-138] and others finding only mild or no distress.[139-141] Some research has shown increased genetic test-related distress in parents with lower education levels.[138] Our primary outcome measure of personal distress will be anxiety, using the 7-item General Anxiety Index (GAD-7).[142] Secondary measures of distress will be depression, as assessed with the 9-item Patient Health Questionnaire (PHQ-9),[142] and self-blame using a novel measure created for BabySeq. The study staff will follow-up and offer clinical support services to any parent who scores above a predetermined threshold for anxiety or distress on the measures, as we did in BabySeq.

Data collection: Surveys at baseline (enrollment), and immediately and 6-months post-disclosure will be brief (15-25 minutes) and offered to both parents, if available. Parent(s) will complete the surveys online via email or text message, on paper, a tablet computer, or verbally with an RA at the HCP office or over the phone. (See our retention plan, above, to encourage completion of the surveys.) *Data collection for Spanish speakers:* We will make all study materials available in Spanish. Several of our outcome measures have been validated in Spanish-speaking populations, including the PSI-4-SF,[143] the Kansas Marital Satisfaction scale,[144] and the GAD-7.[143] Measures that are novel or do not have a Spanish language version will be translated by native Spanish speakers using forward and back translation procedures.

Data analysis**:** We will view the GS arm as non-inferior if upper bounds of confidence intervals for the differences in means on these outcomes (FH+GS arm minus FH arm) are less than the differences in scores on each scale that are considered clinically meaningful. We will conduct per-protocol analyses in which all families who attended disclosure sessions are analyzed. We will use generalized linear models fit with generalized estimating equations to conduct repeated measures analyses and use contrasts to compare means in the two randomization arms. For analyses of personal distress and parent-child relationships per GAD-7 and PSI-4 scores, we will use a log link, given the right-skewed distributions, while analyses of marital satisfaction per the Kansas Marital Satisfaction scale will use an identity link. Missing data will be imputed using fully conditional specification. Models will include terms for time as a categorical variable, interaction between time and randomization arm, and the corresponding baseline measure, where applicable. Based on 1-sided t-tests and non-inferiority bounds of 5 points for the GAD-7, 9 points for the PSI-4 (0.5 sd), and 1.1 points for the Kansas Marital Satisfaction scale (0.5 sd) and assuming complete data from at least 200 (an 80% completion rate) families in each randomization arm, we estimate over 99% power to confirm noninferiority of GS on each measure at $\alpha = 0.016$ (after Bonferroni correction for three outcomes). Actual analyses will probably be even more precise due to the use of repeated measures and imputation of missing data. Also, for a correlation of about 0.5 among repeated observations in the same subject (as observed on multiple outcomes during BabySeq), we find that the sample size needed with 3 observations, compared to a single observation, is about 65% for the same power and alpha levels. We will also run separate regression models that include terms for ethnicity and ethnicity-randomization arm interactions to determine whether outcomes vary by ethnicity and whether any impact of GS varied by ethnicity. Our Stakeholder Board will be encouraged to pose additional questions for analysis, review and present results, and co-author publications.

Aim 2b: To assess the medical impact of GS on infants and their families, we will review medical records and survey parents to track symptoms, laboratory or diagnostic results, new diagnoses, and medical actions attributed to the GS findings. Among infants with an MDR, we will determine whether the MDR: (a) reveals an unsuspected phenotype in the infant or family, (b) explains a family history of a condition, and/or (c) prompts surveillance in the infant or family.

Rationale Aim 2b: Data on medical outcomes will provide insight into the impact of the FHR and GSR on diagnostic thinking and intermediate clinical outcomes.[145]

Methods Aim 2b: *On a yearly basis,* information collected from parents/caregivers via surveys and/or from the medical records will include: Contact information for the child's HCPs, outpatient visits, hospitalizations and surgeries, parent(s) medical visits and/or testing (due to study information), and parental records relevant to reproductive decision-making. Using methods developed for BabySeq,[35] we will create outcome forms specific to each MDR and condition of note on the FHR that list associated diseases, diagnostic and screening tests, and treatments. We will query the infants' medical record to determine if (a) the MDR was a new or known diagnosis, (b) family histories for the MDR diseases had been recorded, and (c) related diagnostic or screening tests were ordered for an MDR or a condition noted on the FHR. If the information collected is incomplete, a study GC or RA will contact the parent(s). We will keep track of emerging signs and symptoms in children with an MDR and will collect the impact on medical outcomes. *The analysis of these data will largely be descriptive, due in part to the nature of the data with heterogeneous diagnoses, but with the increased sample size proposed in this revised resubmission, there will be a larger set of MDRs to explore.*

Aim 2c: To assess the impact of GS in infants on clinical care, we will collect feedback from HCPs throughout the study by monitoring use of the "Genome Resource Center" and conducting interviews with HCPs towards the end of the study.

Rationale Aim 2c: HCPs providing care for our participants are well positioned to identify the benefits and challenges of implementing GS in their healthy patients and more broadly in the populations enrolled.

Methods Aim 2c: We will conduct semi-structured interviews of HCPs who received a GSR. Drs. Holm and Pereira have experience conducting interviews, including in BabySeq and eMERGE.[95] Interviews will be as efficient as possible (target 30 minutes) and we will offer a $50 incentive per interview. We will interview HCPs of infants randomized to the FH+GS arm until we reach thematic saturation, when additional interviews no longer yield novel information,[146] which we expect will be up to 20 HCPs, with the goal of up to 4 HCPs at each site. Our goal is to ensure that a broad range of experiences are represented to capture benefits and challenges that may be unique to the different sites, as well as obtain sufficient information power.[147]. At each site a trained RA, with oversight by an investigator, will conduct the interviews by phone, video-conference (*e.g.,* Zoom), or in person. Drs. Holm and Pereira will lead the development of an interview guide, with input from our Stakeholder Board. The semi-structured format allows us to guide the HCP to topics we want all interviewees to address, while allowing them to share experiences and introduce relevant issues we did not anticipate. Interviews will be audio-record, transcribed, and the data uploaded to Dedoose for analysis. Data analysis*:* Once at least 5 interviews have been transcribed, Drs. Holm and Pereira will work with the project coordinator at BWH to develop a coding scheme utilizing thematic content analysis.[148] Inductive codes will be added to the coding scheme as new themes emerge. Using the coding scheme, we will use standard methods for team-based qualitative analysis with consensus coding.[149]

Exploratory Aim 3: To evaluate healthcare utilization and associated costs of GS.

Rationale Aim 3: The budgetary implications of integrating WGS into the regular practice of medicine is a major concern,[150-153] given the potential for findings to lead to increased monitoring with limited clinical benefits.[150; 152; 153] At present, the vast majority of trials-based work has focused on white participants with medical problems likely to have a genetic basis.[154-156] This project provides a unique opportunity to gather exploratory trials-based economic data about the impact of GS in diverse populations of healthy infants.

Approach Aim 3:

Data will inform analyses from the health sector and societal perspectives.[157] We will expand on approaches we developed for previous studies and use multiple strategies to identify services and costs associated with the care of infants, their parents, and family members.[23; 64; 65] Approaches are summarized in Table 4**.**

Table 4: Healthcare Utilization Analysis Strategy

Approach	Overview of Services Included	Population of Focus
Attributable services	Services that were recommended during disclosure sessions and services patients reported as motivated by BabySeq disclosure	Child and parents
Genomic services	Any genetic or genomic test	Child and parents
All costs	All healthcare, out-of-pocket, and informal health sector costs	Child only

Primary analyses of healthcare utilization and costs will expand an "attributable services" approach implemented in related work we have conducted.[57; 64] We will use the notes from disclosure sessions to identify services that were recommended for infants or parents, and then verify whether the services occurred. By including only services that we can link directly to this study, this approach will produce data with the greatest measurement precision. To identify efficiencies where genetic tests were avoided by having GS, and to identify instances of cascade genetic testing, we will also focus on genetic services that infants and parents received after disclosure sessions. Finally, we will conduct "all costs" analyses where we summarize all health sector costs observed in medical records and supplemented by survey items that ask about hospitalizations, health care visits, genetic services, and familial out-of-pocket expenses. Due to the expansiveness of this approach, "all costs" analyses will focus on costs for the care of the child only. Since standards have not been established about what to report from GS, we will collect data to conduct one-way scenario analyses that provide insight about reporting strategies that vary the following:

- *Definition of attributable services*. To provide a high-side estimate of care that may have been prompted, we will use genomic references, including GeneReviews, OMIM, and primary literature,[158; 159] to identify all possible follow-up services that may be used to screen for conditions identified on the FHR or GSR.
- *Classes of findings reported* (*e.g.*, reporting only findings from an IBA, or only MDR).
- *Conditions reported* (*e.g.*, if we reported findings associated only with pediatric-onset conditions, or conditions on the ACMG SF v2.0 list[115]).
- *Classification criteria* (*e.g.*, if we reported only variants classified as pathogenic)

Intervention costs will include pre-analytics, such as DNA extraction, GS variant classification, and disclosure of results. Post-disclosure costs will use actual cost data when available, updated to the year of analysis using the medical care component of the Consumer Price Index (CPI).[160; 161] Costs will be assigned to other downstream healthcare services by multiplying utilization by cost weights derived from the Centers for Medicare and Medicaid Studies fee schedules.[64] To facilitate analyses from the societal perspective, we will collect data about family out-of-pocket expenses using survey items.[64; 157] We will use generalized linear models with a log link and gamma family error to compare randomization arms on attributable costs for infants and their parents. Cost analyses will be exploratory, but we anticipate that we will have 93% power at α=0.05 (two-tailed) to detect a standardized effect size of d=0.31, which is roughly equivalent to attributable costs in the GS arm being approximately 61% greater than attributable costs in the control arm. We will also run regression models that include terms for ethnicity and ethnicity-randomization arm interactions to determine whether costs overall and/or incremental cost of GS varies by ethnicity.

BARRIERS, LIMITATIONS, AND ETHICAL ISSUES

Participation of AAs and HA populations in genomic health-related research tends to be low as discussed above.[162] In Aim 1, we plan a systematic community engagement effort, and we will work closely with HCPs at the enrollment sites who are highly engaged and committed to bring the potential benefits of genomic medicine to their patients. Since distrust contributes to lack of enrollment, engaging with HCPs who have a relationship with the patients will mitigate this barrier.

The overall sample size is modest, particularly for the assessment of infants who will be found to have MDRs in the GS arm. However, a strength of this project is that it provides a unique opportunity to provide novel insights into how to engage, enroll, conduct GS, and return results, all while studying the impact on a population typically under-represented in biomedical research. In this revision we have increased the sample size to 500 infants enrolled (250 sequenced).

We recognized a number of important ethical issues in this research: (1) There is uncertainty associated with genomic information, especially for the racially and ethnically diverse populations in which penetrance estimates are not as well known. (2) HCPs in this study may be confused by novel information that is outside of their comfort zone and concerned that they will make inappropriate decisions with regard to the patients that are under their care. (3) Parents of the infants enrolled could learn information that makes them anxious, or that causes their HCPs to recommend medical testing that they did not anticipate. In this revised submission, we have shifted more of the responsibility of return of results onto the study GCs, added an HCP educational program, and added the GRC, which will provide consultative resources for the HCPs, as well as participating families.

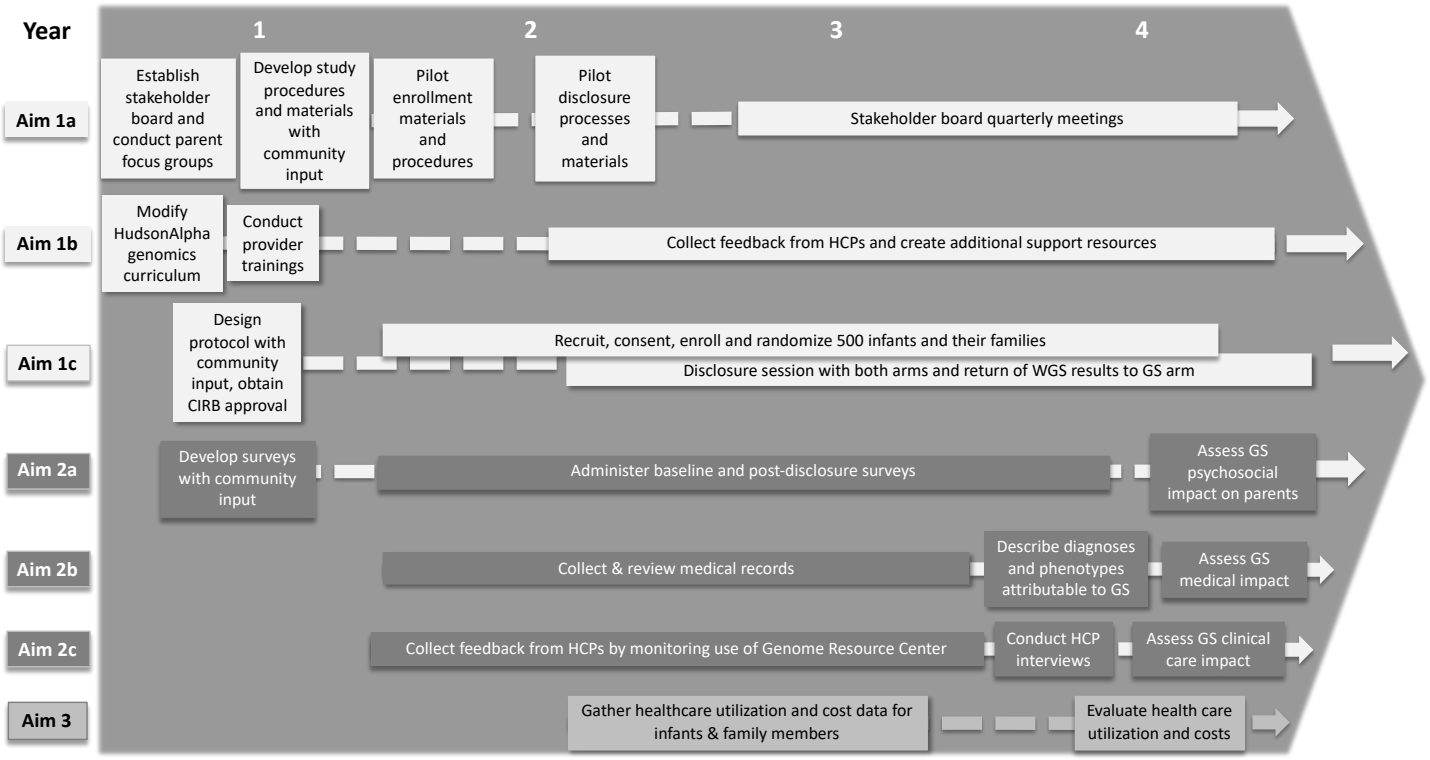
PLANS FOR SUSTAINABILITY

The overall goal of this project is to provide evidence that supports efforts around the dissemination of genomic sequencing as a sustainable screening tool for healthy infants leading to improved health of individuals and the public. As GS prices come down and interpretation becomes more automated, we are on the verge of implementation of GS in pediatrics to inform healthcare. However, it is crucial to provide evidence to guide this implementation down an appropriate pathway and understand the implications of integrating GS into clinical medicine in a generalizable way. We believe that our study will provide such rich evidence in a healthy population of infants and their families. In addition, this study will advance translation of genomic technology from the laboratory to the general pediatric population.

TIMELINE

See separate section.

Timeline


Year
1
2
3
4
Aim 1a
Establish stakeholder board and conduct parent focus groups
Develop study procedures and materials with community input
Pilot enrollment materials and procedures
Pilot disclosure processes and materials
Stakeholder board quarterly meetings
Aim 1b
Modify HudsonAlpha genomics curriculum
Conduct provider trainings
Collect feedback from HCPs and create additional support resources
Aim 1c
Design protocol with community input, obtain CIRB approval
Recruit, consent, enroll and randomize 500 infants and their families
Disclosure session with both arms and return of WGS results to GS arm
Aim 2a
Develop surveys with community input
Administer baseline and post-disclosure surveys
Assess GS psychosocial impact on parents
Aim 2b
Collect & review medical records
Describe diagnoses and phenotypes attributable to GS
Assess GS medical impact
Aim 2c
Collect feedback from HCPs by monitoring use of Genome Resource Center
Conduct HCP interviews
Assess GS clinical care impact
Aim 3
Gather healthcare utilization and cost data for infants & family members
Evaluate health care utilization and costs

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Biosketches

Table of Contents

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: BEGGS, ALAN

eRA COMMONS USER NAME (credential, e.g., agency login): abeggs

POSITION TITLE: Sir Edwin & Lady Manton Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Cornell University, Ithaca, NY	AB	05/1982	Biology
Johns Hopkins University, Baltimore, MD	PHD	10/1987	Human Genetics
Johns Hopkins U. School of Medicine, Baltimore, MD	Postdoctoral Fellow	05/1988	Medical Genetics
Harvard Medical School / Children's Hosp, Boston, MA	Postdoctoral Fellow	05/1992	Molecular Genetics

A. Personal Statement

The Aims of this proposal “Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants” are to explore the implications of genomic sequencing in a diverse cohort of children enrolled as infants and to disseminate findings throughout the. CTSA Network. The ultimate goal is to further develop and optimize the use and application of genomic sequencing data for the clinical care of patients and their families in a pediatric setting. My training is in human genetics, which I have used to understand the genetic and cell biological basis for inherited human developmental and neurologic disorders of newborns and children. Throughout my career, I have used the toolset of human molecular genetics to study normal biology and pathophysiology of a variety of disorders including muscular dystrophies (DMD, BMD), cardiac arrhythmias (LQTS), developmental brainstem defects (CFEOMs), hereditary anemias (DBA), and sudden infant death syndrome (SIDS). A major focus of our work over the years has been on gene discovery and improving methods for identification of pathogenic mutations, with return of these research results to patients in a clinical setting. A primary research focus has been on skeletal muscle-specific genes and human neuromuscular disorders, particularly the muscular dystrophies and non-dystrophic congenital myopathies. Over the past decade, my laboratory has built one of the largest well-characterized registries and DNA/tissue banks of patients representing the full spectrum of congenital myopathies, with which we have carried out extensive genotype-phenotype correlation studies. Significant accomplishments include characterization of patients with Duchenne/Becker and congenital muscular dystrophies, development of rapid and sensitive multiplexed PCR tests for muscular dystrophy that are still used in many clinical diagnostic laboratories worldwide, cloning and characterization of α-actinin genes, and gene discovery in many rare diseases including LQTS, CFEOM, DBA, as well as congenital myopathies. In recent years, we have accomplished many new gene discoveries through the use of whole exome sequencing, and have arranged for clinical confirmation and return of these results in a clinical setting. I am also the founding director of The Manton Center for Orphan Disease Research at Boston Children’s Hospital, which provides resources and a training environment to support research on understudied “orphan diseases”. Through the Center, we support junior faculty with multiyear career development awards, pilot project grants, and access to the Center’s Gene Discovery Core (GDC), which provides genetic and genomic analysis services, and a rich collaborative environment for interactions between clinicians, researchers and bioinformaticians. I am also BCH site PI for a subcontract to the Broad Institute Center for Mendelian Genomics and am active institutionally in developing protocols and pipelines for the routine application of whole exome/genome sequencing in both research and clinical environments. Most recently I have collaborated closely with Drs. Robert Green and Ingrid Holm on the extension and application of new genomic technologies to exploring the risks and benefits of sequencing for newborns and their families. This proposal represents a continuation of this work, for which I am well qualified.

1. Ceyhan-Birsoy O, *et al*. Interpretation of Genomic Sequencing Results in Healthy and Ill Newborns: Results from the BabySeq Project. 2019 Jan;104:76-93. PubMed PMID: 30609409; PubMed Central PMCID: PMC6323417.

2. Beggs AH, *et al*. A multicenter, retrospective medical record review of X-linked myotubular myopathy: The recensus study. Muscle Nerve. 2018 Apr;57(4):550-560. PubMed PMID: 29149770; PubMed Central PMCID: PMC5900738.
3. Holm IA, *et al*. The BabySeq Project: implementing genomic sequencing in newborns. BMC Pediatr. 2018 Jul 9;18(1):225. PubMed PMID: 29986673; PubMed Central PMCID: PMC6038274.
4. Cummings BB, *et al*. Improving genetic diagnosis in Mendelian disease with transcriptome sequencing. Sci Transl Med. 2017 Apr 19;9(386). PubMed PMID: 28424332; PubMed Central PMCID: PMC5548421.

B. Positions and Honors

Positions and Employment

1988 - 1991	Associate, Howard Hughes Medical Institute, Boston, MA
1992 -	Research Associate, Boston Children's Hospital, Dept. Medicine (Genetics & Genomics), Boston, MA
1992 - 1993	Instructor, Harvard Medical School, Department of Pediatrics, Boston, MA
1993 - 1999	Assistant Professor, Harvard Medical School, Department of Pediatrics, Boston, MA
1995 - 1995	Interim Director, DNA Diagnostic Laboratory, Boston University School of Medicine, The Center for Human Genetics, Boston, MA
2000 - 2010	Associate Professor, Harvard Medical School, Department of Pediatrics, Boston, MA
2010 -	Sir Edwin & Lady Manton Professor, Harvard Medical School, Department of Pediatrics, Boston, MA

Other Experience and Professional Memberships

1989 -	Member, American Society of Human Genetics
1993 - 2003	Board Certification in Clinical Molecular Genetics, American Board of Medical Genetics
2000 -	Member, Editorial Board, Journal of Negative Results in Biomedicine
2000 - 2001	Consultant, 5 Year Planning Committee for SIDS Research, NICHD, NIH
2002 - 2007	Scientific Director, Microarray Core Laboratory, Boston Children's Hospital
2005 - 2006	Ad hoc reviewer, NIH Skeletal Muscle & Exercise Physiology Study Section
2006 - 2010	Standing Member, NIH Skeletal Muscle & Exercise Physiology Study Section
2007 - 2009	Ad hoc reviewer, NIH Skeletal Muscle Small Business SEP, ZRG1 MOSS-H 14
2008 -	Director, The Manton Center for Orphan Disease Research, Boston Children's Hospital
2008 -	Member, SAB, A Foundation Building Strength for Nemaline Myopathy, Palo Alto, CA
2008 -	Member, Medical Advisory Committee, Muscular Dystrophy Association
2009 - 2011	Associate Member, The Broad Institute, Cambridge, MA
2009 - 2013	Associate Chief, Research, Boston Children's Hospital
2011 -	Advisory Board Member, Congenital Muscle Disease International Registry (CMDIR)
2011 - 2017	Member, Board of Directors, American Medchem Nonprofit Corporation, Salt Lake City, UT
2011 -	Member, Editorial Board, Skeletal Muscle
2011 - 2014	Member, SAB, IGNITE Orphan Disease Center, Dalhousie Univ, Halifax, Canada
2011 - 2016	Member, Study Section, Committee A, March of Dimes
2013 -	Member, SAB, Audentes Therapeutics, Inc.
2014 -	Member, Editorial Board, Journal of Neuromuscular Diseases
2018-	Associate Director and Genetics Core Director, Boston Children’s Hospital IDDRC
2018 - 2019	Chair, Wellstone Center Evaluation Working Group, NIAMS, NIH

Honors

1985	Dean G. Herberton Evans Fellowship, Johns Hopkins University
1988	Fellowship, Howard Hughes Medical Institute

1992	Fellowship, Charles H. Hood Foundation
2008	Sir Edwin & Lady Manton Professorship of Pediatrics in the Field of Genetics, Harvard Medical School

C. Contribution to Science

1. **Discovery of rare Mendelian disease genes**. With the development of next generation sequencing technologies, recent technological advances have revolutionized our ability to sequence entire exomes and genomes. As founding Director of The Manton Center for Orphan Disease Research, I have built an institutional infrastructure to ascertain, consent, and enroll patients with rare genetic diseases into a research program that allows us to phenotype and genotype patients with unknown diagnoses who otherwise would be discharged and potentially lost to follow up without the benefit of any research investigation. The Center provides expertise in next generation sequencing and analysis to junior clinical and research staff and collaborative support in new gene discovery, which has led to numerous genetic discoveries as well as spawning new research projects throughout the hospital.

    a. Mehta P, *et al*. Novel mutation in *CNTNAP1* results in congenital hypomyelinating neuropathy. Muscle Nerve. 2017 May;55(5):761-765. PubMed PMID: 27668699; PubMed Central PMCID: PMC5366284.
    b. Cao S, *et al*. Homozygous *EEF1A2* mutation causes dilated cardiomyopathy, failure to thrive, global developmental delay, epilepsy and early death. Hum Mol Genet. 2017 Sep 15;26(18):3545-3552. PubMed PMID: 28911200.
    c. Brownstein CA, *et al*. Mutation of *KCNJ8* in a patient with Cantú syndrome with unique vascular abnormalities - support for the role of K(ATP) channels in this condition. Eur J Med Genet. 2013 Dec;56(12):678-82. PubMed PMID: 24176758; PubMed Central PMCID: PMC3902017.
    d. Sankaran VG, *et al*. Exome sequencing identifies *GATA1* mutations resulting in Diamond-Blackfan anemia. J Clin Invest. 2012 Jul;122(7):2439-43. PubMed PMID: 22706301; PubMed Central PMCID: PMC3386831.

2. **Application of genome sequencing in pediatrics**. Through leadership of the BabySeq project and related activities I have been extensively involved in the development of protocols for generation and analysis of genomic sequence data on both healthy and sick infants, children, and adults, and in assessing both benefits and potential risks associated with return of such data in clinical and research settings.

    a. Genetti CA, *et al*. Parental Interest in Genomic Sequencing of Newborns: Enrollment Experience from the BabySeq Project. Genetics in Medicine, In Press, 2018.
    b. Ceyhan-Birsoy O, *et al*. A curated gene list for reporting results of newborn genomic sequencing. Genet Med. 2017 Jul;19(7):809-818. PubMed PMID: 28079900; PubMed Central PMCID: PMC5507765.
    c. Cacioppo CN, *et al*. Expectation versus Reality: The Impact of Utility on Emotional Outcomes after Returning Individualized Genetic Research Results in Pediatric Rare Disease Research, a Qualitative Interview Study. PLoS One. 2016;11(4):e0153597. PubMed PMID: 27082877; PubMed Central PMCID: PMC4833284.
    d. Brownstein CA, *et al*. An international effort towards developing standards for best practices in analysis, interpretation and reporting of clinical genome sequencing results in the CLARITY Challenge. Genome Biol. 2014 Mar 25;15(3):R53. PubMed PMID: 24667040; PubMed Central PMCID: PMC4073084.

3. **Gene discovery and genotype-phenotype correlations in the congenital myopathies**. Following my postdoctoral work on Duchenne and Becker muscular dystrophies, I began my independent research career focused on understanding the genetics of the non-dystrophic congenital myopathies such as nemaline myopathy, centronuclear myopathy, and related conditions. Starting with linkage studies in the early 1990's, we identified two loci for nemaline myopathy (NM) on chromosomes 1 and 2, leading to discovery of mutations for the first two NM genes, *TPM3* and *NEB*. Over the years we contributed to discoveries of seven of the ten known NM genes, four of the six known genes for centronuclear myopathy, and a handful of genes for core myopathies and related neuromuscular diseases. Our new understanding

of the genetic basis for congenital myopathies has led to the appreciation of extensive genetic and phenotypic heterogeneity for these conditions and forced a reevaluation of traditional histopathological diagnostic criteria.

a. Agrawal PB, *et al*. SPEG interacts with myotubularin, and its deficiency causes centronuclear myopathy with dilated cardiomyopathy. Am J Hum Genet. 2014 Aug 7;95(2):218-26. PubMed PMID: 25087613; PubMed Central PMCID: PMC4129406.

b. Gupta VA, *et al*. Identification of *KLHL41* Mutations Implicates BTB-Kelch-Mediated Ubiquitination as an Alternate Pathway to Myofibrillar Disruption in Nemaline Myopathy. Am J Hum Genet. 2013 Dec 5;93(6):1108-17. PubMed PMID: 24268659; PubMed Central PMCID: PMC3852928.

c. Ceyhan-Birsoy O, *et al*. Recessive truncating titin gene, *TTN*, mutations presenting as centronuclear myopathy. Neurology. 2013 Oct 1;81(14):1205-14. PubMed PMID: 23975875; PubMed Central PMCID: PMC3795603.

d. Agrawal PB, *et al*. Nemaline myopathy with minicores caused by mutation of the *CFL2* gene encoding the skeletal muscle actin-binding protein, cofilin-2. Am J Hum Genet. 2007 Jan;80(1):162-7. PubMed PMID: 17160903; PubMed Central PMCID: PMC1785312.

4. **Development and analysis of animal models for neuromuscular disease**. Discovery and creation of faithful animal models for human diseases is a critical aspect of facilitating studies of pathophysiological mechanisms and development of safe and effective therapies. We have actively pursued this with the creation and study of murine models for *Sepn1*-related myopathy, nemaline myopathy (*Cfl2*), myotubular myopathy, T-cap, and more. We have also utilized zebrafish, to create models and conduct drug screens. Finally, we have discovered and characterize several canine models of myotubular myopathy and used these animals to develop gene therapy for this condition.

a. Childers MK, *et al*. Gene therapy prolongs survival and restores function in murine and canine models of myotubular myopathy. Sci Transl Med. 2014 Jan 22;6(220):220ra10. PubMed PMID: 24452262; PubMed Central PMCID: PMC4105197.

b. Lawlor MW, *et al*. Enzyme replacement therapy rescues weakness and improves muscle pathology in mice with X-linked myotubular myopathy. Hum Mol Genet. 2013 Apr 15;22(8):1525-38. PubMed PMID: 23307925; PubMed Central PMCID: PMC3605830.

c. Beggs AH, *et al*. *MTM1* mutation associated with X-linked myotubular myopathy in Labrador Retrievers. Proc Natl Acad Sci U S A. 2010 Aug 17;107(33):14697-702. PubMed PMID: 20682747; PubMed Central PMCID: PMC2930454.

d. Smith LL, *et al*. Bridging integrator 1 (Bin1) deficiency in zebrafish results in centronuclear myopathy. Hum Mol Genet. 2014 Jul 1;23(13):3566-78. PubMed PMID: 24549043; PubMed Central PMCID: PMC4049309.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/alan.beggs.1/collections/48120924/public/

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R01 HD075802-02
BEGGS, ALAN H. (PI)
07/01/14-06/30/20
Genetic screening and therapies for nemaline myopathies
The major goals of this proposal are to complete the identification of pathogenic genes that cause nemaline myopathy, to develop screening assays for all the known gene mutations, to develop zebrafish models of *ACTA1* NM gene mutations, and to use these models for drug discovery.
Role: PI

U01 HG007690, National Human Genome Research Institute (NHGRI)
LOSCALZO, JOSEPH (PI)
04/01/14-06/30/22
Center for Integrated Approaches to Undiagnosed Diseases
This grant supports the Harvard Clinical Site of the Undiagnosed Diseases Network. Dr. Beggs assists with recruitment of patients through the Manton Center for Orphan Disease Research, and participates as a translational scientist in coordinating and interpreting molecular diagnostic testing of patients.
Role: Co-Investigator

UM1 HG008900, National Human Genome Research Institute (NHGRI)
BEGGS, ALAN (PI)
01/14/16-11/30/20
A joint center for Mendelian genomics
The purpose of the Center is to identify new Mendelian disease genes through application of genomic technologies to patients and family members with highly penetrant genetic conditions due to mutations in yet-to-be identified disease genes.
Role: PI

MDA602235, Muscular Dystrophy Association (USA)
BEGGS, ALAN (PI)
02/01/19-01/31/22
Molecular genetics of congenital myopathies
This grant supports development of a congenital myopathy cohort, study of canine and other vertebrate models for some of these diseases, and development of assays for small molecules to treat some of these conditions.
Role: PI

AFM22531, Association Française contre les Myopathies
BEGGS, ALAN (PI)
03/20/2019-03/19/2020
Modeling the heterogeneity of tropomyoson-related congenital myopathies
This is a project to develop mouse and zebrafish models of congenital myopathy caused by mutations of the *TPM2* and *TPM3* genes.
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: **Clement Joseph Bottino**

eRA COMMONS USER NAME (credential, e.g., agency login): cjb25

POSITION TITLE: Instructor in Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Stanford University, Stanford, CA	BA	2001	Human Biology
Columbia University Vagelos College of Physicians & Surgeons, New York, NY	MD	2005	Medicine
Morgan Stanley Children's Hospital of New York-Presbyterian, New York, NY	Residency	2009	Pediatrics
Boston Children's Hospital, Boston, MA	Fellowship	2012	General Academic Pediatrics
Harvard T.H. Chan School of Public Health, Boston, MA	MPH	2012	Clinical Effectiveness

A. Personal Statement

My role on this project is that of study-site champion. I am an academic primary care pediatrician based at Boston Children's Hospital, where I focus on the health and health care of urban underserved populations. Clinical practice is my area of excellence and constitutes approximately 80% of my effort. I have published on a broad range of topics related to primary care pediatrics, including early literacy, asthma, and pa tient-doctor communication. My specific areas of interest and scientific contribution include social determinants of health, healthcare quality improvement, and childhood obesity. I have significant supporting activity in education as a continuity clinic preceptor for the Boston Combined Residency Program in Pediatrics and as co-director of the primary care component of the pediatric clinical clerkship at Harvard School. I have authored two curricula for pediatric care coordinators on social determinants of health, which have been deployed at the national level. I also devote significant effort (approximately 200 hours per year) in direct student mentorship. Taken together, my breadth of experience makes me well suited to be a study-site champion on this NCATS-funded study: "**Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants**".

1. Chen P, Rea C, Shaw R, Bottino CJ. Associations between Public Library Use and Reading Aloud among Families with Young Children. J Pediatr. 2016 Jun;173:221-227.e1. doi: 10.1016/j.jpeds.2016.03.016. PMID: 27056451
2. Lee CC, Holder-Niles FF, Haynes L, Chan Yuen J, Rea CJ, Conroy K, Cox JE, Bottino CJ. Associations Between Patient-Reported Outcome Measures of Asthma Control and Psychosocial Symptoms. Clin Pediatr (Phila). 2018 Nov 21:9922818812479. doi: 10.1177/0009922818812479. PMID: 30461298
3. Bottino CJ, Manji K. Can Clinical Empathy Be Communicated by Text Message? A Case Report. Telemed J E Health. 2019 Feb 26. doi: 10.1089/tmj.2018.0283. PMID: 30807265.

B. Positions and Honors

Positions and Employment

2012-Present Instructor, Pediatrics, Harvard Medical School, Boston, MA
2012-Present Staff Physician, Division of General Pediatrics, Boston Children's Hospital, Boston, MA

Other Experience and Professional Memberships

2009-Present Member, American Academy of Pediatrics
2010-Present Member, Academic Pediatric Association

Honors

2015 Certificate of Excellence in Tutoring, Harvard Medical School
2018 Faculty Teaching Honor Roll, Boston Combined Residency in Pediatrics

C. Contributions to Science:

1. **Social Determinants of Health.** As a clinical fellow in general academic pediatrics, I led a secondary data analysis of *Project Viva*, a prospective longitudinal cohort study of mother-child pairs. We found that infants living in the most urbanized areas had shorter average sleep duration than those living in less urbanized areas. I later led a clinical study assessing urban families' health-related social needs (e.g. food and housing needs) and relationships to diet quality. We found an incomplete overlap between families' reporting of needs and their requests for help with needs, as well as an association between unmet needs and poor diet quality. More recently, I led a study that found Child Life Specialists (pediatric health professionals who work with children on coping with hospitalization) frequently address health-related social needs and family psychosocial issues in addition to standard medical issues.

   a) Bottino CJ, Rifas-Shiman SL, Kleinman KP, Oken E, Redline S, Gold D, Schwartz J, Melly SJ, Koutrakis P, Gillman MW, Taveras EM. The association of urbanicity with infant sleep duration. Health Place. 2012 Sep;18(5):1000-5. doi: 10.1016/j.healthplace.2012.06.007. PMID: 22795497
   b) Bottino CJ, Rhodes ET, Kreatsoulas C, Cox JE, Fleegler EW. Food Insecurity Screening in Pediatric Primary Care: Can Offering Referrals Help Identify Families in Need? Acad Pediatr. 2017 Jul;17(5):497-503. doi: 10.1016/j.acap.2016.10.006. PMID: 28302365
   c) Bottino CJ, Fleegler EW, Cox JE, Rhodes ET. The relationship between housing instability and poor diet quality among urban families. Acad Pediatr. 2019 Apr 12. pii: S1876-2859(18)30598-9. doi: 10.1016/j.acap.2019.04.004. PMID: 30986548
   d) Bottino CJ, Daniels A, Chung M, Dumais C. Child Life Specialists' Experiences Addressing Social Determinants of Health: A Web-Based Survey. Clin Pediatr (Phila). 2019 Apr 2:9922819839233. doi: 10.1177/0009922819839233. PMID: 30939928

2. **Health care quality improvement**. I led the evaluation of a practice-wide initiative aimed at improving immunization rates for pediatric patients. We found that a multidisciplinary team-based approach using care coordination elements produced measurable and sustainable improvements across the practice. More recently, I co-led an initiative aimed at improving rates of iron supplementation for anemic infants. We found that a multipronged improvement intervention helped improve prescription rates for iron supplementation and adherence to guidelines for hemoglobin reassessment.

   a) Bottino CJ, Cox JE, Kahlon PS, Samuels RC. Improving immunization rates in a hospital-based primary care practice. Pediatrics. 2014 Apr;133(4):e1047-54. doi: 10.1542/peds.2013-2494. Epub PMID: 24664096
   b) Rea CJ, Bottino C, Chan Yuen J, Conroy K, Cox J, Epee-Bounya A, Kamalia R, Meleedy-Rey P, Pethe K, Samuels R, Schubert P, Starmer AJ. Improving rates of ferrous sulfate prescription for suspected iron deficiency anaemia in infants. BMJ Qual Saf. 2019 Apr 10. PMID: 30971434.

3. **Childhood obesity.** I have focused on obesity given its high co-morbid prevalence among urban underserved children. My innovations in this space include a home-based health coaching intervention to promote household routines, an evidence-based guideline for management of elevated body mass index, and a model for group visits for patients with elevated body mass index. In a randomized trial, the health coaching intervention was successful at improving sleep duration, television viewing, and body

mass index. In contrast, group visits were unsuccessful in reducing body mass index, although they were associated with high family satisfaction scores.

a) Haines J, McDonald J, O'Brien A, Sherry B, Bottino CJ, Schmidt ME, Taveras EM. Healthy Habits, Happy Homes: randomized trial to improve household routines for obesity prevention among preschool-aged children. JAMA Pediatr. 2013 Nov;167(11):1072-9. doi: 10.1001/jamapediatrics.2013.2356. PMID: 24019074
b) Thaker VV, Lee F , Bottino CJ, Perry CL, Holm IA, Hirschhorn JN, Osganian SK. Impact of an Electronic Template on Documentation of Obesity in a Primary Care Clinic. Clin Pediatr (Phila). 2016 Oct;55(12):1152-9. doi: 10.1177/0009922815621331. Dec 15. PMID: 26676994
c) Bottino CJ, Puente GC, Burrage A, Tannis C, Cheng JK, Epee-Bounya A, Cox JE. Primary Care Group Visits for Childhood Obesity: Clinical Program Evaluation. Clin Pediatr (Phila). 2018 Apr;57(4):442-450. doi: 10.1177/0009922817728696. PMID: 28929794

D. Additional Information: Research Support and/or Scholastic Performance

Past Funding Information:

2016-2018 *Safe and effective delivery of supplemental iron to healthy volunteers – the Iron Babies Study*
Bill and Melinda Gates Foundation
Site investigator (0.1 FTE)
Co-investigator on the pediatric arm of a phase I observational study examining blood markers of iron deficiency and malarial infectivity

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Kurt Derek Christensen, PhD

eRA COMMONS USER NAME (credential, e.g., agency login): KDC123

POSITION TITLE: Instructor in Population Medicine, Harvard Pilgrim Healthcare

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Harvard University	BA	1998	Biochemical Sciences
University of Michigan School of Public Health	MPH	2006	Health Behavior and Health Education
University of Michigan	PhD	2012	Health Behavior and Health Education
Brigham and Women's Hospital and Harvard Medical School	Postdoc	2015	Genetics

A. Personal Statement

I am an Instructor in Population Medicine at the Harvard Pilgrim Health Care Institute and Harvard Medical School whose research focuses on the impact of integrating genomic tools into clinical and research settings. My doctoral training was in health behavior and health education, with a focus on how healthy individuals respond to genetic risk assessments for Alzheimer's disease; and my work as an investigator on the REVEAL Study (R01 HG002213) provided some of the earliest data about the behavioral and psychosocial impact of disclosing genetic risk information about common, complex diseases. I received additional training in genomic variant assessment as part of an NIH-funded NRSA postdoctoral fellowship (F32 HG006993) at Brigham and Women's Hospital, where I developed additional skills in health economics. I continued to expand my focus on the economic impact of genomic sequencing as a co-investigator on a funded NIH supplement to MedSeq Project (U01 HG006500), summarizing the cost impact of genome sequencing in primary care and cardiology settings and methods for conducting these analyses. I have continued this work as a co-investigator on the BabySeq Project (U19 HD077671) examining exome sequencing of healthy and sick newborns. In 2016, I received an NIH-funded K01 award in 2016 to examine the cost-effectiveness of genome sequencing in healthy adults (K01 HG009173). As a Co-Investigator for this project, I will lead work at the Harvard Pilgrim site, and oversee economic analyses in this study, including microcosting analyses of the intervention and the downstream impact of genomic risk disclosure on healthcare utilization and associated costs. I will also contribute to the development of surveys to assess patient-reported outcomes.

a. **Christensen KD,** Vassy JL, Phillips KA, Blout CL, Azzariti DR, Lu CY, et al. Short term costs of integrating whole genome sequencing into primary care and cardiology settings: a pilot randomized trial. Genet Med. 2018;20:1544-53. PMCID: PMC6151171
b. **Christensen KD**, Phillips KA, Green RC, Dukhovny D. Cost analyses of genomic sequencing – lessons learned from the MedSeq Project. Value Health. 2018;21:1054-61.
c. Phillips KA, Deverka, PA, Marshall DA, Wordsworth S, Reiger DA, **Christensen KD**, Buchanan Methodological Issues in assessing the economic value of next-generation sequencing tests: many challenges and not enough solutions. Value Health. 2018;21:1033-42.
d. Hart MR, Biesecker BB, Blout CL, **Christensen KD**, Amendola LM, Bergstrom KL, et al. Secondary findings from clinical genomic sequencing: prevalence, patient perspectives, family history assessment, and healthcare costs from a multi-site study. Genet Med. 2019;21:1100-10. PMID:30287922

B. Positions and Honors

Positions and Employment

1995-1996	Research Assistant, Chemistry, University of Minnesota
1996-1997	Research Assistant, Biochemical Sciences, Harvard Medical School
2005-2006	Student Assistant, Genomics & Public Health, Michigan Center for Genomics and Public Health
2005-	Fellow, Public Health Genetics, Genetic Alliance
2007-2010	Research Assistant, Public Health, University of Michigan
2009	Graduate Student Instructor, Public Health, University of Michigan
2011	Graduate Student Instructor, Public Health, University of Michigan
2012-2015	Postdoctoral Research Fellow, Brigham and Women's Hospital & Harvard Medical School
2015-	Instructor, Department of Medicine, Brigham and Women's Hospital & Harvard Medical School

Honors

2004-2005	University of Michigan School of Public Health Tuition Assistance Scholarship
2005	Genetic Alliance Fellowship
2006-2011	Rackham Merit Fellowship
2008	ISR award to attend ICPSR Summer Program or SRC Summer Institute courses
2008	Department of Health Behavior and Health Education Fellowship
2016	ACMG Top Poster award
2016	Brigham and Women's Hospital Chair's Research Award

C. Contributions to Science

Economic Consequences of Integrating Genomics into Clinical Practice and Research

Concerns are high that the widespread use of genomic sequencing will drive up overall healthcare spending not only due to the costs of testing itself, but also because results may motivate confirmatory testing and follow-up screening that provide minimal clinical benefits. My research shows a limited impact of genomic sequencing on downstream healthcare utilization. This work provides some of the earliest data about the economic consequences of integrating genomics into clinical and research settings to inform policies that will accelerate the responsible use of genomic sequencing in healthcare.

a) **Christensen KD**, Vassy JL, Phillips KA, Blout CL, Azzariti DR, Lu CY, et al. Short term costs of integrating whole genome sequencing into primary care and cardiology settings: a pilot randomized trial. Genet Med. 2018;20:1544-53. PMCID: 6151171
b) **Christensen KD**, Phillips KA, Green RC, Dukhovny D. Cost analyses of genomic sequencing – lessons learned from the MedSeq Project. Value Health. 2018;21:1054-61. PMID:30224109.
c) Hylind RJ, Chandler SF, Beausejour Ladouceur V, Roberts AE, Bezzerides V, **Christensen KD**, et al. Phenotypic characterization of individuals with variants in cardiovascular genes in the absence of a primary cardiovascular indication for testing. Circ Genom Precis Med. 2019;12(3):e002463. PMID:30919684
d) **Christensen KD**, Dukhovny D, Siebert U, Green RC. Assessing the costs and cost-effectiveness of genomic sequencing. J Pers Med. 2015;5(4):470. PMCID:PMC4695866

Health Behavior Responses to Genomic Information

Genomic testing has the potential to motivate individuals to target prevention efforts and modify health behaviors in response to inherited risks. While most studies have shown limited ability of genetic risk information to achieve this, my work as a co-investigator on multiple studies of genetic susceptibility testing has shown that Alzheimer's disease may be a notable exception. Furthermore, whether healthy adults make preventive health behavior changes after a genetic risk assessment may be contingent upon how and why genetic services were obtained.

a. **Christensen KD**, Roberts JS, Whitehouse PJ, Royal CDM, Obisesan TO, Cupples LA, et al. Disclosing pleiotropic effects during genetic risk assessment for Alzheimer's disease: a randomized, controlled trial. Ann Intern Med. 2016;164:155-63. PMCID: PMC4979546
b. **Christensen KD**, Roberts JS, Zikmund-Fisher BJ, Kardia SLR, McBride CM, Linnenbringer E, Green RC. Associations between self-referral and health behavior responses to genetic risk information. Genome Med. 2015;7:10. PMCID: PMC4311425

c. **Christensen KD**, Green RC. How could disclosing incidental information from whole-genome sequencing affect patient behavior? Per Med. 2013;10:377-86. PMCID: PMC3852635
d. **Christensen KD**, Roberts JS, Shalowitz DI, Everett JN, Kim SYH, Raskin L, Gruber SB. Disclosing individual CDKN2A research results to melanoma survivors: interest, impact, and demands on researchers. Cancer Epidemiol Biomarkers Prev 2011;20:522-9. PMCID: PMC3833711

Ensuring the Safety of Genomic Risk Disclosure

There has been longstanding concern that genomic risk information will confuse physicians and lead patients to become anxious, depressed or distressed. As a co-investigator on multiple studies of genomic risk disclosure and contributor to NIH-facilitated consortia, my work has helped to refute those concerns. My work has helped to demonstrate that physicians and patients tend to respond well to genetic risk information, including indications of increased risk for conditions lacking proven prevention strategies.

a. **Christensen KD**, Bernhardt BA, Jarvik GP, Hindorff LA, Ou J, Biswas S, et al. Anticipated responses of early adopter genetic specialists and nongenetic specialists to unsolicited genomic secondary findings. Genet Med. 2018;20:1186-95. PMCID: PMC6103906
b. **Christensen KD**, Uhlmann WR, Roberts JS, Linnenbringer E, Whitehouse PJ, Royal CDM, et al. A randomized controlled trial of disclosing genetic risk information for Alzheimer disease via telephone. Genet Med. 2018;20:132-141. PMCID: PMC5897910
c. Robinson CL, Jouni H, Kruisselbrink TM, Austin EE, **Christensen KD**, Green RC, Kullo IJ. Disclosing genetic risk for coronary heart disease: effects on perceived personal control and genetic counseling satisfaction. Clin Genet. 2016;89:251-7.
d. Green RC, **Christensen KD**, Cupples LA, Relkin NR, Whitehouse PJ, Royal CDM, et al. A randomized non-inferiority trial of condensed protocols for genetic risk disclosure of Alzheimer's disease. Alzheimers Dement. 2015;11:122-30. PMCID: PMC4461546

Understandings of New Technologies

Emerging tools for querying patients' genomes, including whole genome and whole exome sequencing, generate complicated results. As an investigator on studies of genetic testing and population surveys, I have shown that both patients' and providers' understandings of genetics are often limited. At the same time, patients are competent at retaining the test information that is most relevant to them.

a. Roberts JS, Robinson JO, Diamond PM, Bharadwaj A, **Christensen KD**, Lee KB, et al. Patient understanding of, satisfaction with, and perceived utility of whole genome sequencing: findings from the MedSeq Project. Genet Med. 2018;20:1069-76. PMCID: PMC6034997
b. Hock KT, **Christensen KD**, Yashar BM, Roberts JS, Gollust SE, Uhlmann WR. Direct-to-consumer genetic testing: an assessment of genetic counselors' knowledge and beliefs. Genet Med 2011;13: 325-32. PMCID: PMC3804135
c. **Christensen KD**, Jayaratne TE, Roberts JS, Kardia SLR, Petty EM. Understandings of basic genetics in the United States: results from a national survey of black and white men and women. Public Health Genomics 2010;13:467-76. PMCID: PMC3025896
d. Harvey EK, Fogel CE, Peyrot M, **Christensen KD**, Terry SF, McInerney JD. Providers' knowledge of genetics: A survey of 5915 individuals and families with genetic conditions. Genet Med 2007;9:259-67.

Development of Research Protocols

Assessing outcomes from genomic testing requires creative and innovative approaches, especially given the sensitive nature of the information and the diversity of results that genomic sequencing can produce. As an investigator on many studies of genetic testing and population surveys, I have helped to develop protocols that capture high-quality data in ways that minimize respondent burdens.

a. Holm IA, Agrawal PB, Ceyhan-Birsoy O, **Christensen KD**, Fayer S, Frankel LA, et al. The BabySeq Project: implementing genomic sequencing in newborns. BMC Pediatr. 2018;18:225. PMCID: PMC6038274
b. Gray, S.W, Martins Y, Feuerman LZ, Bernhardt BA, Biesecker BB, **Christensen KD**, et al, for the CSER Consortium Outcomes and Measures Working Group. Social and behavioral research in genomic sequencing - approaches from the Clinical Sequencing Exploratory Research Consortium Outcomes and Measures Working Group. Genet Med. 2014;16:727-35. PMCID: PMC416312
c. Roberts JS, Shalowitz DI, **Christensen KD**, Everett JN, Kim SYH, Raskin L, Gruber SB. Returning individual research results: development of a cancer genetics education and risk communication protocol. J Empir Res Hum Res Ethics 2010;5:17-30. PMCID: PMC3159194

d. Vassy JL, Lautenbach DM, McLaughlin HM, Kong SW, **Christensen KD**, Krier JB, Kohane IS, Feuerman LZ, Blumenthal-Barby JS, Roberts JS, Lehmann LS, Ho CY, MacRae CA, Seidman CE, Murray MF, McGuire AL, Rehm HL, Green RC. The MedSeq Project: A randomized trial of integrating whole genome sequencing into clinical medicine. Trials. 2014;15:85. PMCID: PMC4113228

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/kurt.christensen.1/bibliography/42248797/public/

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

Sanford Health 20182750 (Christensen) 01/01/2019-12/31/23 Role: Principal Investigator
Medical/Economic ImpacT and Behavioral Responses to Integrating the Sanford ChipS (METRICS) Study
This goal of this research agreement is to summarize the impact of integrating pharmacogenetic and disease predisposition information into patient care within primary care settings, including the effect on clinician preparedness, provider and patient behaviors, medical and economic outcomes, and familial outcomes.

R01 HG009922 (Green) 09/21/18-06/30/21 Role: Co-Investigator
Experiences and Outcomes in Early Adopters of Predispositional Sequencing
The objective of the proposed research is to aggregate data from, and assess the value of, personal predispositional genome sequencing among participants in present day projects focused on sequencing apparently healthy individuals.

K01 HG009173 (Christensen) 09/01/16-08/31/21 Role: Principal Investigator
Cost-effectiveness of Whole Genome Sequencing of Healthy Adults
The goal of this career development award is to determine the cost-effectiveness of integrating whole genome sequencing into the care of healthy adults. One project will assess the health impact and cumulative healthcare costs of whole genome sequencing five years after participants of a randomized controlled trial received results. A second project will extend these analyses over patients' lifetimes using decision analytic models.

R01 HD090019 (Wu) 09/11/17-05/31/22 Role: Co-Investigator
Precision Medicine and Treatment (PreEMPT) Model
The goals of this project are to (1) develop a microsimulation model of genetic variants and corresponding diseases for newborns; (2) assess the clinical impact, cost, and cost-effectiveness of genome sequencing (GS) in newborns using a microsimulation model; and (3) project the impact of incorporating anticipated research advances into GS for newborns.

RF1 AG047866 (Green) 08/20/15-05/31/20 (NCE) Role: Co-Investigator
Risk Education and Evaluation for Alzheimer's Disease – the Study of Communicating Amyloid Neuroimaging (REVEAL-SCAN)
The goal of this multi-site randomized controlled clinical trial is to understand the impact of disclosing amyloid imaging status on neurocognitive tests and psychological outcomes, and whether disclosure of results biases the responses of patients.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Kelly Moreland East

eRA COMMONS USER NAME (credential, e.g., agency login): KELLYEAST

POSITION TITLE: Clinical Applications Lead, Certified Genetic Counselor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Auburn University	B.S.	12/2007	Microbiology
University of North Carolina Greensboro	M.S.	05/2010	Genetic Counseling

A. Personal Statement

I am a certified genetic counselor and the Clinical Applications Lead at the HudsonAlpha Institute for Biotechnology. I oversee and participate in the delivery of genetic and genomic counseling for clinical services and research projects at HudsonAlpha. I have extensive experience developing scalable models for providing genetic counseling to patient participants and education to non-genetic healthcare providers. We have provided genetic counseling for more than 500 families undergoing whole genome sequencing (WGS) for unexplained developmental delays through a NIH funded CSER Consortium project. A subsequent CSER Consortium project, SouthSeq, aims to provide WGS for 700+ newborns in NICUs across the Southeast. Under my direction, the genetic counseling team at HudsonAlpha developed and implemented a training curriculum for NICU non-genetic providers in SouthSeq, who are responsible for enrolling participants and returning WGS results to families. I have co-chaired working groups on Healthcare Provider Education and Survey Measures and Outcomes within the CSER Consortium. Through involvement with population genetic testing programs such as the Alabama Genomic Health Initiative and Information is Power, my team has returned genetic testing results in a scalable manner to thousands of participants. In 2015, I was part of a team at HudsonAlpha responsible for opening a private practice genomics clinic on campus. This clinic provides clinical evaluation and genetic testing for patients with undiagnosed rare disease, as well as patients seeking elective genomic testing. I have assembled a team of outstanding genetic counselors who work together closely to develop and implement clinical, research, and education projects. Under Dr. Lamb's supervision, I will apply my experience and that of my team to develop the educational material and training as outlined in this proposal.

B. Positions and Honors

Positions and Employment

2009-2010 Graduate Assistant, University of North Carolina at Greensboro, Greensboro, NC
2011-2012 Genetic Counselor, Clearview Cancer Institute, Huntsville, AL
2008- Genetic Counselor, Clinical Applications Lead, HudsonAlpha Institute for Biotechnology, Huntsville, AL

Professional Memberships

2009- National Society of Genetic Counselors
2011-2012 Chair, Education SIG
2016-2018, Abstract Working Group
2011- American College of Medical Genetics and Genomics

Honors

2006	Cellular and Molecular Biology Fellowship, Auburn University
2006-2007	College of Science and Mathematics Fellowship, Auburn University
2008	Comer Medal for Excellence in Biological Sciences, Auburn University
2008	Dean's Medalist, Auburn University
2017	Pacesetter Alumni Award, University of North Carolina Greensboro

C. Contributions to Science

1. **Exploring the role of whole genome sequencing in clinical settings:** I have been an investigator on large research projects aimed at exploring the impact of WGS in various clinical settings. Through an NIH funded CSER Consortium project, we explored the role of WGS in patients with explained developmental delay and intellectual disability. A subsequent CSER Consortium project, SouthSeq, explores the role and usability of WGS in NICU nurseries across the Southeast. In addition to identifying genetic diagnoses, these projects have explored the implementation of WGS within the healthcare system and non-genetics providers.
   a. Amendola LM, Dautenbach D, Scollon S, Bernhardt B, Biswas S, **East K**, ... Jarvik, GP. Illustrative Case Studies in the Return of Exome and Genome Sequencing Results. *Personalized Medicine*. 2015. 12(3):283-295.
   b. Amendola LM, Robinson JO, Hart R, Biswas S, Lee K, Bernhardt BA, **East K**, …Blout C. Why Patients Decline Genomic Sequencing Studies: Experiences from the CSER Consortium. *Journal of Genetic Counseling*. 2018. 27:1220-1227.
   c. Brothers KB, **East KM**, Kelley WV, Wright MF, Westbrook MJ, Rich CA, … Clayton EW. Eliciting Preferences on Secondary Findings: The Preferences Instrument for Genomic Secondary Results (PIGSR). *Genetics in Medicine*. 2016. 19(3):337-344.
   d. **East KM**, Cochran, M, Kelley WV, Greve V, Emmerson, K, Raines G, Cochran JN, Hott AH, Bick D. Understanding the present and preparing for the future: Exploring the needs of diagnostic and elective genomic medicine patients. *Journal of Genetic Counseling*. 2019. 28(2).

2. **Exploring the role of genetic testing for screening purposes in a general population**: I have participated in the development and implementation of several on-going population genetic testing initiatives. The Alabama Genomic Health Initiative is a state-wide research project open that offers genetic screening and biobank repository. Information is Power is an initiative specific to the North Alabama population which offers genetic screening specifically for genes associated with hereditary cancer risk. My team is involved in providing genetic counseling and education to participants and healthcare providers involved in these projects. We are also engaged in research activities exploring the impact of genetic testing for screening purposes in an unselected population.
   a. May T, Cannon A, Moss IP, Nakano-Okano M, Hardy S, Miskell EL, Kelley WV, Curry W, **East KM**, …Korf, B. Recruiting Diversity Where it Exists: The Alabama Genomic Health Initiative. *Journal of Genetic Counseling*. In Press.

3. **Increasing genomic literacy for students, educators, professionals and the public:** As the Clinical Applications Lead in the Educational Outreach department at HudsonAlpha, I manage the development and implementation of educational experiences and materials for a variety of audiences including students, teachers, healthcare providers and trainees, patients and the general public. This includes developing classroom materials for middle and high school students, digital activities and serious games, providing professional development opportunities in genetics for professionals in healthcare and education and increasing the public's understanding of clinical applications of genetics and genomics.
   a. **East KM**, Hott AM, Callanan NP, Lamb NE (2012) Biotech 101: An Educational Outreach Program in Genetics and Biotechnology. Journal of Genetic Counseling, 21, 704-12.
   b. **East KE** and Lamb NE "Genetics/Genomics" In Applied Clinical Informatics for Nurses: Alexander S, Frith KH and Hoy H, editors. Jones and Bartlett Learning 2015.
   c. Loftin M, **East K**, Hott A, and Lamb N. "Touching Triton": Building Student Understanding of Complex Disease Risk. *The American Biology Teacher.* 2016. 78(1). pp 15-21.

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/14WEmMWWqLAAL/bibliography/public/

D. Research Support

Ongoing Research Support

NIH/NHGRI 5U01HG007301-07 (mPI: Cooper, Barsh and Korf) 06/14/2013 - 05/31/2021
Title: South-seq: DNA sequencing for newborn nurseries in the South
The goal of this project is to apply WGS to diagnose neonates with rare disorders, increase participation of individuals from underrepresented racial/ethnic groups in genomics clinical trials, provide educational materials appropriate to diverse audiences, equip non-genetics healthcare providers to return WGS results, assess the impact of WGS testing and results, and engage a broad community to implement safer, more effective, and more equitably distributed genomic medicine.
Role: Genetic Counselor

State of Alabama/UAB (PI: Korf) 10/01/2017 - 09/30/2020
Title: Alabama Genomic Health Initiative
The goal of the Alabama Genomic Health Initiative (AGHI) is to accelerate the discovery of genomic variants with health implications and to bring these discoveries to the citizens of Alabama. Participants will be enrolled into a research study and their genome will be sequenced or genotyped by microarray.
Role: Genetic Counselor

Completed Research Support

NIH/NHGRI 4UM1HG007301-04 (mPI: Cooper and Myers) 06/14/2013 – 07/31/2017
Title: Genomic Diagnosis in Children with Developmental Delay
The goal of this project is to address technological, analytical, and ethical challenges that prevent optimal use of DNA sequencing to improve treatment of diseases and life planning for patients and their families. We are applying next-generation DNA sequencing to meet the diagnostic needs of children with developmental delay, intellectual disability and related health problems.
Role: Genetic Counselor

NIH/NCRR SEPA 5R25OD010981-05 (PI: Lamb) 05/01/2011 - 04/30/2017
Title: It's Complex: Engaging Student Discussions around Complex Genetics and Individualized Medicine
The goal of this project is to create an online classroom activity for use in high schools to highlight the complex interplay between genetic and environmental risk factors in common disease.
Role: Content developer

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Bruce D. Gelb

eRA COMMONS USER NAME (credential, e.g., agency login): brgelb

POSITION TITLE: Gogel Family Professor of Child Health and Development; Professor of Pediatrics and of Genetics and Genomic Sciences

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Amherst College, Amherst, MA	B.A.	05/1980	Chemistry
University of Rochester, Rochester, NY	M.D.	05/1984	Medicine
Babies Hospital, Columbia-Presbyterian, NY, NY		06/1987	Pediatrics
Texas Children's Hospital, Baylor College of Medicine, Houston, TX		06/1991	Pediatric Cardiology

A. Personal Statement

Dr. Gelb's research has focused on human genetics, particularly identifying the causes of congenital heart defects and then elaborating disease pathogenesis and outcomes. Much of the group's work for the past decade has focused on Noonan syndrome and related disorders, which are associated with hypertrophic cardiomyopathy and congenital heart defects such as pulmonic stenosis. The group identified *PTPN11* as the first gene for the trait and have identified several others for these RASopathies. Current work includes studies with fruit flies, mouse models and induced pluripotent stem cells as well as whole exome and genome sequencing for further gene discovery. Through the NHLBI-funded PCGC, Dr. Gelb is studying congenital heart defects as a complex trait using various state-of-the-art genomic approaches including GWAS, exome/genome sequencing and array comparative genomic hybridization. Through the NHGRI-funded CSER network, he is studying the implementation of advanced genomic technologies for the care of children with a variety of genetic traits. Clinically, Dr. Gelb co-directs a Cardiovascular Genetics Program, in which children and adults with genetic-based cardiovascular diseases are evaluated and treated.

B. Positions and Honors

Professional Positions

1984-87 **Resident (Pediatrics),** Babies Hospital, Columbia Presbyterian, New York, NY
1987-91 **Fellow (Pediatric Cardiology)**, Texas Children's Hospital, Baylor College of Medicine
1989-91 **Fellow**, Instit. Of Molec. Genetics, Baylor Coll. of Med. (Mentor: Edward R.B. McCabe, MD, PhD)
1991-97 **Assistant Professor (Pediatrics)**, Mount Sinai School of Medicine, New York, NY
1997-2000 **Assoc. Professor (Pediatr, & Hum Genetics)**, Mount Sinai School of Medicine, New York, NY
2000- **Professor (Pediatrics & Human Genetics)**, Icahn School of Medicine at Mount Sinai, NY, NY
2001-10 **Arthur J. and Nellie Z. Cohen Professor of Pediatrics**, Icahn School of Medicine at Mount Sinai, NY, NY
2006- **Director, Center for Molecular Cardiology**, Icahn School of Medicine at Mount Sinai, NY, NY
2009- **Director, Mindich Child Health and Development Institute**, Icahn School of Medicine at Mount Sinai, New York, NY
2010- **Gogel Family Professor of Child Health and Development,** Icahn School of Medicine at Mount Sinai, New York, NY

Honors and Awards:

1980, Phi Beta Kappa; 1984, Alpha Omega Alpha; 1993, Solomon Silver Award in Clinical Medicine, Mount Sinai School of Medicine; 1997, Young Investigator Award, Eastern Society for Pediatric Research; 2001, American Society of Clinical Investigators; 2004 E. Mead Johnson Award, Society for Pediatric Research; 2008

Norman J. Siegel Award, American Pediatric Society; 2010 National Academy of Medicine; 2018 Jacobi Medallion, Icahn School of Medicine at Mount Sinai

Committees:

1998-08 Council, Eastern Society for Pediatric Research; Program Chair, 2003-2005; President 2005-2008
1998-08 Council, Pediatric Cardiology Society of Greater New York; President 2007-
2003-11 Program Committee, Pediatric Academic Societies; 2009-11 Program Chair
2003-07 Committee on Congenital Heart Defects, American Heart Association
2004-07 Council, Society for Pediatric Research
2008-14 Pediatric Subboard, American Board of Pediatrics
2009-13 Federal Advisory Committee, National Children's Study
2009-13 Scientific Advisory Board, National Marfan Foundation
2012- Council, American Pediatric Society; 2017 Acting Secretary/Treasurer; 2018-19 President
2013- Board of Trustees, International Pediatric Research Foundation (President, 2016-17)
2017- Board Member, American Society of Human Genetics (Treasurer, 2019-21)
2018- Board Member, Pediatric Academic Societies (President, 2018-20)

C. Contribution to Science

The Gelb group studied an autosomal dominant trait called Char syndrome, which includes patent ductus arteriosus among its features. In finding the underlying mutations causing Char syndrome, we discovered the first disease gene for this relatively common form of congenital heart disease. We went on to perform additional studies of the genetics of Char syndrome as well as mechanistic studies of related AP-2 transcription factors.

a. Satoda M, Zhao F, Diaz GA, Burn J, Goodship J, Davidson HR, Pierpont MEM, **Gelb BD**. Mutations in the transcription factor AP-2□ cause Char syndrome, a familial form of patent ductus arteriosus. *Nature Genet* 2000, **25**:42-46.
b. Zhao F, Weismann CG, Satoda M, Pierpont MEM, Sweeney E, Thompson EM, **Gelb BD**. Novel *TFAP2B* mutations causing Char syndrome provide a genotype-phenotype correlation. *Am J Hum Genet* 2001, **69**:695-703. PMCID: PMC1226056
c. Tan CC, *et al*. Transcription factor Ap2δ associates with Ash2l and ALR, a Trithorax family histone methyltransferase, to activate *Hoxc8* transcription. *Proc Natl Acad Sci USA* 2008, **105**:7472-7477. PMCID: PMC2396708 [Role: Senior author]
d. Tan CC, Walsh MJ, **Gelb BD**. *Fgfr3* is a transcriptional target of Ap2δ and Ash2l-containing histone methyltransferase complexes. *PLoS One* 2009, **4**:e8535. PMCID: PMC2795170

The commonest non-chromosomal disorder causing congenital heart disease (CHD) is Noonan syndrome. My research group discovered the first gene mutations causing Noonan syndrome and has gone on to discover additional genes. These discoveries have enabled studies that have shown other genetic traits caused by genes encoding RAS/mitogen-activated protein kinase (MAPK) components, mechanistic studies and ongoing efforts to development meaningful treatments for the RASopathies.

a. Tartaglia M, *et al*. Mutations in *PTPN11*, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. *Nature Genet* 2001, **29**:465-468. [Role: Senior author]
b. Pandit B, *et al*. Gain-of-function *RAF1* mutations cause Noonan and LEOPARD syndromes with hypertrophic cardiomyopathy. *Nature Genet* 2007, **39**:1007-1012. [Role: Senior author]
c. Tartaglia M, *et al*. Gain-of-function *SOS1* mutations cause a distinctive form of Noonan syndrome. *Nature Genet* 2007, **39**:75-79. PMCID: PMC3118925[Role: Senior author]
d. Cordeddu V, *et* al. Mutation in *SHOC2* promotes aberrant protein *N*-myristoylation and underlies Noonan-like syndrome with loose anagen hair. *Nature Genet* 2009, **41**:1022-1026. PMCID: PMC2765465 [Role: Co-senior author]

My research group has explored the role of RAS/MAPK mutations in phenotypes associated with the RASopathies and has explored mechanistic studies of disease pathogenesis. Specifically, we were the first to show that *PTPN11* mutations contribute importantly to the pathogenesis of juvenile myelomonocytic leukemia and that *RAF1* mutations can cause childhood-onset dilated cardiomyopathy. We developed fruit fly models of Noonan syndrome, with which we showed that they had a defined deficit in long-term memory acquistition. We then showed that that deficit was not developmental, implying therapy is possible for the neurocognitive abnormalities in that disorder. We were the first group to model cardiovascular disease using human induced

pluripotent stem cells and then discovered cell non-autonomous effects in RASopathy-associated hypertrophic cardiomyopathy.

a. Pagani MR, Oishi K, **Gelb BD**, Zhong Y. Spacing effect: SHP-2 phosphatase regulates resting intervals between learning trials in long-term memory induction. *Cell* 2009, **139**:186-198. PMCID: PMC2770243 [Role: Co-senior author]
b. Carvajal-Vergara X, *et al.* Patient-specific induced pluripotent stem cell derived models of LEOPARD syndrome. *Nature* 2010, **465**:808-812. PMCID: PMC2885001 [Role: Co-senior author]
c. Dhandapany, PS, *et al*. *RAF1* mutations in childhood-onset dilated cardiomyopathy*. Nature Genet* 2014, **46**:635-639. PMCID: PMC4049514 [Role: Co-senior author]
d. Josowitz R, Mulero-Navarro S, Rodriguez NA, Falce C, Cohen N, Ullian EM, Weiss LA, Rauen KA, Sobie EA, **Gelb BD**. Autonomous and non-autonomous defects underlie hypertrophic cardiomyopathy in BRAF-mutant hiPSC-derived CMs. *Stem Cell Rep* 2016, **7**:355-369. PMCID: PMC5032183.

Congenital heart disease (CHD) appears to be caused primarily by genetic defects but behaves like a complex trait. With the development of newer genomic technologies, it has become possible to assess the roles of various genomic lesions in causing CHD. I have been active in this research arena, particularly through my work as a site Principal Investigator for the NHLBI-funded Pediatric Cardiac Genomics Consortium (PCGC). The PCGC's whole exome sequencing studies with CHD trios has established the role of *de novo* mutations, particularly implicating histone modifying enzyme mutations.

a. Zaidi S *et al*. Increased frequency of *de novo* mutations in histone modifying genes in congenital heart disease. *Nature* 2013, **498**:220-223. [Role: co-senior author]. PMCID: PMC3706629
b. Homsy J, *et al.* De novo mutations in congenital heart disease with neurodevelopmental and other congenital anomalies. *Science* 2015,**350**:1262-1266. [Role: Co-senior author] PMCID: PMC4890146
c. McKean DM, *et al*. Loss of RNA expression and allele specific expression associated with congenital heart disease. *Nature Comm* 2016, **7:**12824. [Role: Co-senior author] PMCID: PMC5052634
d. Jin SC, *et al.* Contribution of rare inherited and *de novo* variants in 2,871 congenital heart disease probands. *Nature Genet* 2017,**49**:1593-1601. [Role: Co-senior author] PMID: 28991257 PMCID: PMC4890146

Genomic data sets generated using next generation sequencing provide opportunities for developing novel analytic approaches. Using PCGC whole exome and R NAseq data, we have developed new methods for identifying copy number variants, mosaic variants, and allele-specific gene expression. We have also established the patterns of DNA methylation across the human developmental spectrum.

a. McKean DM, Homsy J, Wakimoto H, Patel N, Gorham J, DePalma SR, Ware JS, Zaidi S, Ma W, Patel N, Lifton RP, Chung WK, Kim R, Shen Y, Brueckner M, Goldmuntz E, Sharp AJ, Seidman CE*, **Gelb BD***, Seidman JG*. Loss of RNA expression and allele specific expression associated with congenital heart disease. *Nature Comm* 2016, **7:**12824. PMCID: PMC5052634. * indicates equal contribution.
b. Manheimer KB, Richter F, Edelmann LJ, D'Souza SL, Shi L, Shen Y, Homsy J, Boskovski MT, Tai AC, Gorham J, Yasso C, Goldmuntz E, Brueckner M, Lifton RP, Chung WK, Seidman CE, SEidman JG, **Gelb BD**. Robust identification of mosaic variants in congenital heart disease. *Hum Genet* 2018, **137**:183-193. PMID: 29417219
c. Manheimer KB, Patel N, Richter F, Gorham J, Tai AC, Homsy J, Boskovski MT, Parfenov M, Goldmutz E, Chung WK, Brueckner M, Tristani-Firouzi M, Srivastava D, Seidman JG, Seidman CE, **Gelb BD**, Sharp AJ. Robust identification of deletions in exome and genome sequence data based on clustering of Mendelian errors. *Hum Mutation* 2018, epub and in press. [Role: Co-senior author]
d. Gilsbach R, Schwaderer M, Preissi S, Grüning BA, Kranzhöfer D, Schneider P, Nührenberg TG, Mulero-Navarro S, Weichenhan D, Braun C, Dreßsen M, Jacobs AR, Lahm H, Doenst T, Backofen R, Krane M, **Gelb BD**, Hein L. Distinct epigenetic programs regulate cardiac myocyte development and disease in the human heart in vivo. *Nat Commun* 2018, **9**:391. PMCID: PMC5786002

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/sites/myncbi/bruce.gelb.1/bibliography/40322853/public/?sort=date&direction=ascending

D. Ongoing Research Support

T32 (HL007824) (Gelb & Kovacic) 07/01/95-07/30/23
NIH/NHLBI
Training program in molecular and cellular cardiology
The major goal of this award is to provide training in molecular and cellular cardiology to pre-doctoral students and post-doctoral fellows.
Role: PI

UM1 (HL098123) (Gelb) 09/01/09-08/31/20
NIH/NHLBI
Genetics of conotruncal defects and associated neurodevelopmental outcomes
The major goals of this project is to identify genetic causes of conotruncal heart defects and to assess the impact of genetic defects in neurodevelopmental outcomes in subjects with conotruncal heart defects.
Role: PI

U54 (OD020353) (Gelb & Cagan) 08/01/15-07/31/20
NIH Office of the Director
A new disease platform leveraging complex Drosophila and mammalian models
The main goal of Project 3 is to use isogenic human induced pluripotent stems with a range of RASopathy mutations in order to understand the pathogenesis of hypertrophic cardiomyopathies in these genetic traits.
Roles: Project Director (Project 3); Co-Investigator (Project 1)

R35 (HL135742) (Gelb) 02/15/17-01/31/24
NHLBI
Pediatric heart disease: Getting from mutations to therapeutics
The goal of this program is to develop therapies for pediatric cardiovascular diseases, starting with the RASopathies, using fruit fly and induced pluripotent stem cell models of disease.
Role: PI

U01 (HG009610) (Gelb, Horowitc, Kenny & Wasserstein) 08/04/17-05/31/21
NHGRI
Incorporating genomics into the clinical care of diverse NYC children
The goal of this program is to compare different genetic testing and genetic counseling approaches to genetic traits in four broad pediatric medical areas, concentrating on subjects who are underrepresented in medicine.
Role: PI

Recently Completed Support

Million Dollar Bike Ride (Gelb) 02/01/19-01/31/20
University of Pennsylvania The Orphan Disease Center
Advancing a novel therapeutic lead for RASopathies
The goal of this project is to evolve chemicals showing efficacy against fruit fly models of RASopathies to generate more drug-like compounds towards the development of novel therapeutics for the RASopathies.
Role: PI

P30 (ES023515) (Gelb & Wright) 06/18/14-03/31/18
The Mount Sinai Transdisciplinary Center on Early Environmental Exposures
The main goal was to establish a transdisciplinary center to understand how environmental exposures in early lie influence health development, and risk of disease and dysfunction across the life span, in infancy, childhood, adolescence and beyond.
Role: Co-I

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Robert C. Green, MD, MPH

eRA COMMONS USER NAME (credential, e.g., agency login): rcgreen

POSITION TITLE: Director, Genomes2People Research Program, Professor of Medicine, Brigham and Women's Hospital, the Broad Institute and Harvard Medical School; Associate Director for Research, Partners Personalized Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Amherst College, Amherst, MA	BA	05/1976	Biology
University of VA Medical School, Charlottesville, VA	MD	05/1980	Medicine
Emory Univ School of Public Health, Atlanta, GA	MPH	05/2000	Epidemiology

A. Personal Statement

I am a medical geneticist and physician-scientist with a research focus in translational genomics and health outcomes. I have over 20 years of experience directing large multi-disciplinary and multi-institutional projects that have generated empirical data around the medical, behavioral and economic impact of utilizing genomics in the practice of medicine and have led the field in designing and implementing randomized trials in genomic medicine. For example, as PI of the REVEAL Study, continuously funded since 1999, I have led 5 randomized trials that will have enrolled a total of over 1,100 individuals to explore emerging themes in translational genomics of susceptibility genes. As PI of the MedSeq Project within the Clinical Sequencing Exploratory Research Consortium, I directed one of the first randomized trials to examine the impact of whole genome sequencing in the adult practice of medicine. As mPI of the BabySeq Project, within the Newborn Sequencing in Genomic Medicine and Public Health Consortium, I have co-directed a randomized trial to examine the risks and benefits of newborn genome sequencing, which the current proposal will expand upon. As PI of the MilSeq Project, I am leading a pilot project of genome sequencing in active duty members of the US military. I am also co-PI of the Harvard Partners (BWH) site for the Electronic Medical Records and Genomics Network, and a co-investigator within the Partners recruitment site for Precision Medicine Initiative (AllofUs).

I have participated in a number of working groups around policy issues in genomic medicine. In particular, I was co-chair and lead author of the process and publication of the 2013 ACMG recommendations on return of incidental variants in clinical sequencing. I see patients in an adult genetics clinic and am the founding director of the Brigham Preventive Genomics Clinic in Boston, MA.

a. Machini K, Ceyhan-Birsoy O, Azzariti DR, Sharma H, Rossetti P, Mahanta L, Hutchinson L, Mclaughlin H, **Green RC**, Lebo M, and Rehm HL. Analyzing and Reanalyzing the Genome: Findings from the MedSeq Project. The American Journal of Human Genetics. 2019 July. 105(1): 177-88.
b. Berg JS, Agrawal PB, Baily DB, Beggs AH, …, **Green RC**, …, Willig L, Yu TW, Wise AL. Newborn sequencing in genomic medicine and public health (NSIGHT). Pediatrics. 2017 February. 139:e20162252. PMC5260149
c. Vassy JL, Lautenbach DM, McLaughlin HM, Kong SW, Christensen KD, Krier J, Kohane IS, Feuerman LZ, Blumenthal-Barby J, Roberts JS, Lehmann LS, Ho CY, Ubel PA, MacRae CA, Seidman CE, Murray MF, McGuire AL, Rehm HL, **Green RC**. The MedSeq Project: a randomized trial of integrating whole genome sequencing into clinical medicine. Trials. 2014 March. 15(1): 85-97. PMC4113228

d. **Green RC**, Goddard KAB, Jarvik GP, Amendola LM, Appelbaum PS, Berg JS, Bernhardt BA, Biesecker LG, et al. The Clinical Sequencing Exploratory Research Consortium: Accelerating the evidence-based practice of genomic medicine. Am J Hum Genet. 2016 June. 98: 1051-1066. PMC5005464

B. Positions and Honors

Positions and Employment

1980-1981 Intern in Medicine, Rhode Island Hospital, Providence, Rhode Island
1981-1982 International Public Health Training and Service, Johns Hopkins School of Public Health
1982-1985 Resident in Neurology, Longwood Neurology Training Program, Harvard Medical School
1985-1987 Fellow in Behavioral Neurology, Neuroanatomy and Epilepsy, Harvard Medical School
1987-1988 Instructor in Neurology, Harvard Medical School
1988-1996 Director, Emory Neurobehavioral Program and Memory Assessment Clinic
1988-1996 Assistant/Associate (1994) Professor of Neurology, Emory University School of Medicine
1996-1999 Emory Univ MPH Candidate (Epi) & Visiting Prof, College Health Sci, Georgia State Univ
1996-2003 Associate Professor of Neurology, Boston University School of Medicine
2003-2011 Professor of Neurology, Medicine (Genetics) and Epidemiology, Boston Univ School of Medicine
2004-2011 Director, Boston University Alzheimer's Disease Clinical and Research Program
2009-2011 Fellow in Genetics, Harvard Medical School
2011-2017 Associate Professor of Medicine, Brigham and Women's Hospital and Harvard Medical School
2011- Associate Director for Research, Partners HealthCare Personalized Medicine
2013- Associate Member, The Broad Institute of MIT and Harvard
2017- Professor of Medicine, Brigham and Women's Hospital and Harvard Medical School

Honors

1985-1986 AES Lennox Postdoctoral Research Fellowship and EFA Penfield Clinical Research Fellowship
1987 The Children's Hospital United CP Fellowship Award and the Farley Award, Harvard Medical School
1994 Cited in Woodward and White's "Best Doctors in America" for Behavioral Neurology
1999 President, Society for Behav & Cognitive Neurol; Chair, AAN Behav Neurol Section
2003 Fellow of the American Neuropsychiatric Association
2012 BRIght Futures Prize, Brigham and Women's Hospital
2014 Coriell Personalized Medicine Research Award
2015 Fellow of the American College of Medical Genetics and Genomics
2016 Department of Medicine Kenneth L. Baughman Faculty Mentoring Award
2019 BIS Research Top 25 Voices in Precision Medicine

C. Contributions to Science

My work is accelerating the implementation of genomic medicine in the following ways:

1. Since 1999, I have been using the disclosure of *APOE* genotype for risk of Alzheimer's disease as a model to study genetic risk disclosure. I created methods for multi-variant models of genetic risk, demonstrated the unexpected safety of disclosing genetic risk information for common complex diseases and provided experimental evidence for adverse selection in insurance purchase following genetic risk assessment. Data from these trials continue to inform policy issues in predictive genetic testing in common, complex diseases.
    a. Christensen KD, Uhlmann WR, Roberts JS, Linnenbringer E, Whitehouse PJ, Royal CDM, Obisesan TO, Cupples LA, Butson MB, Fasaye GA, Hiraki S, Chen CA, Siebert U, Cook-Deegan R, **Green RC.** A randomized controlled trial of disclosing genetic risk information for Alzheimer disease via telephone. Genet Med. 2018. 20(1): 132-141. PMC5897910
    b. Christensen KD, Roberts JS, Whitehouse PJ, Royal CDM, Obisesan TO, Cupples LA, Vernarelli JA, Bhatt DL, Linnenbringer E, Butson MB, Fasaye G-A, Uhlmann WR, Hiraki S, Cook-Deegan R, **Green RC**, for the REVEAL Study Group: Disclosing pleiotropic effects during genetic risk assessment for Alzheimer's disease. Annals Int Medicine. 2016. 164(3): 155-163. PMC4979546
    c. **Green RC**, Roberts JS, Cupples LA, Relkin NR, Whitehouse PJ, Brown T, Eckert SL, Butson M, Sadovnick AD, Quaid KA, Chen C, Cook-Deegan R, Farrer LA. Disclosure of APOE genotype for risk of Alzheimer's disease. N Engl J Med. 2009 Jul. 361(3): 245-54. PMC2778270

d. **Green RC**, Cupples LA, Go R, Benke KS, Edeki T, Griffith PA, Williams M, Hipps Y, Graff-Radford N, Bachman D, Farrer LA. Risk of dementia among white and African American relatives of patients with Alzheimer disease. JAMA. 2002 Jan. 287(3): 329-36.

2. Genome sequencing in clinical care is becoming feasible as a component of healthcare. Systems will need to be designed to promote clear communication of results and decision support for non-geneticist providers. My scholarship has advanced this area through practice innovations such as the creation of a one-page summary of medically relevant results from sequencing and the need to reduce the risk of insurance discrimination for patients.
    a. Vassy JL, Davis JK, Kirby C, Richardson IJ, **Green RC**, McGuire AL, Ubel PA. How primary care providers talk to patients about genome sequencing results: risk, rationale, and recommendation. J Gen Intern Med. 2018 June. 33(6): 877-885. PMC5975138
    b. Vassy JL, McLaughlin HL, MacRae CA, Seidman CE, Lautenbach D, Krier JB, Lane WJ, Kohane IS, Murray MF, McGuire AL, Rehm HL, **Green RC**. A one-page summary report of genome sequencing for the healthy adult. Public Health Genomics. 2015 April. 18(2): 123-129. PMC43448325
    c. **Green RC**, Rehm HL, Kohane IS. Clinical Genome Sequencing. In: Ginsburg G, Willard H, editors. Genomic and Personalized Medicine. 2nd ed. San Diego: Academic Press/Elsevier. 2013.
    d. Vassy JL, Korf BR, **Green RC**: How to know when physicians are ready for genomic medicine. Sci Trans Med. 2015 May. 7(287): 287fs19. PMC4519005

3. Genome sequencing in clinical practice and in biobanks will identify many disease-associated variants with unproven clinical utility. I have collaborated on several consortia, working groups and policy papers in this area.
    a. Holm IA, Mcguire A, Pereira S, Rehm H, **Green RC**, and Beggs AH. "Returning a Genomic Result for an Adult-Onset Condition to the Parents of a Newborn: Insights From the BabySeq Project." Pediatrics. 2019 January. 143.Suppl: S37-S43. PMC6433124
    b. Wolf SM, Branum R, Koenig BA, Petersen GM, Berry SA, Beskow LM, Daly MB, Fernandez CV, **Green RC**, LeRoy BS, Lindor NM, O'Rourke PP, Breitkopf CR, Rothstein MA, Van Ness B, Wilfond BS: Returning a research participant's genomic results to relatives: Analysis and recommendations. J Law Med Ethics. 2015. 43(3): 440-463. PMC4617203
    c. **Green RC**, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, McGuire AL, Nussbaum RL, O'Daniel JM, Ormond KE, Rehm HL, Watson MS, Williams MS, Biesecker LG. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med. 2013 July.15: 565-574. PMC3727274
    d. Wolf SM, Crock BN, Van Ness B, Lawrenz F, Kahn JP, Beskow LM, Cho MK, Christman MF, **Green RC**, Hall R, Illes J, Keane M, Knoppers BM, Koenig BA, Kohane IS, Leroy B, Maschke KJ, McGeveran W, Ossorio P, Parker LS, Petersen GM, Richardson HS, Scott JA, Terry SF, Wilfond BS, Wolf WA. Managing incidental findings and research results in genomic research involving biobanks and archived data sets. Genet Med. 2012 Apr; 14(4):361-84. PMC3597341

4. Genetic information is increasingly being utilized as part of commercial efforts, including direct-to-consumer genetic testing, to provide consumers with genetic risk information related to common diseases. I have prospectively studied the behavioral and medical impact of direct-to-consumer genetic testing.
    a. Zoltick ES, Linderman MD, McGinniss MA, Ramos E, Ball MP, Church GM, Leonard DGB, Pereira S, McGuire AL, Caskey CT, Sanderson SC, Schadt EE, Nielsen DE, Crawford SD, **Green RC**; for the PeopleSeq Consortium. Predispositional Genome Sequencing in Healthy Adults: Design, Participant Characteristics, and Early Outcomes of the PeopleSeq Consortium. Genome Medicine. 2019 February. 11(1). PMC6391825
    b. T, Vassy JL, van der Wouden C, Roberts JS, Kraft P, **Green RC**: Prescription medication changes following direct-to-consumer personal genomic testing: Findings from the Impact of Personal Genomics (PGen) Study. Gen Med. 2017 May; 19(5):537-545. PMC5362351
    c. Krieger JL, Murray F, Roberts JS, **Green RC**. The impact of personal genomics on risk perceptions and medical decision-making. Nat Biotechnol. 2016 Sep. 34(9): 912-918.

d. Van der Wouden CH, Carere DA, Maitland-van der Zee AH, Ruffin MT, Roberts JS, **Green RC**, for the PGen Study Group: Consumer perceptions of interactions with primary care providers after direct-to-consumer personal genomic testing. Ann Intern Med. 2016 April. 164(8): 513-522.

5. I am currently working on empirical studies and policy statements around what may well be the next major controversy in genomic medicine, i.e. using sequencing for predispositional (screening) purposes.
   a. Ceyhan-Birsoy O, Murry JB, Machini K, Lebo M, Yu TW, Fayer S, Genetti CA, Schwartz TS, Agrawal PB, Parad RB, Holm IA, Mcguire AL, **Green RC**, Rehm HL, and Beggs AH. Interpretation of Genomic Sequencing Results in Healthy and Ill Newborns: Results from the BabySeq Project. The American Journal of Human Genetics 104.1 (2019): 76-93. PMC6323417
   b. Vassy JL, Christensen KD Schonman EF, Blout CL, Robinson JO, Krier JB, Diamond PM, Lebo M, Machini K, Azzariti DR, Dukhovny D, Bates DW, MacRae CA, Murray MR, Rehm HL, McGuire AL, **Green RC**. The impact of whole-genome sequencing on the primary care and outcomes of healthy adult patients: A pilot randomized trial. Ann Int Med. 2017 June. 167:1-12. PMC5856654
   c. Christensen KD, Dukhovny D, Siebert U, **Green RC**. Assessing the costs and cost-effectiveness of genomic sequencing. J Pers Med, 2015;5:(4):470-486. PMC44695866
   d. Vassy JL, Christensen KD, Slashinski MJ, Lautenbach D, Raghavan S, Robinson JO, Blumenthal-Barby J, Feuerman LZ, Lehmann LS, Murray MF, **Green RC**: Someday it will be the norm: physician perspectives on the utility of genome sequencing for patient care. Personalized Medicine. 2015. 12(1): 23-32. PMC4306284

A full list of my published work can be found at the following link:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40321733/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R01 HL143295 Green, Ramachandran Correa, Multi-PIs 07/01/19-06/30/23

Return of Genomic Results and Estimating Penetrance in Population-Based Cohorts

The goal of this project is to develop and implement a genomic return of result (gRoR) process in the Framingham Heart Study and Jackson Heart Study cohorts and explore associated medical, behavioral and economic outcomes.

Role: Multi-Principal Investigator

R01 HG009922 Green 07/01/18-06/30/21

Experiences and Outcomes in Early Adopters of Predispositional Sequencing

The goal of this project is to examine the experiences, attitudes and outcomes of apparently healthy adults who have elected to obtain genome sequencing.

Role: Principal Investigator

RF1 AG047866 Green/Karlawish, Multi-PIs 08/20/15-05/31/20 (NCE)

Impact of Disclosing Amyloid Imaging Results to Cognitively Normal Individuals

This project will examine the impact of learning amyloid imaging results in cognitively normal individuals.

Role: Multi-Principal Investigator

R01 HD090019 Wu, PI 09/11/17-05/31/22

Precision Medicine and Treatment (PreEMPT) Model

The goals of this project are to (1) develop a microsimulation model of genetic variants and corresponding diseases for newborns; (2) assess the clinical impact, cost, and cost-effectiveness of genome sequencing (GS) in newborns using a microsimulation model; and (3) project the impact of incorporating anticipated research advances into GS for newborns.

Role: Subcontract Site Director

U01 HG008685 Weiss, PI 08/01/15-07/31/21

eMERGE Phase III Clinical Center at Partners Healthcare

The goal of this project is to enable genomic research into discovery and implementation by leveraging the Partners Biobank, clinical data in the electronic medical record of over 4 million participants in the Partners Healthcare system. My role is to design and supervise all aspects of the implementation aim (Aim 3) where we will conduct a randomized trial of disclosing medically actionable results to Biobank participants and their physicians.
Role: Co-Principal Investigator

OT2 OD24612 Smoller, Weiss, O'Connor, Karlson, Murphy, mPIs 09/27/16-02/28/23

New England Precision Medicine Consortium

The New England Precision Medicine Consortium includes Partners HealthCare System and it's hospitals, Massachusetts General Hospital and Brigham and Women's Hospital, with Boston University and Boston Medical Center. The goal of this project is to enroll and engage a diverse cohort of 10,000 health system participant-partners who will contribute data and biospecimens to the Precision Medicine Initiative (PMI) Cohort Program to advance the future of precision medicine.
Role: co-Investigator and National Co-Chair Return of Value Committee

Completed Research Support

FA8650-17-2-6704 Green, PI 12/01/16-02/28/20

Enabling Personalized Medicine through Exome Sequencing in the U.S. Airforce

The goal of this project is to conduct a proof-of-concept study to address the widespread implementation and adoption of genomic sequencing in the military.
Role: Principal Investigator

U19 HD077671 Green, PI 09/05/13-08/31/19

Genome Sequence-Based Screening for Childhood Risk and Newborn Illness (The BabySeq Project)

The goals of this project are to quantitatively study the risks and benefits of newborn genome sequencing and to test the feasibility and impact on physicians and parents of genomic sequencing in the newborn period to assess future risk of childhood onset disease, as well as to guide diagnosis and treatment of sick newborns.
Role: Multi-Principal Investigator

U01 HG006500 Green, PI 12/05/11-11/30/17

Integration of Whole Genome Sequencing into Clinical Medicine (The MedSeq Project)

The goal of this multi-disciplinary project is to explore the behavioral impact, health outcomes and downstream health care costs of using whole genome sequencing in the practice of medicine. Over 200 physician-patient dyads in active clinical settings will be studied in a clinical trial format with the actual use of whole genome sequencing in both primary care and specialty care.
Role: Principal Investigator

R01 HG007063 Phillips, PI 06/01/13-01/31/17

Risk-Benefit Trade-Offs for Whole Genome Sequencing

The goal of this project is to evaluate the potential benefit-risk tradeoffs of WGS from the perspectives of patients, providers, the health care delivery system, and society by using systematic and quantitative approaches. The team will leverage a unique opportunity to build upon the first randomized clinical trial of WGS using a general population sample (MedSeq Project, Green, PI), which is being led by Harvard Medical School. The team will examine the translation of this technology into clinical care and health policy before the technology becomes widely implemented-and thus inform its appropriate dissemination.
Role: Subcontract Site Director

R01 HG006615 Holm, PI 02/01/12-01/31/16

Returning Research Results in Children: Parental Preferences and Expert Oversight

The goal of this project is to examine the opinions and choices of parents whose children are enrolled in a research biobank with regard to return of research results.
Role: Co-Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Holm, Ingrid

eRA COMMONS USER NAME (credential, e.g., agency login): ingridholm

POSITION TITLE: Associate Professor of Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Brown University, Providence, RI	BS	05/1979	Psychology
University of Washington, Seattle, WA	Other training	05/1981	Chemistry, Biology
UCLA School of Medicine, Los Angeles, CA	MD	06/1985	Medicine
Residency, Boston Children's Hospital, Boston, MA		06/1988	Pediatrics
Fellowship, Boston Children's Hospital, Boston, MA		06/1992	Genetics
Fellowship, Boston Children's Hospital, Boston, MA		06/1992	Pediatric Endocrinology
Harvard School of Public Health, Boston, MA	MPH	06/2003	Clinical Effectiveness
Children's Mercy Hospital, Kansas City, MO	Certificate	05/2018	Pediatric Bioethics

A. Personal Statement

I am a pediatric geneticist and endocrinologist with broad experience in basic research, clinical research, and clinical practice. My major research interests are in the implementation of genomic medicine, especially in pediatrics, and in the Ethical, Legal and Social Implications (ELSI) related to the impact of return of genomic information to participants and families. I am well-suited to be Co-PI with Dr. Robert Green on our proposal *"Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants".* I was co-PI (with Dr. McGuire) of project 3 of our Newborn Sequencing in Genomic Medicine and Public Health **(**NSIGHT) U19 project, *Genome Sequence-Based Screening for Childhood Risk and Newborn Illness*, also called *BabySeq* (BCH PI: Dr. Alan Beggs, and BWH PI: Dr. Green), which informs the current study. The goals of Project 3, the ELSI arm of the BabySeq project, were to examine the clinical outcomes, benefits, and harms of providing genomic newborn sequencing results and of having a full genomic sequence available as a resource for interrogation in both well and sick infants. In addition, I oversaw the recruitment, IRB issues, consenting, return of results, and data collection in the BabySeq project. I also actively participated in the NSIGHT Ethics and Policy Board, which put forth recommendations regarding the integration of sequencing in the newborn period. I chair the Common Data Elements (CDE) work group (now called the Data Analysis and Sharing work group) to collect genomic and phenotypic CDEs across the 4 sites and deposit in a database overseen by the Newborn Screening Translational Research Network (NBSTRN). My work in BabySeq gives me the experience and expertise to serve Co-PI of the current proposal to enroll a diverse cohort of newborns to study the implementation of whole genome sequencing in under-represented minorities.

a. **Holm IA**, Agrawal PB, Ceyhan-Birsoy O, Christensen KD, Fayer S, Frankel LA, Genetti CA, Krier JB, LaMay RC, Levy HL, McGuire AL, Parad RB, Park PJ, Pereira S, Rehm HL, Schwartz TS, Waisbren SE, Yu TW, the BabySeq Project Team, Green RC, Beggs AH. The BabySeq Project: Implementing Genomic Sequencing in Newborns. BMC Pediatr. 2018 Jul 9;18(1):225. doi: 10.1186/s12887-018-1200-1. PMID: 29986673
b. **Holm IA**. Using Newborn Sequencing to Advance Understanding of the Natural History of Disease. Hastings Cent Rep. 2018 Jul;48 Suppl 2:S45-S46. doi: 10.1002/hast.886. PMID: 30133736
c. **Holm IA**, McGuire A, Pereira S, Rehm H, Green RD, Beggs AH; and the BabySeq Project Team. Returning a genomic result for an adult-onset condition to the parents of a newborn: Insights from the

BabySeq Project. Pediatrics. 2019 Jan;143(Suppl 1):S37-S43. doi: 10.1542/peds.2018-1099H. PMID: 30600270

d. VanNoy GE, Genetti CA, McGuire AL, Green RC, Beggs AH, **Holm IA**; BabySeq Project Group. Challenging the current recommendations for carrier testing in children. Pediatrics. 2019 Jan;143(Suppl 1):S27-S32. doi: 10.1542/peds.2018-1099F. PMID: 30600268

B. Positions and Honors

Positions and Employment

1992 – 2001 Instructor in Pediatrics, Boston Children's Hospital, Boston, MA
1992 – 2003 Assistant in Medicine, Boston Children's Hospital, Boston, MA
2001 – Affiliated staff, Department of Newborn Medicine, Brigham and Women's Hospital, MA
2001 – 2003 Fellow, Harvard Pediatric Health Services Research Fellowship, Boston Children's Hospital and Harvard School of Public Health, MA
2001 – 2011 Associate Director, Children's Hospital Bone Health and DXA Unit, Boston Children's Hospital, Boston, MA
2001 – 2013 Assistant Professor of Pediatrics, Boston Children's Hospital, Boston, MA
2002 – 2013 Director, Phenotyping Core, Program in Genomics, Boston Children's Hospital, MA
2003 – Research Staff, Department of Medicine, Brigham and Women's Hospital, MA
2009 – 2015 Chair, Boston Children's Hospital Biorepository Committee, Boston Children's Hospital, MA
2013 – Associate Professor of Pediatrics, Boston Children's Hospital, Boston, MA
2013 – Associate in Medicine, Boston Children's Hospital, Boston, MA

Other Experience and Professional Memberships

1985 – Member, Massachusetts Medical Society
1989 – Fellow, American Academy of Pediatrics
1989 – Member, American Society for Human Genetics
1991 – 2015 Member, American Federation for Clinical Research
1994 – Member, Lawson Wilkins Pediatric Endocrine Society / Pediatric Endocrine Society
1994 – Member, Board member, Vice president, President, Treasurer, Advances in Mineral Metabolism
1994 – Member, American Society for Bone and Mineral Research
1996 – Member, Endocrine Society
1998 – Fellow, American College of Medical Genetics
1999 – Member, American Medical Association
2001 – Member, Society for Pediatric Research
2001 – 2015 Member, International Society for Clinical Densitometry

Honors

1991 National Research Service Award, NIH
1992 Mallinckrodt Foundation Award, Mallinckrodt Foundation
1992 Physician Scientist Award, NIH
1995 Charles H. Hood Foundation Grant Award, Charles H. Hood Foundation
1995 Genentech Foundation Award, Genentech Foundation

C. Contributions to Science

1. One of my major research interests is on the ELSI related to the impact of return of genomic information to participants and families. I worked with Cincinnati Children's Hospital Medical Center (CCHMC) as co-PI with Dr. John Harley at CCHMC of our joint CCHMC/BCH eMERGE (Electronic Medical Records and Genomics) II site. In eMERGE II, I co-led the Consent, Education, Regulation, and Consultation (CERC) work group and the CERC supplement on patient perspectives on broad consent in biobanks, a large survey across the 9 eMERGE II sites. I now a member of eMERGE III where I co-lead the Return of Results (ROR)/ELSI work group, coordinate participant and health care providers surveys, and consult on pediatric and ELSI issues. I have an R01 (HG010004-01) to study the impact of return of genomic results to health care providers in eMERGE 3.
    a. Sanderson SC, Brothers KB, Mercaldo ND, Clayton EW, Antommaria AH, Aufox S, Brilliant MH, Campos D, Carrel DS, Connolly J, Conway P, Fullerton SM, Garrison NA, Horowitz CR, Jarvik GP, Kaufman D, Kitchner TE, Li R, Ludman EJ, McCarty CA, McCormick JB, McManus VD, Myers MF, Scrol A, Williams JL, Shrubsole MJ, Schildcrout JS, Smith ME, **Holm IA**. Public attitudes towards consent and data sharing in biobank research: a large multi-site experimental survey in the US. Am J Hum Genet, 2017 Feb 4. PMID: 28190457. PMCID: PMC5339111

b. Smith ME, Sanderson SC, Brothers KB, Myers MF, McCormick J, Aufox S, Shrubsole MJ, Garrison NA, Mercaldo ND, Schildcrout JS, Clayton EW, Antommaria AH, Basford M, Brilliant M, Connolly JJ, Fullerton SM, Horowitz CR, Jarvik GP, Kaufman D, Kitchner T, Li R, Ludman EJ, McCarty C, McManus V, Stallings S, Williams JL, **Holm IA**. Conducting a large, multi-site survey about patients' views on broad consent: challenges and solutions. BMC Med Res Methodol. 2016 Nov 24;16(1):162. PMID: 27881091. PMC5122167
c. Antommaria AHM, Brothers KB, Myers JA, Feygin YB, Aufox SA, Brilliant MH, Conway P, Fullerton SM, Garrison NA, Horowitz CR, Jarvik GP, Li R, Ludman EJ, McCarty CA, McCormick JB, Mercaldo ND, Myers MF, Sanderson SC, Shrubsole MJ, Schildcrout JS, Williams JL, Smith ME, Clayton EW, **Holm IA**. AJOB Empir Bioeth. 2018 Sep 21:1-15. doi: 10.1080/23294515.2018.1505783. [Epub ahead of print]. PMID: 30240342
d. Pet DB, **Holm IA**, Williams JL, Myers MF, Novak LL, Brothers KB, Wiesner GL, Clayton EW: Physicians' perspectives on receiving unsolicited genomic results. Genet Med. 2018 Jun 14. doi: 10.1038/s41436-018-0047-z. [Epub ahead of print] PMID: 29904163

2. My work on the ELSI and impact of return of genomic research results in a pediatric setting started with several NIH-funded studies. In addition, I am co-PI with Dr. Joel Hirschhorn on an NICHD-funded study: "*Exome Sequencing in Disorders of Sex Development (DSD) Impact on Patients and Families."* I lead the assessment of the impact of returning genetic testing results to parents with children with DSDs.
   a. Harris ED, Ziniel SI, Amatruda JG, Clinton CM, Savage SK, Taylor PL, Huntington NL, Green RC, **Holm IA**. The beliefs, motivations, and expectations of parents who have enrolled their children in a genetic biorepository. Genet Med. 2012 Mar;14(3):330-7. PubMed PMID: 22241099; PubMed Central PMCID: PMC3763713.
   b. **Holm IA**, Savage SK, Green RC, Juengst E, McGuire A, Kornetsky S, Brewster SJ, Joffe S, Taylor P. Guidelines for return of research results from pediatric genomic studies: deliberations of the Boston Children's Hospital Gene Partnership Informed Cohort Oversight Board. Genet Med. 2014 Jul;16(7):547-52. PubMed PMID: 24406460.
   c. **Holm IA**, Iles BR, Ziniel SI, Bacon PL, Savage SK, Christensen KD, Weitzman ER, Green RC, Huntington NL. Participant satisfaction with a preference-setting tool for the return of individual research results in pediatric genomic research. J Empir Res Hum Res Ethics. 2015 Oct;10(4):414-26. PMID: 26376753.
   d. Ziniel SI, Savage SK, Huntington N, Amatruda J, Green RC, Weitzman ER, Taylor P, **Holm IA**. Parents' preferences for return of results in pediatric genomic research. Public Health Genomics. 2014;17(2):105-14. PubMed PMID: 24642506; PubMed Central PMCID: PMC4073487.
3. As Co-PI with Dr. John Harley at CCHMC of our joint CCHMC/BCH eMERGE II site, I was involved in many aspects of eMERGE II studies to understand the genetics of complex traits
   a. Namjou B, Marsolo K, Todd Lingren T, Ritchie MD, Verma SS, Cobb BL, Perry C, Kitchner TE, Brilliant MH, Peissig PL, Borthwick KM, Williams MS, Grafton J, Jarvik GP, **HolmIA**, Harley JB. A GWAS study on liver function test using eMERGE network participants. PLoS One. 2015 Sep 28;10(9). PMID: 26413716. PMCID: PMC4586138.
   b. Lingren T, Thaker V, Brady C, Namjou B, Kennebeck S, Bickel J, Patibandla N, Ni Y, Van Driest SL, Chen L, Roach A, Cobb B, Kirby J, Denny J, Bailey-Davis L, Williams MS, Marsolo K, Solti I, **Holm IA**, Harley J, Kohane IS, Savova G, Crimmins N. Developing an algorithm to detect early childhood obesity in two tertiary pediatric medical centers. Appl Clin Inform 2016; 7:3-693-706. PMID: 27452794.
   c. Rasmussen LV, Overby CL, Connolly J, Chute CG, Denny JC, Freimuth R, Hartzler AL, **Holm IA**, Manzi S, Pathak J, Peissig PL, Smith M, Williams MS, Shirts BH, Stoffel EM, Tarczy-Hornoch P, Rohrer Vitek CR, Wolf WA, Starren J. Practical considerations for implementing genomic information resources. Experiences from eMERGE and CSER. *Appl Clin Inform.* 2016;7(3):870-88. doi: 810.4338/ACI-2016-4304-RA-0060. PMID: 27652374.
   d. Lingren T, Chen P, Bochenek J, Doshi-Velez F, Manning-Courtney P, Bickel J, Wildenger Welchons L, Reinhold J, Bing N, Ni Y, Barbaresi W, Mentch F, Basford M, Denny J, Vazquez L, Perry C, Namjou B, Qiu H, Connolly J, Abrams D, **Holm IA**, Cobb BA, Lingren N, Solti I, Hakonarson H, Kohane IS, Harley J, Savova G. Electronic Health Record Based Algorithm to Identify Patients with Autism Spectrum Disorder. PLoS One. 2016 Jul 29;11(7):e0159621. doi: 10.1371/journal.pone.0159621. eCollection 2016. PMID: 27472449.

4. I have a long-standing research interest in unraveling the genetic contributions to Sudden Infant Death Syndrome (SIDS) and Sudden Unexpected Death in Childhood (SUDC). I have worked with Dr. Hannah Kinney's group in the Department of Pathology for over 13 years to understand the genetic contributions to SIDS in the context of prenatal alcohol exposure in the Safe Passage Study (PASS), a large, prospective, longitudinal, international study of pregnant women and their babies. I am currently Associate Director (Dr. Richard Goldstein, Director) of the BCH *Robert's Program* for Sudden Unexpected Death in Pediatrics (SUDP) Program and I co-lead the genomic sequencing studies to identify genetic contributions to SUDP.
    a. **Holm IA**, Poduri A, Crandall L, Haas E, Grafe MR, Kinney HC, Krous HF. Inheritance of febrile seizures in sudden unexplained death in toddlers. Pediatr Neurol. 2012 Apr;46(4):235-9. PubMed PMID: 22490769; PubMed Central PMCID: PMC4009678.
    b. Dukes KA, Burd L, Elliott AJ, Fifer WP, Folkerth RD, Hankins GD, Hereld D, Hoffman HJ, Myers MM, Odendaal HJ, Signore C, Sullivan LM, Willinger M, Wright C, Kinney HC. The safe passage study: design, methods, recruitment, and follow-up approach. Paediatr Perinat Epidemiol. 2014 Sep;28(5):455-65. PubMed PMID: 25131605; PubMed Central PMCID: PMC4286367.
    c. Kinney HC, Poduri AH, Cryan JB, Haynes RL, Teot L, Sleeper LA, **Holm IA**, Berry GT, Prabhu SP, Warfield SK, Brownstein C, Abram HS, Kruer M, Kemp WL, Hargitai B, Gastrang J, Mena OJ, Haas EA, Dastjerdi R, Armstrong DD, Goldstein RD. Hippocampal Formation Maldevelopment and Sudden Unexpected Death across the Pediatric Age Spectrum. J Neuropathol Exp Neurol. 2016 Oct;75(10):981-997. PMID: 27612489.
    d. Brownstein CA, Goldstein RD, Kinney HC, Haynes RL, Giles E, Sheidley B, Bainbridge, Haas EA, Mena OJ, Lucas J, Schaber B, **Holm IA**, Poduri AH. SCN1A associated with Two Cases of Sudden Infant Death Syndrome. Epilepsia, 2018 Apr;59(4):e56-e62. Epub 2018 Mar 30.
5. Another focus of my research, related to my work on SIDS and SUDP, is on rare diseases. I led the Patient Engagement Core for the Undiagnosed Diseases Network (UDN) Phase I Coordinating Center and am currently a co-investigator at the UDN Harvard Clinical site in UDN phase 2. I also am co-PI with Dr. Melissa Haendel on a Patient-Centered Outcomes Research Institute (PCORI) study to develop patient self-phenotyping tools to be implemented in patients with rare diseases.
    a. Brownstein CA, **Holm IA**, Ramoni R, Goldstein DB. Data Sharing in the Undiagnosed Diseases Network. Hum Mutat. 2015 Jul 29;PubMed PMID: 26220576.
    b. Philippakis AA, Azzariti DR, Beltran S, Brookes AJ, Brownstein CA, Brudno M, Brunner HG, Buske OJ, Carey K, Doll C, Dumitriu S, Dyke SO, den Dunnen JT, Firth HV, Gibbs RA, Girdea M, Gonzalez M, Haendel MA, Hamosh A, **Holm IA**, Huang L, Hurles ME, Hutton B, Krier JB, Misyura A, Mungall CJ, Paschall J, Paten B, Robinson PN, Schiettecatte F, Sobreira NL, Swaminathan GJ, Taschner PE, Terry SF, Washington NL, Züchner S, Boycott KM, Rehm HL. The Matchmaker Exchange: A Platform for Rare Disease Gene Discovery. Hum Mutat. 2015 Oct;36(10):915-21. PMID: 26295439.
    c. K, Hull SC, **Holm IA**, McDonough TL, Wise AL, Ramoni RB; Members of the Undiagnosed Diseases Network. Implementing the single institutional review board model in the undiagnosed diseases network. Clin Transl Sci. 2017 Sep 25. doi: 10.1111/cts.12512. PMID: 28945957.
    d. Vasilevsky NA, Foster ED, Engelstad ME, Carmody L, Might M, Chambers C, Dawkins HJS, Lewis J, Della Rocca MG, Snyder M, Boerkoel CF, Rath A, Terry SF, Kent A, Searle B, Baynam G, Jones E, Gavin P, Bamshad M, Chong J, Groza T, Adams D, Resnick AC, Heath AP, Mungall C, **Holm** IA, Rageth K, Brownstein CA, Shefchek K, McMurry JA, Robinson PN, Köhler S, Haendel MA. Plain-language medical vocabulary for precision diagnosis. Nat Genet. 2018 Apr;50(4):474-476. doi: 10.1038/s41588-018-0096-x. PMID: 29632381

Complete List of Published Work My Bibliography: https://www.ncbi.nlm.nih.gov/sites/myncbi/1RAmNhf__NJQ-/bibliography/40375340/public/?sort=date&direction=ascending.

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R01 HG010004-01 Holm, Ingrid (PI) 04/01/2018 – 03/31/2021
"Health Care Provider Responses to Receiving Unsolicited Genomic Results"
The objective is to study the impact of return of unsolicited genomic results to health care providers in the Electronic Medical Records and Genomics (eMERGE) Network Phase.

ME-1511-33184 (PCORI) Holm, Ingrid (PI) 08/01/2017 – 07/31/2020
"Realization of a Standard of Care for Rare Diseases Using Patient-Engaged Phenotyping"

The goal is to integrate self-phenotyping into the evaluation of patients with undiagnosed diseases.

R01HD089521 Hirschhorn, Joel (PI) 09/10/16-05/31/21
"Exome Sequencing in Disorders of Sex Development: Impact on Patients and Families"
The goals are to assess the impact of returning genetic testing results of sequencing in patients with DSDs.
Role: Co-PI

U01 HG008701 Harris, Paul (PI) 09/01/2015 – 08/3120/20
"The Electronic Medical Records and Genomics (eMERGE) Network Phase III - Coordinating Center"
I lead the ROR/ELSI work group and consult in issues related to ELSI and pediatrics in eMERGE III.
Role: PI of subcontract

U01HG007690 Loscalzo, Joseph (PI) 04/01/2014 – 07/31/2022
"Center for Integrated Approaches to Undiagnosed Diseases"
The goal is to evaluate patients with undiagnosed diseases as part of a joint Harvard UDN clinical site.
Role: Co-Investigator

NICHD 1R21HD096355-01 Goldstein, Richard (PI) 08/20/2018 – 07/31/2020
Genetics of Sudden Unexpected Death in Pediatrics
The goal is to identify genetic mechanisms associated with Sudden Unexpected Death in Pediatrics (SUDP)
Role: Co-PI with Dr. Goldstein and Dr. Annapurna Poduri

Completed Research Support

U19 HD077671 Green, Robert (PI) 09/05/2013 – 08/31/2019
Genome Sequence-Based Screening for Newborn Illness and Childhood Risk"
This study explores the use of genomic sequence information in the newborn period.
Role: Co-Investigator

U01HG007530 Kohane, Isaac S. (PI) 11/01/2013 – 07/31/2018
"Coordinating Center for the Undiagnosed Diseases Network"
The goal is to oversee a national network to approach the diagnosis of rare undiagnosed diseases.
Role: Co-Investigator

3U01HG008701-02S1 Harris, Paul (PI) 09/28/2016 – 05/31/2017
"Impact of Return of Genomic Results on Health Care Providers – Pilot Project" (Administrative supplement to "The Electronic Medical Records and Genomics (eMERGE) Network Phase III - Coordinating Center")
The goal of the project is to develop a survey of providers who receive genomic results in eMERGE III
Role: PI of subcontract

U01HD045991 Kinney, Hannah (PI) 09/26/2003 – 01/31/2017
"Prenatal alcohol, SIDS, and Stillbirth (PASS) Research Network, Developmental Biology Center"
The goal of this project is to study the interaction of alcohol, SIDS and stillbirths, and genetics.
Role: Co-Investigator

U01HG006828 Harley, John (Co-PI) 05/01/2012 – 04/30/2016
"Better Outcomes for Children: GWAS & PheWAS in eMERGE II"
The goal was for CCHMC and BCH to be an Electronic Medical Records and Genomics (eMERGE) II site.
Role on project: Co-PI

3U01HG006828-02S2 Harley, John (Co-PI) 05/01/2012 – 04/30/2016
"Patient Perspectives on Broad Consent in Biobank Research in the eMERGE" (Administrative Supplement to "Better Outcomes for Children: GWAS & PheWAS in eMERGEII")
Role on project: Co-PI

3U01HG006828-02S1 Harley, John (Co-PI) 05/01/2013 – 04/30/2016
"Pre-emptive Warfarin Genotyping for Children and Adults at Risk for Anticoagulant Management"
(Administrative Supplement to "Better Outcomes for Children: GWAS & PheWAS in eMERGEII")
Role on project: Co-PI

BIOGRAPHICAL SKETCH

NAME: Carol Horowitz

eRA COMMONS USER NAME: P811CHO

POSITION TITLE: Professor of Population Health Science and Policy, Professor of Medicine

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion	FIELD OF STUDY
Cornell University, Ithaca, NY	B.S.	1982	Human Development
Columbia University, New York, NY		1984	Pre-Medical Program
Cornell University, New York, NY	M.D.	1989	Medicine
University of Washington, Seattle, WA	M.P.H.	1995	Public Health

A. Personal Statement

I am a Professor in the Departments of Population Health Science and Policy & Medicine at Mount Sinai, Co-Direct Sinai's Center for Health Equity and Community Engaged Research, a health services researcher and practicing general internist in Harlem. I have been PI and investigator on numerous NIH, CDC and PCORI grants related to chronic disease prevention and control, direct stakeholder engagement for the PCORI-funded NYC Clinical Data Research Network and for Sinai's CTSA, chaired NHGRI's translational genomics consortium, IGNITE and co-chair NHGRI's CSER. I implement and evaluate programs to improve the quality of care and outcomes of diverse adult populations with/at risk for chronic diseases through clinical and community programs. I have an extensive training record spanning 20 years preparing and mentoring trainees in multi-method research, program and intervention development, conducting and analyzing multi-site RCTs, social/environmental, clinical/genetic, behavioral determinants of health and community and stakeholder engagement in research.

B. Positions and Honors

1989-1990 Intern, Albert Einstein College of Medicine, Bronx, NY
1990-1992 Resident, Primary Care Internal Medicine, Albert Einstein
1992-1993 Instructor, Internal Medicine, New York University/Bellevue, NYC, NY
1993-1995 Senior Fellow, Robert Wood Johnson Clinical Scholars Program, Seattle, WA
1993-1995 Instructor, Internal Medicine, University of Washington, Seattle, WA
1996-2008 Assistant Professor, Departments of Health Policy, Mt. Sinai School of Medicine, NY
2008-2016 Associate Professor, Departments of Health Policy, Mt. Sinai School of Medicine
2016- Professor, Department of Population Health Science and Policy, and Department of Medicine, Icahn School of Medicine at Mount Sinai

Other Experience and Professional Memberships

2002- Society of General Internal Medicine, Disparities Taskforce Member
2006-2014 New York City Department of Health, Member, Hemoglobin A1c Registry Advisory Committee
2006- Aetna, Member, Racial and Ethnic Equality External Advisory Committee
2007, 2015 Institute of Medicine- Health Disparities Roundtable
2011-2015 Cornell University, Member, Human Ecology Alumni Board
2012-2017 Member, EAB, Jackson St. U. Cntr of Excellence Minority Health&Health Disparities
2013- 2016 Member, Grameen Health Innovations Board
2013- Member, SGIM Representative, NHGRI Inter-Society Coordinating Committee
2104- Member, Key Faculty, Albert Einstein Diabetes Research Center
2015 Chair, Nickens Award Committee, Society of General Internal Medicine
2015 Panelist, Engagement & Equity Workshop of the PMI Advisory Committee to the NIH Director
2015-2017 Co-Chair, then Chair of NHGIR IGNITE Network
2005- Federal Grant Reviewer: AHRQ, CDC, NIH (NIDDK, NIMHD, Training Awards, Special Emphasis Panels, CLHP Section, NIBIB, SBIR)

2001- Editorial Activities: SGIM-Chaired abstract committees; JGIM and PCHP journals- special editor; Academy Health- Chair social determinants section; Reviewer- multiple medical journals

2017- Co-Chair- NHGRI CSER2 Network

Honors and Awards: Cornell U. Dean's Award- Merit in independent research; Mayoral Award Ithaca, New York, Community Service; Cornell U. Medical College Haas Fellowship for Independent Research; US DHHS Excellence for Contributions to Diabetes; Lighthouse International Partnership Award; Mount Sinai Medicine Community Service Award; Cornell Council of Alumni Women; Public Health Leadership Award; Madrina Three Kings Day Parade; Healthy Communities Promising Practice Award, Rudin NYC Prize for Medicine and Health.

C. Contributions to Science

1. Employing mixed method research, I study reasons for health disparities including challenges adopting healthy lifestyles, with medication adherence, accessing care, and providing care. Findings have informed their fields, such as our sentinel study describing disparities in food availability.
   a. Horowitz CR, Colson KA, Hebert PL, Lancaster K. Barriers to buying healthy foods for people with diabetes: Evidence of environmental disparities. AJPH. 2004;94:1549-54. PMC1448492.
   b. Horowitz CR, Rein SR, Leventhal H. A story of maladies, misconceptions and mishaps: Effective management of heart failure. Soc. Sci. and Med. 2004; 58:631-643. PMC4301306.
   c. Kronish IM, Edmondson D, Goldfinger JZ, Fei K, Horowitz CR. Posttraumatic stress disorder and adherence to medications in survivors of strokes and transient ischemic attacks. Stroke. 2012. 43:2192-7. PMC3404197.
   d. Vedanthan R, Tuikong N, Kofler C, Blank E, Kamano JH, Naanyu V, Kimayo S, Inui TS, Horowitz CR, Fuster V. Barriers and facilitators to nurse management of hypertension: A qualitative analysis from western Kenya. Ethn Dis. 2016; 26:315-22. PMC4948797
2. All my research involves robust stakeholder engagement or community-based participatory research to generate innovative questions, strategies and enable lessons learned to lead to sustainable benefits for at-risk populations. Engagement is responsible for our great successes recruiting and retaining diverse populations in research.
   a. Horowitz CR, Robinson M, Seifer S. Community-based participatory research's journey from margins to mainstream: Are researchers prepared? Circ, 2009; 119; 2633-2642.PMC2796448
   b. Horowitz CR, Brenner BL, Lachapelle S, Amara DA, Arniella G. Effective recruitment and enrollment through community-led strategies. AmJ Preventive Medicine, 2009; 37:S195-200. PMC2810631.
   c. Sisk JE, Horowitz CR, Wang JJ, Hebert PL, McLauglhin MA, Tuzzio L. The success of recruiting minorities, women, and elderly into a randomized controlled effectiveness trial. MS Journal of Medicine, 2008; 75:37-43. PMC4309672.
   d. Kaplan B, Ferryman K, Robinson M, Richardson LD, Caddle-Steele C, Goytia C, Hauser D, Chisolm G, Esmond WA, Gertner M, Horowitz CR. Culture of understanding: Reflections and suggestions from a genomics research community board. Progress in Community Health Partnerships. 2017;11(2):161-165. doi: 10.1353/cpr.2017.0020.
3. Using lessons learned from formative research, we conduct large, multi-site interventions to address disparities through stakeholder-engaged research and teaching, particularly related to chronic disease prevention and control, and genomics, disseminating lessons to inform policy, system and environmental changes. Many of our interventions continue on in clinical and community settings- they are sustained and scaled- after we prove their effectiveness.
   a. Kronish I, Goldfinger JZ, Negron R, Fei K, Arniella G, Horowitz CR. The effect of peer education on stroke prevention: the Prevent Recurrence of All Inner-City Strokes through Education (PRAISE) randomized controlled trial. Stroke, 2014:45; 3330-6. PMC4213208.
   b. Parikh P, Simon EP, Fei K, Looker H, Goytia C, Horowitz CR. Results of a successful pilot

diabetes prevention intervention in East Harlem: Project HEED, AJPH, 2010;100:S232-9. PMC2837455.

c. Sisk JE, Hebert PL, Horowitz CR, McLaughlin MA, Wang J, Chassin MR. Effects of nurse management on the quality of heart failure care in minority communities: a randomized controlled trial. Ann. Internal Medicine. 2006; 145:273-283. PMC4307780.
d. Li K, Cromley E, Fox AM, Horowitz CR. Evaluation of the placement of mobile fruit and vegetable vendors to alleviate food deserts in NYC. Prev.Chr. Disease 2014;11:140086. PMC4164039.

4. We have begun to focus on broader issues that influence heath equity, such as the social determinants, the built environment, and genomic factors. We are among the first cohort of grantees to translate genomic discoveries for diverse populations, to develop new models to build teams of diverse stakeholders (patients, advocates, clinicians, payors, entrepreneurs, funders) together innovate the study of disparities,
   a. Horowitz CR, Ferryman K, Negron R, Sabin T, Rodriguez M, Zinberg RF, Böttinger E, Robinson, MA. Race, genomics and chronic disease: What patients with African ancestry have to say. Journal of Healthcare for the Poor and Underserved. 2017; 28; 248-60. (With invited commentary)
   b. Horowitz CR, Shameer K, Gabrilove J, Atreja A, Shepard P, Goytia CN, Smith GW, Dudley J, Manning R, Bickell NA, Galvez MP. Accelerators: Sparking innovation and transdisciplinary team science in disparities research. J.Env.Res.Public Health. 2017; 14(3): 225. PMC5369061
   c. Tabaei BP, Rundle A, Wu WY, Horowitz CR, Mayer V, Chamany S. Residential socioeconomic, food and built environments and glycemic control in individuals with diabetes in New York City 2007-2013. American Journal of Epidemiology, 2017, https://doi.org/10.1093/aje/kwx300
   d. Sperber NR, Carpenter JS, Cavallari LH, Damschroder L, Cooper-DeHoff RM, Denny JC, Ginsburg GS, Guan Y, Horowitz CR, Levy KD, Levy MA, Madden EB, Matheny ME, Pollin TI, Pratt VM, Rosenman M, Voils CI, Weitzel K, Wilke RA, Wu R, Orlando LA Challenges and strategies for implementing genomic services in diverse settings: experiences from the implementing GeNomics in PracTicE (IGNITE) network. BMC Medical Genomics 2017, 10(1): 35.10(1):35. PMID: 28532511

Complete List of Published Work (>100 articles) in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/carol.horowitz.1/bibliography/43232915/public/?sort=date&direction=ascending

D. Additional Information: Research Support

Ongoing Research Support

NCATS TR001435-01 (Wright) 08/15/15-03/31/20
Conduits: MSHS Translational Science Hub
Conduits is a translational research laboratory, partnering with our diverse patient population, stakeholders, clinicians and scientists to ensure high quality research, research education, and discovery.
Role: Co-Investigator, PI Translational Science Base

NIDDK DK020541-38S1 (Pessin/Stewart) 04/01/15-03/31/20
Einstein-Mt. Sinai Diabetes Research Center
The missions are to provide key methods, technology and infrastructure to further basic diabetes research.
Role: Co-Investigator

NHLBI 1R01HL125487 (Vedanthan) 04/01/15-03/31/20
Bridging Income Generation with Group Integrated Care (BIGPIC)
This multisite, community-based randomized trial in rural western Kenya compares the impact of microfinance groups and group medical visits versus usual care, to reduce cardiovascular disease risk among at-risk adults.
Role: Co-Investigator

PCORI NEN-1508-32252 (Mayer) 03/01/16-2/29/21
The Impact of Medicaid Health Homes on patients with Diabetes
Examine effects of New York State's Medicaid Health Home program (population-targeted policy intervention) on quality of care and patient-centered health outcomes among low-income individuals with diabetes.
Role: Co-Investigator

NHGRI1U01HG009610-01 (Kenny) 06/01/17-05/31/21
Incorporating Genomics into the Clinical Care of Diverse Children
The NYCKidSeq program will assess the clinical utility of genomic medicine in three broad areas of pediatric disorders, while engaging a range of providers and community members to overcome the well-documented barriers to inclusion of under-served and under-represented populations in genomic research.
Role: Co-Investigator

NIEHS P30ES023515 (Wright) 04/01/18-03/31/23
Transdisciplinary Center on Health Effects of Early Environ-mental Exposures
This Center studies how early environmental exposures influence health & disease risk.
Role: PI of Community Outreach and Engagement Core

(Horowitz) 03/15/18-06/30/21
Russell Berrie Foundation
The Russell Berrie Foundation Diabetes Prevention Initiative (RBFDPI)
We will work with the chosen organizations to educate them on best practices for effective community-led diabetes prevention work. Additionally, we will work to provide training and programmatic and evaluation support for both projects over a three-year project period..
Role: Principal Investigator

NHGIR 1 U01 HG010248-01 (Horowitz) 09/18/18-06/30/23
1 U01 HG010248-02S1 09/23/19-06/30/23
GeNYC: Genomic Implementation Research in the Diverse Settings and Populations of New York City
Our stakeholder-engaged team is experienced in conducting clinical trials in diverse populations, including one with >2000 African ancestry patients with high genetic risk for CKD. We aim to implement genomic medicine trials in NYC and study risk-informed disease management in multi-ancestry populations and diverse practices.
Role: Principal Investigator

(Horowitz) 11/01/18 – 09/30/20
WCMC/People-Centered Research Foundation
INSIGHT Network
Mount Sinai is an integral component of the NYC CDRN, offering leadership, expertise and infrastructure for research. By integrating leadership and management with our CTSA, we broaden engagement by developing and employing a novel “accelerator” model and expand research, co-leading the research committee, our academic-community partners lead a PCORI-funded diabetes research study and we participate in numerous PCORnet studies.
Role: Principal Investigator

Completed Research Support

NHGRI 3U01HG007278-04S2 (Horowitz) 08/30/17 – 09/30/19
Genomic Medicine Pilot for Hypertension and Kidney Disease in Primary Care
We will examine the impact of testing and returning results for a genetic variant that increases the risk of chronic kidney disease among hypertensive patients of African ancestry, upon patient-centered outcomes.
Role: Principal Investigator

PCORI (Kaushal) 11/15/15-11/14/18
NYC Clinical Data Research Network
Build and implement a network to facilitate patient-centered clinical research.
Role: Director, Patient Engagement, Site PI for Mount Sinai

NIH (Orlando) 07/0117-04/30/18
Implementation, Adoption, and Utility of Family History in Diverse Care Settings
Mount Sinai will be responsible for recruiting and consenting 300 diverse patients from two Mount Sinai outpatient clinics located in New York City.
Role: Sub PI

PCORI (Jay) 6/01/15-12/31/17
Short- and Long-term Effects of Antibiotics on Childhood Growth
This observational study explores the association between antibiotic use and obesity.
Role: Site PI

NHGRI U01HG007278S1 11/01/16-10/31/17
Supplement to Genomic Medicine Pilot for Primary Care
This supplement studies the epigenomics of genomics and obesity, focused on new discovery of association between high risk APOL1 variants and obesity.
Role: PI

NHLBI 1U01HL114200-01 (Fuster) 05/01/12-03/31/17
Hypertension Care in Rural Kenya
Using multidisciplinary implementation, determine the impact of community health workers, using tailored behavioral communication and a smartphone tool linked to an EHR, on BP control in rural western Kenya.
Role:Co-I

NIMHD 2R24MD001691-09 (Horowitz) 04/01/13-3/31/17
Disseminating Effective Community-Led Programs to Eliminate Diabetes Disparities
This program is disseminating Project HEED, an evidence-based weight loss intervention for adults at risk for developing diabetes utilizing innovative dissemination methods, including social networks and social media.
Role: PI

CDC/FPHNY Contract No.80636 (Horowitz) 09/30/14-09/29/17
Partnerships to Improve Community Health (PICH)
The Partnerships to Improve Community Health (PICH) grant aims to address chronic disease through mitigating related factors such as tobacco use and exposure, poor nutrition, and physical inactivity.
Role: Site PI for Borough of Manhattan

NHGRI 1U01HG007278-01(Horowitz) 06/01/13-04/30/17
Genomic Medicine Pilot For Hypertension And Kidney Disease In Primary Care
The multisite RCT studies the effects and challenges of incorporating genomic risk information in clinical care for patients of African ancestry with hypertension at risk for chronic kidney disease and generates new insights on how genomic medicine approaches impact in primary care and in underserved, diverse communities.
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Anna Chesson Edens Hurst

eRA COMMONS USER NAME (credential, e.g., agency login): ACEHurst

POSITION TITLE: Assistant Professor, Department of Genetics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
North Carolina State University - Raleigh, NC	BS	05/2005	Biological Sciences
University of South Carolina School of Medicine - Columbia, SC	MS	05/2007	Genetic Counseling
Medical University of South Carolina – Charleston, SC	MD	05/2011	Medicine
Wake Forest Baptist Medical Center – Winston Salem, NC		06/2014	Pediatrics residency
University of Alabama at Birmingham – Birmingham, AL		06/2016	Medical Genetics residency

A. Personal Statement

As a pediatric medical geneticist also trained in genetic counseling, I have an interest in researching novel ways to communicate the concept of genetic testing and results with patients and families. My clinical interests include dysmorphology and the genetic basis of congenital anomalies, multiple malformation syndromes, skeletal dysplasias, intellectual disabilities and developmental delays. I am also interested in emerging technologies such as whole genome sequencing as a method of achieving diagnoses more efficiently.

I have recently started my first faculty position at University of Alabama at Birmingham as an assistant professor on a clinician-educator tract. My clinical responsibilities include general genetics and dysmorphology evaluations, skeletal dysplasia clinics, and serving as a pediatric clinician in UAB's Undiagnosed Diseases Program. My educational efforts focus on teaching pediatric residents and genetic counseling students about the fundamentals of medical genetics, embryology, and dysmorphology. In an attempt to learn more and develop my research experience, I completed the 2016-7 Rare Disease Clinical Research Training Program through Children's National Medical Center in Washington, D.C.

I am currently involved in several clinical research studies. 1) I am the primary investigator for "Children's of Alabama Genome Sequencing," a research project providing Whole Genome Sequencing (WGS) for 200 children with undiagnosed, rare disorders who are followed by multiple subspecialists. I have designed and implemented a program that diagnoses rare diseases while also analyzing the economic utility of genomic sequencing. Current funding is provided by Children's of Alabama and the HudsonAlpha Institute for Biotechnology 2) I am also a co-investigator in the Alabama Genomic Health Initiative, which will provide genotyping and actionable secondary findings to 10,000 general population individuals and WGS results to approximately 500 individuals with undiagnosed diseases. My role in AGHI is co-chair of the genomics committee, and I focus on organizing the variant review committee and return of results. 3) I am a co-investigator for South-Seq, an NIH NHGRI-funded Clinical Sequencing Evidence-Generating Research study using genomic sequencing to diagnose infants with rare diseases admitted to neonatal intensive care units across our region. 4) I am also leading a research study using novel Facial Dysmorphology Novel Analysis computer software tools to detect subtle dysmorphic features in patients with neurofibromatosis type 1. While

in medical genetics residency, I completed laboratory research with David Bedwell, PhD investigating nonsense suppression pharmacological agents in fibroblasts from patients with Mucolipidosis II alpha/beta and III alpha/beta.

It is my hope that participation in the current projects would develop my research skills while expanding the scope of genetic testing availability to minority populations in the south and improving the communication of genetic information.

B. Positions and Honors

Board Certification, Licensure, and Employment:

2011-2014	North Carolina Medical License valid
2014	Board certification in Pediatrics, American Board of Pediatrics
2014-current	Alabama Medical License valid
2016-current	Assistant Professor, Department of Genetics, University of Alabama at Birmingham
2017	Board certification in Clinical Genetics, American Board of Medical Genetics and Genomics

Memberships:

2005-2007	MUSC Medical Graduate Student Association
2006-2007	National Society of Genetic Counselors (NSGC) and Cancer Special Interest Group
2008-2011	South Carolina Medical Association
2007-2011	Southern Medical Association
2009-2011	American Academy of Neurology student member
2011-2014	North Carolina Pediatrics Society
2012-2014	NC. Pediatrics Society Committee on Children with Special Needs
2012-2014	North Carolina Medical Society
2009-2015	American Academy of Pediatrics
2013-current	American College of Medical Genetics
2016-current	Facial Dysmorphology Novel Analysis, Scientific Advisory Board member

Honors:

2001-2005	North Carolina State University Park Scholar, Phi Beta Kappa, Phi Kappa Phi, Phi Eta Sigma
2005	North Carolina State University Student Commencement Speaker
2008	Perry V. Halushka Student Research Day (Medical University of South Carolina) – Second Place Winner in Oral Category; *Expanding the Female Neurologic Phenotype of Duplicated Xp Syndrome*
2008	Scholarship recipient from K&L Gates Law Firm to attend the Treumen Katz Center for Pediatric Bioethics at Seattle Children's Hospital conference "*Predicting Our Future: Genetic Testing in Children and Their Families*
2016-2017	Scholarship recipient and participant in the Rare Disease Clinical Research Training Program, Children's National Medical Center, Washington, DC.

C. Contributions to Science

1. As a clinical geneticist, I believe accurate phenotyping and description of the varied presentations of genetic syndromes is important for contribution to clinical care and diagnosis. I collaborate with other physicians in neurology, endocrinology, orthopedics, and other subspecialties to manage patients with genetic disorders, reporting cases of unusual presentation and significance

a. Edens AC, Lyons MJ, Duron RM, DuPont BR, Holden KR. 2011 "*Autism in two females with duplications involving Xp11.22-p11.23.*" Developmental Medicine and Child Neurology. 53(5): 463-6. PMID 21418194

b. Hurst ACE, Williams CL, Nelson KR, Stolerman ES, Robin NH. *Nevoid Basal Cell Carcinoma Syndrome with Nystagmus and Immobile First Digit Interphalangeal Joints: Expanding the Phenotype of PTCH1 Duplications.* 2015. Annals of Pediatrics and Child Health. 3(9):1090-1095.
c. Upadia J, Oakes J, Hamm A, Hurst AC, Robin, NH. *Foramen magnum compression in Coffin-Lowry syndrome: A case report.* 2017. American Journal of Medical Genetics Part A. 173(4):1087-1089. PMID 28190284

2. I am interested in the science of dysmorphology and its use in clinical phenotyping for patients with genetic conditions. I have authored publications about the genetic physical exam for oncologists, and review pieces for pediatricians describing the current use of facial recognition software in clinical practice.

a. Hurst ACE, Robin NH. *The Genetic Evaluation of the Child with Cancer*. Book Chapter In: Pediatric Cancer Genetics. Robin NH, Farmer M, editors. 2017.
b. Hurst, ACE. *Facial Recognition Software in Clinical Dysmorphology*. Curr Opinion in Peds. 2018; 30(6):701-706. PMID 30407972
c. Hurst ACE, Robin NH. *The Next-Generation of Dysmorphology*. 2020. (In review)

3. I am involved in utilizing advancing genetic testing technologies, such as genome sequencing and SNP-based microarrays, to detect rare causes of genetic disease.

a. Ashraf A, Hurst AC, Garg A. *Extreme hypertriglyceridemia, pseudohyponatremia, and pseudoacidosis in a neonate with lipoprotein lipase deficiency due to segmental uniparental disomy*. Journal of Clinical Lipidology. 2017. 11(3):757-62. PMID 28438574
b. Hiatt S, Neu MB, Ramaker RC, Hardigan AA, Prokop JW, Hancarova M, Prchalova D, Havlovicova M, Prchal J, Stranecky V, Yim DKC, Powis Z, Keren B, Nava C, Mignot C, Rio M, Revah-Politi A, Hemati P, Stong N, Iglesias AD, Suchy SF, Willaert R, Wentzensen IM, Wheeler PG, Brick L, Kozenko M, Hurst ACE, Wheless JW, Lacassie Y, Sedlacek Z, Cooper GM. *De novo mutations in the GTP/GDP-binding region of RALA, a RAS-like small GTPase, cause intellectual disability and developmental delay*. PLOS Genetics. 2018;14(11). PMID 30500825.
c. Kerr E, Stuhlmiller G, Maha G, Koester RP, Ladd MA, Mikhail FM, Hurst ACE. Maternal Uniparental Isodisomy for Chromosome 6 Discovered by Paternity Testing: A Case Report. Molecular Cytogenetics. 2018; 11(60). PMID 30598700.

4. As many children with genetic disorders have complex special healthcare needs, I am interested in care coordination and addressing medical and psychosocial needs of children with life-limiting conditions. I also have written summary review pieces to assist with complex care management, summarizing known literature for rare conditions.

a. Haldeman-Englert CR, Hurst ACE, Levine MA. *Disorders of GNAS Inactivation*. 2017 Oct 26. In: Adam MP, Pagon RA, et al, editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from: http://www.ncbi.nlm.nih.gov/books/NBK459117/. PMID 29072892
b. Nagaswaran S, Hurst ACE, Radulovic A. *Unexpected Survivors: Children with life-limiting conditions of uncertain prognosis. American Journal of Hospice and Palliative Medicine*. 2018. 35(4):690-696. PMID 29121791

D. Additional Information: Research Support and/or Scholastic Performance

<u>Ongoing Research</u>

Genomic Sequencing for Children with Rare Mendelian Disorders. ("Children's of Alabama Genome Sequencing")
Funding: University of Alabama at Birmingham, Children's of Alabama, and HudsonAlpha Institute for Biotechnology
August 2016-ongoing
PI: Anna Hurst, MD
IRB-approved (IRB-170314004)
We are identifying a cohort of 200 children with rare, undiagnosed conditions and using whole genome sequencing (WGS) to seek diagnoses in an effort to provide personalized medical management. An

additional focus will be an economic analysis of the tests and procedures patients experienced prior to WGS.
Role: PI

Alabama Genomic Health Initiative.
Funding: State of Alabama
October 2016-ongoing
IRB-approved (X170214002).
The AGHI seeks to build a biobank of genomic samples from over 10,000 individuals from throughout the state of Alabama. Healthy participants receive actionable findings from the American College of Medical Genetics and Genomics Secondary Findings v2.0 list, obtained through a genotyping array. A subset of individuals with phenotypes (~150) will be enrolled for Whole Genome Sequencing (WGS) in an effort to diagnose rare diseases.
PI: Bruce Korf, MD, PhD, Greg Barsh, MD, PhD, Matt Might, PhD
Role: Co-Investigator. Co-Chair of the Sequencing Committee. Enrollment, examination and return of results for patients who receive genome sequencing.

South-Seq, a Clinical Sequencing Evidence-Generating Research project.
Funding: NHGRI
2017-ongoing
IRB-approved
This project will enroll infants with rare diseases admitted to neonatal intensive care units across the Deep South (AL, MS, LA, KY) and use genomic sequencing to diagnose rare diseases. We seek to enroll participants from diverse, underserved backgrounds
PI: Bruce Korf, MD, PhD, Greg Barsh, MD, PhD, Greg Cooper, PhD
Role: Co-Investigator. Phenotyping participants, interpreting variants, returning results, and educating non-genetics medical professionals.

Delineating the Facial Phenotype of Neurofibromatosis Type I Using Facial Dysmorphology Novel Analysis
Funding: None
2016-ongoing
IRB-approved (X160803001)
We partnered with Facial Dysmorphology Novel Analysis (FDNA), which offers a computer modeling system to detect subtle dysmorphic findings in photographic images, to explore if there is a recognizable facial phenotype in patients with Neurofibromatosis type I (NF1). Our role involves gathering photographs of patients with NF1 and subdividing groups based on mutation type. I mentored a medical student to be involved with this project through the American College of Medical Genetics Summer Scholar Program.
PI: Anna Hurst, MD
Role: Primary Investigator

22q11.2 Deletion Fluorescent In Situ Hybridization (FISH) Utilization Practices in the Regional Neonatal Intensive Care Unit.
Funding: None, guidance from Chief Quality Resident Program at University of Alabama at Birmingham
2014-ongoing
Developed a strategy for testing infants with cardiovascular lesions for genetic disorders focus on the specific lesion. Framed as a quality improvement project aimed at improving the selection of patients for which 22q11.2 FISH probes are ordered. Project began while I was a trainee and as a faculty member, I mentored a pediatric cardiology fellow to transfer this work to the pediatric Cardiovascular Intensive Care Unit at Children's of Alabama.
PI: Anna Hurst, MD

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Korf, Bruce

eRA COMMONS USER NAME (credential, e.g., agency login): bkorf1

POSITION TITLE: Chief Genomics Officer

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Cornell University, Ithaca, NY	AB	06/1974	Genetics
Rockefeller University, New York, NY	PHD	05/1979	Genetics and Cell Biology
Cornell University Medical College, New York, NY	MD	05/1980	
Children's Hospital, Boston, Boston, MA	Resident	06/1982	Pediatrics Residency
Harvard Medical School Genetics Training Program, Boston, MA	Postdoctoral Fellow	06/1985	Medical Genetics Fellowship
Harvard-Longwood Neurology Training Program, Boston, MA	Resident	06/1985	Neurology residency (child neurology)

A. Personal Statement

I am a medical geneticist with a strong interest and background in the integration of genetics and genomics into medical practice. I was chair of the UAB Department of Genetics for 15 years from 2003-2018 and subsequently assumed a new role as Assoc dean for Genomic Medicine and Chief Genomics Officer for UAB Medicine. I also co-direct the UAB-HudsonAlpha Center for Genomic Medicine. I play an active role in several genomic medicine-related clinical and research activities. I am the contact PI for the All of Us Southern Network, part of the national All of Us Research Program. In this capacity I coordinate enrollment into All of Us for 11 sites in Alabama, Mississippi, and Louisiana and also serve as chair of the All of Us 'Omics Committee. Together with colleagues at HudsonAlpha I am co-PI of SouthSeq, a project which is part of the Clinical Sequencing Evidence-Generating Research Consortium (CSER); I also serve as co-chair of the CSER steering committee. SouthSeq is focused on whole genome sequencing of babies in the special care nursery who have phenotypes suggestive of a genetic etiology. We are also doing a clinical trial regarding return of results, comparing return by a certified genetic counselor with that by trained non-geneticist staff in the nursery. I am also co-PI and principal architect of the Alabama Genomic Health Initiative, which is supported by the state of Alabama. We are providing genotyping and return of medically actionable data to 10,000 people in the state, and also performing whole genome sequencing and return of results of pathogenic, likely pathogenic, and selected variants of unknown significance that may constitute a diagnosis for individuals with phenotypes suggestive a genetic condition. In the population sequencing cohort we have enrolled more than 5,000 participants and returned results to approximately 1.5%. Finally, I direct the UAB Undiagnosed Diseases Program, which provides multidisciplinary evaluations to children and adults with undiagnosed disorders; most have genome sequencing as part of their evaluations. On a national level, I am on the steering committee of the Global Genomic Medicine Collaborative and serve as president of the American College of Medical Genetics and Genomics Foundation. I also serve as editor-in-chief of the American Journal of Human Genetics. Through these activities, I am well positioned to serve as the site PI for our participation in this newborn sequencing project.

1. Kalia SS, Adelman K, Bale SJ, Chung WK, Eng C, Evans JP, Herman GE, Hufnagel SB, Klein TE, Korf BR, McKelvey KD, Ormond KE, Richards CS, Vlangos CN, Watson M, Martin CL, Miller DT. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017 Feb;19(2):249-255. PubMed PMID: 27854360.

2. Bowdin S, Gilbert A, Bedoukian E, Carew C, Adam MP, Belmont J, Bernhardt B, Biesecker L, Bjornsson HT, Blitzer M, D'Alessandro LC, Deardorff MA, Demmer L, Elliott A, Feldman GL, Glass IA, Herman G, Hindorff L, Hisama F, Hudgins L, Innes AM, Jackson L, Jarvik G, Kim R, Korf B, Ledbetter DH, Li M, Liston E, Marshall C, Medne L, Meyn MS, Monfared N, Morton C, Mulvihill JJ, Plon SE, Rehm H, Roberts A, Shuman C, Spinner NB, Stavropoulos DJ, Valverde K, Waggoner DJ, Wilkens A, Cohn RD, Krantz ID. Recommendations for the integration of genomics into clinical practice. Genet Med. 2016 Nov;18(11):1075-1084. PubMed PMID: 27171546; PubMed Central PMCID: PMC5557020.
3. Coulter M, Colvin C, Korf B, Messiaen L, Tuanama B, Crowley M, Crossman DK, McCormick K. Hypomagnesemia due to two novel TRPM6 mutations. J Pediatr Endocrinol Metab. 2015 Nov 1;28(11-12):1373-8. PubMed PMID: 26226117.
4. Manolio TA, Abramowicz M, Al-Mulla F, Anderson W, Balling R, Berger AC, Bleyl S, Chakravarti A, Chantratita W, Chisholm RL, Dissanayake VH, Dunn M, Dzau VJ, Han BG, Hubbard T, Kolbe A, Korf B, Kubo M, Lasko P, Leego E, Mahasirimongkol S, Majumdar PP, Matthijs G, McLeod HL, Metspalu A, Meulien P, Miyano S, Naparstek Y, O'Rourke PP, Patrinos GP, Rehm HL, Relling MV, Rennert G, Rodriguez LL, Roden DM, Shuldiner AR, Sinha S, Tan P, Ulfendahl M, Ward R, Williams MS, Wong JE, Green ED, Ginsburg GS. Global implementation of genomic medicine: We are not alone. Sci Transl Med. 2015 Jun 3;7(290):290ps13. PubMed PMID: 26041702; PubMed Central PMCID: PMC4898888.

B. Positions and Honors

Positions and Employment

1985 - 1986	Instructor in Neurology, Harvard Medical School, Boston, MA
1986 - 1993	Assistant Professor of Neurology, Harvard Medical School, Boston, MA
1986 - 1999	Director, Clinical Genetics Program, Children's Hospital, Boston, Boston, MA
1993 - 2009	Associate Professor of Neurology (Pediatrics), Harvard Medical School, Boston, MA
1998 - 1999	Associate Chief, Division of Genetics, Children's Hospital, Bostonq, Boston, MA
1999 - 2002	Medical Director, Harvard-Partners Center for Genetics and Genomics, Boston, MA
2003 -	Wayne H. and Sara Crews Finley Endowed Chair of Medical Genetics, University of Alabama at Birmingham, Birmingham, AL
2003 - 2018	Professor and Chair, Department of Genetics, University of Alabama at Birmingham, Birmingham, AL
2006 - 2018	Director, Heflin Center for Genomic Sciences, University of Alabama at Birmingham, Birmingham, AL
2014 -	Co-Director, UAB-HudsonAlpha Center for Genomic Medicine, University of Alabama at Birmingham, Birmingham, AL
2018 -	Chief Genomics Officer, UAB Medicine, Birmingham, AL

Other Experience and Professional Memberships

1988 -	Chair, Medical Advisory Committee, Children's Tumor Foundation
1996 - 2002	Member, Board of Directors, American College of Medical Genetics
1998 - 2014	Associate Editor, Education, Genetics in Medicine
1999 - 2002	Vice President, Clinical Genetics, American College of Medical Genetics
1999 - 2006	Member, Liaison Committee on Medical Education
2002 - 2004	President, Association of Professors of Human and Medical Genetics
2002 - 2005	Member, Editorial Board, American Journal of Human Genetics
2003 - 2006	Member, Board of Directors, American Society of Human Genetics
2003 - 2008	Member, Board of Scientific Counselors, National Cancer Institute
2009 - 2011	President, American College of Medical Genetics
2009 - 2013	Member, Board of Scientific Counselors, National Human Genome Research Institute
2012 -	President, ACMG Foundation for Genetic and Genomic Medicine
2012 - 2013	Member, Blue Ribbon Panel on Intramural Research Program, National Human Genome Research Institute

2013 - Chair, External Advisory Board, Neurofibromatosis Therapeutic Acceleration Project

Honors

2007 Medical Honoree, Children's Tumor Foundation, NE Chapter
2009 ASHG Award for Excellence in Genetics Education, American Society of Human Genetics
2014 AAAS Fellow, American Association for the Advancement of Science

C. Contribution to Science

1. The UAB Medical Genomics Laboratory is regarded internationally as the gold standard in NF genetic testing, including NF1, NF2, and schwannomatosis, as well as other Ras pathway disorders. The laboratory has identified several genotype-phenotype correlations in NF1. In addition, it has characterized the natural history of Legius syndrome, associated with SPRED1 mutation, and identified LZTR1 as being responsible for some cases of schwannomatosis not associated with SMARCB1 mutation.

   a. Koczkowska M, Chen Y, Callens T, Gomes A, Sharp A, Johnson S, Hsiao MC, Chen Z, Balasubramanian M, Barnett CP, Becker TA, Ben-Shachar S, Bertola DR, Blakeley JO, Burkitt-Wright EMM, Callaway A, Crenshaw M, Cunha KS, Cunningham M, D'Agostino MD, Dahan K, De Luca A, Destrée A, Dhamija R, Eoli M, Evans DGR, Galvin-Parton P, George-Abraham JK, Gripp KW, Guevara-Campos J, Hanchard NA, Hernández-Chico C, Immken L, Janssens S, Jones KJ, Keena BA, Kochhar A, Liebelt J, Martir-Negron A, Mahoney MJ, Maystadt I, McDougall C, McEntagart M, Mendelsohn N, Miller DT, Mortier G, Morton J, Pappas J, Plotkin SR, Pond D, Rosenbaum K, Rubin K, Russell L, Rutledge LS, Saletti V, Schonberg R, Schreiber A, Seidel M, Siqveland E, Stockton DW, Trevisson E, Ullrich NJ, Upadhyaya M, van Minkelen R, Verhelst H, Wallace MR, Yap YS, Zackai E, Zonana J, Zurcher V, Claes K, Martin Y, Korf BR, Legius E, Messiaen LM. Genotype-Phenotype Correlation in NF1: Evidence for a More Severe Phenotype Associated with Missense Mutations Affecting NF1 Codons 844-848. Am J Hum Genet. 2018 Jan 4;102(1):69-87. PubMed PMID: 29290338; PubMed Central PMCID: PMC5777934.

   b. Rojnueangnit K, Xie J, Gomes A, Sharp A, Callens T, Chen Y, Liu Y, Cochran M, Abbott MA, Atkin J, Babovic-Vuksanovic D, Barnett CP, Crenshaw M, Bartholomew DW, Basel L, Bellus G, Ben-Shachar S, Bialer MG, Bick D, Blumberg B, Cortes F, David KL, Destree A, Duat-Rodriguez A, Earl D, Escobar L, Eswara M, Ezquieta B, Frayling IM, Frydman M, Gardner K, Gripp KW, Hernández-Chico C, Heyrman K, Ibrahim J, Janssens S, Keena BA, Llano-Rivas I, Leppig K, McDonald M, Misra VK, Mulbury J, Narayanan V, Orenstein N, Galvin-Parton P, Pedro H, Pivnick EK, Powell CM, Randolph L, Raskin S, Rosell J, Rubin K, Seashore M, Schaaf CP, Scheuerle A, Schultz M, Schorry E, Schnur R, Siqveland E, Tkachuk A, Tonsgard J, Upadhyaya M, Verma IC, Wallace S, Williams C, Zackai E, Zonana J, Lazaro C, Claes K, Korf B, Martin Y, Legius E, Messiaen L. High Incidence of Noonan Syndrome Features Including Short Stature and Pulmonic Stenosis in Patients carrying NF1 Missense Mutations Affecting p.Arg1809: Genotype-Phenotype Correlation. Hum Mutat. 2015 Nov;36(11):1052-63. PubMed PMID: 26178382; PubMed Central PMCID: PMC5049609.

   c. Piotrowski A, Xie J, Liu YF, Poplawski AB, Gomes AR, Madanecki P, Fu C, Crowley MR, Crossman DK, Armstrong L, Babovic-Vuksanovic D, Bergner A, Blakeley JO, Blumenthal AL, Daniels MS, Feit H, Gardner K, Hurst S, Kobelka C, Lee C, Nagy R, Rauen KA, Slopis JM, Suwannarat P, Westman JA, Zanko A, Korf BR, Messiaen LM. Germline loss-of-function mutations in LZTR1 predispose to an inherited disorder of multiple schwannomas. Nat Genet. 2014 Feb;46(2):182-7. PubMed PMID: 24362817; PubMed Central PMCID: PMC4352302.

   d. Messiaen L, Yao S, Brems H, Callens T, Sathienkijkanchai A, Denayer E, Spencer E, Arn P, Babovic-Vuksanovic D, Bay C, Bobele G, Cohen BH, Escobar L, Eunpu D, Grebe T, Greenstein R, Hachen R, Irons M, Kronn D, Lemire E, Leppig K, Lim C, McDonald M, Narayanan V, Pearn A, Pedersen R, Powell B, Shapiro LR, Skidmore D, Tegay D, Thiese H, Zackai EH, Vijzelaar R, Taniguchi K, Ayada T, Okamoto F, Yoshimura A, Parret A, Korf B, Legius E. Clinical and mutational spectrum of neurofibromatosis type 1-like syndrome. JAMA. 2009 Nov 18;302(19):2111-8. PubMed PMID: 19920235.

2. I have played a visible role nationally and internationally in genetics and genomics education, and in the integration of genetics and genomics into medical practice. I served as president of the American College of Medical Genetics and Genomics, and as a member of the committee on incidental findings from genomic sequencing. I also chaired the committee of the Intersociety Coordinating Committee of NHGRI that formulated competences in genomic medicine for clinicians. I have chaired three national conferences on medical genetics professional education.

   a. Korf BR, Blitzer MG, Demmer LA, Feldman GL, Watson MS. Report on the Banbury Summit Meeting on medical genetics training in the genomic era, 23-26 February 2014. Genet Med. 2017 Sep;19(9)PubMed PMID: 28640242; PubMed Central PMCID: PMC5589971.
   b. Vassy JL, Korf BR, Green RC. How to know when physicians are ready for genomic medicine. Sci Transl Med. 2015 May 13;7(287):287fs19. PubMed PMID: 25971999; PubMed Central PMCID: PMC4519005.
   c. Korf BR, Berry AB, Limson M, Marian AJ, Murray MF, O'Rourke PP, Passamani ER, Relling MV, Tooker J, Tsongalis GJ, Rodriguez LL. Framework for development of physician competencies in genomic medicine: report of the Competencies Working Group of the Inter-Society Coordinating Committee for Physician Education in Genomics. Genet Med. 2014 Nov;16(11):804-9. PubMed PMID: 24763287.
   d. Korf BR. The medical genetics residency milestones. J Grad Med Educ. 2014 Mar;6(1 Suppl 1):87-90. PubMed PMID: 24701269; PubMed Central PMCID: PMC3966601.

3. I serve as PI of the Neurofibromatosis Clinical Trials Consortium, which conducts clinical trials of targeted therapies for all forms of neurofibromatosis. I also lead a research effort at UAB aimed at development of mutation-targeted therapies for NF1.

   a. Cannon A, Chen MJ, Li P, Boyd KP, Theos A, Redden DT, Korf B. Cutaneous neurofibromas in Neurofibromatosis type I: a quantitative natural history study. Orphanet J Rare Dis. 2018 Feb 7;13(1):31. PubMed PMID: 29415745; PubMed Central PMCID: PMC5803843.
   b. Packer RJ, Fisher MJ, Cutter G, Cole-Plourde K, Korf BR. Neurofibromatosis Clinical Trial Consortium. J Child Neurol. 2018 Jan;33(1):82-91. PubMed PMID: 29246097.
   c. Payne JM, Barton B, Ullrich NJ, Cantor A, Hearps SJ, Cutter G, Rosser T, Walsh KS, Gioia GA, Wolters PL, Tonsgard J, Schorry E, Viskochil D, Klesse L, Fisher M, Gutmann DH, Silva AJ, Hunter SJ, Rey-Casserly C, Cantor NL, Byars AW, Stavinoha PL, Ackerson JD, Armstrong CL, Isenberg J, O'Neil SH, Packer RJ, Korf B, Acosta MT, North KN. Randomized placebo-controlled study of lovastatin in children with neurofibromatosis type 1. Neurology. 2016 Dec 13;87(24):2575-2584. PubMed PMID: 27956565; PubMed Central PMCID: PMC5207004.
   d. Li K, Turner AN, Chen M, Brosius SN, Schoeb TR, Messiaen LM, Bedwell DM, Zinn KR, Anastasaki C, Gutmann DH, Korf BR, Kesterson RA. Mice with missense and nonsense NF1 mutations display divergent phenotypes compared with human neurofibromatosis type I. Dis Model Mech. 2016 Jul 1;9(7):759-67. PubMed PMID: 27482814; PubMed Central PMCID: PMC4958313.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/bruce.korf.1/bibliography/public/

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

1T2OD026548-01, National Institute of Health
Co-PI's –Korf/Lewis
07/01/2018-06/30/2023
Southern All of Us Network

The goal of this project is to gather data from 20,000 participants per year to accelerate research and improve health. This is a participant-engaged, data-driven enterprise supporting research at the intersection

of human biology, behavior, and genetics to produce new knowledge with the goal of developing more effective ways to treat disease

W81XWH-12-1-0155, Department of Defense
Korf, Bruce (PI)
08/15/17-08/14/21
The NF Clinical Trials Consortium
This is a multicenter clinical trials award intended to perform clinical trial studies in patients with NF. UAB is a patient recruitment site, but also serves as the coordinating center for the consortium. Note: This award has been renewed for another five years beginning May 2017.
Role: PI

1T32HG008961, NHGRI
Korf, Bruce (PI)
06/01/16-05/30/21
UAB-HudsonAlpha Genomic Medicine Training Program
The UAB-HudsonAlpha Genomic Medicine Research Training Program trains postdoctoral fellows from MD, PhD, and MDPhD backgrounds, focusing on genomic medicine in clinical research.
Role: PI

U01HG007301, NIH
Cooper, Gregory (PI)
08/01/17-07/31/21
Clinical sequencing across communities in the Deep South
This project is part of the NHGRI Clinical Sequencing Exploratory Research Program. We are using whole genome sequencing to establish diagnoses of newborns in the special care nursery and testing the ability to support nursery staff in return of genomic results to parents.
Role: CPI

Completed Research Support

OT2OD025284, NIH
Korf, Bruce (PI)
08/26/17-05/31/18
Southern All of Us Network
I am PI of the Southern All of Us Network, which consists of a set of health provider organizations in Alabama, Mississippi, and Louisiana that will be recruiting participants for the national All of Us program.
Role: PI

F100225004-UAB, Department of Defense
Korf, Bruce (PI)
02/07/13-02/06/18
A Phase II Study of Everolimus (RAD001) for children with Neurofibromatosis Type I and Chemotherapy-Refractory Radiographic Progressive Low-Grade Glioma
Study of the efficacy of everolimus in treatment of low grade glioma in children with NF1. I serve as site PI for the UAB data collection site.
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Neil Edward Lamb, Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): NEILLAMB

POSITION TITLE: Vice President for Educational Outreach, Faculty Investigator

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Auburn University	B.S.	05/1990	Molecular Biology
Emory University	Ph.D.	05/1997	Genetics and Molecular Biology

A. Personal Statement

I am the Vice President for Educational Outreach at the HudsonAlpha Institute for Biotechnology. I oversee all educational programming developed at the institute, ranging from elementary school to graduate students and from hands on lab kits to digital media activities. I have extensive experience in education, combined with a strong working knowledge of the genetics and genomics fields. During my time as a faculty member at Emory, I transitioned from running a sequencing laboratory to focusing on the educational needs of the Department of Human Genetics. I directed and served as the primary teacher for the Medical Genetics course, created undergraduate and graduate learning activities that cut across multiple disciplines, and became a frequent public spokesperson about genetics and the medical, ethical and social implications of the field. The opportunity to reach individuals across an even broader range of ages and backgrounds led me to HudsonAlpha, where I have assembled a well-qualified team of educators, scientists and assessment experts. We have developed several hands-on and digital activities that link biology and genetic concepts to real-world applications and careers. These have been adopted by Alabama's statewide math and science program, and annually reach over 60,000 middle and high school students. All activities are linked to state science standards and include extensive educator background materials. My team also crafts and oversees professional development opportunities that update both content and pedagogical skills for Alabama educators, including an annual guidebook that highlights new genetic discoveries and connects the discovery to science, health and career and technical state standards. We have developed a number of undergraduate course modules for metagenomics and clinical sequencing. In terms of public outreach, I author a blog called "Shareable Science" to help explain relevant biotechnology concepts and have crafted a public discussion series that regularly educates over 300 individuals each semester. Since January of 2015, the Education Outreach group offers a series of Continuing Medical Education (CME) courses that are approved for CME credits by the Medical Association of the State of Alabama (MASA). The series, titled "Genetics in your practice", is aimed at physicians and nurse practitioners and consists of three courses per year. This cumulative experience of my team will allow me to develop the educational material and training as outlined in this proposal.

B. Positions and Honors

Positions and Employment

1997-1999 Director of Family Programming and Communications, Oak Grove UMC, Atlanta, GA
1999-2006 Assistant Professor, Emory University, Atlanta, GA
2001-2005 Director, Center for Medical Genomics, Emory University, Atlanta, GA

2005-2006 Director of Education, Department of Human Genetics, Emory University, Atlanta, GA
2006-2013 Director of Educational Outreach, HudsonAlpha Institute for Biotechnology, Huntsville, AL
2013- Vice President for Educational Outreach, HudsonAlpha Institute for Biotechnology, Huntsville, AL

Professional Memberships

1999- American Society of Human Genetics
2003-2005 Member, Information and Education Committee
2007 Chair, Information and Education Committee
2003- National Science Teachers Association
2010- National Association of Biology Teachers
2016- Alabama Science Teachers Association

Honors

1994-1996 NIH Training Grant Fellow
1996 American Society of Human Genetics Outstanding Predoctoral Basic Research Award
2002 Emory University School of Medicine - Dean's Golden Apple Award for Teaching
2005 Woodruff Leadership Academy fellow – Emory University Woodruff Health Science Center
2005 National Council of Churches – Human Biotechnology Policy Development Committee
2008 Alabama Math Science and Technology Initiative – Friend of AMSTI
2018 Faraday Science Communicator Award – National Science Teachers Association

C. Contributions to Science

1. **Understanding the molecular contributors to chromosome nondisjunction:** My training was in human genetics, specifically the molecular factors association with chromosome movement during meiosis. Using a combination of linkage-based mapping, STR molecular profiling and computational modeling, I analyzed the association between altered meiotic recombination and different patterns of chromosome nondisjunction for trisomy 21. My work confirmed aberrant recombination as the first molecular correlate for chromosome aneuploidy. After graduate school, and throughout my time at Emory University as a faculty member, I continued this collaboration with Stephanie Sherman.
   a. Lamb, N.E., Freeman, S.B., Savage-Austin, A., Avramopoulos, D., Gu, Y., Hallberg, A., Hersey, J., Pettay, D., May, K.M., Saker, D., Shen, J., Taft, L., Mikkelsen, M., Hassold, T.J., Petersen, M., and Sherman, S.L. (1996). Susceptible chiasmate configurations of chromosome 21 predispose to nondisjunction in both maternal meiosis I and meiosis II. Nature Genetics, 14, 400-405.
   b. Lamb, N.E., Feingold, E., and Sherman, S.L. (1997). Predicting meiotic exchange patterns from recombination data: an application to humans. Genetics, 146, 1101-1117.
   c. Lamb NE, Yu K, Shaffer J, Feingold E, Sherman SL (2005) Association between Maternal Age and Meiotic Recombination. American Journal of Human Genetics, 76, 91-99.
   d. Lamb NE, Sherman SL, Hassold TJ (2005) Effect of meiotic recombination on the production of aneuploid gametes in humans. Cytogenet Genome Res 2005, 111, 250-255.

2. **Increasing genomic literacy for students, educators, professionals and the public:** Upon joining HudsonAlpha, I focused my efforts on developing programs to create more genetically literate citizens. This includes developing classroom materials for middle and high school students, crafting immersive experiences to grow the biotechnology workforce, providing ongoing training for professionals in healthcare, education and law, and increasing the public's understanding of the growing role of genomics. Many of these programs integrate rigorous assessment methods, allowing us to quantitate the impact of our efforts.
   a. East KM, Hott AM, Callanan NP, Lamb NE (2012) Biotech101: An Educational Outreach Program in Genetics and Biotechnology. Journal of Genetic Counseling, 21, 704-12.
   b. Loftin M, Lamb NE (2013) Too New for Textbooks: The Biotechnology Discoveries and Applications Guidebook. The American Biology Teacher, 75(7), 480-485.
   c. East KE and Lamb NE "Genetics/Genomics" In Applied Clinical Informatics for Nurses: Alexander S, Frith KH and Hoy H, editors. Jones and Bartlett Learning 2015.

d. Loftin M, East KM, Hott AM, Lamb NE. “Touching Triton”: Building Student Understanding of Complex Disease Risk. *The American Biology Teacher*. 2016; 78(1):15-21.

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/neil.lamb.1/bibliography/47980228/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

University of Alabama at Birmingham (PI: Kimberly) 05/06/2019 - 04/30/2024
NIH/NCATS 1UL1TR003096
Center for Clinical and Translational Science

Dr. Lamb will work with Drs. Michael, Allen and Hood (UAB) to coordinate the activities fulfilling the Community and Collaboration specific aims including implementing the Collaboratory Platform, arranging Community Engagement mini-sabbaticals and working with CCTS Community and Collaboration for dissemination and education. Role: Co-Investigator

NIH/NHGRI 1R25HG010028 (PIs: Barsh and Korf) 09/24/2018 – 08/31/2023
Summer Undergraduate Research Experiences in Genomic Medicine (SURE-GM)

This R25 grant will leverage and build on the environment at UAB and HudsonAlpha to develop Summer Undergraduate Research Experience in Genomic Medicine (SURE-GM)**,** a two consecutive summer program tailored for HBCU undergraduate students that will provide them with the necessary skills, exposures, and experiences to succeed in graduate and/or professional training in genomic sciences. Role: Co-Investigator

NIH/NIGMS 5R25GM129867-02 (PI: Lamb) 09/10/2018 – 07/31/2023
Filtered: a story-driven digital learning platform for bioinformatics and infectious disease

Filtered allows students to approach real-world problems using 21st century skills, pulling multiple lines of evidence from molecular biology, human genetics, population biology and evolution as they draw connections between their classroom lessons, personal interests and present-day applications.

NSF EPSCoR OIA-1826781 (PI: Schmutz) 10/01/2018 – 09/30/2022
RII Track-2 FEC: Functional Analysis of Nitrogen Responsive Networks in Sorghum

This grant will establish a partnership for cutting edge plant genomic research between two EPSCoR regions of Alabama and Nebraska. The team at University of Nebraska-Lincoln will contribute their expertise in plant transformation and automated phenotyping using their new state-of-the-art LemnaTeC high-throughput system for imaging large plants. The team at HudsonAlpha Institute for Biotechnology will contribute dedicated outreach for agricultural biotechnology education and genomic and molecular analysis of plant networks. We will combine these advanced tools to better understand the regulation of a complex agronomic trait of agricultural, economic, and environmental importance: how nitrogen affects plant growth and development. Role: Co-PI

The Boeing Company (PI: Lamb) 01/01/2018 – 12/31/2021
Launching Aspiring Biotechnology Students (LABS)

This program equips students from disadvantaged and underrepresented populations with the knowledge and skills to confidently take the “next step” towards entry into STEM-based college or post-secondary training programs.

NIH/NHGRI 5T32HG008961 (PIs: Barsh and Korf) 06/01/2016 - 05/31/2021
UAB-HudsonAlpha Genomic Medicine Training Program

The purpose of this training grant is to recruit trainees from various disciplines and provide mentorship and clinical research training in genomic medicine. Role: Co-Investigator and Content Mentor

Alabama Department of Education (PI: Lamb) 10/01/2019 – 09/30/2020
Alabama Department of Education Science Teacher Training

This project supports life science education across the State of Alabama through engaging student experiences, interactive classroom resources and education professional learning opportunities.

NSF S-STEM 1356579 (PI: Moriarity) 09/01/2014 - 08/31/2020
UHOP Scholarship Program

Personnel at the HudsonAlpha Institute for Biotechnology teach the course BYS 491-01 (Principles of research techniques and lab skills) to cohorts of students in the UHOP program and provide weekly professional development seminars for the students. Role: Co-Investigator

Completed Research Support

NIH/NHGRI 4UM1HG007301-04 Revised (PIs: Cooper and Myers) 06/14/2013 – 07/31/2017
Genomic Diagnosis in Children with Developmental Delay

The goal of this project is to address technological, analytical, and ethical challenges that prevent optimal use of DNA sequencing to improve treatment of diseases and life planning for patients and their families. We are applying next-generation DNA sequencing to meet the diagnostic needs of children with developmental delay, intellectual disability and related health problems. Role: Co-Investigator

NIH/NCRR SEPA 5R25OD010981-05 (PI: Lamb) 05/01/2011 - 04/30/2017
It's Complex: Engaging Student Discussions around Complex Genetics and Individualized Medicine

The goal of this project is to create an online classroom activity for use in high schools to highlight the complex interplay between genetic and environmental risk factors in common disease.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Matthew S Lebo

eRA COMMONS USER NAME (credential, e.g., agency login): LEBOMS

POSITION TITLE: Director of Bioinformatics, Partners HealthCare Personalized Medicine (PPM); Director, Laboratory for Molecular Medicine (LMM), PPM; Assistant Professor in Pathology, Harvard Medical School, Brigham and Women's Hospital

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Boston University, Boston, MA	B.A.	2002	Mathematics and Biology
University of Southern California, Los Angeles, CA	Ph.D.	2008	Computational Biology and Bioinformatics
University of Southern California, Los Angeles, CA	Post-Doc	08-09	Molecular and Computational Biology
Harvard Medical School, Boston, MA	Fellow	09-11	Clinical Molecular Genetics

A. Personal Statement

My current role, as well as many of the past and current projects on which I've worked, position me well to help drive the aims of this proposal. Currently, I serve as both the Director of Bioinformatics within a personalized medicine center and as Director of the Laboratory for Molecular Medicine (LMM), a CLIA-certified molecular diagnostics laboratory. Along with my training in computational biology, my roles allow me to drive forward the routine use of clinical computational biology in translational and clinical applications. I direct all bioinformatics activities for Partners Personalized Medicine, driving activities in clinical molecular genetic testing, translational research projects, software development, and the Partners Biobank. As Director of the LMM, I lead our clinical genome/exome sequencing pipelines, with a major focus in genomic based screening of healthy individuals. Under my leadership our bioinformatics has managed a clinical genomic interpretation pipeline for over 6 years, continuously updating and validating the workflow to provide accurate and efficient workflows for the clinical interpretation team. This includes identifying variants, annotating and filtering them to likely candidates, and assessing pathogenicity. I also have managed our variant assessment process, leading to one of the first publications detailing standardized methodology for variant interpretation, and helped develop a novel algorithm for copy-number variant calls from targeted next-generation sequencing data. Additionally, I am working on multiple efforts focused on clinical sequencing, variant interpretation, and return of results to patients using exome and genome sequencing focusing on healthy and sick adults (MedSeq), healthy and sick newborns (BabySeq), active armed forces members (MilSeq), and large biobank cohorts (eMERGE, Partners Biobank, and Geisinger MyCode). For these efforts, I interpret and sign-out reports, direct the clinical bioinformatics activities, and oversee the management of the projects at our laboratory.

B. Positions and Honors

Positions and Employment

2009 – 10 Research Fellow in Genetics with Heidi Rehm, Ph.D., Brigham and Women's Hospital, Boston, MA

2010 – 11 Post-Doctoral Associate at Molecular Diagnostics Laboratory with D. Alexa Sirko-Osadsa, Ph.D., Genzyme Genetics, Westborough, MA
2011 – 17 Instructor in Pathology, Departments of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA
2011 – 13 Assistant Laboratory Director, Laboratory for Molecular Medicine (LMM), Partners Personalized Medicine (PPM), Partners HealthCare System, Cambridge, MA
2011 – 13 Senior IS Domain Specialist, Partners Center for Personalized Genetic Medicine (PCPGM), Partners HealthCare System, Cambridge, MA
2013 – Director of Bioinformatics, Partners Personalized Medicine (PPM), Partners HealthCare System, Cambridge, MA
2013 – 18 Associate Laboratory Director, Laboratory for Molecular Medicine (LMM), Partners Personalized Medicine (PPM), Partners HealthCare System, Cambridge, MA
2017 - Assistant Professor in Pathology, Departments of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA
2018 - Director of the Laboratory for Molecular Medicine, Partners Personalized Medicine (PPM), Partners HealthCare System, Cambridge, MA

Other Experiences and Professional Memberships
2010 – Member, American College of Medical Genetics
2010 – 11 Trainee Member, Working-group on Microarray Technology in Neoplastic Disorders, American College of Medical Genetics Laboratory Quality Assurance Committee
2015 – Member, Association for Molecular Pathologists
2017 – Informatics Subdivision Leadership; Program Committee Representative, Association for Molecular Pathologists
2018 – Member, Genomic Medicine Resource Committee, College of American Pathologists

Certification
2011 American Board of Medical Genetics, Clinical Molecular Geneticist

C. Contributions to Science

Clinical molecular genetics is increasingly being supported by in-depth bioinformatics algorithms. These algorithms not only need to be able to handle large amounts of complex data, but also need to produce meaningful results. We have developed and validated many algorithms in this space, including VisCap, a novel approach to CNV calling from NGS data whose description is current under revision. My current work focuses on implementing translational and clinical bioinformatic processes into active practice, with much of the work centered around large multi-center projects.

1. Jordan DM, Kiezen A, Baxter SM, Agarwala V, Green RC, Murray MF, Pugh T, **Lebo MS**, Rehm HL, Funke BH, Sunyaev SR. Development and Validation of a Computational Method for Assessment of Missense Variants in Hypertrophic Cardiomyopathy. Am J Hum Genet. 2011 Feb 11;88(2):183-92.
2. Pugh TJ, Amr SS, Bowser MJ, Gowrisankar S, Hynes E, Mahanta LM, Rehm HL, Funke B, **Lebo MS**. VisCap: Inference and visualization of germline copy number variants from targeted clinical sequencing data. Genet Med. 2015 Dec 17. PMID: 26681316.
3. Amr SS, Al Turki SH, **Lebo M**, Sarmady M, Rehm HL, Abou Tayoun AN. Using large sequencing datasets to refine intragenic disease regions and prioritize clinical variant interpretation. Genet Med. 2016 Sep 22. PMID: 27657688.
4. Lincoln SE, Truty R, Lin CF, Zook J, Paul J, Ramey V, Salit M, Rehm HL, Nussbaum R, **Lebo M**. A Rigorous Interlaboratory Examination of the Need to Confirm NGS-Detected Variants by an Orthogonal Method in Clinical Genetic Testing. bioRxiv 335950; doi: https://doi.org/10.1101/335950.

There is also a tremendous need in the clinical and research genomics communities for tools that process and analyze genome scale data accurately and efficiently. Analysis of such data still requires specialized staff to establish and maintain analysis pipelines and tools. With the increasing commoditization of genome scale analyses and their implementation in the clinic it is vital to create easy to use systems that allow practicing medical geneticists and physicians to access and interpret patient data. This drives a key focus to my work, namely infrastructure for variant classification and interpretation. Due to experience gathered working as a

geneticist, I'm involved in two major efforts (ClinGen and the Canadian Open Genetics Repository) that focus on the sharing and disseminating of standards, tools, and data among clinical and translational laboratories.

1. Duzkale H, Shen J, McLaughlin H, Alfares A, Kelly M, Pugh T, Funke B, Rehm H, **Lebo M**. A systematic approach to assessing the clinical significance of genetic variants. Clin Genet. 2013 Nov;84(5):453-63 PMID: 24033266
2. Lerner-Ellis J, Wang M, White S, **Lebo MS**; and the Canadian Open Genetics Repository Group. Canadian Open Genetics Repository (COGR): a unified clinical genomics database as a community resource for standardising and sharing genetic interpretations. J Med Genet. 2015 Apr 22. pii: jmedgenet-2014-102933. PMID: 25904639.
3. Amendola LM, Jarvik GP, Leo M, McLaughlin HM, Akkari Y, Amaral MD, Berg J, Biswas S, Bowling KM, Conlin LK, Cooper GM, Dorschner MO, Dulik MC, Ghazani AA, Ghosh R, Green RC, Hart R, Horton C, Johnston JJ, **Lebo MS**, Milosavljevic A, Ou J, Pak CM, Patel RY, Punj S, Richards CS, Salama J, Strande NT, Yang Y, Plon SE, Biesecker LG, Rehm HL. Performance of ACMG/AMP variant interpretation guidelines among nine laboratories in the Clinical Sequencing Exploratory Research consortium. Am J Hum Genet. 2016 Jun 2;98(6):1067-76. PMID: 27181684.
4. **Lebo MS**, Zakoor KR, Chun K, Speevak MD, Waye JS, McCready E, Parboosingh JS, Lamont RE, Feilotter H, Bosdet I, Tucker T, Young S, Karsan A, Charames GS, Agatep R, Spriggs EL, Chisholm C, Vasli N, Daoud H, Jarinova O, Tomaszewski R, Hume S, Taylor S, Akbari MR, Lerner-Ellis J. Data sharing as a national quality improvement program: reporting on BRCA1 and BRCA2 variant-interpretation comparisons through the Canadian Open Genetics Repository (COGR). Genet Med. 2017. PMID: 28726806.

Genomic sequencing is starting to be used as a screening tool for healthy individuals in the translational and clinical research communities. I've been involved in numerous large-scale projects that identify individuals with risks of Mendelian conditions, and returning these variants to patient participants. The tools developed by my team have annotated and filtered the genomic information of >70,000 individuals across a variety of projects, identifying numerous individuals who are at risk of developing serious disease prior to the onset of symptoms.

1. Dewey FE, Murray MF, Overton JD, Habegger L, Leader JB, Fetterolf SN, O'Dushlaine C, Van Hout CV, Staples J, Gonzaga-Jauregui C, Metpally R, Pendergrass SA, Giovanni MA, Kirchner HL, Balasubramanian S, Abul-Husn NS, Hartzel DN, Lavage DR, Kost KA, Packer JS, Lopez AE, Penn J, Mukherjee S, Gosalia N, Kanagaraj M, Li AH, Mitnaul LJ, Adams LJ, Person TN, Praveen K, Marcketta A, **Lebo MS**, Austin-Tse CA, Mason-Suares HM, Bruse S, Mellis S, Phillips R, Stahl N, Murphy A, Economides A, Skelding KA, Still CD, Elmore JR, Borecki IB, Yancopoulos GD, Davis FD, Faucett WA, Gottesman O, Ritchie MD, Shuldiner AR, Reid JG, Ledbetter DH, Baras A, Carey DJ. Distribution and clinical impact of functional variants in 50,726 whole-exome sequences from the DiscovEHR study. Science. 2016 Dec 23;354(6319). PMID: 28008009.
2. Haggerty CM, James CA, Calkins H, Tichnell C, Leader JB, Hartzel DN, Nevius CD, Pendergrass SA, Person TN, Schwartz M, Ritchie MD, Carey DJ, Ledbetter DH, Williams MS, Dewey FE, Lopez A, Penn J, Overton JD, Reid JG, **Lebo M**, Mason-Suares H, Austin-Tse C, Rehm HL, Delisle BP, Makowski DJ, Mehra VC, Murray MF, Fornwalt BK. Electronic health record phenotype in subjects with genetic variants associated with arrhythmogenic right ventricular cardiomyopathy: a study of 30,716 subjects with exome sequencing. Genet Med. 2017. PMID: 28471438.
3. Vassy JL, Christensen KD, Schonman EF, Blout CL, Robinson JO, Krier JB, Diamond PM, **Lebo M**, Machini K, Azzariti DR, Dukhovny D, Bates DW, MacRae CA, Murray MF, Rehm HL, McGuire AL, Green RC. The Impact of Whole-Genome Sequencing on the Primary Care and Outcomes of Healthy Adult Patients: A Pilot Randomized Trial. Ann Intern Med. 2017. PMID: 28654958.
4. Cirino AL, Lakdawala NK, McDonough B, Conner L, Adler D, Weinfeld M, O'Gara P, Rehm HL, Machini K, Lebo M, Blout C, Green RC, MacRae CA, Seidman CE, Ho CY, for the MedSeq Project. A Comparison of Whole Genome Sequencing to Multigene Panel Testing in Hypertrophic Cardiomyopathy Patients. Circ Cardiovasc Genet. 2017 2017 Oct;10(5). pii: e001768. PMID: 29030401

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1RQNgwxrdmB57/bibliography/53894569/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R01 HL143295 7/1/19-6/30/23 Role: Co-Investigator
(Green/Ramachandran/Correa)
Return of Genomic Results and Estimating Penetrance in Population-Based Cohorts
The goals of this project are to develop and implement a genomic return of results (gRoR) process in the Framingham Heart Study and Jackson Heart Study cohorts and explore associated medical, behavioral and economic outcomes. We plan to automate and streamline genomic variation interpretation and will evaluate aggregate penetrance for Mendelian diseases.

OT2OD02750 (Gabriel/Rehm/Topper) 9/25/18-08/31/23 Role: Co-PI
NIH
Broad-LMM-Color Genome Center for All of Us
The goal of this project is to provide genomic data in the form of genotyping arrays and whole genome sequencing on one million participants in the All of Us research program and return clinically meaningful results to participants.

1 R01 HG010372-01 (Cassa) 09/24/18-06/30/23 Role: Co-Investigator
NIH
Integrated Pathogenicity Assessment of Clinically Actionable Genetic Variants
The goals of this project include 1) improved computational predictions of structural and functional impact, 2) assessment of phenotypic impact using measures of selective constrain and 3) development of a Bayesian statistical framework to assess clinical risk.

U41 HG006834 (Rehm/Martin/Ledbetter) 08/01/17-07/31/21 Role: Co-Investigator
NIH/NHGRI
The Clinical Genome Resource
This project serves to collect and organize genomic data from many sources into a free and publicly accessible environment and enable expert curation of that data for use in improving healthcare and biomedical research.

R01 HG009174 (Murphy/Rehm) 09/28/16-8/31/20 Role: Co-Investigator
NIH/NCBI
Developing i2b2 into a Health Innovation Platform for Clinical Decision Support in the Genomics Era
The goal of this project is to provide the laboratory perspective on how the HIP-CDS app should be constructed, to validate functionality, and to ensure this work is well coordinated with efforts throughout the genetics community.

U01 HG008685 (Weiss, et al.) 09/01/15 – 03/31/20 Role: Co-Investigator
NIH/NHGRI
eMERGE Phase III Clinical Center at Partners HealthCare
The discovery and clinical use of genetic variants associated with both rare Mendelian and more common complex diseases promises to dramatically change the practice of medicine. The eMERGE III Clinical Center at Partners HealthCare will leverage a large Biobank and a rich electronic medical record to define the phenotypic impact of mutations emerging from sequencing and then return results on selected variants to Biobank participants using a clinical trial.

U01 HG008676 (Rehm, et al.) 09/01/15-03/31/20 Role: Co-Investigator
NIH/NHGRI
eMERGE III Central Sequencing, Genotyping and Interpretation Facility
The Central Sequencing and Genotyping Facility composed of the Laboratory for Molecular Medicine (LMM) at Partners HealthCare and the Genomics Platform at the Broad Institute provides high-quality sequencing and interpretation for the eMERGE Network. The project is identifying clinically relevant genetic variants and supporting their return to study sites. Through this project, researchers are able to identify causes of human disease and facilitate the integration of genetics into the practice of medicine.

Completed Research Support

UM1HG008900 (MacArthur/Rehm) 01/14/16-11/30/19 Role: Co-Investigator
Joint Center for Mendelian Genomics
NIH/NHGRI
Clinical sequencing has become a frontline strategy for diagnosing rare, severe disease, particularly in pediatrics: 10% of pediatric admissions and up to 20% of infant deaths derive from Mendelian disease. However, the capability for generating sequence data far outstrips the capability to accurately interpret these data, and over half of patients with suspected genetic disorders do not currently receive a genetic diagnosis. Our Center will contribute substantially to the establishment of a comprehensive catalog of the genetic causes of Mendelian diseases, thus improving disease diagnosis rates as well as building the biological understanding needed to develop more effective therapeutics.

U19 HD077671 (Green/Beggs) 09/05/13-8/31/18 Role: Co-Investigator
NIH/NICHD
Genome Sequence-Based Screening for Childhood Risk and Newborn Illness
The major goal of the grant is to evaluate the outcomes of two cohorts of newborns (240 NICU babies and 240 well-nursery babies) who will be randomized to receive or not receive whole genome sequencing in their clinical care.

U41 HG006834 (Rehm, et al) 08/01/16-07/31/17 Role: Co-Investigator
NIH/NHGRI
A Unified Clinical Genomics Variant Database
Hundreds of thousands of disease-causing variants have been identified in patients with disease, yet only a small fraction of that data, and the interpretation of it, is accessible to researchers and clinicians. This project will serve to collect and organize genomic data from many sources into a free and publicly accessible environment and enable expert curation of that data for use in improving healthcare and biomedical research.

U01 HG006500 (Green) 12/05/11-05/31/17 Role: Co-Investigator
NIH/NHGRI
Integration of Whole Genome Sequencing into Clinical Medicine
The major goal of the grant is to evaluate the outcomes of two cohorts of patients (100 patients with cardiomyopathy and 100 healthy individuals) who are randomized to receive or not receive whole genome sequencing in their clinical care.

BCB2012 #5434 (Lerner-Ellis and Lebo) 07/01/13 – 03/31/17 Role: Co-PI
Genome Canada
Development of a unified Canadian clinical genomic database as a community resource for standardizing and sharing genetic interpretations
Clinical molecular laboratories across Canada are focused on providing high quality genetic testing, yet lack standardization and infrastructure for scaling as the need for their services grow. This grant is focused on developing standard processes and tools for laboratories, particularly around variant assessment, and on removing the typical barriers and silos within the laboratories by utilizing common infrastructure to share variant classifications and interpretations. The result of the first two parts of the project will enable us to create a database of consensus level interpretations across the Canadian clinical laboratory community.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Amy L. McGuire

eRA COMMONS USER NAME (credential, e.g., agency login): amcguire

POSITION TITLE: Leon Jaworski Professor of Biomedical Ethics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Pennsylvania, Philadelphia, PA	B.A.	05/95	Psychology
University of Houston Law Center, Houston, TX	J.D.	05/00	Law
Institute for Medical Humanities, University of Texas Medical Branch, Galveston, TX	Ph.D.	12/04	Humanities/Ethics

A. Personal Statement

I have a long track record of conducting ELSI research using a range of qualitative, quantitative, legal, and mixed methods and experience leading large research groups as PI or Co-PI. My research focuses on legal and ethical issues in human genomics and innovative neurotechnologies, and my group is currently working on projects related to research ethics in areas such as genomic data sharing and return of genetic research results, informed consent and governance in biobanking, and the psychosocial impact and policy challenges of the clinical integration of adaptive deep brain stimulation and genome sequencing technologies. I have served on the Advisory Council for the National Human Genome Research Institute (NHGRI) and its Genomics and Society Working Group and have served as a member of several other national committees that explore ethical issues in genome research and its responsible integration into clinical practice, including: NIH 1000 Genomes Samples/ELSI Workgroup, NIH All of Us Research Program, NIH Electronic Medical Records in Genomics Network (eMERGE), Clinical Sequencing Exploratory Research Consortium Outcomes and Measures Working Group co-Chair, Clinical Sequencing Evidence Generating Research Consortium ELSI and Diversity Working Group co-Chair, Consent and Community Participation Workgroup, NIH Advisory Committee to the Director Working Group on Participant and Data Protection, and the X Prize in Genomics Ethics Advisory Board. Drawing on my extensive expertise in conducting ELSI research, as well as my directly related work as Co-PI of Project 3 on the BabySeq Project (U19HD077671), I will help oversee all activities proposed for this project to explore the longitudinal impact of clinically integrating newborn genome sequencing.

B. Positions and Honors

Positions:

2004-2009	Assistant Professor, Center for Medical Ethics and Health Policy, Baylor College of Medicine (BCM), Houston, TX
2009-2012	Associate Professor, Center for Medical Ethics and Health Policy, BCM, Houston, TX
2009-2012	Associate Director of Research, Center for Medical Ethics and Health Policy, BCM, Houston, TX
2012-present	Professor, Center for Medical Ethics and Health Policy, BCM, Houston, TX
2012-present	Director, Center for Medical Ethics and Health Policy, BCM, Houston, TX

Honors:

1995	BA, *summa cum laude,* University of Pennsylvania

2000 JD, *summa cum laude,* University of Houston Law Center
2004 PhD, *with distinction,* Institute for the Medical Humanities, University of Texas Medical Branch
2008 Fulbright & Jaworski L.L.P. Faculty Excellence Award for Educational Leadership
2009 Fulbright & Jaworski L.L.P. Faculty Excellence Award for Teaching and Evaluation
2012 Leon Jaworski Professorship in Biomedical Ethics

Competitive Teaching Fellowships:
2001-2004 Medical Jurisprudence Fellowship, University of Texas Medical Branch (UTMB)
2005-2007 Educational Scholars Fellowship, Baylor College of Medicine (BCM)

Committees and Service Responsibilities:
2014-present Association of Bioethics Program Directors, Vice President and President-elect
2012-present Genomics and Society Working Group
2011-present National Advisory Council for Human Genome Research, NIH-NHGRI, Member
2007-2011 NIH Electronic Medical Records in Genomics Network (eMERGE), ELSI Consent and Community Participation Workgroup, Coordinator: Ellen Wright Clayton (Vanderbilt University), Member, Data Sharing Focus Group, Chair
2008-2011 NIH 1000 Genomes Project, Samples/ELSI Workgroup, Member
2007-2009 NIH Advisory Committee to the Director (ACD), Working Group on Participant and Data Protection (PDP) for the Genetic Association Information Network (GAIN) and Genome-wide Association Studies (GWAS), Member
2007-2009 Personalized Health Care Working Group (PHC), American Health Information Community (AHIC), Office of the National Coordinator for Health Information Technology (ONC HIT), Secretary of the Department of Health and Human Services (DHHS), Member; Confidentiality, Privacy, and Security Sub-Committee, Co-Chair
2001-present American Society for Bioethics and the Humanities, Member
2004-present BCM Institutional Review Board, Member
2006-present American Society for Human Genetics, Member
2006-present X Prize Foundation, X Prize in Genomics, Ethics and Social Issues Advisory Board, Member

C. Contribution to Science

1. I was Co-I and ethics consultant on the first whole genome sequence and have written extensively on ethical issues arising in the field of genomics. Through publications related to scientific advancements in the field of genomics over the past twelve years, I have identified and provided recommendations for the responsible management of ethical issues in genomic science, such as the return of research results, obligations to third-party relatives, and future use of genomic information. These contributions have informed practical guidelines, for example for reporting genomic research results and reporting incidental findings in genomic medicine.
    a. **McGuire AL**, Joffe S, Koenig BA, Biesecker BB, McCullough LB, Blumenthal-Barby JS, Caulfield T, Terry SF, Green RC. Ethics and Genomic Incidental Findings. Science 340, 2013: 1047-1048. PMCID: PMC3772710.
    b. Wheeler DA, Srinivasan M, Egholm M, Shen Y, Chen L, **McGuire A**, He W, Chen YJ, Makhijani V, Roth GT, Gomes X, Tartaro K, Niazi F, Turcotte CL, Irzyk GP, Lupski JR, Chinault C, Song XZ, Liu Y, Yuan Y, Nazareth L, Qin X, Muzny DM, Margulies M, Weinstock GM, Gibbs RA, Rothberg JM; The complete genome of an individual by massively parallel DNA sequencing. Nature, 452, 2008: 872-877. PMID 18421352.
    c. **McGuire AL**, Caulfield T, Cho M. Research ethics and the challenge of whole genome sequencing. Nature Reviews Genetics 9, 2008: 152-156. PMCID: PMC2225443.
    d. **McGuire AL**, Cho MK, McGuire SE, Caulfield T. The future of personal genomics. *Science* 317, 2007: 1687. PMCID: PMC2220016.

2. Much of my work has focused on issues of data sharing, privacy and identifiability in genomics. I was among the first to study research participants' perspectives on sharing their genomic information, serving as PI of a randomized trial of consent for genomic data sharing. More recently, I have been exploring, as PI

of an R01 project, commons theory and design principles for sharing genomic and other health data in a medical information commons.

a. Deverka PA, Majumder MA, Villanueva AG, Anderson M, Bakker AC, Bardill J, Boerwinkle E, Bubela T, Evans BJ, Garrison NA, Gibbs RA, Gentleman R, Glazer D, Goldstein MM, Greely H, Harris C, Knoppers BM, Koenig BA, Kohane IS, La Rosa S, Mattison J, O'Donnell CJ, Rai AK, Rehm HL, Rodriguez LL, Shelton R, Simoncelli T, Terry SF, Watson MS, Wilbanks J, Cook-Deegan R, **McGuire AL**. Creating a data resource: what will it take to build a medical information commons? Genome Med. PMCID:PMC5610432
b. Cook-Deegan R, **McGuire AL**. Moving beyond Bermuda: Sharing data to build a medical information commons. *Genome Research.* 2017;27(6):897-01.
c. **McGuire AL**, Oliver JM, Slashinski MJ, Graves JL, Wang T, Kelly PA, et al. To share or not to share: A randomized trial of consent for data sharing in genome research. Genet Med. 13(11), 2011: 948-955. PMCID: PMC3203320.
d. **McGuire AL**, Gibbs RA. No longer de-identified. Science. 312, 2006: 370-371. PMID 16627725.

3. Since 2010, I have been engaged in research on the clinical integration of whole genome and whole exome sequencing. I served as Co-PI and Co-I of two of the nine funded Clinical Sequencing Exploratory Research (CSER) studies, am Co-PI of one of the six funded studies in the new Clinical Sequencing Evidence Generating (CSER2) program, and I am Co-PI on one of the funded Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) studies, leading the ELSI component of each of these projects. I was the inaugural co-chair of the Outcomes and Measures Working Group of the CSER Consortium and coordinated efforts across all nine sites to harmonize measures to facilitate consortium-wide analyses, and the inaugural co-chair of the ELSI and Diversity Working Group of the CSER2 Consortium. These projects are ongoing and to date have generated several publications related to the ethical issues of clinical integration of genomic sequencing.
    a. Wolf SM, Amendola LM, Berg JS, Chung WK, Clayton EW, Green RC, Harris-Wai J, Henderson GE, Jarvik GP, Koenig BA, Lehmann LS, **McGuire AL**, O'Rourke P, Somkin C, Wilfond BS, Burke W. Navigating the research-clinical interface in genomic medicine: analysis from the CSER Consortium. *Genetics in Medicine* 20, 2018: 545-553. PMCID: PMC5832495.
    b. Vassy JL, Christensen KD, Schonman EF, Blout CL, Robinson JO, Krier JB, Diamond PM, Lebo M, Machini K, Azzariti DR, Dukhovny D, Bates DW, MacRae CA, Murray MF, Rehm HL, **McGuire AL**, Green RC; MedSeq Project. The Impact of Whole-Genome Sequencing on the Primary Care and Outcomes of Healthy Adult Patients: A Pilot Randomized Trial. Ann Intern Med. 167, 2017: 159-169. PMCID: PMC5856654.
    c. Frankel LA, Pereira S, **McGuire AL**. Potential Psychosocial Risks of Sequencing Newborns. Pediatrics 137 Suppl 1, 2016: S24-29. PMID: 26729699.
    d. Gray SW, Martins Y, Feuerman LZ, Bernhardt BA, Biesecker BB, Christensen KD, Joffe S, Rini C, Beenstra D, **McGuire AL**. Social and Behavioral Research in Genomic Sequencing: Approaches from the Clinical Sequencing Exploratory Research Consortium Outcomes and Measures Working Group. *Genetics in Medicine* 16, 2014: 727-735. PMCID: PMC4163120.

4. As the next generation sequencing (NGS) industry continues to grow, a challenge is to address policy concerns related to the clinical uptake of this technology. In this area, I served as PI on a study exploring key policy challenges in the areas of regulation, reimbursement, intellectual property, and data sharing. For this project, we identified existing laws and guidelines that may be applicable to genomic research and medicine in order to discern where gaps in regulations and policies have arisen or may occur. We then conducted a modified policy Delphi to prioritize policy concerns and develop ethically appropriate recommendations for new approaches to these existing methods.
    a. Messner DA, Koay P, Al Naber J, Cook-Deegan R, Majumder M, Javitt G, Dvoskin R, Bollinger J, Curnutte M, **McGuire AL**. Barriers to clinical adoption of next-generation sequencing: a policy Delphi panel's solutions. Per Med. 14, 2017: 339-354. PMCID: PMC5722256.
    b. Deverka PA, Kaufman D, **McGuire AL**. Overcoming the reimbursement barriers for clinical sequencing. *JAMA* 2014; 312(18): 1857-1858. PMC: PMC5087268.
    c. Curnutte MA, Frumovitz KL, Bollinger JM, **McGuire AL**, Kaufman DJ. Development of the clinical next-generation sequencing industry in a shifting policy climate. *Nat Biotechnol*. 2014; 32(10): 980-982. PMC: PMC5125294.

d. Kaufman D, Curnutte M, **McGuire AL**. Clinical integration of next generation sequencing: A policy analysis. *J Law Med Ethics*. 2014; 42 Suppl 1: 5-8. PMC: PMC5095695.

5. The genomic direct-to-consumer (DTC) market has raised significant policy, ethical, and empirical questions, which I have studied with great interest. I conducted the first public opinion survey of DTC genetic services and found general interest in these services, especially for medical care purposes, and an expectation that physicians would be able to help interpret the information. I have also studied the potential impact of DTC testing on the health care system. Most recently, I have focused my research in this area on how to build and maintain public trust as new uses of DTC genetic databases, including law enforcement uses, are revealed.
    a. Ram N, Guerrini CJ, **McGuire AL**. Genealogy databases and the future of criminal investigation. Science. 360, 2018:1078-1079. PMID: 29880677.
    b. Caulfield T, **McGuire AL**. Direct-to-Consumer Genetic Testing: Perceptions, Problems and Policy Responses. Ann. Rev. Med. 63, 2012: 23-33. PMID: 21888511.
    c. **McGuire AL**, Burke W. Health System Implications of Direct-to-Consumer Personal Genome Testing. Public Health Genomics 14(1), 2011: 53-58. PMCID: PMC3025885.
    d. **McGuire AL**, Diaz C, Wang T, Hilsenbeck S. Social Networkers' Attitudes toward Direct-to-Consumer Personal Genome Testing. The American journal of bioethics: Am J Bioeth. 9, 2009: 3-10. PMCID: PMC2792120.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/amy.mcguire.1/bibliography/public/

D. Research Support

Ongoing Research Support

R01 CA237118 (Cook-Deegan, McGuire) 04/01/2019 – 03/31/2023
The Sulston Project: making the knowledge commons for interpreting genomic cancer variants more effective
The goal of this study is to carefully examine the challenges of developing a sustainable commons for inherited cancer risk variants to generate policy solutions for the most important and feasible issues identified.

U01 HG006485 (Plon, Parsons, McGuire) 08/07/2017 – 05/31/2021
Evaluating Utility and Improving Implementation of Genomic Sequencing for Pediatric Cancer Patients in the Diverse Population and Healthcare Settings of Texas
This project compares targeted cancer panel tests to germline whole exome sequencing of childhood cancer patients to assess clinical and perceived utility of these tests, as well as uptake and impact of recommended follow-up testing for family members.

U01 HG006485-S1 (Plon, Parsons, McGuire) 09/11/2018 – 05/31/2020
Evaluating Utility and Improving Implementation of Genomic Sequencing for Pediatric Cancer Patients in the Diverse Population and Healthcare Settings of Texas – Administrative Supplement
The goal of this supplement project is to develop and validate a novel measure of perceived utility in genomic medicine by exploring perceptions of utility of clinical genome sequencing across individuals participating in Clinical Sequencing Evidence-Generating Research consortium projects.

U01 HG006485-S2 (Plon, Parsons, McGuire) 09/19/2019 – 08/31/2020
Evaluating Utility and Improving Implementation of Genomic Sequencing for Pediatric Cancer Patients in the Diverse Population and Healthcare Settings of Texas – Administrative Supplement
The goal of this supplement project is to explore perceived utility in genomic medicine among adolescent and young adult patient-participants who are undergoing sequencing in the KidsCanSeq Study.

U01 HG007292-06S1 (Goddard, Wilfond) 09/13/2018 – 05/31/2020
Exome Sequencing in Diverse Populations in Colorado and Oregon – Administrative Supplement
This supplement project will validate key harmonized measures being administered across the Clinical Sequencing Evidence-Generating Research consortium.
Role: Co-Investigator

R01 MH114854 (Lazaro-Munoz, McGuire, Goodman) 09/15/2017 – 08/31/2021

Neuroethics of Adaptive Deep Brain Stimulation Systems Targeting Neuropsychiatric and Movement Disorders
This project is developing an ethically justified and empirically informed policy framework for the responsible research and translation of adaptive deep brain stimulation (aDBS) systems by identifying the most pressing neuroethics issues related to aDBS research and translation from the perspective of diverse stakeholders across multiple clinical research contexts.

UM1 HG008898 (Gibbs) 01/14/2016 – 11/30/2020
Genomic Architecture of Common Disease in Diverse Population
The major goals of the Human Genome Sequencing Center at Baylor College of Medicine are to support a broad range of activities that address biomedical questions using high-throughput sequencing.
Role: Co-Investigator

R01 HG008918 (McGuire) 09/05/2013 – 06/30/2020
Building the Medical Information Commons: Participant Engagement and Policy
This project will establish the foundation for developing a sustainable ethical and policy framework for data sharing in networked environments aiming to broadly share diverse sources of medical, health, and genomic data for research use and clinical application.

Completed Research Support

U19 HD077671 (Green, Beggs) 09/05/2013 – 09/30/2019
Genome sequence-based screening for childhood risk and newborn illness
R01 HG008918-S1 (McGuire, Cook-Deegan) 09/11/2017 – 06/30/2019
Building the Medical Information Commons: Participant Engagement and Policy – Administrative Supplement
FA8650-16-2-6704 (Green) 12/01/2016 – 03/31/2019
Enabling Personalized Medicine through Exome Sequencing in the U.S. Air Force
U54 HG006542 (Valle, Lupski) 12/01/2017 – 11/30/2018
Baylor-Johns Hopkins Center for Mendelian Genetics
U01 HG006500 (Green) 12/05/2011 – 05/31/2017
Integration of Whole Genome Sequencing into Clinical Medicine
U01 HG006485 (Plon, Parsons) 12/05/2011 – 05/31/2017
Incorporation of Genomic Sequencing into Pediatric Cancer Care
R01 HG007063-01 (Phillips) 02/15/2013 – 01/31/2016
Evaluating Benefit-Risk Trade-offs for Clinical Use of Whole Genome Sequencing
R01 HG006460 (McGuire) 08/01/2012 – 07/31/2016
Clinical Integration of Whole Genome Sequencing: A Policy Analysis
R01 HG006460-S1 (McGuire) 08/01/2015 – 07/31/2016
Clinical Integration of Whole Genome Sequencing: A Policy Analysis
R21 HG006612 (Clayton) 09/23/2011 – 08/31/2013
Returning Research Results of Pediatric Genomic Research to Participants
UH3 DK083990-02 (Versalovic) 08/01/2010 – 08/31/2014
The Human Microbiome in Pediatric Abdominal Pain and Intestinal Inflammation
R01 HG004853 (McGuire) 07/01/2009 – 06/30/2013
Ethical, Legal, and Social Dimensions of Human Microbiome Research
R01 HG004333 (McGuire) 08/02/2007 – 07/31/2010
The Ethics of Consent for the Public Release of Potentially Identifiable DNA Data

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Stacey Pereira

eRA COMMONS USER NAME: pereira_s

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Clark University, Worcester, MA	B.A.	05/2004	Psychology
Rice University, Houston, TX	M.A.	12/2010	Anthropology
Rice University, Houston, TX	Ph.D.	06/2014	Anthropology
Baylor College of Medicine, Houston, TX	Postdoctoral	06/2016	Ethical, Legal, and Social Issues (ELSI) in Genomics

A. Personal Statement

I am a sociocultural anthropologist with over nine years' experience conducting research on ethical and social implications (ELSI) in genomics using both qualitative and quantitative research methods. My current research focuses on the harms and benefits associated with the implementation of genomic sequencing into clinical care of different populations, including newborns, active duty military personnel, cardiovascular patients, and healthy adults. My primary responsibly on these projects has been to lead the development of both qualitative and quantitative data collection tools and the analysis and interpretation of data assessing the impacts of genomic sequencing. The proposed project builds logically on my previous work. I will bring my experience from the BabySeq Project and the survey tools my colleagues and I have already developed for BabySeq to the proposed project. Leveraging these materials and experience, I will be able to adapt and develop the survey instruments described in Aim 2 to successfully assess outcomes in this project. I will contribute to data analysis by providing content expertise and helping with the interpretation of the findings. I will present and write papers to disseminate research results. I have a history of successful collaboration with members of this team on multiple projects.

a. **Pereira, S,** Smith, HS, Frankel, L, Robinson, JO, Islam, R, Christensen, KD, Genetti, CA, Blout, CL, Parad, RB, Agrawal, P, Waisbren, SE, Yu, T, Holm, IA, Beggs, AH, Green, RC, McGuire, AL. The Impact of Newborn Genomic Sequencing on the Parent-Child Relationship in the BabySeq Project. Talk given at the American Society for Bioethics and Humanities Annual Meeting, October 2019, Pittsburgh, PA**.** (*manuscript on these data in development*)

b. Malek, J, **Pereira, S**, Robinson, JO, Gutierrez, AM, Slashinski, MJ, Parsons, DW, Plon, SE, McGuire, AL. Responsibility, Culpability, and Parental Views on Genomic Testing for Seriously Ill Children. Genetics in Medicine. 2019; 21:2791-2797.

c. **Pereira, S**, Robinson, JO, Gutierrez, AM, Petersen, D, Hsu, RL, Lee, CH, Schwartz, TS, Holm, IA, Beggs, AH, Green, RC, McGuire, AL, for The BabySeq Project Group. Perceived Benefits, Risks, and Utility of Newborn Genomic Sequencing in the BabySeq Project. Pediatrics. 2019; 143(s1): S6-S13.

d. Frankel, LA, **Pereira, S**, McGuire, AL. Potential Psychosocial Risks of Sequencing Newborns. Pediatrics. 2016; 137(S1): 24-29.

B. Positions and Honors

Positions

2003-2005	Research Assistant, Depression in Ethnically Diverse, Low-Income Adolescents Research Project, Clark University, Worcester, MA
2010	Instructor, Rice University, Houston, TX
2009-2011	Research Consultant, The Rapid Assessment of Hospital Procurement Barriers in Donation Project, Virginia Commonwealth University
2010-2014	Research Assistant, Center for Medical Ethics and Health Policy, Baylor College of Medicine (BCM), Houston, TX
2014-2016	Postdoctoral Associate, Center for Medical Ethics and Health Policy, BCM, Houston, TX
2016-2018	Instructor, Center for Medical Ethics and Health Policy, BCM, Houston, TX
2018-present	Assistant Professor, Center for Medical Ethics and Health Policy, BCM, Houston, TX

Honors

2004	BA, *summa cum laude*, Clark University
2014	Gardner Award for Best Dissertation in the Social Sciences Nominee, Rice University

C. Contributions to Science

1. Harms and benefits of sequencing newborns: With decreasing costs and increasing utility of genomic information across various stages of life, many believe that the integration of genomic sequencing into clinical care of newborns is inevitable. Previous research assessing risks of returning genomic results had often focused on risks and benefits associated with individuals receiving their own genetic risk information. Recognizing the unique issues associated with sequencing individuals at birth and providing predictive information to parents that could have lifelong impacts on the family, NHGRI and NICHD launched the Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) program to study the impact of sequencing newborns. I am a Co-Investigator on the BabySeq Project, one of the four funded NSIGHT projects. I am primarily responsible for leading the development of data collection tools and analysis of data assessing the impact of integrating exome sequencing into the clinical care of newborns via longitudinal surveys with parents and the clinicians providing care to these newborns. I am also leading a qualitative project about parents' decisions to receive (or not) adult-onset genomic results for their children to better understand how parents made that decision and elucidate the motivations, concerns, and values that underlie such choices. Data analysis is ongoing, but early results suggest that parents who enrolled in the BabySeq study anticipate benefits of genomic sequencing that clinicians may not, and that providing exome sequencing to newborns does not disrupt family bonding. Relevant research products from this ongoing project include:

    a. **Pereira, S,** Robinson, JO, Gutierrez, AM, Petersen, D, Hsu, RL, Lee, CH, Schwartz, TS, Holm, IA, Beggs, AH, Green, RC, McGuire, AL, for The BabySeq Project Group. Perceived Benefits, Risks, and Utility of Newborn Genomic Sequencing in the BabySeq Project. Pediatrics. 2019; 143(s1): S6-S13.

    b. **Pereira, S**, Petersen, D, Robinson, JO, Frankel, L, Christensen, KD, Waisbren, SE, Holm, IA, Beggs, AH, Green, RC, McGuire, AL. The impact of newborn genomic sequencing on families: Findings from the BabySeq Project. Talk given at the American Society of Human Genetics Annual Meeting, October 2018, San Diego, CA.

    c. **Pereira, S**, Wright Clayton, E. Commercial Interests, the Technological Imperative, and Advocates: Three Forces Driving Genomic Sequencing in Newborns. Hastings Center Special Report Supplement; The Ethics of Sequencing Newborns: Reflections and Recommendations. 2018. July/August: S2-6.

    d. Frankel, LA, **Pereira, S**, McGuire, AL. Potential Psychosocial Risks of Sequencing Newborns. Pediatrics. 2016; 137(S1): 24-29.

2. Stakeholders' perspectives on biobanking and data sharing: While serving as a research assistant for a local cancer research biobank funded by the Cancer Research Prevention Institute of Texas (CPRIT), I conducted a 3-year ethnographic project exploring issues related to banking, sharing, and research use of human biospecimens and genomic data. Investigating the meanings and values various stakeholders assigned to the biospecimens and resulting genomic data, this work formed an analysis of cancer biobanking and the larger social and economic context in which it takes place. Along with my colleagues, we also identified biobank professionals' motivations and barriers to sharing biospecimens and explored biobank participants' understanding of and willingness to allow their genomic data to be shared for research via an open access database. My work with this cancer biobank resulted in 5 conference presentations, 3 peer-reviewed publications, and a successful dissertation that was nominated for the Gardner Award for Best Dissertation in the Social Sciences at Rice University.

    a. **Pereira, S**. Motivations and Barriers to Sharing Biological Samples: A Case Study. Journal of Personalized Medicine. 2013; 3(2):102-110.

    b. **Pereira, S**, Gibbs, RA, McGuire, AL. Open Access Data Sharing in Genomic Research. Genes. 2014; 5:739-747.

    c. Becnel, LB, **Pereira, S**, Drummond, JA, Gingras, MC, Covington, KR, Kovar, CL, Doddapaneni, HV, Hu, J, Muzny, D, McGuire, AM, Wheeler, DA, Gibbs, RA. An Open Access Pilot Freely Sharing Cancer Genomic Data from Participants in Texas. Scientific Data. 2016; 16(3): 160010.

    d. **Pereira, S**. "Mutations are our Currency:" The Value of Genomic Data in the Information Economy. Talk given at the HeLEX Translation in Healthcare—Exploring the Impact of Emerging Technologies conference, June 2015, University of Oxford, Oxford, United Kingdom.

3. Impact of genomic sequencing on healthy adults: As genomic sequencing is being introduced into clinical care, there is a great need for research exploring the impact of genomic information on individuals to ensure that sequencing is integrated responsibly. Previous research had generally focused on response to genetic information in affected individuals. Because next generation sequencing technologies and advances in genomic science make routine genomic screening of healthy individuals a distinct possibility, it is imperative to explore the impact of genomic information on healthy individuals. Using mixed methods, my colleagues and I have empirically studied how apparently healthy adults understand, use, and respond to receiving genomic information. My ongoing research in this space includes my work as a Co-Investigator on the MilSeq Project, where we are providing exome sequencing to active-duty Airmen in the United States Air Force. My role on this project is to lead the development, administration, and analysis of surveys with Airmen and their clinicians to assess the impact of integrating sequencing into the clinical care of this unique population. I also serve as a Co-Investigator on the PeopleSeq Project, a multi-site collaborative project seeking to understand the long-term medical, behavioral, and economic impacts of performing genomic sequencing in healthy individuals by surveying and interviewing people who have undergone sequencing via a variety of commercial and research programs. My role on this project is to provide expert input on the development and analysis of longitudinal surveys, and to lead the qualitative aim of this project where we are interviewing participants who receive unanticipated genomic findings to better understand the experience and value of receiving predispositional genomic information.

    a. **Pereira, S**, Robinson, JO, Hsu, RL, Petersen, DK, Majumder, M, Parasidis, E, Mehlman, MJ, Christensen, KD, Maxwell, MD, Blout, C, Lebo, M, Brenner, R, Gardner, C, De Castro, M, Green, RC, McGuire, AL. Airmen's attitudes toward genomic sequencing in the US Air Force: Results from the MilSeq Project. Talk given at the American Society for Bioethics and Humanities Annual Meeting, October 2018, Anaheim, CA.

    b. Zoltick, ES, Linderman, MD, Nielsen, DE, Betting, WN, McGinniss, MA, Ramos, E, Ball, MP, Leonard, DGB, **Pereira, S**, Sanderson, SS, Crawford, SD, Green, RC, the PeopleSeq Consortium. Temporal Differences in Concerns, Motivations, and Attitudes regarding Predispositional Genome Sequencing among Healthy Adults: Findings from the PeopleSeq Consortium. Poster presented at the American Society of Human Genetics Annual Meeting, October 2018, San Diego, CA.

    c. Caskey CT, Gonzalez-Garay ML, **Pereira S**, McGuire AL. Adult Genetic Risk Screening. Annual Review of Medicine. 2014; 65: 1-17.

d. Gonzalez-Garay ML, McGuire AL, **Pereira S**, Caskey CT. Personalized Genomic Disease Risk of Volunteers. Proceedings of the National Academy of Sciences. 2013 Oct 15; 110(42): 16957-62.

4. Ethical, Legal, and Social Issues in Genomics and Healthcare: I have researched and written on several novel issues in genomics and healthcare more generally, including the way genomic researchers address the issue of returning results to research participants in their informed consent documents, psychiatric genomics researchers' perspectives toward returning research results to individuals participants, the role of genomic sequencing in cases of unexplained, sudden death, the issue of whether people should profit from sharing their genomic information, and intergenerational differences in views toward health privacy.

   a. **Pereira, S**, Robinson, JO, Peoples, HA, Gutierrez, AM, Majumder, MA, McGuire, AM, Rothstein, MA. Do privacy and security regulations need a status update? Perspectives from an intergenerational survey. PLOS ONE. 2017; 12(9): e0184525.
   b. **Pereira, S**, Oliver Robinson, J, McGuire, AL. Return of individual genomic research results: what do consent forms tell participants? European Journal of Human Genetics. 2016; 24(11): 1524-1529.
   c. Roberts, JL, **Pereira, S**, McGuire, AL. Should you profit from your genome? Nature Biotechnology. 2017; 35(1): 18-20.
   d. **Pereira, S**. "DNA is information, and genetics is information technology:" Reconsidering the genetic code. American Journal of Bioethics. 2019; 19(1): 75-76.

My Bibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/stacey.pereira.1/bibliography/52623250/public/?sort=date&direction=descending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

Precision Medicine and Population Health Grant, BCM (Pereira) 07/2019 – 06/2020
Clinical Impact and Perceived Utility of Genomic Cardiovascular Disease Risk Information in a Precision Medicine for Population Health Initiative
This project seeks to assess the clinical impact and perceived utility of genomic cardiovascular disease risk information in a genomics-enabled learning health system project.
Role: Principal Investigator

R01 MH114854 (Lazaro-Munoz, McGuire, Goodman) 09/2017 – 08/2021
Neuroethics of Adaptive Deep Brain Stimulation Systems Targeting Neuropsychiatric and Movement Disorders
This project is developing an ethically-justified and empirically-informed policy framework for the responsible research and translation of adaptive deep brain stimulation (aDBS) systems by identifying the most pressing neuroethics issues related to aDBS research and translation from the perspective of diverse stakeholders across multiple clinical research contexts.
Role: Co-Investigator

1R01HG009922-01A1 (Green) 09/2018 – 03/2021
Experiences and Outcomes in Early Adopters of Predispositional Sequencing
This project seeks to systematically study the medical, behavioral, and economic impact of Predispositional genomic sequencing in ostensibly healthy individuals.
Role: Co-Investigator

R00HG008689 (Lázaro-Muñoz) 07/2017 – 06/2020
Return of Results from Psychiatric Genomics Research: Attitudes and Barriers

This study examines ethical, policy, scientific, and medical issues that influence the management of return of results in psychiatric genomics by studying the perspectives of psychiatric genomics researchers around the world regarding the return of results to individual participants in their research.
Role: Co-Investigator

Completed Research Support

U19 HD0077671 (Green, Beggs) 9/2013 – 9/2019
Genome Sequence-Based Screening for Newborn Illness and Childhood Risk
The major goals of this study are to explore the implications, challenges, and opportunities associated with the use of genomic sequence information in the newborn period by generating high-quality whole exome sequencing data and returning the results of this data to research participants.
Role: Co-Investigator

FA8650-16-2-6704 (Green) 12/2016 – 12/2018
Enabling Personalized Medicine through Exome Sequencing in the U.S. Air Force
This project investigates how military healthcare providers incorporate genomic information into active duty service members' medical care and studies the impact receiving this information has on medical, behavioral and healthcare utilization outcomes for study participants.
Role: Co-Investigator

Cancer Prevention and Research Institute of Texas (CPRIT)
RP101353-P04 (Gibbs) 08/2010 – 02/2014
Tumor Banking for Genomic Research and Clinical Translation
The goal of this project is to establish a state-wide cancer tissue repository and to link samples with clinical and genomic data.
Role: Research Assistant

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Rehm, Heidi Lee

eRA COMMONS USER NAME (credential, e.g., agency login): HLREHM

POSITION TITLE: Professor of Pathology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Middlebury College, Middlebury, VT	B.A.	05/1992	Molecular Biology & Biochemistry
Harvard Medical School, Boston, MA	M.M.Sc.	02/1995	Medical Science
Harvard University	Ph.D.	03/2000	Genetics
Howard Hughes Medical Institute, Boston, MA	Postdoc	12/2001	Neurobiology
Harvard Medical School, Boston, MA	ABMG Fellowship	09/2003	Clinical Molecular Genetics

A. Personal Statement

I am a board-certified clinical laboratory geneticist and genomic medicine researcher. I am a leader in defining standards for the interpretation of sequence variants and best practices for supporting genetic and genomic testing. I am a principal investigator of ClinGen, providing free and publicly accessible resources to support the interpretation of genes and variants. I also co-lead the Broad Center for Mendelian Genomics focused on discovering novel rare disease genes and co-lead a Genome Center to support sequencing of the All of Us Research Program cohort. I am a strong advocate and pioneer of open science and data sharing, working to extend these approaches through my role as Vice Chair of the Global Alliance for Genomics and Health. More recently in my role as the Chief Genomics Officer at MGH I have been working to standardize and support the implementation of genomic medicine across Massachusetts General Hospital. A few review articles and commentaries that I have written are listed below:

Rehm HL. A new era in the interpretation of human genomic variation. *Genet Med*. 2017; 19(10):1092-95.
Rehm HL. Evolving health care through personal genomics. *Nat Rev Genet*. 2017;18(4):259-267.
Aronson SJ, **Rehm HL**. Building the foundation for genomics in precision medicine. *Nature*. 2015;526 (7573):336-42.
Rehm HL, Fowler DM. Keeping up with the genomes: scaling genomic variant interpretation. Genome Med. 2019;12(1):5.

B. Positions and Honors

Positions and Licensure

2000 - 2002 Post-doctoral Research Associate in Neuroscience and Genetics with David P. Corey, Ph.D., Howard Hughes Medical Institute and Harvard Medical School, Boston, MA
2002 - 2008 Instructor in Pathology, Department of Pathology, Brigham and Women's Hospital (BWH) and Harvard Medical School (HMS), Boston, MA
2002 - Geneticist, Laboratory for Molecular Medicine, Partners HealthCare Personalized Medicine (PPM), Boston, MA
2005- Board-certified and maintenance of certification in Clinical Molecular Genetics and Genomics
2006 - 2015 Director, Clinical Molecular Genetics Training Program, Harvard Medical School, Boston, MA
2008 - 2013 Assistant Professor of Pathology, BWH and HMS, Boston, MA
2009 - 2018 Chief Laboratory Director, Laboratory for Molecular Medicine, PPM, Boston, MA
2013 - 2018 Associate Professor of Pathology, Department of Pathology, BWH and HMS, Boston, MA
2014 - Institute Member, Broad Institute of Harvard and MIT, Cambridge, MA

2015 - Medical Director, Clinical Research Sequencing Platform, Broad Institute, Cambridge, MA
2018 - Chief Genomics Officer, Department of Medicine, Massachusetts General Hospital (MGH)
2018 - Professor of Pathology, Departments of Pathology, BWH, MGH and HMS, Boston, MA

Other Experience and Professional Membership

1996 – Member, American Society of Human Genetics
2001 – Fellow, American College of Medical Genetics
2009 – 2010 President, New England Regional Genetics Group
2009 – 2014 Member, Advisory Board, Coalition Usher Syndrome for Research
2009 – 2012 Scientific Advisor, Generation Health, Inc.
2011 – 2015 Member, ACMG Laboratory QA Committee & Interpretation of Sequence Variants Workgroup
2011 – 2012 Co-Chair, ACMG Next Generation Sequencing Standards and Guidelines Workgroup
2011- 2015 Co-Chair, Genomic Medicine Committee, Partners Healthcare
2011 - 2015 Scientific Advisory Boards of Multiple Companies: GenomeQuest, Knome, Complete Genomics, Omicia, Ingenuity/Qiagen
2012 – 2016 Advances in Genome Biology and Technology Planning Committee
2013 – 2018 Co-Chair, Biomedical Research Institute Genomics Center, Brigham and Women's Hospital
2013 – 2015 Scientific Advisory Board, Ontario Institute for Cancer Research
2014 - 2016 Expert Advisory Group, NHGRI ELSI R21 "Patient Safety in Genome Medicine"
2014 - 2016 Expert Advisory Board, Inherited Neuropathy Consortium
2014 - 2016 Advisory Board, PoliSeq: Clinical Integration of Next Generation Sequencing R01
2014 - 2017 Scientific Advisory Board, Steven Scherer Autism Research, Ontario Genomics Institute
2015 - 2018 Council Member, Human Genome Organisation International
2014 - 2019 Council Member, Human Genome Variation Society
2016 - 2018 BD2K Grant – David Haussler
2016- Steering Committee (Vice Chair 2018-now), Global Alliance for Genomics and Health
2016- External Advisory Board, Ensembl, European Bioinformatics Institute
2017- Scientific Advisory Board, Genome Medical, Inc
2018-2019 External Advisory Panel, TOPMed, NHLBI
2018- External Advisory Panel, CSER, NHGRI
2019- Board of Regents, National Library of Medicine

Honors

2006	Tomorrow's PIs (promising young investigator)	Genome Technology
2006	Partners in Excellence Award (for work integrating genetic data into the Electronic Medical Record)	Partners Healthcare System
2010	40 Under 40 Award (business and civic leadership)	Boston Business Journal
2012	The CLARITY Challenge (genome interpretation)	Boston Children's Hospital
2013	Editor's Choice Award for GeneInsight	BioIT World
2014	BWPO Physician Recognition Award for Clinical Innovation	Brigham and Women's Hospital

C. Contribution to Science

1. **Open data sharing.** It is becoming increasingly clear that open data sharing is a critical requirement for advancing our understanding of the role of genomic variation in human health and disease (Aronson and Rehm 2015). To that end, I have taken a strong position on the importance of open data sharing, actively participating in many aspects of the Global Alliance for Genomics and Health (GA4GH 2016), including the launch of the federated Matchmaker Exchange platform for rare disease data sharing (Philippakis *et al,* 2015). I also have played a major role in leading the way for clinical and research laboratories to share data openly in ClinVar as highlighted in ClinGen's marker paper (Rehm *et al,* 2015).

a. Global Alliance for Genomics and Health. A federated ecosystem for sharing genomic, clinical data. Science. 2016 Jun 10;352(6291):1278-80.
b. Philippakis AA, Azzariti DR, Beltran S, Brookes AJ, Brownstein CA, Brudno M, Brunner HG, Buske OJ, Carey K, Doll C, Dumitriu S, Dyke SO, den Dunnen JT, Firth HV, Gibbs RA, Girdea M, Gonzalez M, Haendel MA, Hamosh A, Holm IA, Huang L, Hurles ME, Hutton B, Krier JB, Misyura A, Mungall CJ, Paschall J, Paten B, Robinson PN, Schiettecatte F, Sobreira NL, Swaminathan GJ, Taschner PE, Terry

SF, Washington NL, Züchner S, Boycott KM, **Rehm HL**. The Matchmaker Exchange: A Platform for Rare Disease Gene Discovery. Hum Mutat. 2015;36(10):915-21.

c. Aronson SJ, **Rehm HL.** Building the foundation for genomics in precision medicine. Nature. 2015;526(7573):336-42.

d. **Rehm HL,** Berg JS, Brooks LD, Bustamante CD, Evans JP, Landrum MJ, Ledbetter DH, Maglott DR, Martin CL, Nussbaum RL, Plon SE, Ramos EM, Sherry ST, Watson MS; ClinGen. ClinGen - The Clinical Genome Resource. N Engl J Med. 2015 May 27

2. **Curated genomic knowledgebases.** To best support the use of genomics in the practice of medicine, accurate and reliable resources of curated genomic knowledge are needed. I am addressing this need through my leadership in ClinGen where I have worked to organize efforts across the community to enable expert curation of genomic knowledge and deposition into freely available knowledgebases including the ClinGen website (for gene-level resources such as demonstrated in DiStefano et al 2019) and the ClinVar database. We have also worked with clinical laboratories who share data in ClinVar to resolve differences in variant classification, (Harrison et al 2017, Harrison et al 2018), ensuring patients receive the most accurate and up-to-date interpretations of their variants. Most recently I have taken on a leadership role in supporting gnomAD.

a. DiStefano MT, Hemphill SE, Oza AM, Siegert RK, Grant AR, Hughes MY, Cushman BJ, Azaiez H, Booth KT, Chapin A, Duzkale H, Matsunaga T, Shen J, Zhang W, Kenna M, Schimmenti LA, Tekin M, **Rehm HL**, Tayoun ANA, Amr SS; ClinGen Hearing Loss Clinical Domain Working Group. ClinGen expert clinical validity curation of 164 hearing loss gene-disease pairs. *Genet Med*. 2019 Mar 21.

b. Harrison SM, Dolinksy JS, Chen W, Collins CD, Das S, Deignan JL, Garber KB, Garcia J, Jarinova O, Knight Johnson AE, Koskenvuo JW, Lee H, Mao R, Mar-Heyming R, McFaddin AS, Moyer K, Nagan N, rentas S, Santani AB, Seppälä EH, Shirts BH, Tidwell T, Topper S, Vincent LM, Vinette K, **Rehm HL**. Scaling resolution of variant classification differences in ClinVar between 41 clinical laboratories through an outlier approach. *Hum Mutat*. 2018;39(11): 1641-1649.

c. Harrison SM, Dolinsky JS, Knight Johnson AE, Pesaran T, Azzariti DR, Bale S, Chao EC, Das S, Vincent L, **Rehm HL**. Clinical laboratories collaborate to resolve differences in variant interpretations submitted to ClinVar. Genet Med. 2017;19(10):1096-1104.

d. Ceyhan-Birsoy O, Machini K, Lebo MS, Yu TW, Agrawal PB, Parad RB, Holm IA, McGuire A, Green RC, Beggs AH, **Rehm HL**. A curated gene list for reporting results of newborn genomic sequencing. *Genet Med*. 2017;19(7):809-81.

3. Interpretation of genomic variants. One of the most challenging aspects of genomics is the interpretation of the clinical relevance of genomic variants. The literature is teeming with false claims of variant pathogenicity and this has led to patient harm. Previously I built and directed a clinical laboratory (Partners LMM) that established itself as one of the highest quality laboratories for clinical interpretation of genetic testing results and I have made substantial contributions to the field over the past 10 years. I helped organize and lead a workshop on “Investigating causality of sequence variants in human disease” which was subsequently written up as a guideline and published in Nature (MacArthur et al, 2014). Subsequently, I co-led a workgroup through the American College of Medical Genetics and Genomics to develop guidelines for the interpretation of sequence variants (Richards et al. 2015). Most recently I have supported ClinGen’s efforts to refine the 2015 ACMG/AMP guidelines for variant interpretation and guide ClinGen’s Expert Panels in the development of disease specific specifications of the 2015 ACMG/AMP guidelines. Many publications and white papers are now located here https://clinicalgenome.org/working-groups/sequence-variant-interpretation/ These efforts are improving the standards by which genetic data is interpreted and used for patient care.

a. Amendola LM, Jarvik GP, Leo MC, McLaughlin HM, Akkari Y, Amaral MD, Berg JS, Biswas S, Bowling KM, Conlin LK, Cooper GM, Dorschner MO, Dulik MC, Ghazani AA, Ghosh R, Green RC, Hart R, Horton C, Johnston JJ, Lebo MS, Milosavljevic A, Ou J, Pak CM, Patel RY, Punj S, Richards CS, Salama J, Strande NT, Yang Y, Plon SE, Biesecker LG, **Rehm HL.** Performance of ACMG-AMP Variant-Interpretation Guidelines among Nine Laboratories in the Clinical Sequencing Exploratory Research Consortium. Am J Hum Genet. 2016 Jul 7;99(1):247.

b. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, **Rehm HL.** Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-23

c. MacArthur DG, Manolio TA, Dimmock DP, **Rehm HL**, Shendure J, Abecasis GR, Adams DR, Altman RB, Antonarakis SE, Ashley EA, Barrett JC, Biesecker LG, Conrad DF, Cooper GM, Cox NJ, Daly MJ, Gerstein MB, Goldstein DB, Hirschhorn JN, Leal SM, Pennacchio LA, Stamatoyannopoulos JA, Sunyaev SR, Valle

D, Voight BF, Winckler W, Gunter C. Guidelines for investigating causality of sequence variants in human disease. Nature. 2014 Apr 24;508(7497):469-76 NIHMSID #628939.

d. Duzkale H, Shen J, McLaughlin H, Alfares A, Kelly M, Pugh T, Funke B, **Rehm H,** Lebo M. A systematic approach to assessing the clinical significance of genetic variants. Clin Genet. 2013; 84(5):453-63.

4. **Supporting genomics in the practice of medicine.** In addition to supporting the interpretation of genomic variants, there are many other aspects of genomic medicine that must be supported for effective integration into medical practice. Over ten years I worked closely with a software engineering team to guide the development of GeneInsight, a genetic knowledgebase and reporting system that aids in high quality, consistently generated and accurate clinical reports from large scale sequencing tests (Aronson et al. 2011). We also launched an innovative clinician-facing tool, GeneInsight Clinic, to support electronic delivery of results to ordering clinicians with EHR integration as well as automated updating of genetic results through an application called (Aronson et al. 2012) that was subsequently the subject of an NIH grant to evaluate clinician usability. This software was sold by Partners Healthcare to a commercial vendor in 2016. I have also led efforts within the MedSeq Study to develop a robust process for whole genome interpretation, returning both diagnostic and secondary findings, in a format that is straightforward enough for a cardiologist or primary care physician to consume as summarized in McLaughlin et al. 2015 and Vassy et al. 2015 and later used in the NIH-funded BabySeq Study (Ceyhan-Birsoy et al 2019).

a. Vassy JL, McLaughlin HL, MacRae CA, Seidman CE, Lautenbach D, Krier JB, Lane WJ, Kohane IS, Murray MF, McGuire AL, **Rehm HL**, Green RC; A One-Page Summary Report of Genome Sequencing for the Healthy Adult. Public Health Genomics. 2015; PMID: 25612602.

b. McLaughlin HM, Ceyhan-Birsoy O, Christensen KD, Kohane IS, Krier J, Lane WJ, Lautenbach D, Lebo MS, Machini K, MacRae CA, Azzariti DR, Murray MF, Seidman CE, Vassy JL, Green RC, **Rehm HL**; MedSeq Project. A systematic approach to the reporting of medically relevant findings from whole genome sequencing. BMC Med Genet. 2014 Dec 14;15:134.

c. Aronson SJ, Clark EH, Varugheese M, Baxter S, Babb LJ, **Rehm HL.** Communicating new knowledge on previously reported genetic variants. Genet Med 2012;14(8):713-719.

d. Aronson SJ, Clark EH, Babb LJ, Baxter S, Farwell LM, Funke BH, Hernandez AL, Joshi VA, Lyon E, Parthum AR, Russell FJ, Varugheese M, Venman TC, **Rehm HL.** The GeneInsight Suite: A platform to support laboratory and provider use of DNA-based genetic testing. Hum Mutat 2011;32(5):532-536.

5. **Best practices for genetic and genomic testing.** I have been a leader in the development of standards and best practices for genetic and genomic testing. I led the development of the 2013 clinical standards for next generation sequencing (NGS) through the ACMG (Rehm et al, 2013) and contributed to a paper to evaluate the role of orthogonal confirmation in NGS (Lincoln et al. 2019). I co-led efforts to standardize sequencing and analysis approaches across laboratories (eMERGE Consortium, 2019) and reported on the benefits and approaches to reanalysis of genomic testing results in both diagnostic and incidental contexts (Machini et al, 2019).

a. **Rehm HL**, Bale SJ, Bayrak-Toydemir P, Berg JS, Brown KK, Deignan JL, Friez MJ, Funke BH, et al. ACMG Clinical Laboratory Standards for Next Generation Sequencing. Genet Med 2013; 15(9):733-47.

b. Lincoln SE, Truty R, Lin CF, Zok JM, Paul J, Ramey VH, Salit M, **Rehm HL**, Nussbaum RL, Lebo MS. A Rigorous Interlaboratory Examination of the Need to Confirm Next-Generation Sequencing-Detected Variants with an Orthogonal Method in Clinical Genetic Testing. J Mol Diagn. 2019 21(2):318-329.

c. eMERGE Consortium. Harmonizing Clinical Sequencing and Interpretation for the eMERGE III Network. Am J Hum Genet. 2019 Sep 5;105(3):588-605.

d. Machini K, Ceyhan-Birsoy O, Azzariti DR, Sharma H, Rossetti P, Mahanta L, Hutchinson L, McLaughlin H; MedSeq Project, Green RC, Lebo M, **Rehm HL**. Analyzing and Reanalyzing the Genome: Findings from the MedSeq Project. Am J Hum Genet. 2019 Jul 3;105(1):177-188.

Complete List of >200 Published Works in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1jKFg7dtkhvk-/bibliography/public/

D. Research Support

Ongoing Research Support

U01HG008676 (Rehm/Lennon) 09/01/15-05/31/20 Role: Multi-Principal Investigator

eMERGE III Central Sequencing, Genotyping and Interpretation Facility

The Central Sequencing and Genotyping Facility composed of the Laboratory for Molecular Medicine at Partners HealthCare and the Genomics Platform at the Broad Institute will provided high-quality sequencing and interpretation for the eMERGE Network to enable return of results to biobank participants at the study sites.

UM1HG008900 (MacArthur/Rehm) 01/14/16-11/30/20 Role: Multi-Principal Investigator
Joint Center for Mendelian Genomics
The Joint Center for Mendelian Genomics will contribute substantially to the establishment of a comprehensive catalog of the genetic causes of Mendelian diseases, thus improving disease diagnosis rates as well as building the biological understanding needed to develop more effective therapeutics.

R01HG009174 (Murphy/Aronson/MacRae/Rehm) 09/28/16-08/31/20 Role: Multi-Principal Investigator
Developing i2b2 into a Health Innovation Platform for Clinical Decision Support in the Genomics Era
The goal is to provide the laboratory perspective on how the HIP-CDS app should be constructed, to validate functionality, and to ensure this work is well coordinated with efforts throughout the genetics community.

U41HG006834 (Rehm/Martin/Ledbetter) 08/01/17-07/31/21 Role: Multi-Principal Investigator
Clinical Genome Resource
This project serves to collect and organize genomic data from many sources into a free and publicly accessible environment and enable expert curation of that data for use in improving healthcare and biomedical research.

R01HG009141 (Rehm/Quinlan) 9/13/17-6/30/21 Role: Multi-Principal Investigator
A Powerful Web-based Discovery Platform for Rare Disease Genetics
The goals of this project are to build an interactive software platform including, GEMINI and seqr, to support gene discovery for rare diseases.

R01HD090019 (Wu) 09/11/17-05/31/22 Role: Co-Investigator
Precision Medicine and Treatment (PreEMPT) Model
The goals of PreEMPT are to develop a microsimulation model of genetic variants and corresponding newborn diseases, assess the clinical impact and cost-effectiveness of genome sequencing (GS) in newborns using a microsimulation model and project the impact of incorporating research advances into GS for newborns.

OT2OD02750 (Gabriel/Rehm/Topper) 9/25/18-08/31/23 Role: Multi-Principal Investigator
Broad-LMM-Color Genome Center for All of Us
The goal of this project is to provide genomic data in the form of genotyping arrays and genome sequencing on one million participants in the All of Us research program and return clinically meaningful results to participants.

U24HG010262 (Philippakis/Carroll/Grossman/Hall/Hall/Haussler/Paten) 9/19/18-6/30/23 Role: Co-Investigator
The AnVIL Data Ecosystem
The goal of this project is to create an ecosystem of cloud-based applications that will enable the NHGRI to store, share and analyze datasets at unlimited scale. This architecture will interoperate with other key NIH data environments as part of a federated genomic data commons.

T32HG010464 (Smoller/Rehm) 5/22/19-4/30/24 Role: Multi-Principal Investigator
Partners Healthcare Training Program in Precision Medicine and Genomic Medicine
The training grant is designed to provide rigorous, interdisciplinary training of postdoctoral scientists in the translational genomic, clinical and computational sciences that are driving a new era of precision and genomic medicine.

U01CA242954 (Cline) 7/1/19-6/30/22 Role: Co-Investigator
Eliminating variants of uncertain significance in BRCA1, BRCA2 and beyond
We will leverage and integrate secure data collection technology for genetic variation and combine these with functional experiments, to provide broadly-applicable approaches to understand rare variants.

R01HL143295 (Green/Ramachandran/Correa) 7/1/19-6/30/23 Role: Co-Investigator
Return of Genomic Results and Estimating Penetrance in Population-Based Cohorts
The goals of this project are to develop and implement a genomic return of results (gRoR) process in the Framingham Heart Study and Jackson Heart Study cohorts and explore associated medical, behavioral and economic outcomes. We plan to automate and streamline genomic variation interpretation and will evaluate aggregate penetrance for Mendelian diseases.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Hana Zouk

eRA COMMONS USER NAME (credential, e.g., agency login): HZOUK1

POSITION TITLE: Instructor of Pathology, Harvard Medical School
Assistant Director, Laboratory for Molecular Medicine (LMM), Partners Personalized Medicine, Partners HealthCare System

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
American University of Beirut, Beirut, Lebanon	B.Sc	06/2003	Biology
McGill University, Montreal, Quebec, Canada	M.Sc	05/2006	Human Genetics
McGill University, Montreal, Quebec, Canada	Ph.D	05/2013	Human Genetics
Harvard University, Cambridge, MA	ABMGG	08/2016	Clinical Molecular Genetics

A. Personal Statement

My current role, as well as my past and current projects, position me well to help drive the aims of this proposal. The skill set accrued throughout my research and specifically my fellowship training, will allow me to support this effort, as I have specific training and proficiency in the assessment of novel and rare variants as well as reporting of clinical genetic results. I have a diverse background in human genetics, where my early pre-doctoral and doctoral training focused on sorting out molecular etiologies of complex genetic diseases. I investigated the contribution of common genetic variation of well-established and novel genes to complex disorders, including mental health disorders and diabetes. My clinical molecular genetics fellowship allowed me to apply my genetics background toward the interpretation of human genetic variation identified through various clinical molecular diagnostic tests that cover a wide variety of genetically heterogenous disease including hearing loss, cardiomyopathies, rasopathies, connective tissue and pulmonary disorders. During my fellowship I determined the pathogenic variant spectrum in the *EDA1* X-linked hypohidrotic ectodermal dysplasia (XLHED) gene and identified EDA1 domains that are most commonly affected in XLHED patients. I then used this information to adapt ACMG variant classification guidelines for *EDA1* variant interpretation. I have recently completed my fellowship and have been granted active candidate status by the American Board of Medical Genetics and Genomics (ABMGG) as I will be taking my board exam later this year. In my current role as an assistant laboratory director at the CLIA-certified laboratory for molecular medicine (LMM), I am actively involved in the final interpretation and sign-out of clinical genetic tests. Such expertise would make me well positioned to help achieve the objectives outlined in the current proposal.

B. Positions and Honors

Positions and Employment

2002-2003 Student Research Volunteer, Department of Biology, American Univeristy of Beirut, Beirut, Lebanon
2003-2006 MSc Candidate (Dr. Gustavo Turecki), Department of Human Genetics, McGill University, Montreal, Canada
2006-2013 PhD Candidate (Dr. Constantin Polychronakos), Department of Human Genetics, McGill University, Montreal, Canada
2008-2011 Teaching Assistant (Introduction to Chemistry), eConcordia (Concordia University), Montreal, Canada
2014-2016 ABMGG Clinical Molecular Genetics Fellow, Harvard University
2016- Instructor, Department of Pathology, Massachusetts General Hospital and Harvard Medical School

2016- Assistant Laboratory Director, Laboratory of Molecular Medicine, Partners HealthCare | Personalized Medicine

Other Experience and Professional Memberships

2006 Member, American Society of Human Genetics
2017- Member, American College of Medical Genetics

Honors

2003-2005 McGill Group for Suicide Studies Scholarship
2007-2008 Montreal Children's Hospital Research Institute Student Scholarship
2008-2011 Fonds de Recherche en Santé au Québec (FRSQ) Doctoral Training Award
2010 The Foundation of Stars Graduate Student Prize of Excellence

Certification

2017- American Board of Medical Genetics and Genomics, Clinical Molecular Genetics

C. Contribution to Science

1. My early training focused on investigating impulsive-aggressive behaviors (IABs) in suicide. Both impulsivity and aggressivity have been shown to be important behavioral correlates of suicide, both clinically and biologically, but it was unclear how they might mediate suicide risk. This work shows that impulsive suicides were characterized by greater psychiatric comorbidity, increased levels of aggression and were more likely to be affected by negative life events. For a molecular genetics standpoint, these publications also show that one serotonin receptor (5-HT1B) promoter variant significantly influence levels of aggressive behaviors in suicide completers, suggesting that aggression plays a role as an intermediate phenotype that increases propensity to suicide. Both studies highlight the importance of the role of IABs in mediating suicide at both clinical and biological levels.

    a. **H. Zouk,** M. Tousignant, M. Seguin, A. Lesage & G. Turecki. Characterization of impulsivity in suicide completers: Clinical, behavioral and psychosocial dimensions. *Journal of Affective Disorders*, 92 (2-3): 195-204, 2006.
    b. **H. Zouk,** A. McGirr, V. Lebel, G. Rouleau, C. Benkelfat & G. Turecki. The effect of genetic variation of the serotonin 1B receptor gene on impulsive-aggressive behavior and suicide. *American Journal of Medical Genetics: Neuropsychiatric Genetics,* 144(8): 996-1002, 2007.

2. While still in the realm of complex genetics, my research shifted focus to another disease area, where we sought to functionally evaluate the mechanism of association of two novel genetic loci to type 1 diabetes, including one locus that encompasses a single gene whose function was unknown at the time. These studies highlight the difficulty in transitioning from genetic associations to functional studies, which are essential in bridging genetic predisposition with biological mechanisms underlying the immune dysregulation associated with disease.

    a. **H. Zouk,** L. Marchand & C. Polychronakos. Study of transcriptional effects in cis at the IFIH1 locus. PLoS One, 5(7): e11564, 2010.
    b. **H. Zouk**, L. Marchand, Q. Li & C. Polychronakos. Functional characterization of the Thr946Ala SNP at the type 1 diabetes *IFIH1* locus. *Autoimmunity*, 47(1): 40-5, 2014.
    c. **H. Zouk**, E. d'Hennezel, X. Du, H. Ounissi, C.A. Piccirillo & C. Polychronakos. Functional evaluation of the role of CLEC16A at the chromosome 16p13 locus. Clinical and Experimental Immunology,175(3):485-97, 2014.

3. One of the focuses of my current work is on detection and clinical interpretation of human DNA sequence variation in patients afflicted with a genetic disorder. Specifically, I am interested in employing domain analysis approaches for clinical interpretation of sequence variants identified in individuals with X-linked hypohidrotic ectodermal dysplasia (XLHED) and using this information to develop more specific guidelines for the clinical interpretation of sequence variants identified in individuals with XLHED. This approach can

be extended to other disease-causing genes to ultimately better understand and improve novel variant assessment. A manuscript describing these findings is currently in preparation for submission

a. **H. Zouk**, M.W. Dillon, H.L. Rehm & S.S. Amr. The *EDA1* variant spectrum in X-linked hypohidrotic ectodermal dysplasia. *Manuscript in preparation*.

D. Research Support

Ongoing Research Support

5R01HG010372-02 (Cassa) 09/24/18-06/30/23 Role: Co-Investigator
NIH
Integrated Pathogenicity Assessment of Clinically Actionable Genetic Variants
This project aims to improve computational predictions of structural and functional impact; assess phenotypic impact using measures of selective constraint; and development of a Bayesian statistical framework to assess clinical risk.

1 U01 HG008676 (Rehm/Lennon) 09/01/15 – 03/31/20 Role: Co-Investigator
NIH/NHGRI
eMERGE III Central Sequencing, Genotyping and Interpretation Facility
The Central Sequencing and Genotyping Facility composed of the Laboratory for Molecular Medicine (LMM) at Partners HealthCare and the Genomics Platform at the Broad Institute provides high-quality sequencing and interpretation for the eMERGE Network. The project is identifying clinically relevant genetic variants and supporting their return to study sites. Through this project, researchers are able to identify causes of human disease and facilitate the integration of genetics into the practice of medicine.

Letters of Support

Institutional Support and Financial Commitments

CTSA Support

Stakeholder Board

Clinical Recruitment Support

Stakeholder Engagement

Single IRB Agreement

Consultancy Agreement

BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

Paul J. Anderson, M.D., Ph.D.
Chief Academic Officer and Senior Vice President of Research
K Frank Austen Professor of Medicine, Harvard Medical School

75 Francis Street, Boston MA 02115
Tel: 617-732-8990, Fax: 617-732-5343
Email: panderson@bwh.harvard.edu

February 27, 2020

Robert C. Green, MD, MPH
Department of Medicine, Division of Genetics
Brigham and Women's Hospital
41 Avenue Louis Pasteur, Suite 301
Boston, MA 02115

Dear Robert,

It is with great pleasure that I write this letter in strong support of your U01 grant resubmission entitled, "Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants."

The proposal that you and your team have envisioned is a significant step into the future where preventive genomic information may be responsibly, appropriately and successfully integrated into the practice of medicine, even in very early infancy. The practical knowledge gained from the implementation of this project will have an immense impact on molding how genomic information will be further integrated into newborn care and I was particularly pleased to learn of the focus on enrolling individuals from diverse racial and ethnic backgrounds, which is well aligned with our institution's goals for current and future research.

We are delighted facilitate an increased sample size and to express our institutional support by providing internal funding of $25,000 per year over 4 years ($100,000 total) in addition to the NIH award, if it is successful.

I will be keenly interested in following the progress of this exciting project and will be delighted to provide any additional support that is needed to make sure it is successful.

Yours sincerely,

Paul Anderson, MD, PhD
Senior Vice President, Research and Education
Chief Academic Officer

ARIADNE LABS

BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL
HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

March 4, 2020

Robert C. Green, MD, MPH
Genomes2People Research Program
Division of Genetics, Department of Medicine
Brigham and Women's Hospital
41 Avenue Louis Pasteur, Suite 301
Boston, MA 02115

Dear Robert,

Thank you so much for sharing with me the detailed plans for your NIH U01 resubmission entitled, "Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants."

As a practicing primary care physician and Executive Director of Ariadne Labs (110-person health systems innovation center at Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health), I have followed your prior work in both MedSeq (U01 HG006500) and BabySeq (U19 HD077671) with great interest. It is so closely aligned with our goals of developing and implementing simple, scalable solutions that dramatically improve healthcare to save lives and reduce suffering around the world. Indeed, sharing technology, tools and healthcare innovation with individuals and populations in all settings, with an enhanced focus on low-resource settings, is of the utmost importance to us.

You and the remarkable team you established for the original BabySeq Project have already proven the incredible value of the protocol you completed, and I'm simply delighted to see it being scaled in both number (to include a total of 500 infants and their families) and diversity (with inclusion of diverse families from underrepresented populations) as part of your plans to expand these cohorts in Boston, New York and Alabama.

401 Park Drive
Landmark Center
Floor 3 East
Boston, MA 02215

www.ariadnelabs.org
Tel: (617) 384-6555
Fax: (617) 384-8727
abitton@ariadnelabs.org

Your research program and our work at Ariadne Labs are very well aligned and we have already begun to work together on a number of areas related to preventive genomics and precision public health. If your proposal to NCATs if funded, **we are prepared to assist the work with significant in-kind support in the form of dedicated time from our staff scientific and implementation specialist resources**. We are excited to help you expand the scope and/or scale of the project, and to support you with other resources that we may find fit to yield the greatest impact.

I wish you the best of luck for a successful submission.

Sincerely,

Asaf Bitton MD, MPH
Executive Director, Ariadne Labs
Brigham and Women's Hospital | Harvard T.H. Chan School of Public Health

Icahn School of Medicine at Mount Sinai

Dennis S. Charney, MD
Anne and Joel Ehrenkranz Dean,
Icahn School of Medicine at Mount Sinai
President for Academic Affairs,
Mount Sinai Health System
Professor, Departments of Psychiatry, Neuroscience, and Pharmacological Sciences

Mount Sinai Health System
One Gustave L. Levy Place, Box 1217
New York, NY 10029-6574
T 212-241-5674
F 212-824-2302
dennis.charney@mssm.edu

June 19, 2019

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital
41 Avenue Louis Pasteur, EC Alumnae Building, Suite 301
Boston, Massachusetts 02115

Ingrid A. Holm, MD, MPH
Associate Professor of Pediatrics, Harvard Medical School
Division of Genetics and Genomics, Boston Children's Hospital
3 Blackfan Circle, CLSB 15022, Mailstop BCH3150
Boston, Massachusetts 02115

Dear Drs. Green and Holm:

I am writing in my role as Dean of the Icahn School of Medicine to provide my enthusiastic support for your grant proposal entitled "*Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants*," which is in response to NIH PAR-19-099 entitled "Limited Competition: Clinical and Translational Science Award (CTSA) Program: Collaborative Innovation Award (U01 Clinical Trial Optional)." I am delighted to have our institution be an active participating site, overseen by two outstanding investigators here, Bruce Gelb, M.D. and Carol Horowitz, M.D.

Mount Sinai's strategic plan emphasizes genomic medicine, both in research and clinical implementation. We are actively pursuing numerous efforts in this arena. Because our institution serves a remarkably diverse population such as the heavily Hispanic and African-American communities in Harlem, we are developing particular expertise in community-engaged research in genomic medicine. For instance, the NIH-funded Clinical Sequencing Evidence-Gathering Research (CSER) project here called NYCKidSeq, for which Drs. Horowitz and Gelb, are Principal Investigators, is specifically focused on whole genome sequencing of children with certain medical conditions drawn from diverse communities. Our recruitment of subjects from diverse backgrounds is exceeding 70%. We are also leverage our community partners through a long-standing community engagement board that Dr. Horowitz oversees. These experiences and expertise will greatly benefit the project that you are now proposing.

One of the greatest current challenges in genomic medicine is determining how to use the burgeoning sequencing capabilities at it applies to population screening. Your previous accomplishment with BabySeq were groundbreaking and have greatly informed our thinking about how to proceed with this genetics-first approach for well pediatric patients. Thus, we are thrilled to partner with you for the new randomized clinical trial, for which 500 infants of diverse backgrounds will undergo either standard care or whole genome sequencing in order to determine the impact of such sequencing medically and psychosocially. This is a logical extension of the work we are doing in NYCKidSeq. I would add that we already have health economists at Mount Sinai examining issues related to clinical utility for that project, expertise that will be important for the work in your proposed Aim 3.

Mount Sinai has an active CTSA program called Conduits, led by Rosalind Wright, M.D., M.P.H. Our institution has been highly supportive of this mission-critical project, providing space and supplemental resources for the support of the translational research endeavor that this underpins. The resources of Conduits will be fully available to Drs. Gelb and Horowitz for this new project.

Finally, Mount Sinai is fully committed to the success of genomic medicine for pediatric patients, being overseen at our institution by Dr. Gelb in his role as Director of the Mindich Child Health and Development Institute. The School will continue to provide him with resources needed for implementing pediatric precision medicine at Mount Sinai, including those that can be used to augment this project as needed.

I wish great success with your application for this important proposal, which is at the cutting edge of genomic medicine research.

Sincerely,

Dennis S. Charney, MD
Anne and Joel Ehrenkranz Dean,
Icahn School of Medicine at Mount Sinai
President for Academic Affairs,
Mount Sinai Health System

Boston Children's Hospital
Until every child is well™

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Gary R. Fleisher, MD
Chairman, Department of Pediatrics
Physician-in-Chief, Pediatrician-in-Chief, Boston Children's Hospital
Egan Family Foundation Professor, Harvard Medical School
300 Longwood Avenue, Boston, Massachusetts 02115
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gary.fleisher@childrens.harvard.edu

July 1, 2019

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital
41 Avenue Louis Pasteur, EC Alumnae Building, Suite 301
Boston, MA 02115
Email: rcgreen@bwh.harvard.edu

Ingrid A. Holm, MD, MPH
Associate Professor of Pediatrics, Harvard Medical School
Division of Genetics and Genomics, Boston Children's Hospital
3 Blackfan Circle, CLSB 15022
Boston, MA 02115
Email: Ingrid.holm@childrens.harvard.edu

RE: Proposal: "Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants"; Grant: NIH PAR-19-099 entitled "Limited Competition: Clinical and Translational Science Award (CTSA) Program: Collaborative Innovation Award (U01 Clinical Trial Optional)"

Dear Drs. Green and Holm,

It is with great pleasure that I provide this letter conveying my enthusiastic support for your proposal to NIH PAR-19-099 entitled, "Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants". By forming new collaborations between CTSA sites at Harvard Medical School, Ichan School of Medicine at Mount Sinai, and the University of Alabama at Birmingham, you have assembled an interdisciplinary team that will implement newborn genomic sequencing in novel environments and explore its impacts within diverse populations. Your proposal will allow us to reach more patients and provide the insights necessary to adapt this technology for further dissemination.

I enthusiastically support your approach of recruiting 500 infants from general pediatrics clinics serving diverse populations in Boston, New York City, and Birmingham, including the Boston Children's Hospital Primary Care Clinic (CHPCC). By conducting a randomized controlled trial of whole-genome sequencing, your proposal will be the first to study medical, behavioral and economic outcomes of newborn genomic medicine in representative populations. Additionally, your approach will thoughtfully explore the impact of genomic information on family functioning and development. These data are crucial for further dissemination and implementation of the

technology in general pediatrics clinics throughout our specific healthcare system and across the country.

For example, while next-generation sequencing has been clinically available for years, little is known about its utility as a population-based screening tool. Your pilot study, BabySeq, was the first clinical trial to ask these questions in a methodical way and truly laid the groundwork for implementing genome sequencing into the care of newborns. The clear next step in understanding utility in the general population is to expand the infrastructure and procedures developed in BabySeq to a more diverse cohort across the country. Data from this new study will inform how our practice begins using genomic sequencing to screen our large population of pediatric patients seen annually, including the many new babies establishing care each week. In addition, this project will provide some of the first crucial insights into the psychological and behavioral outcomes of newborn genomic sequencing in minority populations, including African American and Spanish-speaking Hispanic families.

Finally, a well-recognized roadblock to the implementation of genomic sequencing is efficiency of the consent process and return of results. I admire the goals of your project to develop innovative solutions to streamline these steps, including creating educational materials for patients, training new providers to provide genetic services, and arranging telemedicine consults. These tools and techniques will be crucial for establishing genomic screening as a routine procedure in our pediatric clinics.

This collaborative research project will create innovative solutions to increase the efficiency of newborn genomic sequencing and improve health of individuals and the public. The data generated will support our institutional efforts around the dissemination of genomic sequencing as a sustainable screening tool for healthy infants. Your proposal is a bold and innovative strategy to explore newborn genomic sequencing as a screening tool in diverse populations and will help to advance translation of this technology from the laboratory to the general newborn population.

This proposal is strengthened by your experience in conducting a randomized controlled trial to study the clinical implementation of genomic information, by the innumerable hours you have spent considering the most ethical and clinically useful approach to genomic information, and by your outstanding leadership and diplomacy. I look forward to working with this forward-thinking and highly respected team.

Sincerely,

Gary R. Fleisher, M.D.

Mount Sinai *The Mindich Child Health and Development Institute*

February 25, 2020

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital
41 Avenue Louis Pasteur, EC Alumnae Building, Suite 301
Boston, Massachusetts 02115

Ingrid A. Holm, MD, MPH
Associate Professor of Pediatrics, Harvard Medical School
Division of Genetics and Genomics, Boston Children's Hospital
3 Blackfan Circle, CLSB 15022, Mailstop BCH3150
Boston, Massachusetts 02115

Dear Drs. Green and Holm:

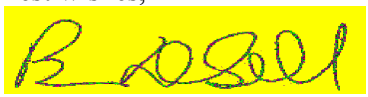
While I am a site Principal Investigator for your grant proposal entitled "*Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants*," which is in respond to NIH PAR-19-099 entitled "Limited Competition: Clinical and Translational Science Award (CTSA) Program: Collaborative Innovation Award (U01 Clinical Trial Optional)," I am writing in my role as Director of the Mindich Child Health and Development Institute (MCHDI).

At Mount Sinai, the MCHDI is in charge of pediatric precision medicine, which is part of an overall institutional commitment to precision medicine more broadly. For the MCHDI, it is one of our three current strategic initiatives. Thus, we view the success of your proposed project, for which we will collaborate as mission critical.

In order to enhance the ability to recruit sufficient subject numbers for this study, the MCHDI is delighted to commit to providing $10,000 per year for Years 2-4 of this project if funded. We believe that this modest investment of philanthropic funds will bring rich scientific rewards.

Good luck with this application!

Best wishes,



Bruce D. Gelb, M.D.
The Gogel Family Professor of Child Health and Development
Professor of Pediatrics and Genetics & Genomic Sciences
Director, Mindich Child Health and Development Institute

UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

February 27, 2020

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital

Ingrid A. Holm, MD, MPH
Associate Professor of Pediatrics, Harvard Medical School
Division of Genetics and Genomics, Boston Children's Hospital

Dear Dr. Green and Dr. Holm,

On behalf of the Center for Clinical and Translational Science (CCTS) at the University of Alabama at Birmingham (Hub), it is my great pleasure to provide this letter of support for your proposal to the CTSA Collaborative Innovation Award program, entitled, "*Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants*". This multi-site research initiative, – drawing on research expertise at Harvard Medical School, Mount Sinai, Boston Children's, Brigham and Women's Hospital and UAB, – involving the efficiency of newborn genomic sequencing has the tremendous potential to improve the health and well-being of our pediatric patients and their families.

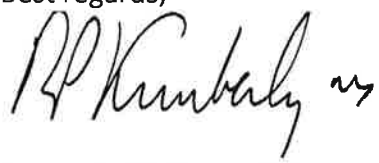
You have assembled an impressive, transdisciplinary team that will implement newborn genomic sequencing in a range of environments and explore its impacts within diverse populations. Your strategy of recruiting 500 infants from general pediatrics clinics to conduct a randomized controlled trial of whole-genome sequencing will be the first to study medical, behavioral and economic outcomes of newborn genomic medicine in representative populations. Your approach will also allow investigation of the impact of genomic information on families and will offer the first crucial insights into the psychological and behavioral outcomes of newborn genomic sequencing in underrepresented minority populations.

The CCTS is dedicated to improving health and elevating health equity in a region of the country disproportionately burdened by chronic disease. The CCTS leverages multidisciplinary expertise and cutting-edge capacity available within an 11-institution Partner Network spanning Alabama, Mississippi and Louisiana to advance the platform for integrating genomic information to guide disease prevention, diagnosis, and treatment. The CCTS Partner Network provides a fertile environment to accomplish this goal toward improved health through interdisciplinary teamwork, engaged communities and innovative approaches.

CCTS
Center for Clinical and Translational Science
1924 7th Avenue South
Mailing Address:
PCAMS 111 | 1720 2ND AVE S | BIRMINGHAM AL 35294-0007
phone: 205.934.7442 | fax: 205.934.3749
email: ccts@uab.edu | www.uab.edu/ccts

The proposed collaboration, which builds on foundational work for implementing genome medicine into the care of newborns (BabySeq study), will take the vital step of expanding the methodology to a more diverse population. The CCTS will support $10,000 per year for Years 2-4 of this project, if awarded, to increase recruitment and enrollment for this study. The insights developed by your collaborative team will increase the efficiency of newborn genomic sequencing as a sustainable screening tool for healthy infants. The CCTS looks forward to being part of this important effort.

Best regards,



Robert P. Kimberly, MD
Howard L. Holley Professor of Medicine
Director, Center for Clinical and Translational Science
Senior Associate Dean for Clinical and Translational Research, UAB School of Medicine
Associate Vice President for Medicine and Biomedical Research
University of Alabama at Birmingham

PARTNERS HEALTHCARE | FOUNDED BY BRIGHAM AND WOMEN'S HOSPITAL AND MASSACHUSETTS GENERAL HOSPITAL

February 27, 2020

Robert C. Green, MD, MPH
Department of Medicine, Division of Genetics
Brigham and Women's Hospital
41 Avenue Louis Pasteur, Suite 301
Boston, MA 02115

Dear Robert,

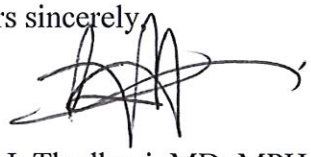
It is with great pleasure that I write this letter in strong support of your U01 grant resubmission entitled, "Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants."

The proposal that you have orchestrated will have a great impact on the future of preventive genomics and personalized medicine, beginning at the infant stage of life. It is also great to see plans for whole genome sequencing and its integration into clinical care expanded into diverse populations responsibly

I am happy to assist you with enrolling an increased sample in addition to the NIH award if it is selected for funding.

I will be delighted to follow the progress of this project and give you my strongest support.

Yours sincerely,



Ravi I. Thadhani, MD, MPH

Ravi I. Thadhani, M.D., MPH
Chief Academic Officer, Partners HealthCare | Professor of Medicine, Harvard Medical School
Dean for Academic Programs at Partners HealthCare, Harvard Medical School

Prudential Tower, 800 Boylston Street, Boston, MA 02199
Tel: 617 278-1140, Email: rthadhani@partners.org

Children's
of Alabama

July 9, 2019

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital

Ingrid A. Holm, MD, MPH
Associate Professor of Pediatrics, Harvard Medical School
Division of Genetics and Genomics, Boston Children's Hospital

Dear Dr. Green and Dr. Holm:

It is with great pleasure that I write in support of your proposal to NIH PAR-19-099 entitled, "*Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants*". By forming new collaborations between CTSA sites at Harvard Medical School, Mount Sinai and University of Alabama at Birmingham, you have assembled an interdisciplinary team that will implement newborn genomic sequencing in novel environments and explore its impacts within diverse populations.

Children's of Alabama provides ongoing support of genomic research projects, including direct funding support of over $300,000 for the Genomic Sequencing for Children with Rare Mendelian Disorders (100 Genomes at Children's of Alabama) study. We also are an enrollment site for whole genome sequencing of neonatal and pediatric patients in the NIH-funded CSER2 Consortium SouthSeq and state-funded Alabama Genomic Health Initiative projects. We view genomic sequencing as a means to enhance medical care for children with rare diseases, and we also see future opportunities for sequencing to improve newborn screening and pediatric healthcare.

Your proposed approach to recruit **500** healthy newborns would provide pediatricians with critical information to serve as a resource for informing clinical care during infancy and early childhood. Additionally, this approach will thoughtfully explore the impact of genomic information on family functioning and development. Your study truly holds the potential to move the field of newborn screening into a new era.

Our knowledge of genetics is constantly evolving, making it of utmost importance to have an efficient and well-planned methodology for issuing revised genomic reports and tracking healthcare utilization associate with genomic sequencing. You have assembled a forward-thinking interdisciplinary team that is prepared to take on this great task, and I applaud your thoughtful effort and approach on this important topic.

Russell Campus
1600 7th Avenue South Birmingham, Alabama 35233 tel 205.939.9621 fax 205.939.9189 ChildrensAL.org

I believe this is an important initiative and along with the 100 Genomes at Children's of Alabama project, AGHI, and other initiatives that are currently being pursued at Children's of Alabama, this effort will continue to help children in our region.

We wish you success in your efforts and remain available to be helpful to ensure the success of the program as a whole.

Very truly yours,

Mike Warren

Wm. Michael Warren, Jr.
President and CEO
Children's of Alabama

WMWJr:kes

HARVARD CATALYST
Harvard Clinical & Translational Science Center

HARVARD UNIVERSITY

July 1, 2019

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital
41 Avenue Louis Pasteur, EC Alumnae Building, Suite 301
Boston, MA 02115
Email: rcgreen@bwh.harvard.edu

Ingrid A. Holm, MD, MPH
Associate Professor of Pediatrics, Harvard Medical School
Division of Genetics and Genomics, Boston Children's Hospital
3 Blackfan Circle, CLSB 15022
Boston, MA 02115
Email: Ingrid.holm@childrens.harvard.edu

Re proposal: "Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants"
Grant: NIH PAR-19-099 entitled "Limited Competition: Clinical and Translational Science Award (CTSA) Program: Collaborative Innovation Award (U01 Clinical Trial Optional)"

Dear Dr. Green and Dr. Holm:

It is with great pleasure that I write to provide this letter to convey my enthusiastic support for your grant proposal entitled, "*Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants*". As Dean for Clinical and Translational Research and Director of Harvard Catalyst | The Harvard Clinical and Translational Science Center, which includes Brigham and Women's Hospital and Boston Children's Hospital, I am excited about the scientific questions you are asking surrounding the application of genome sequencing in the newborn arena. This proposal will capitalize on the successes and infrastructure of your BabySeq Project and will provide valuable insights around the medical, behavioral and economic outcomes after the recruitment of a more diverse and representative population at three CTSA sites.

I am excited to be a part of this innovative project and to contribute to the much-needed discussion around the utility of genomic sequencing. Your plan to meld together the best ideas from three of the leading CTSAs to address sscientific questions surrounding the application of genome sequencing in the newborn arena is innovative and collaborative. The proposed project involves conducting a new randomized controlled trial of whole genome sequencing in order to determine medical, behavioral and economic outcomes after the recruitment of a more diverse and representative population at three CTSA sites. Your proposal will allow us to better understand the impacts of newborn genomic medicine in a more representative population.

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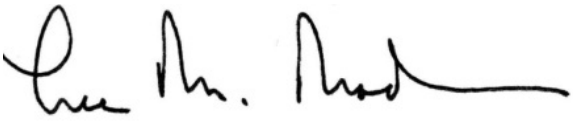
Harvard Clinical & Translational Science Center

HARVARD UNIVERSITY

I applaud you for the creation of this important grant proposal which will bring together the CTSA sites at Harvard Medical School (Brigham and Women's Hospital and Boston Children's Hospital), Mount Sinai, and University of Alabama. You have my full and complete support for your application. You have assembled a forward-thinking interdisciplinary team that is prepared to take on this great task, and I applaud your thoughtful effort and approach on this important topic.

Best regards,



Lee M. Nadler, M.D.
Virginia and D. K. Ludwig Professor of Medicine
Dean for Clinical and Translational Research
Harvard Medical School

Mount Sinai *Conduits*
Institutes for Translational Sciences

July 2, 2019

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital
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Boston, Massachusetts 02115

Ingrid A. Holm, MD, MPH
Associate Professor of Pediatrics, Harvard Medical School
Division of Genetics and Genomics, Boston Children's Hospital
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Boston, Massachusetts 02115

Dear Drs. Green and Holm:

I am the Dean for Translational Biomedical Sciences at Mount Sinai and oversee ConduITS, our CTSA program. In that capacity, I am delighted to provide my full support for your grant proposal entitled "Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants," which is in response to NIH PAR-19-099 entitled "Limited Competition: Clinical and Translational Science Award (CTSA) Program: Collaborative Innovation Award (U01 Clinical Trial Optional)." As our site's PIs, Carol Horowitz and Bruce Gelb, have shared the details of the proposed randomized clinical trial, which will compare whole genome sequencing with return of results to standard care for 500 young infants who are ostensibly well. This type of work is well within the ambit of our CTSA program and aligns extremely well with Mount Sinai's focus on genomic medicine. Of note, Dr. Horowitz directs the stakeholder engagement for our CTSA and has built strong partnerships and programs to effectively engage, recruit and retain diverse populations in research.

As you know, this grant opportunity specifies the inclusion of sites with active CTSA programs. ConduITS' objectives are at the forefront of translating scientific discoveries into treatments for patients. To achieve excellence in clinical and translational science, our programs offer diverse expertise and services. Of particular use for this proposal, Conduits offers the Centers for Community and Academic Research Partnerships (CCARP), Office of Research Services (ORS), the Clinical Research Center (CRC), and the Center for Patient Oriented Research, Training, Education, and Development (CePORTED). CCARP was founded to enhance health care, improve health outcomes, and better understand and address health problems in minority and underserved communities. It instills the importance and benefits of community-engaged and health disparities research, employ these research methods, and translate study's results back to the communities studied. CCARP builds and fosters strong relationships of mutual trust and respect between community representatives and Mount Sinai faculty. Special emphasis is placed on community leaders' ability to shape research and work with Mount Sinai to transform research operations. Additionally, CCARP trains and mentors researchers to conduct research with local communities more effectively. These partnerships provide opportunities for community and faculty to develop research partnerships with the goal of translating study results into action and policy change. This highlights the synergies between the missions of ConduITS and this proposal.

Mount Sinai *Conduits*
Institutes for Translational Sciences

ORS serves ISMMS and the entire Mount Sinai Health System as a central resource that assists the research community with navigation of internal infrastructure and external research agencies. ORS offers investigators and research teams the Research Roadmap and Research 411, which provides guidance and responses to questions regarding research infrastructure and resources; training and education; orientation; consulting for ClinicalTrials.gov registration and reporting, IND/IDE submission, protocol development and patient recruitment and retention strategies. The ORS is the point of contact for the Trial Innovation Network (TIN), a collaborative national network that focuses on multi-site studies and supports operation innovation, excellence and collaboration and leverages the expertise and resources of the CTSA Program. Locally, our CTSA has extensive experience in participation in multicenter clinical research studies with diverse patient populations, and will provide access to resources, infrastructure, organizational processes, training for staff and junior faculty and continuity to facilitate the trial's ability to successfully accomplish its stated objectives.

The Clinical Research Unit (CRU) provides nursing support and specimen processing resources for investigators involved in clinical research. It is the hub for conducting clinical and translational research at Icahn School of Medicine. There are currently approximately 90 active protocols under the auspices of the CRU, representing studies in virtually every discipline, institute, and department throughout the Mount Sinai Health System (MSHS).

At Icahn School of Medicine at Mount Sinai, we also engage the research community and its affiliates through the Center for Patient Oriented Research, Training, Education, and Development (CePORTED). CePORTED provide rigorous and unique educational opportunities for trainees from multiple healthcare professions in diverse stages of training to educate and train them to pursue careers in clinical and translational research to improve patient outcomes and the surrounding communities.

Our CTSA team looks forward to working with Drs. Gelb and Horowitz on this important study. We will certainly make every effort to accommodate them with the resources of ConduITS.

Sincerely,

Rosalind J. Wright

Rosalind J. Wright, MD, MPH
Dean for Translational Biomedical Sciences
Principal Investigator, NCATS-funded Institute for Translational Sciences
Horace W. Goldsmith Professorship in Children's Health Research
Professor, Pediatrics, Pulmonary and Critical Care
Professor, Environmental Medicine & Public Health
Icahn School of Medicine at Mount Sinai
1468 Madison Ave
New York, NY 10029

June 27, 2019

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital

Ingrid A. Holm, MD, MPH
Associate Professor of Pediatrics, Harvard Medical School
Division of Genetics and Genomics, Boston Children's Hospital

Dear Dr. Green and Dr. Holm,

On behalf of the Center for Clinical and Translational Science (CCTS) at the University of Alabama at Birmingham (Hub), it is my great pleasure to provide this letter of support for your proposal to the CTSA Collaborative Innovation Award program, entitled, "*Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants*". This multi-site research initiative, – drawing on research expertise at Harvard Medical School, Mount Sinai, Boston Children's, Brigham and Women's Hospital and UAB, – involving the efficiency of newborn genomic sequencing has the tremendous potential to improve the health and well-being of our pediatric patients and their families.

You have assembled an impressive, transdisciplinary team that will implement newborn genomic sequencing in a range of environments and explore its impacts within diverse populations. Your strategy of recruiting 500 infants from general pediatrics clinics to conduct a randomized controlled trial of whole-genome sequencing will be the first to study medical, behavioral and economic outcomes of newborn genomic medicine in representative populations. Your approach will also allow investigation of the impact of genomic information on families and will offer the first crucial insights into the psychological and behavioral outcomes of newborn genomic sequencing in underrepresented minority populations.

The CCTS is dedicated to improving health and elevating health equity in a region of the country disproportionately burdened by chronic disease. The CCTS leverages multidisciplinary expertise and cutting-edge capacity available within an 11-institution Partner Network spanning Alabama, Mississippi and Louisiana to advance the platform for integrating genomic information to guide disease prevention, diagnosis, and treatment. The CCTS Partner Network provides a fertile environment to accomplish this goal toward improved health through interdisciplinary teamwork, engaged communities and innovative approaches.

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1924 7th Avenue South
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The proposed collaboration, which builds on foundational work for implementing genome medicine into the care of newborns (BabySeq study), will take the vital step of expanding the methodology to a more diverse population. The insights developed by your collaborative team will increase the efficiency of newborn genomic sequencing as a sustainable screening tool for healthy infants. The CCTS looks forward to being part of this important effort.

Best regards,

Robert P. Kimberly, MD
Howard L. Holley Professor of Medicine
Director, Center for Clinical and Translational Science
Senior Associate Dean for Clinical and Translational Research, UAB School of Medicine
Associate Vice President for Medicine and Biomedical Research
University of Alabama at Birmingham

March 4, 2020

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital
41 Avenue Louis Pasteur, Boston, MA 02115

Dear Dr. Green,

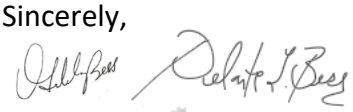
It has been a pleasure participating in your original BabySeq project and thus we would like to lend our support to your new proposed project, "*Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants*."

We enrolled in your original BabySeq project as new parents almost four years ago, and have also participated in other research studies in the past. We are both from minority backgrounds and recognize that medical research and healthcare have alarming disparities for those with racial and ethnic minority backgrounds. We are excited to be part of this new initiative to expand the BabySeq project with a targeted focus on families from African American and Hispanic American communities. This is especially important given the majority of participants in the original study self-identified as White.

Our daughter was in the BabySeq control group and didn't receive genome sequencing in the project. However, since BabySeq was the first study to offer this technology to healthy infants, we have a unique perspective as parents who have been through the consent process and agreed to participate in this type of research. We are willing to provide input on your study materials and participate in group meetings especially throughout the first year of your new project.

We understand that other stakeholders will include community members, clinicians, advocates, and researchers, and appreciate that we will receive a stipend as compensation for our time. Given our background and experience, we look forward to helping design a successful project that is respectful of all participants. Thank you for including us in this important work and good luck with your application!

Sincerely,



Gabriela and Delante Bess

BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL
HARVARD MEDICAL SCHOOL

Cheryl R. Clark MD, ScD
Director, Health Equity Research & Intervention Unit
Center for Community Health and Health Equity
Hospitalist, Brigham Health Hospital Medicine Unit
Assistant Professor, Harvard Medical School

February 29, 2020

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital
41 Avenue Louis Pasteur, Boston MA 02115

Dear Robert,

It has been a pleasure working with you on the All of Us research program and as a colleague at Brigham and Women's Hospital, and I am proud to support your new proposed research project, *"Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants"*.

I currently serve as the engagement co-lead of the All of Us research program, through which physicians recruit diverse patients for precision medicine studies. This program includes providing DNA samples and has a specific focus on engaging and recruiting a representative cohort. More than 60% of participants are from populations traditionally underrepresented in biomedical research.

In my research as a social epidemiologist, I have studied the ways that social determinants of health, including discrimination and distrust influence health care utilization and health outcomes. Throughout my career, I have had success recruiting diverse populations in research. One study specifically looked at the importance trusted physicians as brokers of information when parents of young women and girls of African descent considered vaccination against STDs (e.g. HPV), which is a highly stigmatizing issue. In another project we were successful recruiting 1,000 women who spoke a diversity of non-English languages by working with trusted clinicians.

The goal of your new project is to explore the impact of genomic sequencing in infants from ethnically and racially diverse backgrounds across the US who have historically been underrepresented in genomic research. It will be critical to consider community input in this project to address potential issues of distress, mistrust, fear and stigma. I have experience and expertise in community based participatory

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research (CBPR) principles, which prioritize the collaborative effort between researchers and community residents through all stages of the research process.

I appreciate that you are including an intentional community engagement strategy in your resubmission and assembling a group of stakeholders including patients, community members and clinicians across all study sites. It will be my honor to participate in a community-engaged advisory committee for this research.

Sincerely,

Cheryl Clark MD, ScD
Investigator, *All of Us* Research Program New England
Brigham and Women' Hospital

February 24, 2020

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital
41 Avenue Louis Pasteur, Boston MA 02115

Dear Robert,

It has been a pleasure working with you as a researcher, colleague and advisor and thus I am pleased to lend my support to your new proposed project, *"Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants"*.

I have helped advise several of your genomic sequencing studies to help increase diversity among participants. Together we have achieved funding and crafted strategies to increase engagement, recruitment and retention of participants from minority populations.

The goal of your new project is to explore the impact of genomic sequencing in infants from ethnically and racially diverse backgrounds across the USA who have historically been underrepresented in genomic research. It is essential to address potential issues of distress, mistrust, fear and stigma within minority communities that have been historically marginalized in genomic research. I appreciate your efforts to craft an intentional community engagement strategy and am excited to be a part of your new Stakeholder Board.

This group will include diverse patients, advocates, and clinicians from all study sites, who will review and provide feedback on your study design, recruitment strategy and genomic reports. I look forward to partnering with investigators so we can engage and serve diverse populations in an ethically appropriate manner. I am confident that input from myself and other members will help ensure this project is acceptable to traditionally underserved populations.

I understand that participation as a stakeholder will involve one in-person kickoff meeting and monthly remote meetings throughout Year 1, then quarterly remote meetings throughout Years 2-4. I appreciate that all travel expenses will be provided and that I will receive an annual stipend as compensation for my time. I look forward to continuing our partnership to help bring the potential of genomic medicine to all people rather than worsening existing healthcare disparities. Best of luck with your application.

Sincerely,

Tshaka Cunningham, Ph.D.
Executive Director, Faith-Based Genetic Research Institute
(www.fbgri.org)

VANDERBILT UNIVERSITY MEDICAL CENTER

Institute for Medicine and Public Health

February 26, 2020

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital
41 Avenue Louis Pasteur, Boston MA 02115

Dear Robert,

It is with great pleasure that I write to provide this letter of support for your revised R01 grant proposal titled, *"Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants."* As a practicing obstetrician and researcher, I recognize the importance of advancing newborn screening for all communities.

I currently serve as a genetic epidemiologist, Director of the Division of Quantitative Sciences in the Department of Obstetrics and Gynecology and Director of Women's Health Research center. My research is focused on understanding and identifying genetic risk factors for complex diseases with a specific focus on diseases that disproportionately impact minorities. It is essential to address potential issues of distress, mistrust, fear and stigma within research for these participants. I appreciate your efforts to craft an intentional community engagement strategy and am excited to be a part of your new Stakeholder Board.

I look forward to partnering with diverse patients, community advocates, and clinicians from all study sites so we can engage and serve diverse populations in an ethically appropriate manner. I am confident that input from myself and other members will help ensure this project is acceptable to traditionally underserved populations.

I understand that participation as a stakeholder will involve one in-person kickoff meeting and regular remote meetings throughout Year 1, then quarterly remote meetings throughout Years 2-4. I appreciate that all travel expenses will be provided and that I will receive an annual stipend as compensation for my time.

I am excited to be a part of this effort and wish you the best of luck with your application.

Sincerely,

Digna Velez Edwards, PhD, MS

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March 3, 2020

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital
41 Avenue Louis Pasteur, Boston MA 02115
Ingrid A. Holm, MD, MPH
Associate Professor of Pediatrics, Harvard Medical School
Division of Genetics and Genomics, Boston Children's Hospital
3 Blackfan Circle, Boston MA 02115

Dear Dr. Green and Dr. Holm,

I am happy to write and offer my support towards your new proposed project, "*Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants*."

It is so important to bring diverse perspectives to research, and I am excited to be a part of your new Stakeholder Board for this study. I understand that this project involves genome sequencing in healthy babies recruited from diverse families in the Birmingham area. As a community member, I will be happy to review and provide feedback on your engagement materials, recruitment strategy, study design and genomic reports.

To make sure research participants feel valued and respected, it is important to address potential issues from the beginning of the project. I appreciate your efforts to include representatives from the community and am glad to contribute. I understand that participation as a stakeholder will involve one in-person meeting and regular remote meetings throughout Year 1, then quarterly remote meetings throughout Years 2-4. I appreciate that travel expenses will be provided and that I will receive an annual stipend as compensation for my time. I look forward to working with other board members including researchers, clinicians and community members from all three sites (Boston, New York and Birmingham).

I am glad that this project is focused on bringing genomic sequencing to a more representative population and wish you good luck with your application.

Sincerely,
Sarita Edwards

UAB SCHOOL OF PUBLIC HEALTH

February 27, 2020

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital
41 Avenue Louis Pasteur, Boston MA 02115

Dear Robert,

It is with great pleasure that I write in support for your revised R01 grant proposal titled, *"Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants."* The study, in partnership with the University of Alabama at Birmingham, Mount Sinai, and Boston Children's Hospital, will explore the impact of genomic information in families from diverse backgrounds. I believe this data is crucial for further clinical implementation of this technology.

I am currently an Assistant Professor in the Department of Health Behavior at the University of Alabama at Birmingham School of Public Health. My research is focused on the ethics of engaging marginalized and stigmatized populations in scientific research, and seeks to inform ethical practice and policies by centering the values and preferences of stakeholders. My research background and expertise in public health, community engagement and bioethics will allow me to provide input on potential issues of distress, mistrust, fear and stigma for the children and families in your study.

I am excited to be a part of your new Stakeholder Board. I am looking forward to working with this board to provide ongoing feedback as you develop each stage of the study along with minority communities. Developing a strong communal relationship while incorporating sensitivity and cultural diversity will help the study team earn the trust of community members and ensure participants are treated as valued members of a partnership.

I agree to the terms that participation as a stakeholder will involve one in-person kickoff meeting and regular remote meetings throughout Year 1, then quarterly remote meetings throughout Years 2-4. I appreciate that all travel expenses will be provided and that I will receive an annual stipend as compensation for my time.

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UAB SCHOOL OF PUBLIC HEALTH

I am excited to be a part of this effort and wish you the best of luck with your application. I look forward to working with you to conduct a successful project.

Sincerely,

Faith E. Fletcher

Faith E. Fletcher, PhD, MA
Assistant Professor
Department of Health Behavior
University of Alabama at Birmingham School of Public Health

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March 8, 2020

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital
41 Avenue Louis Pasteur, Boston, MA 02115

Dear Dr. Green,

It has been a pleasure participating in your original BabySeq project and thus I would like to lend my support to your new proposed project, "*Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants.*"

I enrolled in your original BabySeq project as a new mom four years ago, and your team has been great to work with throughout the process. My son was among the group that received genome sequencing as a healthy newborn. We ended up learning information that was medically relevant for him as well as several other family members. Since BabySeq was the first study to ever sequence healthy infants, I understand how unique our family's experience is. I am willing to provide input on your new study and feel that I can bring an important perspective as a parent who has actually participated in a similar research study.

I am enthusiastic about your new proposed project to bring genomic sequencing to more families from diverse backgrounds. The goal of your new study is to recruit 500 babies across the U.S., with a special focus on families from African American and Hispanic American communities. You are planning to work with a variety of "stakeholders" including researchers, clinicians and community members as part of the project development. Given my family's past participation in research, I look forward to being able to use my experiences to help inform the design of this project during discussions with the other members of the Stakeholder Board.

I understand that participation as a stakeholder will involve reviewing study materials and participating in team calls, and appreciate that I will receive an annual stipend as compensation for my time. I look forward to working with other stakeholders and the study team to design a successful project that is respectful of all participants. I'm honored to help support the cause!

Sincerely,

Alyssa Carter Gracia

UHealth
UNIVERSITY OF MIAMI HEALTH SYSTEM

UNIVERSITY OF MIAMI
MILLER SCHOOL
of MEDICINE

February 26th, 2020

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital
41 Avenue Louis Pasteur, Boston MA 02115

Dear Robert,

It has been a pleasure working with you in the Hispanic Community Health Study/ Study of Latinos (SOL) which is a NIH-funded multi-center epidemiologic study in Hispanic/Latino populations to assess the role of acculturation in the prevalence and development of disease, and to identify factors playing a protective or harmful role in the health of Hispanics/Latinos. We have also had the pleasure of interacting through the NIH's All of Us Research Program as I am one of the co-investigators and Regulatory/Ethics lead for the SouthEast Enrollment Center (SEEC) consortium member as well as co-Chair of the All of Us' Resource Access Board (RAB).

In my role as a research assistant professor at the Miller School of Medicine in Miami, my scholarly research is devoted to identifying and analyzing the social, ethical and legal (ELSI) dimensions of novel and disruptive genetic technologies. My multicultural/ethnic background has helped inform my unique expertise in comparative policy and ethics. It would be a pleasure to support this application to educate and empower historically underrepresented and underserved minority populations to participate in genomic research studies and have equal access to precision medicine care.

Even before joining together as collaborators on numerous projects, I had been following the groundbreaking work you had done in "Genome Sequence-Based Screening for Childhood Risk and Newborn Illness". I am excited to hear you are submitting a new proposal and it would be an honor to join in on this project.

I would be delighted to partake in the stakeholder board to provide ongoing feedback as the project team develops the protocol, recruitment strategy and genomic reports. In collaboration with the entire team, I am confident that we will be able to effectively establish and maintain trust filled relationships with all participants in the study. I understand that participation as a stakeholder will involve one in-person kickoff meeting and monthly remote meetings throughout

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UHealth
UNIVERSITY OF MIAMI HEALTH SYSTEM

UNIVERSITY OF MIAMI
MILLER SCHOOL
of MEDICINE

Year 1, then quarterly remote meetings throughout Years 2-4. I appreciate that all travel expenses will be provided and that I will receive an annual stipend as compensation for my time.

I look forward to continuing our partnership to help bring the potential of genomic medicine into clinical care for all patients. My absolute best wishes for your application!

(Ms.) Rosario Isasi, JD, MPH
Assistant Professor (Research)
Dr. John T. Macdonald Foundation Department of Human Genetics
Institute for Bioethics and Health Policy
John P. Hussman Institute for Human Genomics
Interdisciplinary Stem Cell Institute
University of Miami Leonard M. Miller School of Medicine

July 2, 2019

Carol Horowitz MD, MPH
Professor
Department of Population Health Science and Policy
Icahn School of Medicine at Mount Sinai
1 Gustave L. Levy Place, Box 1077

Dear Carol,

It has truly been a joy to work with you these past years, so I would like to lend my enthusiastic support for you and Bruce Gelb in taking this next step forward with this new proposed project *"Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants."*

I am thrilled to have been involved with so many projects throughout our time working together, beginning with our community initiated diabetes prevention program, HEED. As an advisor on our Genetic and Genomic Stakeholder Board, my colleagues and I have been able to focus on issues pertaining to race, ancestry and genomics, which helped us bring GUARDD, (part of IGNITE I) to fruition with great success. Thanks to suggestions that the Board has come up with, we were able to recruit a population that is often apprehensive about research, in a limited time span, and retain an incredible majority of this population over the course of the study.

We have continued our successful partnership with NYCKidseq (part of CSER2). I personally have taken on the responsibility of the CSER engagement workgroup co-chair, and co-authored various papers about my experiences with community based participatory research and stakeholder engagement in genomics, one of which was included in a Martin Luther King special edition of the Journal of Health Care for the Poor and Underserved. I am greatly encouraged by the work that we have been able to do together in connecting

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academics with community stakeholders and informing research at all levels. As a result of our collaboration, I have had the pleasure of attending talks where I have been able to disseminate information about the importance of inclusivity in research to genomics researchers of primarily European Ancestry. It is of the utmost importance that we continue to bring the diverse voices that are often lacking into the research community.

As a Board, our group has the ability to build stakeholder-academic collaborations in order to inform and create more impactful research. Contributing to and engaging in conversation with patient representatives, community organizers, providers and researchers has been a key method of exploring genomics research from a distinctive and vital perspective, as well as informing recruitment and retention strategies. Our track record as community-academic partners in GUARDD, NYCKidseq and other projects has been a shining star in the field of research. We know our work has and will continue to enhance the likelihood that genomic research will benefit all people, including low-income, underrepresented minority patients most likely to suffer from poor health and least likely to gain from scientific discoveries first.

I believe that you will be able to do great things with this new randomized clinical trial you propose with infants of diverse backgrounds. Along with the rest of the Board, I hope to continue our partnership designing, executing and disseminating this kind of research on a larger scale.

Wishing you great success.

Mimsie Robinson

Pastor Mimsie Robinson
Associate Pastor

SBLRC
South Bay Latino Research Center

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital
41 Avenue Louis Pasteur, Boston MA 02115

March 2, 2020

Dear Robert,

It has been a pleasure working with you as a researcher and colleague and thus I am pleased to offer my full support to your new proposed project, *"Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants".*

I serve as Principal Investigator of the San Diego Field Center and Chair of the Steering Committee for the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), which is multi-site epidemiologic study of Latino health among 16,000 individuals in four US cities, focusing on cardiovascular risk factors and psychosocial variables. By fostering mutual respect and earning the trust of communities involved, we have been able to learn more about chronic diseases, risks and protective factors in Hispanics/Latinos and share results to improve public health at the local level.

It has been exciting to collaborate with you on the PopSeq project to return genomic results within the HCHS/SOL cohort, and I look forward to working with you on your new proposed study. The goal of this new project is to explore the impact of genomic sequencing in infants from ethnically and racially diverse backgrounds across the USA who have historically been underrepresented in genomic research. As I am a bilingual, bicultural Hispanic/Latino physician with expertise in community-based participatory research, I am confident that I can advise on important ethical considerations and how to effectively engage with the community at each stage of the study.

To ensure participants feel valued throughout the research process, it is important to address potential issues of distress, mistrust, fear and stigma before we begin recruitment. I appreciate your efforts to craft an intentional community engagement strategy and am excited to be a part of your new Stakeholder Board. I understand that participation as a stakeholder will involve one in-person kickoff meeting and regular remote meetings throughout Year 1, then quarterly remote meetings throughout Years 2-4. I appreciate that travel expenses will be provided and that I will receive an annual stipend as compensation for my time. I am glad to be partnering with other researchers, clinicians and community members so we can engage and serve diverse populations in an ethically appropriate manner.

I look forward to working with you on another grant to help bring the potential of genomic medicine to all populations. My best wishes for your application.

Sincerely,

G A Talavera

Gregory A Talavera, MD, MPH

March 4, 2020

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital
41 Avenue Louis Pasteur, Boston MA 02115

Ingrid A. Holm, MD, MPH
Associate Professor of Pediatrics, Harvard Medical School
Division of Genetics and Genomics, Boston Children's Hospital
3 Blackfan Circle, Boston MA 02115

Dear Dr. Green and Dr. Holm,

It is my pleasure to support your new proposed project, "Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants."

I understand that the goal of your new project is to explore the impact of genomic sequencing in infants from ethnically and racially diverse backgrounds across the US, including those recruited from the Birmingham area. It is critical for scientists to listen to the community when planning research and I am happy to provide my input. I appreciate the significance of the project and I look forward to being able to use my experiences to help inform the design.

This new Stakeholder Board that you are putting together will include researchers, healthcare providers, former research participants and community members from each site. I understand that participation will involve one in-person meeting and regular remote meetings throughout Year 1, then quarterly remote meetings throughout Years 2-4. I appreciate that travel expenses will be provided and that I will receive an annual stipend as compensation for my time.

To ensure participants feel valued throughout the research process, it is important to address potential issues of distress, mistrust, fear and stigma from the very beginning. I am hopeful that input from myself and other board members will help ensure this project is acceptable and helpful to populations who traditionally suffer from healthcare disparities. I am glad to be partnering with the study team and wish you good luck with your application.

Best,

Angela G Williams

February 26, 2020

Carol Horowitz, MD, MPH

Professor

Department of Population Health Science and Policy

Icahn School of Medicine at Mount Sinai

1 Gustave L. Levy Place, Box 1077

Dear Carol,

It has been a pleasure working with you as a researcher, colleague and community member and thus I am pleased to lend my support to your new proposed project, *"Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants"*.

I have been an advisor on your existing Genetic and Genomic Stakeholder Board for the past 2 years providing my input as a Certified Midwife and former GUARDD research study participant. Together we have advised a number of research studies regarding engagement, recruitment and retention of participants from minority populations. I am encouraged by the progress we have made connecting academics with members of the community to build trust and mutual respect.

It is essential to bring diverse perspectives to research, and so I am excited to be part of an entirely new Stakeholder Board being developed specifically for your proposed research project. This study of genome sequencing in healthy babies from African American and Hispanic families is an ambitious effort, and it will be critical to consider community input in the project. I will be happy to review and provide feedback on your engagement materials, recruitment strategy, study design and genomic reports. I look forward to working with other stakeholders including researchers, clinicians, community members and former research participants of diverse backgrounds.

This new Stakeholder Board will be important for every step of your research to address potential issues of distress, mistrust, fear and stigma. I am confident that input from myself and other board members will help ensure this is project is acceptable to traditionally underserved populations. I look forward to

continuing our partnership to help bring the potential of genomic medicine to all people rather than worsening existing healthcare disparities.

Sincerely,

Trinisha Williams, CM, LM, MPH, FACCE, LCCE, LC

Director of Midwifery

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Boston Children's Hospital
Until every child is well™

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Boston Children's Primary Care at Longwood
300 Longwood Avenue, BCH 3081, Boston, MA 02115
617-355-7701 | bostonchildrens.org

July 1, 2019

Robert C. Green, MD, MPH
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Ingrid A. Holm, MD, MPH
Associate Professor of Pediatrics, Harvard Medical School
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3 Blackfan Circle, CLSB 15022
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Re proposal: "Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants"
Grant: NIH PAR-19-099 entitled "Limited Competition: Clinical and Translational Science Award (CTSA) Program: Collaborative Innovation Award (U01 Clinical Trial Optional)"

Dear Dr. Green and Dr. Holm:

It is a great pleasure to provide this letter to convey my enthusiastic support for your grant proposal entitled, "*Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants*". As a primary care pediatrician and Associate Director of the Boston Children's Hospital Primary Care Clinic (CCHPC), I am excited about the scientific questions you are asking surrounding the application of genome sequencing in the newborn arena. This proposal will capitalize on the successes and infrastructure of your BabySeq Project and will provide valuable insights around the medical, behavioral and economic outcomes after the recruitment of a more diverse and representative population. The proposed project involves conducting a new randomized controlled trial of whole genome sequencing that will allow us to better understand the impacts of newborn genomic medicine in a diverse population. I have a keen interest in the potential for genomics to inform pediatric care and a deep understanding of how genetic information can affect parents.

I am excited that you will be recruiting patients from CCHPC into your study. As you know, we have extensive experience, and the infrastructure, in conducting research projects and recruiting patients into research studies. In addition we have worked with Dr. Holm in the past to recruit patients for genomic studies. CCHPC has a satellite clinic at the Martha Elliot Health Center, and I am excited that Dr. Clement Bottino, a primary care pediatrician at both the Longwood and Martha Elliot sites, will be a co-investigator on your grant as the CCHPC "clinical champion". We provide care to a socially, medically and racially diverse population, which is approximately 50% Hispanic, and is approximately 40% African American and 10% White, with 50% identifying themselves as "more than one race". Our 16,000 patients include approximately 700 newborns per year just at the Longwood site. We therefore feel that it is very feasible to recruit 50 participants a year between the Longwood and Martha Elliot CCHPC sites.

I am excited to be a part of this innovative project and to contribute to the much-needed discussion around the utility of genomic sequencing. You have my full and complete support for your application. You have assembled a forward-thinking interdisciplinary team that is prepared to take on this great task, and I applaud your thoughtful effort and approach on this important topic.

Boston Children's Hospital
Until every child is well™

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Boston Children's Primary Care at Longwood
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617-355-7701 | bostonchildrens.org

Best regards,

Ronald Samuels, MD, MPH
Associate Director, Children's Hospital Primary Care at Longwood
Assistant Professor of Pediatrics, Harvard Medical School

Icahn School of Medicine at Mount Sinai

Kravis Children's Hospital
Divison of General Pediatrics

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June 18, 2019

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Boston, Massachusetts 02115

Dear Drs. Green and Holm:

I am writing in my role as Chief of the Division of General Pediatrics within the Department of Pediatrics to provide my enthusiastic support for your grant proposal entitled "*Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants*," which is in respond to NIH PAR-19-099 entitled "Limited Competition: Clinical and Translational Science Award (CTSA) Program: Collaborative Innovation Award (U01 Clinical Trial Optional)." For this project, 300 infants aged 1-6 months will be recruited for a randomized clinical trial that will compare genome sequencing to standard care, emphasizing the recruitment of individuals who are ethnically and racially diverse.

The Division of General Pediatrics oversees Mount Sinai Pediatric Associates Practice, which provides comprehensive medical care to children from birth through adolescence and has been recognized as a New York State Level 3 Primary Care Medical Home. The practice provides medical care to approximately 9,900 patients with over 23,000 visits per year. Relevant to your proposed project, we see an average of 17 newborns per week, nearly all of whom receive ongoing care in our practice. Our patient population is primarily racial and ethnic minority; 40% are Hispanic, 34% African- American, 19% other, 4% white, 2% Indian/Southeast Asian, and <1% Asian.

The practice comprises 16 attending physicians, who supervise 62 pediatric and triple board residents. The majority of the patients come from East Harlem, Central Harlem, and the Bronx. Approximately 87% are covered by Medicaid/S-CHIP. A very high percentage of our patients will meet your goals with respect to diversity in race and ethnicity.

We have a well-established track record on recruiting subjects for a wide variety of research protocols in our clinic. We are already working through the protocol for recruiting children in our practice to Mount Sinai's extensive biobank, BioMe. While your protocol, which includes return of results, will be more complex, I feel confident that we can partner strongly with the Principal Investigators, Drs. Bruce Gelb and Carol Horowitz, to be successful in recruiting for this clinical trial. I am an experienced clinical researcher with experience in clinical trials and provision of study results, and I am fully prepared to meet regularly with the PIs when the trial starts in order to devise successful strategies, tweak those as we gain experience with the protocol, etc.

Our group wishes you success with the application for this important proposal. We look forward to working together in the not-too-distant future.

Sincerely,

Karen M. Wilson

Karen M. Wilson
Debra and Leon Black Professor and Division Chief of General Pediatrics
Vice-Chair for Clinical and Translational Research

UAB MEDICINE
PEDIATRICS

Children's of Alabama

February 14, 2020

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital

Ingrid A. Holm, MD, MPH
Associate Professor of Pediatrics, Harvard Medical School
Division of Genetics and Genomics, Boston Children's Hospital

Dear Dr. Green and Dr. Holm:

We are pleased to write in support of your proposal entitled, "Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants". As a teaching clinic in the University of Alabama (UAB) Pediatric Residency Program, we currently mentor 90 physicians-in-training for both pediatrics and combined Med/Peds careers. Participating in this project will provide exposure for these young physicians to the tremendous benefits, as well as the challenges, that genomic information can produce in the context of pediatric health care.

Our Primary Care Clinic is located within the Children's of Alabama facility but is part of the University of Alabama Department of Pediatrics. We provide primary care for a population of roughly 4200 patients ages birth through 18 years, with 8000-9000 clinical encounters per year. We average 25 new babies recruited into the practice each month, most of whom are born at the University of Alabama Women and Infant's Center (WIC) and who will have at least 5 visits in the first 6 months of life. Our Academic General Pediatrics faculty serve as supervising physicians in both the WIC Newborn Nursery (with approximately 3500 term and late preterm newborns admitted each year) and in the Primary Care Clinic. Therefore, there is ample access to newborns who could be candidates for your study.

The majority (75-80%) of our patient population is insured by Alabama Medicaid. We also have a substantial number of patients covered by the Medicaid expansion program, as well as private insurance and a few uninsured patients. The majority (80%) of our patients are African-American, with 8% white, 8% Hispanic, and 2% Asian.

Our clinic has worked with and supported a number of research projects conducted by investigators at UAB. Our most recent studies have focused on children over 2 years of

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age, so there will be no "competition" with other investigators for these young infants. Because we have worked with researchers at UAB, I am confident the research team will have a good experience working with our clinic staff and physicians. As a pediatric practice associated with an academic institution, we are eager to support research which has the potential to improve the health of children. In addition, practicing in a relatively resource-limited environment (Alabama being a poor state, and many of our patients living at or below the poverty level), we are excited for our patients to be afforded the opportunity to participate in this study. We also feel that working with our practice may be advantageous for the overall study, since we have a large percentage of African-American and Hispanic patients, a characteristic of our population which might be different from other potential sites.

You have assembled a forward-thinking interdisciplinary team involving 3 CTSA sites-Harvard Medical School (Brigham and Women's Hospital and Boston Children's Hospital), Mount Sinai and University of Alabama at Birmingham, that is prepared to take on this great task, and I applaud your thoughtful effort and approach on this important topic. It has become clear that the next frontier in the application of clinical genomics and genomic medicine is in the newborn population and your proposed approach to recruit 500 healthy newborns would provide pediatricians with critical information to serve as a resource for informing clinical care during infancy and early childhood.

I am particularly impressed with your plans to not only investigate how genomic information may impact patient care through the early years of development of the healthy and ill newborn cohorts, but also to thoughtfully explore the parent's reactions to this genomic information as their child grows.

I am excited to be part of this innovative project and to contribute to the much-needed discussion around the utility of genomic sequencing. We believe that this is an important initiative for children in our region.

Sincerely,

Terry Wall

Terry Wall, MD, MPH
John W. Benton Endowed Chair in General Pediatrics
Professor and Division Director, Academic General Pediatrics
University of Alabama at Birmingham
Medical Director, Clinical Informatics, Children's of Alabama

Over the Mountain Pediatrics

3300 Cahaba Road, Suite 102 • Birmingham, AL 35223 • **Main:** 205.870.7292 • **Fax:** 205.638.9996

July 10th, 2019

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital

Ingrid A. Holm, MD, MPH
Associate Professor of Pediatrics, Harvard Medical School
Division of Genetics and Genomics, Boston Children's Hospital

Dear Dr. Green and Dr. Holm:

It is with great pleasure that I write in support of your proposal to NIH PAR-19-099 entitled, "*Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants*". By forming new collaborations between CTSA sites at Harvard Medical School, Mount Sinai and University of Alabama at Birmingham, you have assembled an interdisciplinary team that will implement newborn genomic sequencing in novel environments and explore its impacts within diverse populations.

Over the Mountain Pediatrics provides comprehensive medical care to children from birth through adolescence. The practice provides medical care to approximately 11,000 patients with over 29,500 visits per year. They see an average of 80 newborns per week whom receive ongoing care in the practice. The patient population is a variety of races and ethnicities: 72% Caucasian, 21% African American, 6% other, 3% Hispanic/Latino, 1% Asian, <1% Pacific Islander and <1% American Indian/Alaskan native. The majority of the patients come from the suburbs of Birmingham, Alabama. 39% of patients are on Medicaid.

As a pediatrician, I am passionate about improving the quality of care received by children and their families. I am excited about the scientific questions you are asking surrounding the application of genome sequencing in the newborn arena and I enthusiastically support your approach of conducting a new RCT of whole genome sequencing (WGS) in order to determine medical, behavioral and economic outcomes after the recruitment of a more diverse and representative population at 3 CTSA sites. Your proposal will allow us to better understand the impacts of newborn genomic medicine in a more representative population.

Our knowledge of genetics is constantly evolving, making it of utmost importance to have an efficient and well-planned methodology for issuing revised genomic reports and tracking healthcare utilization associated with genomic sequencing. Your study truly holds the potential to move the field of newborn screening into a new era.

I am excited to be a part of this innovative project and to contribute to the much-needed discussion around the utility of genomic sequencing.

Sincerely,

Elizabeth W. Luke, MD
Over the Mountain Pediatrics

July 1, 2019

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Division of Genetics, Brigham and Women's Hospital
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Associate Professor of Pediatrics, Harvard Medical School
Division of Genetics and Genomics, Boston Children's Hospital
3 Blackfan Circle, CLSB 15022
Boston, MA 02115
Email: Ingrid.holm@childrens.harvard.edu

Re proposal: "Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants"

Grant: NIH PAR-19-099 entitled "Limited Competition: Clinical and Translational Science Award (CTSA) Program: Collaborative Innovation Award (U01 Clinical Trial Optional)"

Dear Dr. Green and Dr. Holm:

It is with great pleasure that I write to provide this letter to convey my enthusiastic support for your grant proposal entitled, "*Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants*". I am excited about the scientific questions you are asking surrounding the application of genome sequencing in the newborn arena. This proposal will capitalize on the successes and infrastructure of your BabySeq Project and will provide valuable insights around the medical, behavioral and economic outcomes after the recruitment of a more diverse and representative population at three CTSA sites.

As you know, I am the Associate Project Director for the Longitudinal Pediatric Data Resource (LPDR) at the Newborn Screening Translational Research Network (NBSTRN), an effort that is dedicated to improving the health outcomes of newborns with genetic or congenital disorders by means of an infrastructure that allows investigators access to robust resources for research performed in the newborn period. The LPDR is a secure informatics system designed to enable enhanced data collection, sharing, management and analysis for conditions identified as part of newborn screening or for conditions that may benefit from newborn screening. During the BabySeq Project, I worked closely with your team to aid in the deposit of data collected from BabySeq participants into the LPDR. By depositing these common data elements, your team helped facilitate the dissemination of new findings and fostered the secondary use of the original data sets. By utilizing the LPDR the common data elements, phenotypic and genomic data generated by the BabySeq Project has now become an invaluable and enduring resource for secondary analysis by researchers and will accelerate the adoption of genomic sequencing information across the lifespan.

I am excited to be a part of this innovative project and to contribute to the much needed discussion around the utility of genomic sequencing. The proposed project involves conducting a new randomized controlled trial of whole genome sequencing in order to determine medical, behavioral and economic outcomes after the recruitment of a more diverse and representative population at three CTSA sites. I am excited to work with your team on this new project to aid in the deposit of data collected from participants into the LPDR. By depositing these common data elements, we will continue to facilitate the dissemination of new findings and build even large data sets for secondary research. Your proposal will allow us to better understand the impacts of newborn genomic medicine in a more representative population.

I am excited to be part of this exciting project and to provide the NBSTRN infrastructure for data sharing thought the LPDR.

Sincerely,

Amy Brower

Amy Brower, PhD
Associate Project Diretor NBSTRN
American College of Medical Genetics and Genomics

LSU Health NEW ORLEANS

School of Medicine
Department of Genetics

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital

Ingrid A. Holm, MD, MPH
Associate Professor of Pediatrics, Harvard Medical School
Division of Genetics and Genomics, Boston Children's Hospital

Dear Dr. Green and Dr. Holm,

I am pleased to extend my strong support for your collaborative study, entitled "*Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants*," in response to the CTSA Collaborative Innovation Award Program (PAR-19-099). Your initiative, in partnership with the University of Alabama at Birmingham, Mount Sinai and Harvard Medical School, is a bold and innovative approach to leverage genomic information to study medical, behavioral and economic outcomes of newborns in a diverse population. Additionally, your approach will thoughtfully explore the impact of genomic information on family functioning and development. These data are crucial for further dissemination and implementation of the technology in general pediatrics clinics across the country.

Louisiana State University Health Sciences Center (LSUHSC) has a tradition of using state-of-the art approaches and novel methodologies to elucidate genetic mechanisms of disease, genomics-based precision medicine, bioinformatics and population genomics. Of note, our Pediatrics Department is the backbone of Louisiana Children's Medical Center, the only pediatric hospital in the state. Medical geneticists and genetics counselors with cross-appointments in the Department of Genetics serve a diverse population of pediatric patients. We have an ongoing collaborative effort with Hudson-Alpha Institute for Biotechnology, another member of the UAB-led Center for Clinical and Translational Sciences, led by one of our pediatric cardiovascular surgeons who is using whole genome sequencing of pediatric patients to seek established and novel pathogenic mutations associated with congenital cardiovascular defects. The institution's mission is to drive innovation in research, training, clinical service and faculty development in a spirit of collaborative partnership and community engagement to advance the usefulness of genetics and genomics to improve health. While next-generation sequencing has been clinically available for years, little is known about its utility as a population-based screening tool. Building on your previous work, this proposal will extend methodologies for implementing genome sequencing into the care of newborns to a more diverse cohort across the country. This project will provide some of the first crucial insights into the psychological and behavioral outcomes of newborn genomic sequencing in minority populations.

On behalf of my colleagues at LSUHSC, I am excited to learn about the advances in genomic medicine enabled by your study and look forward to exploring ways to disseminate this knowledge to the benefit of our communities in Louisiana.

Most Sincerely,

Lucio Miele, MD, PhD
Cancer Crusaders Endowed Professor in Cancer Research
Professor and Department Head, LSU School of Medicine, Department of Genetics
Director for Inter-Institutional Programs, LSU Stanley Scott Cancer Center and Louisiana Cancer Research Consortium
Co-Director and Site Lead, Center for Clinical and Translational Science
Louisiana State University Health Sciences Center

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June 28, 2019

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital

Ingrid A. Holm, MD, MPH
Associate Professor of Pediatrics, Harvard Medical School
Division of Genetics and Genomics, Boston Children's Hospital

Dear Drs. Green Holm,

We are pleased to offer our enthusiastic support for your proposal to the CTSA Collaborative Innovation Award program, entitled, "*Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants*". You have assembled an impressive, transdisciplinary team that will implement newborn genomic sequencing in novel environments and explore its impacts within diverse populations. Your bold strategy of recruiting 500 infants from general pediatrics clinics to conduct a randomized controlled trial of whole-genome sequencing will be the first to study medical, behavioral and economic outcomes of newborn genomic medicine in representative populations. Your approach will also allow investigation of the impact of genomic information on family functioning and development.

At the University of Mississippi Medical Center (UMMC) is dedicated to educating health professionals, catalyzing scientific discoveries and delivering world class clinical care to improve the health of our state and region, which are affected by disparities in and disproportionate burden of diseases including hypertension, stroke, metabolic disease and obesity. As part of its strategic goals, UMMC embraces a culture of patient- and family-centered care that is further enhanced by our institution's agility to respond to paradigm-shifting opportunities in genomics and precision medicine.

This collaborative research project will create innovative solutions to increase the efficiency of newborn genomic sequencing and improve health of individuals and the public. You have proposed an innovative strategy to explore newborn genomic sequencing as a screening tool in diverse newborn populations, which has the tremendous potential to improve the health and well-being of our pediatric patients and their families. The UMMC Department of Pediatrics has built reliable capacity to facilitate implementation of research opportunities that can further the goals of this project. On behalf of UMMC, we look forward to following your work and learning how we may be able extend this kind of initiative to the communities we serve in Mississippi.

Best regards,

Richard L. Summers, MD
Professor of Emergency Medicine
Associate Vice Chancellor for Research

Robert D Annett, PhD
Vice Chair for Research
Department of Pediatrics

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July 1, 2019

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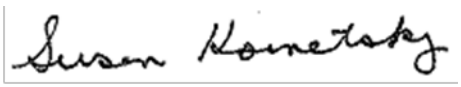
Re proposal: "Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants"
Grant: NIH PAR-19-099 entitled "Limited Competition: Clinical and Translational Science Award (CTSA) Program: Collaborative Innovation Award (U01 Clinical Trial Optional)"

Dear Dr. Green and Dr. Holm:

It is a great pleasure to provide this letter of agreement to serve as the Central IRB (CIRB) for your grant proposal entitled, "*Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants*". This proposal brings together Boston Children's Hospital, Brigham and Women's Hospital, Baylor College of Medicine, Icahn School of Medicine at Mount Sinai, and University of Alabama at Birmingham. The Boston Children's Hospital has extensive experience serving as the CIRB for a number of studies. In addition, the Boston Children's Hospital IRB worked with the Brigham and Women's Hospital IRB on the previous BabySeq project.

Sincerely,



Susan Kornetsky, MPH
Director of Clinical Research Compliance
Boston Children's Hospital

Human Research Committee
Brigham and Women's Hospital
Massachusetts General Hospital
McLean Hospital

July 2, 2019

RE: Title: Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants / NIH PAR-19-099
Relying Site PI: Robert C. Green, MD, MPH

Dear Dr. Green,

This letter confirms the willingness of the Brigham and Women's Hospital to cede review of this protocol to another IRB. It is our understanding that Boston Children's Hospital will likely serve as the single IRB: Brigham and Women's Hospital is willing to rely upon their IRB review.

Sincerely,

Maria E. Sundquist, MPA
Asst. Director, External IRB Programs
Partners HealthCare System, Inc.
399 Revolution Drive – Suite 710
Somerville, MA 02145
857-282-1902
msundquist@partners.org

Mount Sinai

Icahn School of Medicine at Mount Sinai
Mount Sinai Beth Israel
Mount Sinai Brooklyn
The Mount Sinai Hospital
Mount Sinai Queens
New York Eye and Ear Infirmary
of Mount Sinai
Mount Sinai St. Luke's
Mount Sinai West

Program for the Protection of Human Subjects
Institutional Review Boards

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Re: NIH Policy on the Use of a Single Institutional Review Board of Record for Multi-Site Research

The Program for the Protection of Human subjects (PPHS) at the Icahn School of Medicine at Mount Sinai (ISMMS) understands that the new NIH Policy on the Use of a Single Institutional Review Board of Record for Multi-Site Research establishes the expectation that all sites participating in multi-site studies, involving non-exempt human subjects research and funded by the National Institutes of Health (NIH), will use a single Institutional Review Board (sIRB) to conduct the ethical review required by the Department of Health and Human Services regulations for the Protection of Human Subjects.

When ISMMS will be a relying site (regardless of whether ISMMS is the prime awardee), the ISMMS IRB agrees to cooperate with the Single IRB plan when the Reviewing IRB is either:

- accredited and utilizing the SMART IRB Master Common Reciprocal Institutional Review Board Authorization Agreement (SMART IRB Agreement), or
- an external IRB with which ISMMS already has an existing master agreement.

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

June 14, 2019

Re: Letter of Support for use of single Institutional Review Board (sIRB) for "Limited Competition: Clinical and Translational Science Award (CTSA) Program: Collaborative Innovation Award"

Dear Dr. Bruce Korf,

Please accept this letter in support of your grant application for " Limited Competition: Clinical and Translational Science Award (CTSA) Program: Collaborative Innovation Award". The purpose of this letter is to demonstrate support for use of a single Institutional Review Board (sIRB) for the project. We understand that the National Institute of Health (NIH) Policy on the Use of a sIRB for Multi-site Research establishes the expectation that all sites participating in multi-site studies involving non-exempt human subjects research funded by the NIH will use a sIRB to conduct the ethical review. The University of Alabama at Birmingham recognizes the need for efficient study implementation while complying with the NIH sIRB policy.

This letter serves as confirmation that the University of Alabama at Birmingham is willing to rely on Boston Children's Hospital IRB for this project. The University of Alabama at Birmingham has agreed to rely on Boston Children's Hospital IRB in the past, so the arrangement allowing The University of Alabama at Birmingham to cede IRB review to Boston Children's Hospital IRB may proceed quickly upon approval to move forward with your project.

Sincerely,

Adam McClintock, MBA, CIP
Director, UAB Office of the IRB
701 20th St. South, Suite AB470
Birmingham AL 35294

Baylor College of Medicine
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OFFICE OF RESEARCH
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July 9, 2019

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital
41 Avenue Louis Pasteur, EC Alumnae Building, Suite 301
Boston, Massachusetts 02115

Ingrid A. Holm, MD, MPH
Associate Professor of Pediatrics, Harvard Medical School
Division of Genetics and Genomics, Boston Children's Hospital
3 Blackfan Circle, CLSB 15022, Mailstop BCH3150
Boston, Massachusetts 02115

Re: Statement of Intent to abide by NIH Policy on the Use of a Single Institutional Review Board (sIRB) for Multi-Site Research

Dear Drs. Green, Holm:

This letter is to confirm that Baylor College of Medicine agrees to participate in the NIH fuded multi-site research study entitled "Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants." The principal investigator for Baylor College of Medicine is Amy L. McGuire, JD, PhD.

Baylor College of Medicine is a subawardee. The Boston Children's Hospital IRB has been designated to serve as the IRB of record for all U.S. based study sites in keeping with the NIH Policy on the Use of a Single Institutional Review Board (sIRB) for Multi-Site Research. All participating sites will adhere to the NIH Policy on the Use of a Single Institutional Review Board (sIRB) for Multi-Site Research policy. The Boston Children's Hospital IRB will coordinate collection of local context information from all participating sites, as well as disseminate BCM IRB-approved protocol documents and consent forms.

The following are the registration numbers issued to the IRB of record by the HHS Office for Human Research Protections:

IRB00000352 IRB00010042

The following are the participating sites:

Harvard Medical School (Brigham and Women's Hospital and Boston Children's Hospital), Mount Sinai School of Medicine, University of Alabama, and Baylor College of Medicine.

Sincerely,

Leanne Scott

Leanne Scott
Senior Director, Sponsored Programs

March 4, 2020

Robert C. Green, MD, MPH
Professor of Medicine, Harvard Medical School
Division of Genetics, Brigham and Women's Hospital

Ingrid A. Holm, MD, MPH
Associate Professor of Pediatrics, Harvard Medical School
Division of Genetics and Genomics, Boston Children's Hospital

Dear Robert and Ingrid,

I am writing to express my enthusiastic support of your proposal to NIH PAR-19-099 entitled, "*Implementation of Whole Genome Sequencing as Screening in a Diverse Cohort of Healthy Infants*". As a clinical molecular geneticist, I recognize the growing need to generate empirical data on the clinical utility of predispositional genome sequencing in infants and I am thrilled to support this project.

As you know, I served as a co-I during the BabySeq Project. I played an integral role in the creation of the pipeline for gene interpretation and developed criteria for interpretation of over 1500 disease-associated genes (Ceyhan-Birsoy O, et al. *Genetics in Medicine*. 2017). I recognize the truly visionary nature and potential of studying whole genome sequencing (WGS) as screening in a generalizable, diverse population of infants in their first 6 months of life. I am particularly interested in working with you and the outstanding team you have assembled to implement revisable reporting of existing genomic data sets to identify reportable genetic variants based on our evolving understanding of the medical genome.

I look forward to working with you as a consultant on this study. I understand that this will require me to attend one meeting in Boston per project year and to participate in teleconference calls as needed. I understand that this grant will provide an hourly consultant fee for time spent working on this project, totaling 40 hours annually for the first and fourth project years and 20 hours annually for the second and third project years. I wish you success with your application.

Sincerely,

Ozge Ceyhan-Birsoy