Molecular Genetics and Metabolism Reports 38 (2024) 101037

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

ScreenPlus: A comprehensive, multi-disorder newborn screening program

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ARTICLE INFO

Keywords:
Newborn screening
Pilot studies
Expanded conditions
ELSI
Ethics
Research

ABSTRACT

The increasing availability of novel therapies highlights the importance of screening newborns for rare genetic disorders so that they may benefit from early therapy, when it is most likely to be effective. Pilot newborn screening (NBS) studies are a way to gather objective evidence about the feasibility and utility of screening, the accuracy of screening assays, and the incidence of disease. They are also an optimal way to evaluate the complex ethical, legal and social implications (ELSI) that accompany NBS expansion for disorders. ScreenPlus is a consented pilot NBS program that aims to enroll over 100,000 infants across New York City. The initial ScreenPlus panel includes 14 disorders and uses an analyte-based, multi-tiered screening platform in an effort to enhance screening accuracy. Infants who receive an abnormal result are referred to a ScreenPlus provider for confirmatory testing, management, and therapy as needed, along with longitudinal capture of outcome data. Participation in ScreenPlus requires parental consent, which is obtained in active and passive manners. Patient-facing documents are translated into the ten most common languages spoken at our nine pilot hospitals, all of which serve diverse communities. At the time of consent, parents are invited to receive a series of online surveys to capture their opinions about specific ELSI-related topics, such as NBS policy, residual dried blood spot retention, and the types of disorders that should be on NBS panels. ScreenPlus has developed a stakeholder-based, collective funding model that includes federal support in addition to funding from 14 advocacy and industry sponsors, all of which have a particular interest in NBS for at least one of the ScreenPlus disorders. Taken together, ScreenPlus is a model, multi-sponsored pilot NBS program that will provide critical data about NBS for a broad panel of disorders, while gathering key stakeholder opinions to help guide ethically sensitive decision-making about NBS expansion.

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https://doi.org/10.1016/j.ymgmr.2023.101037
Received 5 December 2023; Accepted 8 December 2023

1. Introduction

Since the discovery that phenylketonuria is an easily diagnosed, preventable cause of intellectual disability, newborn screening (NBS) has become a critical component of preventable healthcare and is considered one of the greatest public health successes in the twentieth century [1–4]. The development of multiplex and DNA technologies has dramatically increased the potential of NBS, enabling screening of an increasing quantity and complexity of disorders and prompting questions about the appropriateness of expanded NBS panels. In the United States, disorders can be added to routine NBS panels through state legislation and/or are nominated for consideration on the Recommended Uniform Screening Panel (RUSP). The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC), a committee of physicians, scientists, bioethicists, researchers, and parents, was established in 2003 to make national-level, evidence-based recommendations about which disorders should be included in the RUSP [5]. As of August 2023, 37 core disorders are included on the RUSP [6].

Compiling an evidence base to nominate disorders for the RUSP is often challenging; for instance, many disorders under consideration are rare, phenotypically variable, or have a poorly defined natural history or unclear treatment outcomes. Without sufficient published literature on certain rare diseases, assessing the "magnitude and certainty of net benefit to the population" screened – a requirement for ACHDNC recommendation – is often difficult or impossible [7]. Given that individuals with these potentially life-threatening disorders may benefit from early detection through screening, gathering, evaluating, and disseminating data about these disorders is crucial.

NBS pilot studies can provide an integral platform to collect objective evidence about the feasibility and effectiveness of screening for a condition, which can then be used to inform decision-making processes about whether to include a condition or not in a NBS program. Pilot studies typically involve screening a subset of newborns for a particular condition and can evaluate the accuracy of screening tests, the ability to confirm diagnoses, and the impact of early detection on patient outcomes. In fact, Public Health Law 113–240 Sec 116 of the Newborn Screening Saves Lives Reauthorization Act of 2014 encourages researchers to "conduct pilot studies on disorders recommended by the Advisory Committee to ensure that screenings are ready for nationwide implementation" [8]. Dialogue and debate regarding several recently added RUSP disorders have benefitted from pilot studies, including mucopolysaccharidosis type I (MPS I) [9,10], X-linked adrenoleukodystrophy [11], and spinal muscular atrophy [12,13]. A recent ACHDNC Evidence Report for the addition of MPS I noted that, "the most relevant evidence regarding newborn screening programs comes from population-based programs or evaluations of screening with diagnostic confirmation" [14].

Because of the rarity of most candidate NBS disorders, it is important that pilot programs be conducted in as large a population as feasible to increase the likelihood of detecting affected infants. A recent panel on modernizing the newborn screening system found broad agreement among experts that collaboration is needed between stakeholders across sectors, including government, researchers, laboratories, and patient advocates [15]. Such collaboration can facilitate the sharing of expertise and resources, which can ultimately improve the quality of NBS programs and increase the likelihood of detecting affected infants [16]. However, in practice, there are few NBS pilot programs that have been structured to enable this kind of collaboration.

NBS pilot programs that include parental informed consent are in an optimal position to evaluate the complicated ethical, legal, and social implications (ELSI) associated with screening for an increasingly complex range of disorders, as there is direct contact with an engaged population. These ELSI concerns are considerable, ranging from the impact of uncertainty and false positives on families to whether or not certain types of disorders with varying severities of clinical presentation should be included in NBS panels. The Bioethics and Legal Workgroup for the Newborn Screening Translational Research Network identified key questions regarding the ELSI of NBS and noted the substantial gap that currently persists in availability of robust ELSI data. As such, the Workgroup has encouraged NBS pilot studies to include a rigorous assessment of these important ELSI questions [17].

A previous NBS pilot study conducted by ScreenPlus investigators enrolled and screened over 65,000 infants for five lysosomal storage disorders (LSDs). The study demonstrated that it is not only possible to implement a multi-site, multi-disorder pilot program, but that most parents are amenable to participate and have their child screened [18]. These findings led to the conceptualization of ScreenPlus, a comprehensive, multi-disorder pilot NBS program. ScreenPlus aims to generate critical data about the appropriateness and feasibility of multi-tiered screening for a fluid panel of complex disorders in the diverse population of New York City. By partnering with the New York State Newborn Screening Program, ScreenPlus has the potential to provide valuable insights into the effectiveness of NBS for these disorders that can directly inform population-wide implementation. Infants identified with a disorder on the ScreenPlus panel will be followed by study geneticists to better understand the clinical impacts of early identification. Importantly, ScreenPlus will also integrate ELSI studies, including parent surveys and a qualitative study, to characterize parental opinions towards, and experiences with the NBS system. A novel financial and administrative infrastructure has been developed to ensure the program can be implemented at scale, with the input of advocacy groups and experts in biochemistry, genetics, and NBS ethics. ScreenPlus is guided by Scientific and Community Advisory Boards, who provide expert input into the technical operation of the study, study materials, family support, and community engagement.

In this report, we describe ScreenPlus' approaches for assessing the feasibility and outcomes of screening for multiple disorders, evaluating the logistical and technical constraints of implementing a consented NBS pilot in a diverse population, and capturing parents' informational preferences and values about NBS. The size and scope of ScreenPlus will provide a comprehensive, inclusive, and evidence-based approach to significantly enhance our understanding of the implications of screening for complex disorders, facilitate other large-scale pilot NBS programs by sharing mechanistic insights, and guide population-wide decision-making about NBS.

2. Methods

2.1. Study design

Over a five-year period, ScreenPlus aims to enroll and screen over 100,000 infants born in eight high birth rate, ethnically diverse pilot hospitals in New York for a flexible panel of genetic disorders. Screen positive infants have confirmatory testing and follow up as needed, with capture of long term follow up data. This study also involves an evaluation of the ethical, legal, and social implications (ELSI) of screening newborns for complex disorders, which will be done via online surveys directed towards ScreenPlus parents who opt to participate, and qualitative interviews with families of infants who are identified through ScreenPlus and/or through routine NBS. The study has been approved by a single Institutional Review Board (sIRB) through the Biomedical Research Alliance of New York (BRANY; Protocol #19–10-212) and is registered on clinicaltrials.gov (NCT05368038).

2.2. Financial infrastructure

To implement this program at scale and provide robust, consented pilot NBS data to a range of important stakeholders, a stakeholder-based collective funding model that includes federal (NIH R01HD073292), advocacy and industry sponsors has been developed. This model allows for a diverse range of sponsors to support the program and obtain data of interest in a mutually beneficial and cost-effective manner. ScreenPlus

has engaged 14 advocacy and industry sponsors who are each interested in the feasibility and outcome of screening for one or more ScreenPlus disorders. Sponsor contracts are generally based on time and/or participant accrual in an effort to align with the study's recruitment goals. The implementation of these efforts will be reported in a future manuscript.

2.3. Study recruitment

Eligible newborns are recruited primarily through active, on-site recruitment, which our previous study found as the most effective in engaging parents right after birth [18]. All newborns (0–4 weeks old) born at a pilot hospital are eligible to participate, regardless of sex, gestational age, or health status. Active recruitment involves a face-to-face discussion with parents on the maternity wards in the days after they have given birth. Each pilot hospital supports a full-time study coordinator tasked with recruitment and informed consent.

An explicit goal of this study is to recruit the populations reflective of the diverse communities served by the pilot hospitals. Most study recruiters are bilingual or multilingual, and hospital translation services are available for non-English speaking parents. To ensure our linguistically diverse population has information available in their preferred language, study materials (e.g., brochures, posters, surveys) are available in ten languages (English, Spanish, Bengali, Hindi, simplified Chinese, Russian, Arabic, Urdu, Albanian, and French), reflecting the most prominent languages spoken across our pilot hospitals. Additional languages will be added as needed throughout the study period based on the primary language collected by recruiters. Parents are provided with study brochures, and materials are made available on the hospital floors and in discharge packets. An electronic-based consent (e-Consent) is used to facilitate consent discussions, providing information and resources to aid parental decision-making. Patient-facing study materials were developed with input from our Community Advisory Board (CAB), which consists of parents of children affected by a ScreenPlus disorder and Family Support group leaders. They continue to provide invaluable feedback about the type and amount of information provided and the comprehensiveness of the materials through our annual ScreenPlus CAB meetings. Furthermore, parents provide feedback on the consent process and materials after their decision. This feedback, along with insights the study coordinators gain during their interactions, is used to refine the study materials.

In addition to active, direct in-person consenting, ScreenPlus engages other approaches. In response to the COVID-19 pandemic, which substantially impacted clinical operations and the implementation of clinical research protocols, innovative recruitment and consenting strategies were needed for research teams across specialties to avoid infection risk and minimize disruption of already overburdened clinicians [19,20]. ScreenPlus addressed this by adopting a flexible recruitment approach that allows recruiters to provide materials to families without direct contact (e.g., food trays with a brochure personalized with a short, handwritten introductory note, email/text or MyChart message, QR codes on materials) and/or the option of directly engaging new parents by phone, rather than in-person, while utilizing the same consent timing, script, and materials.

Another recruitment modality utilizes a passive approach where parents who are in the hospital when our recruiters are not present, and parents who would prefer not to interact with additional staff (i.e., study recruiters) have an opportunity to enroll in the study. QR codes on the patient facing materials bring parents to an eligibility form and, when appropriate, to multi-lingual consent forms.

Recruitment strategies are harmonized across the sites, and information on the type of interaction(s) (i.e., in-person, phone, MyChart, passive) and outcome (i.e., enrolled, declined, undecided, unavailable) of each attempt made by the recruiters are systematically collected for each attempt interaction with families. This data collection enables the ScreenPlus team to identify the most effective recruitment approaches, with the dual goals of enhancing the efficiency of our own program and sharing our strategies with other pilot NBS teams to enable them to maximize recruitment and productivity.

2.4. ScreenPlus panel

All consented newborns are screened for a panel of disorders that can be altered as the study progresses, with the following 14 disorders selected for inclusion in the initial panel: Acid Sphingomyelinase Deficiency (ASMD, or Niemann-Pick type A and B), Ceroid Lipofuscinosis type 2 (CLN2), Cerebrotendinous Xanthomatosis (CTX), Fabry Disease, GM1 gangliosidosis, Gaucher Disease, Lysosomal Acid Lipase deficiency (LAL—D), Metachromatic Leukodystrophy (MLD), Mucopolysaccharidosis (MPS) II (Hunter Syndrome), MPS IIIb (Sanfilippo type 3b), MPS IVa (Morquio syndrome), MPS VI (Maroteaux-Lamy syndrome), MPS VII (Sly Syndrome), Niemann-Pick Disease Type C (NPC). These disorders were selected based on having met the criteria: 1) a dried blood spot (DBS) assay that can be multiplexed and that is high-throughput, reasonably priced, and has had positive baseline validation studies; 2) significant morbidity or mortality if untreated; 3) a pediatric phenotype; and 4) an FDA-approved treatment(s) or treatment(s) currently in a clinical trial. The assays for the disorders in the initial panel were developed, multiplexed, and validated by the ScreenPlus laboratory teams (MG, JO, MM, HM, DO), with the study PI (MW) ensuring that the clinical criteria for each disorder was met. The ScreenPlus panel is flexible, so that if a disorder is added to the RUSP and/or the NYS routine NBS panel, it will be removed from the panel. As such, we anticipate the removal of MPS II from the panel, as it has been added to the RUSP and will soon be added to New York's routine panel. Similarly, if other disorders fulfill criteria, they will be assessed for inclusion by the same teams to ensure consistent interpretation of the criteria.

2.5. Screening/assay procedures

ScreenPlus uses an analyte-based, multi-tiered screening platform to evaluate and enhance screening accuracy (**Table 1**). All tiers of testing are performed using the same DBS obtained for routine NBS and are integrated into operating procedures at NYS Newborn Screening Laboratory. First-tier screening is performed using a megaplex liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay [21]. First-tier screening for ASMD, CLN2, Fabry, Gaucher, GM1, LAL—D, MPS II, MPS IIIb, MPS IVa, MPS VI and VII is enzyme-based, whereas first-tier screening for CTX, MLD, and NPC is a biomarker-based assay (**Table 1**). Infants who have an abnormal screen for a disorder on the first-tier assay have their DBS sent for second-tier (biomarker or enzyme, when applicable) and third-tier (targeted gene sequencing) testing which is done in parallel until evidence of second-tier accuracy is shown.

Table 1
ScreenPlus multi-tier testing.

Disorder	First Tier	Second Tier	Third Tier
ASMD	ASM activity	Lyso SPM	*SMPD1* sequencing
CLN2	TPP1 activity	–	*TPP1* sequencing
CTX	Bile terol-glucuronide	7alpha12alphaC4	*CYP27A1* sequencing
Fabry	GLA activity	Lyso-Gb3	*GLA* sequencing
Gaucher	ABG activity	Lyso-Gb1	*ABG* sequencing
GM1	β-galactosidase activity	A2G2, dp5 [22]	*GLB1* sequencing
LAL	LAL activity	–	*LAL* sequencing
MLD	C16:0 sulfatide	ARSA activity	*MLD* sequencing
MPS II	I2S activity	GAGs	*IDS* sequencing
MPS IIIB	NAGLU activity	GAGs	*NAGLU* sequencing
MPS IVA	GALNS activity	GAGs	*GALNS* sequencing
MPS VI	Arylsulfatase B activity	GAGs	*ARSB* sequencing
MPS VII	β-glucuronidase activity	GAG	*GUSB* sequencing
NPC	Bile Acid B [23]	–	*NPC1, NPC2* sequencing

Second-tier testing is performed in lab(s) of ScreenPlus collaborators who are experts in the specific NBS assay and third-tier testing is conducted at the NYS Newborn Screening Laboratory.

2.6. Referrals, diagnostic evaluations, and treatment

In general, enzyme activities that fall below 20% of the daily mean activity (DMA) are retested in duplicate; this cut-off is based on data from the previously discussed LSD pilot screen in New York [24]. Samples for which the average of the three replicates falls below 15% of the DMA are sent onwards for second-tier biochemical analysis and third-tier DNA sequencing will be performed.

Infants who meet pre-specified criteria (ex. abnormal first- and second-tier results and at least one pathogenic, likely pathogenic, or variant of uncertain significance in the relevant disease gene) are then referred for confirmatory testing. All infants referred for confirmatory testing are referred to a ScreenPlus site medical geneticist, who conducts a clinical examination and disease-specific confirmatory testing, such as leukocyte enzyme activity for several of the LSDs. Definitions of true positive, uncertain, and false positive cases have been created for each disorder based on biochemical, sequencing, and clinical results.

All infants with confirmed cases of a ScreenPlus disorder are monitored carefully by their physician, who will typically be the ScreenPlus site co-investigator/medical geneticist. Treatment and clinical trial decisions are made at the discretion of that physician, with disease-specific experts available for consultation as needed. These medical decisions are impartial to whether a treatment or clinical trial is sponsored by a ScreenPlus funder.

2.7. Ethical, legal, and social implications (ELSI)

Parent engagement is at the core of the ScreenPlus program, and the study evaluates parent perspectives and experiences with NBS through integrated, mixed-methods ELSI sub-studies. All parents are invited to complete a brief feedback survey about the consenting process, and parents who choose not to participate are offered decliner surveys to provide insight on the full spectrum of opinions around decision-making. Additionally, parents who opt-in to participate in ELSI surveys during the consent process are sent a flexible, adaptive series of short (approximately 10–15 min) questionnaires related to expanded NBS, NBS policies, DBS retention and use, whole genome sequencing, and other key topics related to the future of NBS. Surveys continue to be added to the series to address emerging issues in the field. All surveys capture demographic data, including self-reported ancestry, education, economic status, and include optional questions about religious and political leanings. This self-reported data will also be used to assess if our recruitment and survey data represents the diverse demographics in our pilot hospital neighborhoods.

To explore the ways in which NBS impacts parents who receive positive or uncertain results, and to learn how the NBS community can better support these parents, a qualitative sub-study will be conducted. Parents of at least one child between six months and 2 years of age who receive a positive or uncertain screening result for a ScreenPlus disorder or for other disorders with complex and variable clinical presentations (e.g., Pompe disease, MPS I, X-linked adrenoleukodystrophy, and Krabbe disease) and who live in the United States will be eligible to participate. The study consists of an in-depth, semi-structured interview that will cover the parent's NBS narrative and how NBS has changed their family's life, including their financial circumstances, mental and physical health, and overall family bonding. Interviews will also explore the impact of NBS on future reproductive decision-making. These interviews will explicitly explore the concept of uncertainty and how families cope with this uncertainty in their daily lives. While our recent study found that parents of children with rare diseases diagnosed through NBS have lower odds of experiencing stress or depression [25], the myriad of ways in which NBS changes lives, and the support systems families need, have yet to be described.

3. Anticipated impact

There are several overall objectives of the project. First, we will define the analytic and clinical validity of multi-tiered screening assays for the ScreenPlus disorders. This includes correlations between screening results during first-, second-, and third-tier analyses, the positive predictive value (PPV) of screening assays, along with rates of false positives and false negatives for candidate disorders. Second, we will determine disease incidence in an ethnically diverse population. As this is a consented study, there may be limitations in the populations reflected in the study. However, the study is designed to be accessible to the diverse populations served by the hospital sites and we anticipate that our recruitment and engagement strategies will result in a diverse sample of infants screened. Third, we will assess the impact of early diagnosis and treatment on health outcomes, using longitudinally collected clinical, biomarker, radiographic, and biochemical data. Additionally, we will evaluate the overall effectiveness of our recruitment and consent processes, which can be used to inform future newborn screening and broader clinical research, as well as consent processes for routine NBS. Furthermore, parent opinions and perspectives about the NBS system, the ScreenPlus program, and the future of NBS will provide information on parental values and the potential benefits and harms of such a program. Finally, outcomes related to the implementation and infrastructure of ScreenPlus will be key to this work. Given the rarity of many candidate disorders for NBS, pilot studies must be implemented at scale to capture disorders in the population. Developing a study that can accommodate a cohort of over one hundred thousand newborns requires a level of support that no individual sponsor can provide alone. We have worked to create a cost-sharing financial infrastructure to enable this large clinical research program to operate at scale across institutions and sponsors. Recording the challenges, advantages, and overall process of building the ScreenPlus infrastructure using an implementation science framework will help provide guidance to researchers for future NBS pilot studies.

4. Conclusions

Rapid advancement of NBS technology demands rigorous, objective evidence of the appropriateness of candidate disorders for NBS. The ScreenPlus program will provide important data about the implementation of NBS for a flexible panel of rare disorders. In screening over 100,000 infants, surveying tens of thousands of parents, interviewing parents of children with positive or uncertain results, and following children clinically who receive a confirmatory diagnosis, we will gain a nuanced understanding of the logistical challenges of screening for these disorders, the implementation challenges with building a study of this magnitude, and parental perspectives towards NBS. We are rigorously assessing the factors that increase parental hesitancy towards NBS, the information that parents want – and do not want – from the NBS system, and how communication of results can be improved. We will also collect NBS narratives from parents of children who have the unique experience of receiving positive or uncertain results, which may provide important information about the potential harms of NBS.

There are several limitations in the design of the ScreenPlus study that should be discussed. First, pilot hospitals were selected with the aim of recruiting from high birth rate systems that serve linguistically and ethnically diverse communities of New York; however, most hospitals are NBS referral centers within the New York Metropolitan Area, which limits the geographic diversity of the population. An additional limitation is that our surveys are mainly conducted with parents who consent to participate and while parents who have declined to participate in ScreenPlus pilot screening are eligible to complete opinion surveys, it is anticipated that only a very small proportion of dissenting parents will choose to do so. This may limit generalizability to all parents as well as

introduce a potential for non-response bias in these surveys, in which participants who decline to participate are systematically different from those who complete the surveys, as the survey sample only includes those motivated to complete it [26].

Ultimately, NBS is a complex system that includes blood spot testing, storage and research, parent engagement and education, communication of results and follow-up, and policy-level processes for expansion. The ScreenPlus program will comprehensively address how the NBS system can expand ethically and appropriately, considering the values and preferences of a range of stakeholders. We anticipate that ScreenPlus will provide critical information to policymakers, rare disease advocates, and researchers that will continue to shape and strengthen the NBS system as technology continues to advance.

Funding

Research reported in this publication was supported by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under Award Number R01HD073292. This work is support by grants from Abeona Therapeutics, Alexion Pharmaceuticals, the Michael, Marcia and Christa Parseghian Endowment for Excellence in Niemann Pick Type C Research doing business as the Ara Parseghian Medical Research Fund at Notre Dame, BioMarin Pharmaceutical, Cure Sanfilippo Foundation, Dana's Angels Research Trust, Firefly Fund, Genzyme Corporation, Noah's Hope - Hope4Bridget Foundation, Orchard Therapeutics, Passage Bio, Sio Gene Therapies, Takeda Pharmaceuticals, Travere Therapeutics, and Ultragenyx Pharmaceutical. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or above-named sponsors.

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Declaration of Competing Interest

MW has received consulting and speaker fees from Sanofi Genzyme, Takeda, and Orchard Therapeutics.

Data availability

No data was used for the research described in the article.

Acknowledgments

We are grateful to our Community Advisory Board (Amy Blum, National Gaucher Foundation; Pam Crowley-Andrews, Firefly Fund; Justin Hopkin, National Niemann-Pick Disease Foundation; Jack Johnson, Fabry Support and Information Group; Maria Kefalas, Cure MLD; Terri Klein, National MPS Society; Amy Fenton Parker, Batten Disease Support and Research Initiative; Dean Suhr, MLD Foundation; Sean Kassen and Cindy Parseghian, Ara Parseghian Medical Research Foundation; Cara O'Neill, Cure Sanfilippo Foundation; Christine Waggoner, Cure GM1), Scientific Advisory Board (Drs. Robert Desnick, Michael Gelb, Aaron Goldenberg, Dieter Matern, Joseph Muenzer, Forbes D. Porter, Michael Watson and Joseph Orsini) Disease Expert Panels (Drs. Laura Adang, Elizabeth Berry-Kravis, Jaap-Jan Boelens, Margo Breilyn, Andrea De Barber, Maria Escolar, Tzippi Falik-Zaccai, Can Ficioglou, Roberto Guigliani, Jeanine Jarnes, Austin Larson, Heather Lau, Paul Levy, Eric Mallack, Marc Patterson, Forbes Denny Porter, Debra Regier, Robert Steiner, Chet Whitley), and the Office of Biotechnology and Business Development, Department of Finance, and Research Administration for the Department of Pediatrics at the Albert Einstein College of Medicine for their generous donations of time and expertise.

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