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Project Baby Bear: Rapid precision care incorporating rWGS in 5 California children's hospitals demonstrates improved clinical outcomes and reduced costs of care

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Summary

Genetic disorders are a leading contributor to mortality in neonatal and pediatric intensive care units (ICUs). Rapid whole-genome sequencing (rWGS)-based rapid precision medicine (RPM) is an intervention that has demonstrated improved clinical outcomes and reduced costs of care. However, the feasibility of broad clinical deployment has not been established. The objective of this study was to implement RPM based on rWGS and evaluate the clinical and economic impact of this implementation as a first line diagnostic test in the California Medicaid (Medi-Cal) program. Project Baby Bear was a payor funded, prospective, real-world quality improvement project in the regional ICUs of five tertiary care children's hospitals. Participation was limited to acutely ill Medi-Cal beneficiaries who were admitted November 2018 to May 2020, were <1 year old and within one week of hospitalization, or had just developed an abnormal response to therapy. The whole cohort received RPM. There were two prespecified primary outcomes—changes in medical care reported by physicians and changes in the cost of care. The majority of infants were from underserved populations. Of 184 infants enrolled, 74 (40%) received a diagnosis by rWGS that explained their admission in a median time of 3 days. In 58 (32%) affected individuals, rWGS led to changes in medical care. Testing and precision medicine cost $1.7 million and led to $2.2–2.9 million cost savings. rWGS-based RPM had clinical utility and reduced net health care expenditures for infants in regional ICUs. rWGS should be considered early in ICU admission when the underlying etiology is unclear.

Introduction

Genetic disorders are a leading contributor to morbidity and mortality in the neonatal and pediatric intensive care unit (ICU) in the United States. Approximately 7% to 10% of the 4 million infants born in the U.S. each year are admitted to a neonatal intensive care unit (NICU) for the diagnosis and treatment of an acute illness.[1–4] A recent review of billing data suggests that approximately 1% of all NICU admissions have one of 116 billing codes suggestive of a genetic disease.[5] In other studies, approximately 15% of babies admitted to high acuity units appear to have a genetic disorder.[6] At one children's hospital, genetic disorders and malformations were the most common cause of mortality, accounting for more than one-third of all deaths.[7]

Our previous work, and that of many other groups, has demonstrated that early institution of genome-wide sequencing is associated with both a shorter time to diagnosis and an increased diagnostic yield when compared with standard-of-care testing that includes gene panels and chromosome microarrays.[8–16]

Recently, we and others have shown that, when common non-genetic reasons for admission are excluded, rapid whole-genome sequencing (rWGS) provides a diagnosis for 21% to 57% of children in intensive care settings, including those without a high pre-test probability of a genetic disorder.[6] The benefit of rWGS has been associated with high satisfaction and perceived utility among physicians.[17] Among parents, rWGS has extremely low levels of perceived harm or decisional regret and very high perceived utility, including when testing does not yield a diagnosis.[18]

In precision medicine, clinicians incorporate information about an individual's genetic makeup and other factors to help determine specific treatment and prevention strategies.[19] rWGS, and the system of care that surrounds it, is sometimes referred to as rapid precision medicine (RPM).

At the time of the project initiation, studies at single-site academic centers had demonstrated significant improvement in clinical outcomes as the result of early genome-wide

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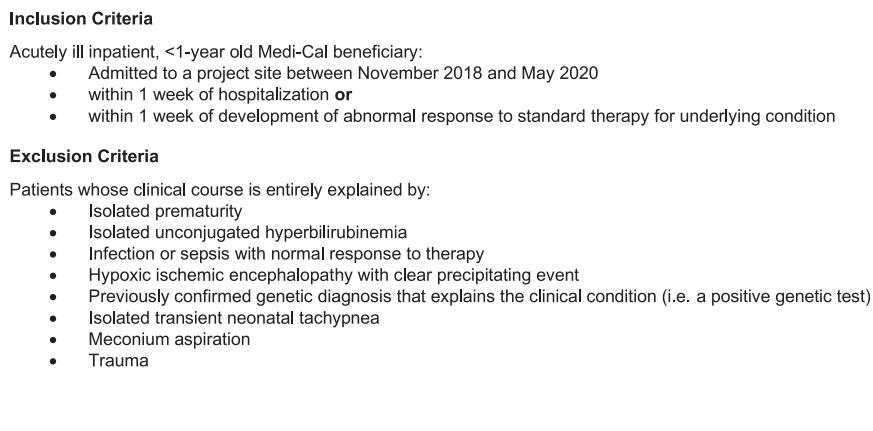

Figure 1. Inclusion and exclusion criteria
Criteria used to identify acutely ill infants without a clear non-genetic etiology.

sequencing.[11,20] Moreover, although currently relatively expensive, prospective, single-site studies have reported that early genome-wide sequencing yields substantial reductions in the cost of care when compared to testing with chromosome microarray, the current standard of care.[4,21,22]

Medicaid and commercial insurers in Wisconsin began limited coverage of outpatient WGS in 2011.[23] More recently, a commercial insurer has issued specific coverage criteria for rWGS in critically ill children on the basis of published studies.[24] Nevertheless, despite evidence that sequencing improves clinical outcomes, reduces net costs of care, and leads to high provider and parental satisfaction, routine implementation in ICUs and coverage by payors has remained a challenge.

In 2018, the California state legislature appropriated funds for Project Baby Bear (PBB) and commissioned this study to determine whether the economic and clinical benefits of genome-wide sequencing could be achieved more widely, outside of single-site research settings, and whether its accompanying system of care was scalable to the population covered by the state's Medicaid program, known as Medi-Cal.

The objective of this project was to implement and identify, in the real-world setting, the clinical and economic effects of deploying rWGS-informed RPM for critically ill children who receive care in multiple ICU settings across California and are insured by the Medi-Cal program.

Subjects and methods

The institutional review boards at all sites reviewed the project and determined it to be a quality improvement project. Parents or legal guardians provided consent for rWGS. Data sharing was performed in adherence with state and federal regulations governing the sharing of protected health information.

Project design and participants

PBB was a multi-site quality improvement project of the deployment of rWGS in intensive care settings. Hospitals were selected that were geographically spread throughout the state with patients from rural and urban populations as well as a substantial number of children covered by Medi-Cal (see Figure S1). Five tertiary care children's hospitals that had California Children's Services-accredited regional neonatal and pediatric ICUs were selected: Valley Children's Hospital (VCH); Children's Hospital of Orange County (CHOC); University of California–San Francisco Benioff Children's Hospital Oakland (UCSF BCHO); University of California Davis Children's Hospital (UCD); and Rady Children's Hospital–San Diego (RCHSD). Rady Children's Institute for Genomic Medicine (RCIGM) served as the project's coordinating center.

Participation was limited to any Medi-Cal beneficiary admitted between November 2018 and May 2020 who was acutely ill, without a clear non-genetic etiology, and less than 1 year old, and who had been hospitalized 1 week or less or who had developed an abnormal response to standard therapy for an underlying condition within the preceding week (Figure 1). Sex was determined on the basis of clinical examination; race and ethnicity were derived from parental report.

Genome sequencing and interpretation

Clinical rapid whole-genome sequencing (rWGS) or, in cases deemed too clinically unstable to wait, ultra-rapid trio WGS (urWGS)[6,14] with targeted phenotype-driven analysis was performed on all patients. The methods have been previously published in detail.[6,14] In brief, clinical features representative of each child's illness were identified by the ordering provider. Polymerase chain reaction free 2 × 101 nt rWGS was performed to at least 40-fold coverage with instruments developed by Illumina (San Diego, California). Clinical molecular geneticists interpreted variants according to standard clinical guidelines (Table S7).[25] Genomic sequence interpretation was generally performed as singleton probands with single-site testing of available parental DNA. However, because of the reduced time to diagnosis, urWGS tests were analyzed as familial trios where possible.[6]

All reported variants were confirmed by Sanger sequencing, multiplex-ligation-dependent probe amplification, or chromosomal microarray, as appropriate. Secondary findings were not systematically sought or reported, but medically actionable incidental findings were reported if families consented to receiving this information. Using the consensus recommendations of the American College of Medical Genetics and Genomics, a diagnosis was considered to be made if pathogenic or likely pathogenic variants were identified in a genomic locus that the bedside providers agreed led to the disease causing the critical illness.[25]

Outcome measures

There were two prespecified primary outcomes—changes in medical care because of rWGS results and changes in the cost of care because of rWGS at 4 months, 12 months, and 18 years after return of results.

Changes in medical care for each patient were reported in structured self-administered questionnaires completed by the physician who ordered rWGS. Questionnaire items focused on

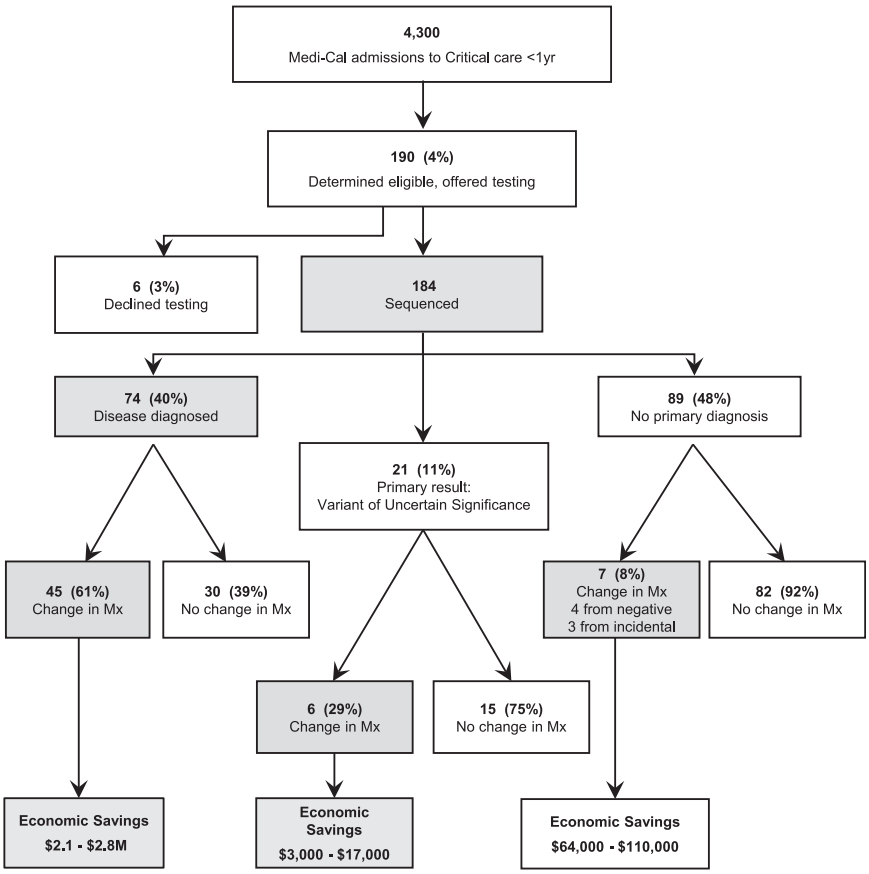

Figure 2. Project enrollment and outcomes
Enrollment and testing outcomes for Project Baby Bear.

changes in length of stay and surgical, medical, and dietary changes (see supplemental information). All changes in medical care reported in questionnaires were reviewed with the primary treatment group at monthly conferences. Each infant was categorized into one of three groups: no change in medical care (group 1); changes in medical care that did not alter long-term outcomes, length of stay, or major procedures performed (group 2); or changes in medical care that altered long-term outcomes, length of stay, and/or major procedures performed (group 3).

We knew from experience that the babies receiving rWGS diagnoses would suffer from genetic diseases that are rare, and this would make it difficult to identify matched controls who were diagnosed without rWGS. Moreover, there is insufficient information in the medical literature to establish routine medical management practices for many of these rare diseases.[6,8,11] Consequently, we used a model-based expert elicitation process to estimate how a clinician would manage each baby's rare disease in the absence of rapid genome sequencing.[26]

As described in previous work, counterfactual care pathways were developed to describe what would have happened to babies in group 3 in the absence of rWGS.[9,11] Where possible, this comparison pathway was determined by identification of similar historical cases with the same disease or through a literature review followed by consensus expert opinion from the treating site physicians. Two physicians with expertise in modeling counterfactual pathways (L.F. and D.D.) reviewed any estimated changes in length of stay, major procedures performed, or improvements in outcome in the babies receiving rWGS. The description of cases and counterfactual pathways are outlined further in the supplemental notes. Where there was uncertainty about what value to assign to changes in length of stay or survival, physicians at the treating sites estimated a range. In situations where the RCIGM physicians disagreed with the treating team's estimates, the RCIGM team assigned the value that minimized the estimated cost savings. Thus, all cost savings analysis was based on conservative assumptions. We estimated costs of avoided procedures, avoided tests, and avoided hospital days from concurrent billing data. This modeling and methods for estimating cost savings are further detailed in the supplemental information.

Changes in the cost of care dependent on turnaround time of rWGS were determined in a post hoc analysis. To evaluate the effect of slower versus faster testing on utilization and costs, the RCIGM team estimated how longer turnaround times (7 days or 14 days versus 3 days) would have increased inpatient stay for each of the patients who received significant benefit from sequencing. More detailed analytic methods are described in the supplemental information.

Results

Participant demographics and diagnostic yield of testing

The project enrolled 184 babies. The provision of rWGS and support for RPM cost $1.7 million. Enrolled babies across all sites represented an average of 4% of the Medi-Cal admissions at these sites (Figure 2). The majority of patients were from historically underrepresented groups; 55% of children were identified by their parents as "Hispanic" and only 15% as both "white" and "non-Hispanic" (Table 1).

rWGS proved to be a valuable tool in clinical decision-making. Of the 184 babies sequenced in this project, rare genetic diseases that explained the infant's admission were diagnosed in 74 babies (40%), genetic variants of uncertain significance (VUSs) were identified in 21 babies (11%), and no diagnosis was made in 89 babies (48%) (Figure 2). Most diagnoses were of very rare disorders that would not be expected to have been seen by the child's providers previously in their careers. Although disease estimates are limited by the availability of molecular testing, 37 of the 73 diagnosed genetic diseases thought by the providers to explain the child's admission to the

Table 1. Demographic characteristics of the 184 PBB probands

Race	Total (184)	Hispanic (101, 55%)	Non-Hispanic[a] (83, 45%)
African American	22 (12%)	2	20
Asian	10 (5%)	0	10
White	87 (47%)	59	28
Native Hawaiian or other Pacific Islander	1 (1%)	0	1
Other	54 (29%)	40	14
Unknown	9 (5%)	0	9
Refused	1 (1%)	0	1
Sex			
Male	107 (58%)		
Female	71 (39%)		
Unknown/undetermined/not available	6 (3%)		

[a]Includes one who identified as "East Indian," four who identified as "Middle Eastern," nine who refused to select, and 11 who marked "other."

ICU have a reported incidence of less than one per million births. Sixty-eight of these 74 primary genetic diseases were diagnosed in individual patients in the project, and the other six conditions were diagnosed in two patients each (Table S5).

Physicians initially reported that rWGS-informed RPM led to changes in medical care in 61 of the 184 infants tested (33%). However, with further review, the anticipated changes did not occur in three infants and so these infants were classified as having no change in medical care. Consequently, 58 of 184 babies (32%) sequenced underwent at least one change in medical care (Figure 2, Table 2). No significant differences were seen in diagnostic yield or change in medical care across racial, ethnic, or sex categories.

Changes in medical care

Precision medicine informed by rWGS of critically ill babies with unclear etiology of symptoms resulted in at least one change in the medical care of 58 babies (32%). Specifically, 24 children had changes in surgeries, 23 had changes in medication, nine had dietary changes, and 14 had other changes in care. No children had changes in proposed organ or tissue transplantation (Table 2).

Except for one baby with malignant hyperthermia, changes in longer-term outcomes were deemed too speculative to be confident about cost savings or improved quality of life beyond the initial episode of care. Therefore, we modeled changes in cost during the initial episode of care and not at 4 months, 12 months, and 18 years following return of the rWGS result.

Effects on health care costs

In 27 of the 58 children for whom medical care changed as a result of rWGS, there was no change in length of stay or in major procedures performed and, thus, no substantial effect on health care costs. In the remaining 31 children whose medical care changed substantially because of rWGS, a detailed analysis of the effects of rWGS on hospital costs was performed (See Table S3 and supplemental notes for more details). In several children, diagnosis led to interventions that increased the costs of care. For example, in site one, case 17, the child was identified to be at risk for thyroid disease and laboratory testing for this was ordered. These changes in the costs of care were included in the modeling. In all such children, these costs were more than offset by avoidance of other costly procedures or reduction in length of hospitalization. In the 30 babies with a change in length of stay, between 457 and 592 days were avoided because of rWGS results. There were no babies for whom we estimated an increase in length of stay or for whom a major procedure was performed that would not have been performed in the absence of rWGS.

In several cases, a non-diagnostic genome led to cost savings. For example, in site one, case 2, the child had intractable seizures that required significant respiratory support and failed to respond to typical anti-seizure medicines. rWGS was non-diagnostic and review of the raw data established high-confidence coverage of all the genetic etiologies of neonatal seizures that have specific therapies beyond standard treatment. The ability to dramatically reduce the post-test likelihood of a treatable seizure disorder provided the parents (and providers) with reassurance that they were not missing a prognosis altering intervention. This allowed the parents to make the informed decision to move their baby to comfort care.

Estimated cumulative savings due to rWGS for the 31 children were between a $2.2 million and $2.9 million reduction in hospital costs and professional fees. Averaged over the 184 babies in PBB, savings were approximately $12,041 to $15,786 per child sequenced, more than offsetting the $9,492 cost of rWGS and precision medicine per child (Table 3).

Between 89% and 93% of estimated savings derived from reduced length of stay and, to a substantially lesser degree, avoided major procedures, such as tracheostomies

Table 2. Number of infants with a change in care due to an rWGS result

Intervention type	n
Any change	58
Surgical (n = 24)	
Surgical procedure added	5
Surgical procedure removed	16
Surgical procedure changed	5
Medication (n =23)	
Medication added	16
Medication stopped	8
Medication changed	0
Dietary (n = 9)	
Diet changed	9
Length of hospital course (n = 30)	
Hospital days added	0
Hospital days avoided	30

Please note that children may have experienced more than one change, for example, a medicine added and a medicine stopped.

and gastrostomy tube insertions (see Table S3 for more details). Approximately 7% to 11% of estimated savings derived from avoided diagnostic tests, such as chromosomal microarrays (see Tables S2 and S3 for more details of avoided testing and consequent economic impact).

As reported above, median turnaround time for provisional rWGS results was 3 days. Post hoc sensitivity analysis of turnaround times from an average of 3 days to 7 or 14 days showed that fewer inpatient days were avoided and proportionately less cost savings were realized with an increased time to result (Table 3). More detailed analysis can be seen in Table S4.

Discussion

With the exception of one non-randomized retrospective study looking at a longer turnaround time exome test,[27] studies performed in the carefully controlled environment of clinical research have reproducibly found genome-wide sequencing to be effective for diagnosis and management of undiagnosed infants in ICUs and to result in reductions in health care costs.[6,8,11,14–16,20–22,28–34] PBB demonstrates the feasibility of deploying rWGS-informed RPM into routine care across multiple sites to help vulnerable patients in a cost-effective manner while achieving diagnosis and change-in-medical-care rates comparable to previously published studies. Test results influenced the decisions physicians and families made about the care of babies with rare genetic diseases. These decisions, in turn, substantially reduced the cost of caring for babies receiving rWGS compared to babies with similar conditions who did not have access to rWGS. These savings were dependent on the speedy return of test results and more than compensated for the cost of performing rWGS.

An earlier study using similar methods in a cohort of 42 babies estimated cost reductions of approximately $800,000 in hospital and professional fees, or approximately $19,000 per baby.[11] These savings were slightly larger than the estimated gross savings of $12,041 to $15,786 per child sequenced in the current project. Given that the earlier study and the current project were conducted on relatively small cohorts of babies and that there was substantial variation across babies in the effects of rWGS on resource use and costs, the differences between the two studies in estimated cost savings per baby sequenced are relatively small. These results suggest that such cost savings are scalable across multiple institutions.

Although making a genetic diagnosis may provide immense lifelong benefits, its greatest utility occurs when made early in the course of care when more definitive health care decisions have yet to be made and less irreversible damage has occurred. This requires early identification of at-risk children, rapid testing, and prompt intervention.[6]

Most health care cost savings were due to reductions in the length of stay. Conclusive diagnosis allowed for more confident prognosis. In some instances, this empowered parents to shift to comfort care or to definitively move infants to life-prolonging measures, such as a home ventilator and tracheostomy.

This project used inclusion criteria similar to our previous NSIGHT2 study;[6] however, a substantially smaller proportion of children covered by Medi-Cal at PBB sites received rWGS than we expected at the outset. In NSIGHT2, 43% of babies admitted to the one study ICU were deemed eligible for testing. In the current study, enrollment of Medi-Cal babies ranged from 3% to 13% of admitted babies. This, in part, reflects a reduction in enrollment at the midpoint of the project because of uncertainty at sites about exceeding the prespecified 100-genome mark and awareness that there was a limited number of tests available. Discussions with colleagues and a review of cases suggested that this perceived budget limitation may have pushed providers toward selecting cases with a potentially higher diagnostic yield. Others perceived a delay in changing their practice. Specific physicians identified a "learning curve" as they transitioned from genomic testing on those with a high suspicion of genetic disorder to proactively testing all children without a clear indication for admission. Interestingly, there is no difference in the change in management rate between this study, which had a higher diagnostic yield, and NSIGHT2 (see Table S6), suggesting that rWGS has clinical utility in a larger proportion of ICU infants than tested herein.

In previous research studies, over half of all eligible families declined enrollment.[6,35] By comparison, following explanation of the test, only six families were known to decline clinical consent for genomic sequencing in this project. This observation suggests that a substantial barrier to consent for genome sequencing in previous studies was most likely

Table 3. Savings of rWGS and hypothetical savings with turnaround times extended to 7 and 14 days

	3-day turnaround[a]		7-day turnaround		14-day turnaround	
	Low[b]	High[b]	Low	High	Low	High
Cost savings for system	$2.2 m	$2.9 m	$1.7 m	$2.4 m	$1.1 m	$1.7 m
Cost savings per child	$12,041	$15,786	$9,517	$13,250	$6,216	$9,132

[a]Actual rWGS turnaround time in this study.
[b]Low and high calculations reflect the lower and upper estimates of changes in care.

more related to resistance to research enrollment and broad public data sharing than concerns about genomic testing.

This project was further limited by the failure to systematically collect physician- and parent-reported measures of harm and benefit, although the absence of reported harms is encouraging. The lack of systematic data collection about perceived harm may mean that harms are underreported; this concern is somewhat allayed by our group's prior research.[17,18]

Further, the methods to estimate cost savings have intrinsic limitations. Specifically, physicians in the project may have an unconscious bias to inflate length of stay or costs in the absence of rWGS. We attempted to mitigate this by using a second tier of experts who could modify length-of-stay estimates or cost savings they perceived as exaggerated. Similarly, we could not accurately project or measure long-term benefits for most children or their families. Our deliberately conservative approach may lead to a significant underestimation of the real benefits accrued.

Our choice to use hospital costs, rather than third party payments, to measure savings carries significant benefits in generalizability and scaling across health care delivery systems. However, it is limited by the methods that are used to calculate costs; it does not, for example, distinguish between fixed costs (e.g., the building) and marginal costs (e.g., test reagents or staffing). Further, the benefits of cost savings are not equally realized between health care institutions and payors. However, the exact distribution of these savings is dependent on the reimbursement model.

Finally, the speed with which families move to make end-of-life decisions based on rWGS results and the degree of prognostic certainty is not uniform and may not be consistent across cultures. This may limit generalization of such findings beyond the U.S. health care context.

In conclusion, the five-site quality improvement project known as Project Baby Bear developed a real-world system for the rapid delivery of whole-genome sequencing that improved outcomes and decreased costs of care. This project has demonstrated that hospitals and payors with similar systems of rapid precision medicine can deploy rWGS for critically ill children in a cost-effective manner.

Data and code availability

Case report forms, details of all genetic disease diagnoses, and detailed case level analysis of economic outcomes is provided in the supplemental information. All reported genomic variants have been submitted to ClinVar (ClinVar: 506081) (https://www.ncbi.nlm.nih.gov/clinvar/submitters/506081/). Genomic sequencing was performed clinically and at the request of the sponsor; permission was not sought for wider data sharing. Therefore, raw genomic data will not be made publicly available.

Supplemental information

Supplemental information can be found online at https://doi.org/10.1016/j.ajhg.2021.05.008.

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Declaration of interests

D.D. reports previous consulting fees from Audentes, Biomarin, Ichorion, and Complete Genomics. D.D. serves on a scientific advisory board for Taysha Gene Therapies. D.D. is an inventor on U.S. patent 8718950B2 assigned to The HudsonAlpha Institute for Biotechnology. The remaining authors declare no competing interests.

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