Advanced Genomics for Critically Ill Children

Final Report

Period covering August 1, 2019 – June 30, 2020

Variety Children's Hospital D/B/A Nicklaus Children's Health System

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EXECUTIVE SUMMARY

Nicklaus Children's Hospital is one of the nation's first hospitals offering precision and personalized medicine to support children's medical care, health and wellness. Over the course of this demonstration pilot ("Project Baby Manatee"), rapid whole genome sequencing (rWGS) has shown great potential as the standard of care for testing of critically ill infants and children in intensive care units (NICU, PICU, CICU) with illnesses of unknown etiology. This expensive test typically takes several weeks to return the results, but at Nicklaus Children's Hospital we are able to offer rWGS with a turnaround time of a few days, thanks to a collaboration with Rady Children's Institute for Genomic Medicine. While rWGS is still moving from an investigational tool to a standard of care, it has proven to be of great value and potentially lifesaving by providing genetic diagnoses. This is particularly true with ultra-rare genetic disorders in infants where symptoms may not align with documented cases and single gene or gene panel diagnostic tests may not exist. Compared to traditional genetic tests, where diagnosis may be delayed or even missed, rWGS has a high diagnostic yield (40%-70%).

Over a period of 11 months, Project Baby Manatee:

- Completed rWGS on 50 children and families
- Provided diagnoses for 20 children and families (40%)
- Led to change in care for 19 patients (38%), either through finding appropriate treatment or through avoiding unnecessary, invasive, or high-risk procedures
- Diagnosed 23 rare genetic conditions
- Achieved a 2.5-day turnaround time for provisional results for ultra-rapid cases and a 4-day turnaround for rapid cases
- Reduced healthcare costs and downstream spending primarily by empowering doctors to eliminate unnecessary procedures and discharge children sooner
- Offered referrals for mental health counseling to 18 parents experiencing elevated levels of depression
- Saved $3,764,250 by using rWGS instead of standard of care, yielding a $2,884,250 return on investment

Our Health Outcomes research team, including a licensed mental health counselor, interviewed 47 caregivers and administered standard psychological assessments to them at both the time of enrollment and the return of results. At both time points, between 28-43% of caregivers were experiencing elevated levels of depression and/or anxiety. Interviewers provided referrals to the 18 participants who scored above the clinical cutoff for depression. In interviews, most caregivers expressed gratitude for this attention given to their mental health. While most also wished for a diagnosis and clear treatment indications from rWGS, they also had appropriate expectations and understanding of the process. Even those who did not obtain a diagnosis were satisfied with the testing process and found the results useful, recommending it strongly for other families in similar situations. Clear communication by culturally and linguistically competent study coordinators and other research and clinical personnel were important to the overall positive clinical experience of rWGS at Nicklaus Children's Hospital.

The introduction of genome sequencing in some of the most vulnerable of children had a profound impact on three key dimensions of healthcare (Figure 1):

1. Beneficial changes in clinical management by providing timely diagnostic and prognostic information.
2. Improved healthcare experience for families by providing mental health support for parents, reducing uncertainty and empowering families to make informed medical decisions.
3. Lowered the cost of delivering care by reducing unnecessary tests, procedures and time spent in the hospital.

Figure 1 Three key dimensions of healthcare impacted by rWGS

To successfully provide rapid precision medicine for South Florida's most vulnerable children, the program depended on the participation of a multi-disciplinary team, including medical doctors, clinical research coordinators, a genetic counselor, researchers, psychologists, psychotherapists, health economists, laboratory personnel, administrative and support staff. Precisely coordinated teamwork, coupled with a rapid test turnaround time, led to the project's dramatic success. We would like to recognize and thank the interdisciplinary team (see Appendix C) who worked tirelessly to ensure that eligible children had access to this powerful test.

Through robust stewardship of the Florida State Appropriation funds, the Nicklaus Children's team successfully enrolled and sequenced 50 patients. Thanks to these funds, low-income families have gained access to genomic testing traditionally only available to those of exceptional means. The pilot program resulted in estimated savings of over **$3.76** million, yielding an estimated **$2.88** million return on investment. The state funds are now fully expended and, as required by legislation, the following summary and analysis serve as the final report to the Florida Department of Health. It reports the clinical outcomes for children in Project Baby Manatee and estimates the effects of providing rWGS on healthcare expenditures.

Respectfully submitted,

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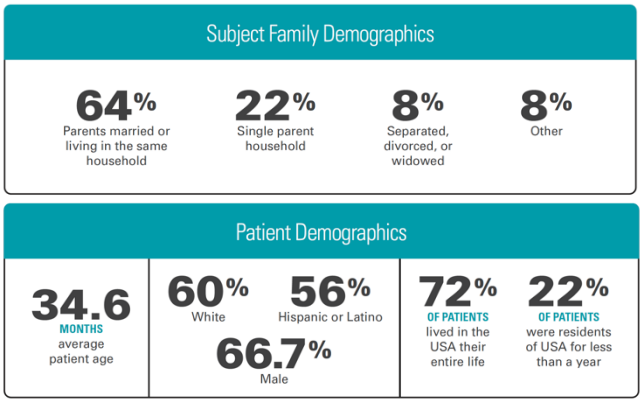
PROJECT DESCRIPTION

Project Baby Manatee employed rWGS as part of the Personalized Medicine Initiative at Nicklaus Children's Hospital. This pilot program has provided diagnoses of rare genetic diseases in critically ill children. Instead of a lengthy "diagnostic odyssey" for poorly defined diseases of undetermined causes, with rWGS we are often able to offer treatments that target specific conditions with known causes. Timely diagnosis can shorten length of stay and help avoid unnecessary tests and procedures, possibly preventing further irreversible harm. This report provides data on changes in clinical management and cost savings to justify future coverage of this technology by payors. The ultimate vision is to make this technology available to all critically ill children with undefined diagnoses for which standard genetic tests fail, thereby averting a long and costly diagnostic odyssey.



A total of 50 participants were included in the study. Although 51 were initially enrolled, one person withdrew after consenting (but before collection of their blood sample) after consulting with their extended family. The average age of children who participated in the study was 34.6 months and two thirds were male (66.7%). A total of 60% of children were identified by their parents as White, including 42% who also identified as Hispanic/Latino and 18% as non-Hispanic/Latino. An additional 26% of the children were identified by their parents as Black/African American, including 4% Hispanic/Latino and 22% non-Hispanic/Latino. In total, 56% of the children were identified as Hispanic/Latino. Most of the children (72%) had lived in the United States their entire lives.

PARENT DEMOGRAPHICS	AVERAGE AGE	WHITE	COLLEGE GRADUATE	AT LEAST 1 YEAR COLLEGE *or specialized training*	HIGH SCHOOL GRADUATE
MOTHERS	31.9	62%	28%	22%	20%
FATHERS	35	60%	28%	20%	20%

Like the children, the majority of caregivers (56%) identified as Hispanic/Latino, including 41% who also identified as White and 1% who identified as Black/African American. The remaining 44% of caregivers were non-Hispanic/Latino, including 19% identifying as White and 24% identifying as Black/African American. The majority of the children's parents were married or

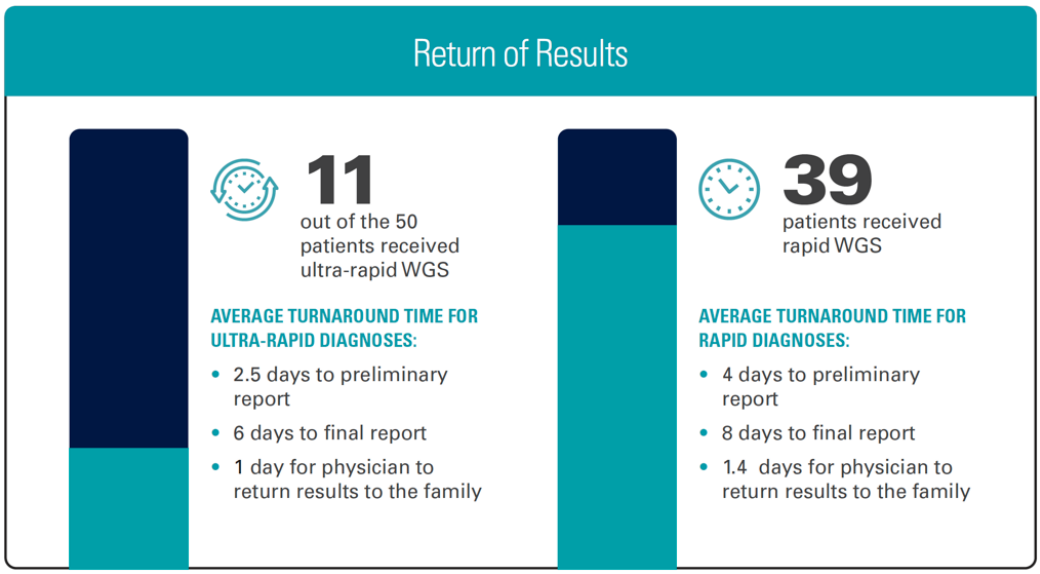
living in the same household (64%), followed by single (22.0%), other (8.0%), and either separated, divorced, or widowed (8.0%). The average age of the parents in the study was 31.9 years and 35.0 years for mothers and fathers respectively. Parents mostly had standard college or university graduation (28.0%), followed by partial college (at least one year) or specialized training (20.0-22.0%), and high school graduation (20.0%).

IMPROVED DIAGNOSTIC RATES AND MANAGEMENT

DIAGNOSTIC YIELD

20
out of 50 patients (40%) received genetic diagnoses based on WGS

Two types of WGS tests were performed: rapid (rWGS) and ultra-rapid (urWGS). Ultra-rapid testing was selected when delivery of the genetic diagnoses were critical for clinical management. Twenty out of fifty patients (40%) received genetic diagnoses based on WGS (Appendix A, Table 1).



Each participant received a written technical report of the WGS test results, including a negative genome clinical report or an analysis of genetic variants that included the following information:

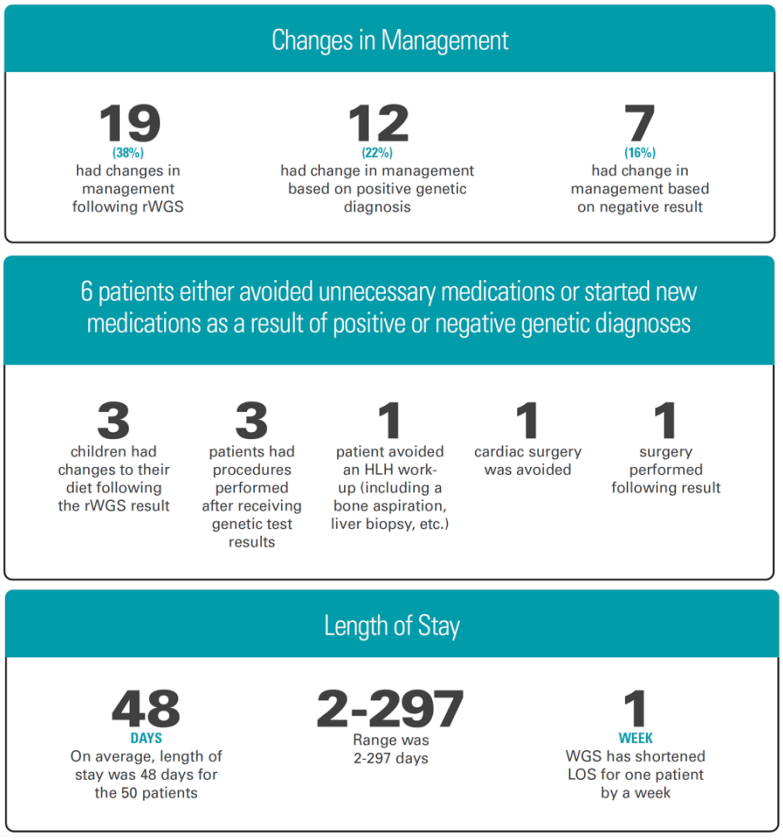
- Pathogenic or likely pathogenic phenotypically related variants;
- Variants of uncertain significance (VUS);
- In a gene that strongly overlapped with the phenotype of a patient for which the mode of inheritance matched what is known about the gene of interest;
- Pathogenic or likely pathogenic variants identified in a gene for a recessive condition in trans with a VUS;
- Compelling VUS within a gene of uncertain significance when supporting information that suggested pathogenicity;

- Incidental findings defined as pathogenic variants in medically-actionable genes unrelated to phenotypes when the caregivers opted-in to receive such results.

TYPES OF GENETIC DISEASES DIAGNOSED

The clinical presentations and disease symptoms of the 50 children enrolled in Project Baby Manatee were extremely varied (Appendix A, Table 2). The most common presentations of illness in which a genetic disease was diagnosed by rWGS were respiratory problems (36%), cardiovascular problems (36%), seizures (32%), brain disorders (32%), and metabolic issues (24%). Furthermore, the clinical presentations of genetic diseases observed among children in this cohort frequently differed from classic presentations in older children, making them much more difficult to diagnose in the absence of rWGS.

The genetic diseases diagnosed in Project Baby Manatee are documented in Appendix A, Table 1 alongside the incidence of the disease. Eight of the diagnosed genetic diseases have an incidence of less than one in one million births or is of unknown incidence. Each of the genetic diseases were diagnosed just once in the Baby Manatee population. These conditions are so rare that many treating physicians had never seen them before, increasing the probability that these disorders would generally go underdiagnosed without rWGS.



The rWGS also led to changes in the clinical management of 38% of Project Baby Manatee children (Appendix 1, Table 3). In these situations, results empowered clinicians and parents to quickly make informed decisions that typically altered the course of the child's hospitalization and led to the initiation of new procedures and medications, or the avoidance of unnecessary ones.

All detected novel diagnostic mutations were submitted to ClinVar, a freely accessible, public archive of reports of the relationships among human genetic variations and phenotypes with supporting evidence. These reports can be found at

https://www.ncbi.nlm.nih.gov/clinvar/submitters/506081/ using submission IDs SUB7860354 and SUB7860438.

CASE 31: TREATMENT AND PREVENTION OPTIONS FOR BABY AND MOTHER

Case 31 was admitted to the Neonatal Intensive Care Unit (NICU) at Nicklaus Children's Hospital just two days after his birth. The baby was unable to feed properly and developed severe metabolic acidosis, a condition in which too much acid accumulates in the body. The baby also had an excessive amount of fluid in his lungs and an abnormal heart anatomy, among other medical complications.

The rapid whole genome sequencing revealed mutations in two genes. One mutation was in the gene (NDUFA1) associated with Complex I-deficient Leigh syndrome, a severe neurological disorder characterized by the progressive loss of mental and motor abilities. Because of this finding, doctors were able to offer treatment of daily oral doses of B vitamins and the antioxidant CoQ10, which have been shown to improve lactic acid levels and improve brain lesions in patients with NDUFA1-related X-linked Leigh syndrome. The second mutation was detected in the SCN1A gene, associated with a spectrum of seizure disorders. While the baby was not presenting symptoms of seizure disorders at the time, the information is valuable for prevention and treatment of future illness.

Additionally, an incidental finding was detected: a pathogenic heterozygous variant in the CHEK2 gene that is associated with higher susceptibility to breast and colorectal cancer. These results indicated that the baby's mother was also susceptible to these cancers. The results of rWGS for this family not only lead to clearer prevention and treatment options for baby, but also equipped the mother with vital information she can use to make important healthcare decisions toward reducing her own cancer risk.

IMPROVED EXPERIENCE OF CARE: HEALTH OUTCOMES

PARTICIPANTS

For the Health Outcomes portion of our study, 47 caregivers from 31 families participated in interviews about their experience with rWGS. Participants also completed two standardized screening measures to assess depression and anxiety. Both interviews and screening were conducted at two time points: time of enrollment (TOE) and return of results (ROR). The majority of caregivers (64%) enrolled in this study were mothers.

RATES OF DEPRESSION AND ANXIETY

Anxiety and depression levels were assessed using standardized self-report questionnaires: Generalized Anxiety Disorder-7 scale (GAD-7) and Patient Health Questionnaire 9 (PHQ-9) were used to assess anxiety and depression scores in the caregivers. The importance of mental health support for parents is evident in their elevated levels of depression and anxiety. Between 28-43% of caregivers scored above the clinical cutoff (scores $\geq$ 10) for anxiety or depression at the time of enrollment and return of results (Figure 2). The 18 parents who scored above the clinical cutoff for depression were offered referrals for assistance.

Figure 2: Depression and anxiety levels at time of enrollment and return of results

Depression levels PHQ-9	Levels of Depression: Score	Time of Enrollment n (%)	Return of Results n (%)
Below clinical cutoff	Minimal (0-4)	19 (40.4)	13 (41.9)
	Mild (5-9)	15 (31.9)	6 (19.4)
Above clinical cutoff	Moderate (10-14)	4 (8.5)	7 (22.6)
	Moderately Severe (15-19)	3 (6.4)	3 (9.7)
	Severe (20-27)	6 (12.8)	2 (6.5)
Total participants		47 (100)	31 (100)
Total participants above clinical cutoff for depression		**13 (27.6)**	**12 (38.7)**

Anxiety levels GAD-7	Levels of Anxiety: Score	Time of Enrollment n (%)	Return of Results n (%)
Below clinical cutoff	Minimal (0-4)	19 (40.4)	11 (35.5)
	Mild (5-9)	8 (17.0)	9 (29)
Above clinical cutoff	Moderate (10-14)	5 (10.6)	2 (6.5)
	Moderately Severe (15-19)	10 (21.3)	6 (12.8)
	Severe (20-27)	5 (10.6)	3 (6.4)
Total participants		47 (100)	31 (100)
Total participants above clinical cutoff for anxiety		**20 (42.5)**	**11 (35.5)**

MAJOR THEMES AT TIME OF ENROLLMENT

In the interviews conducted a time of enrollment, the top three predominant themes discussed were: parental expectations, consenting and understanding, and psychological responses (Figure 3). For a full description of these and other themes, please see Appendix A, Table 4.

Parental expectations: Wanting answers

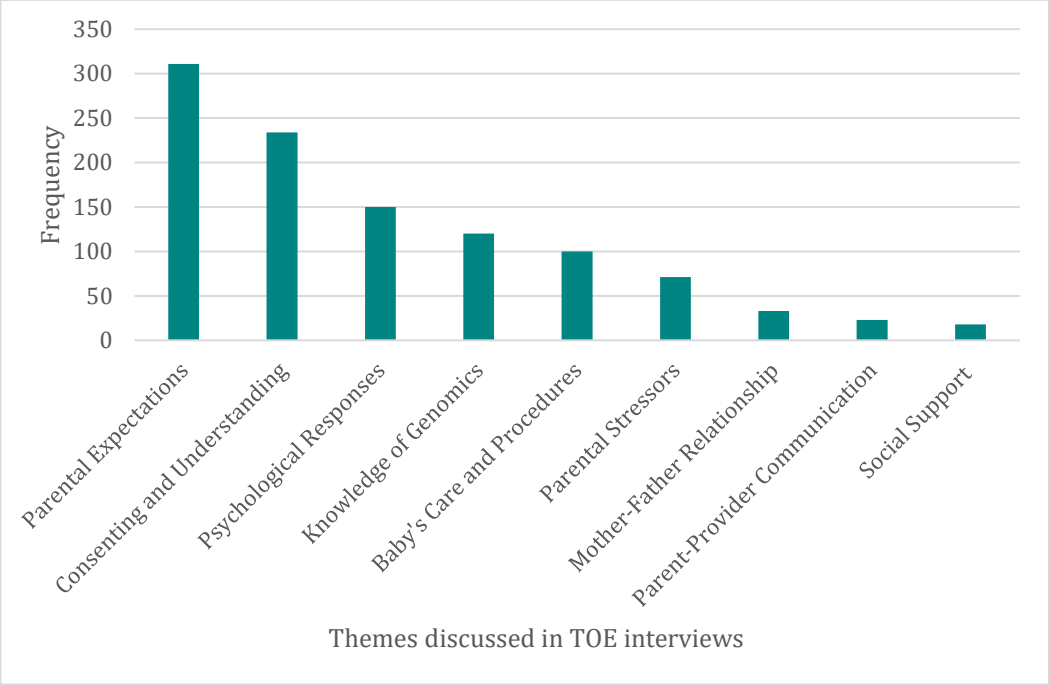
The majority of parents reported the expectation that they would "get an answer" as their reason for enrollment. For example, one parent noted, "I'm hoping that they find something that we didn't already know so then that would help us treat her." Another parent similarly expressed "the hope to obtain a diagnosis and that that diagnosis has a treatment." These statements reveal that some parents expect not just answers alone, but answers that would

lead to treatments. A smaller number of parents hoped that the answer would be one of no genetic findings for fear of the implications of such a diagnosis. One parent said, "I just want to be back home, [and hope that] nothing's wrong with her, and we don't need to study her or anything." In parents' expressions of distress regarding the possibility of a genetic diagnosis, we see the importance of mental health support for families undergoing WGS.

Psychological responses: Roller coaster emotions

Even at the time of enrollment, the majority of parents reported on the ups and downs of their psychological responses to their child's illness. As one parent put it, "we're having good days and bad days." Another said, "It's been an experience like living on a roller coaster, because all of a sudden, we were at the top, very hopeful, and suddenly, two days later, things came tumbling down." These statements further emphasize the need for psychological support, particularly for parents of children in intensive care settings.

Figure 3: Frequency of themes discussed in Time of Enrollment interviews



Consenting and understanding: Quality communication, appropriate expectations

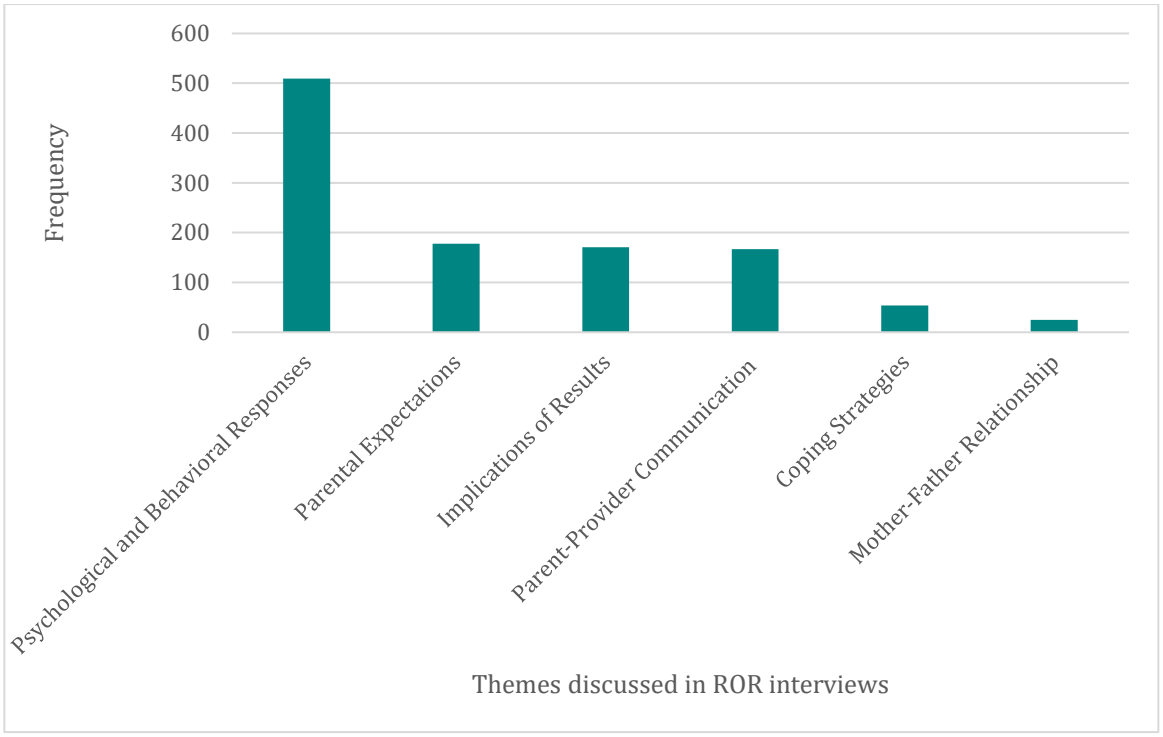
Although most parents hoped for answers at the time of enrollment, they also generally understood that such answers were not guaranteed. Most expressed that since the research and clinical teams explained the process so thoroughly, they were able to adjust their expectations accordingly. The consent procedures also made them feel that they understood the implications of the results and their rights as participants. As one parent noted, "It was explained to me well, very detailed. So, I felt confident signing and all, because I understood

what they were showing me and what they were saying." Although some caregivers had initial apprehensions that may have deterred them - for example, about how the costs of the test would be covered - study coordinators were able to explain the process well enough that patients felt comfortable participating. We credit the study coordinators' success to their extensive knowledge and training; the compassion and empathy they demonstrated for families; and their ability to communicate in culturally and linguistically appropriate ways as Spanish-English bilingual professionals. These qualities will be essential for members of clinical teams if and when rWGS is implemented as the standard of care in pediatric hospitals.

MAJOR THEMES AT RETURN OF RESULTS

The top three predominant themes discussed during the return of results (ROR) interviews were: psychological and behavioral responses to results; parental expectations; and implications of results (Figure 4). For a full description of these and other themes, please see Appendix A, Table 4.

Figure 4: Frequency of themes discussed in Time of Enrollment interviews



Psychological and behavioral responses: Satisfaction, utility, and information seeking

The majority of parents reported satisfaction with the process from start to finish. As one parent stated, "Well, it's a beautiful experience because we can also find out what we [the parents] have or don't have." Some parents commented that they found the test useful because of its impact for their child's treatment, either now or in the future. As one parent commented, if a genetic finding could offer "possible solutions, possible treatments, possible medication in the future that will have a positive change and something – it would be an excellent impact in that kid's life."

Even in instances where rWGS did not detect the causative gene(s) for their child's symptoms, parents were positive about the experience. One mother who did not get a result from the tests stated she felt "quite comfortable because it's something that leaves you at peace to know…that the test is quite comprehensive, and that they didn't find anything; it gives you peace of mind that something won't come up in the future." Similarly, whether or not parents got a result, they reported the test as being useful. Another parent stated, "I believe the test is really important, because it plays a fundamental role in discovery." Most indicated that they would recommend rWGS to others and expressed the hope that it would be available to other parents in the future: "I would love it if in the future, the insurance companies would support this because there are truly kids who need this and the parents can't pay for this."

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The majority of parents were satisfied with the test and information provided by the clinical and research teams. Some, however, felt as though they wanted more information and did their own searching on the internet. One reported, "I tried to Google stuff and, you know, it is not only extremely hard to understand, it is limited too…a lot of it was vague and it did not really amount to anything." This caregiver's statement underscores the need for the team to provide as many resources as possible, particularly internet resources that are reliable, accurate and easy to comprehend.

Parental expectations: Changes in treatment

Parents whose children received a diagnosis most frequently reported that they expected it would lead to a change in their child's treatment. One father stated enthusiastically, "Oh wow, totally. You know, just getting…a good jump start on speech, occupational, physical [therapy], everything. You know, just gonna stay ahead of it." Another parent expressed that, while they eventually expect a change in treatment, they understand that there is still much to learn about their child's genetic condition: "As the doctor told me, it's like this gene is still under study. It's a gene that's very newly discovered or something like that…like, maybe within 5 years or 3 years, more would be discovered, but right now, they know very little. But well, you always start

somewhere. Right?" Through effective communication with the provider, this parent was able to form appropriate short-term expectations and long-term hopes.

Implications of results: Future planning, future hopes

Parents expressed that these results would not only have immediate impact on their child's treatment, but also important future implications, including decisions related to family planning. Speaking of an affected gene found in her own genome, one mother reflected, "I do have something I would pass on to other children and I would definitely think twice and have to put a lot more thought and research into that." For another parent, the rWGS testing experience and the finding of a pathogenic gene have helped her decide not to have more children. She noted, "I've thought about it. I think that my priority is my baby. I think that, it's a special case in which he demands a lot of attention, a lot of time. So, I don't even feel prepared, and I don't see the possibility of wanting to have a baby soon because of that." Empowered with critical genomic information, this mother is able to make the best decision for her family.

"I think I feel more hopeful now that we have the results. They seem to think that they can figure it out. You know, that this is treatable, so that gives me hope."

No matter the test results, most parents remained hopeful. One parent stated, "I'm going to believe that…something's going to come up, that she's going to be able to get help. She's going to be able to live a productive life, and that's what we're focusing on." Another parent noted, "I think I feel more hopeful now that we have the results. They seem to think that they can figure it out. You know, that this is treatable, so that gives me hope."

CASE 34: NEW INFORMATION, ESSENTIAL SUPPORT

Case 34 was a 15-year-old boy with an existing genetic diagnosis of chromosome 13q33 microdeletion. This rare chromosomal disorder causes multiple body malformations, delays in the acquisition of skills associated with the coordination of mental and muscular activity, and intellectual disability. The boy now depended on a tracheostomy/ventilator to breath and a gastrostomy tube to feed. He was admitted to the Pediatric Intensive Care Unit (PICU) at Nicklaus Children's Hospital for infusion treatment and ongoing medical management due to an increase in the frequency of his seizures that did not seem to improve with treatment and could not be explained by his existing diagnoses.

The rapid whole genome sequence revealed critical new information: a pathogenic variation in the CARKD gene. This variation is associated with a brain disorder called autosomal recessive progressive encephalopathy, early-onset, with brain edema and/or leukoencephalopathy 2. This

condition overlaps with the chromosome 13 deletion that was previously reported and subsequently explained the boy's recently deteriorating condition.

During her interview at the time of study enrollment, the boy's mother reported symptoms of severe depression and suicidal ideation. The study interviewer, a licensed mental health counselor, performed clinical follow-up and coordinated appropriate referrals for the mother to receive the psychological care she needed. At her second interview, the mother expressed enormous gratitude for the assistance received since she recognized that taking care of her mental health would have a direct impact on her son's care and wellbeing. Regarding the interview and psychological screening of parents, she believes "this process should be done for parents when they hear the news about genetic tests…because we didn't have the same support when we got the [initial] results for our son." The mother wished for a similar interdisciplinary focus on the parent and child's wellbeing when she received her son's first genetic diagnosis soon after his birth. That initial diagnosis had a detrimental impact on her mental health that was never addressed. In contrast, in the experience of rWGS at Nicklaus Children's, "I felt support," she said. "I felt that people were trying to protect me and protect our son of any negative feelings or anything. I felt very, very good. And it was exceptional."

The results of rWGS also helped dissipate the mother's experience of guilt regarding her son's current clinical presentation. Before the test, she worried that she may have inadvertently caused her son's sudden and inexplicable health deterioration due to mismanagement of his chronic illness. The results of this test proved that his condition was caused by a genetic condition, and not any previous medical treatment. This knowledge allows the boy's mother to make educated decisions regarding possible experimental treatment options, as well as consult with experts in other medical specialties in an effort to provide her son with the best possible quality of life.

The Neonatal and Cardiac Intensive Care Units at Nicklaus Children's Hospital count on the expertise of a Clinical Psychologist who provides preventive and therapeutic clinical interventions to the parents in these units. The hospital recognizes the importance of immediately addressing the emotional impact that a severe medical condition can have on the mental health and overall wellbeing of the parents of a critically ill child and, consequently, on their ability to care for their children both at the hospital and at home.

Case 34 demonstrates the need for qualified mental health professionals to address the psychological needs of parents when they receive the results of genetic testing. Referring parents for appropriate care can benefit both them and their children in a time of crisis and in the long term.

REDUCING HEALTH DISPARITIES

Our research has also identified some common pitfalls in implementing genomic testing. Ethnically diverse communities still experience a lack of referrals, difficulty in traveling to

outpatient visits and a cultural mismatch with providers. As genomic sequencing transitions from outpatient to inpatient settings, it presents an opportunity to close this health disparity gap. By implementing and researching rWGS in pediatric intensive care settings, Nicklaus Children's is helping to address these and other common barriers faced by underserved families.

COST-SAVINGS AND COST-EFFECTIVENESS OF RWGS

METHODOLOGY OVERVIEW

The clinical benefits of genome sequencing in diagnosing rare conditions are clear. But is rWGS cost effective? The analysis of our health economics team points to yes.

The team analyzed data from 59 critically ill patients who received rWGS in comparison with a control group of 268 patients that received current standard-of-care genetics evaluations (chromosome microarray, small gene panels or single-gene testing). One patient was excluded from this analysis because of age (older than 18 years) and five patients were excluded based on a possible diagnostic odyssey prior to rWGS. We also included patients from the pilot study that started prior to the beginning of the period covered by state appropriation funds, in order to increase the total number of subjects in the analysis and ensure the validity of the results.

The outcome measures included (1) cost savings, (2) diagnostic yield (the proportion of patients receiving a disease diagnosis following a test), (3) length of diagnosis odyssey (time measured from when the first test was performed to the posting of the results provisional genetic diagnosis), and (4) survival. Three cost analyses were performed including a cost savings analysis and two cost-effectiveness analyses (CEAs): one for overall survival (OS) and one for diagnostic yield (DY).

Figure 5: Incremental cost-effectiveness ratio

$$ICER = \frac{Cost(A) - Cost(B)}{Benefit(A) - Benefit(B)}$$

These analyses were expressed in terms of two common metrics: 1) the incremental cost-effectiveness ratio (ICER), defined by the difference in cost between two possible interventions, divided by the difference in their effect (see Figure 5) and 2) the net monetary benefit (NMB), representing the difference between the benefits associated with rWGS (expressed in monetary value) and the amount invested (total costs attributable to the use of rWGS). The willingness to pay threshold, representing the ability of the decision-maker to pay per life year gained due to rWGS, was set at $50,000, one of the standard accepted thresholds in health economics.

BASELINE CHARACTERISTICS OF PARTICIPANTS

Although there were significant differences in some baseline characteristics between treated and control groups, we were able to adjust our analysis to account for these differences in order to produce valid results. The mean age difference was statistically significant between the treated group and the control group (1166 *vs.* 87 days, p<0.001). There was also a statistically significant difference in the hospital location (recruitment source) of the patients: a larger proportion of the treated group were located in the PICU and other hospital floors, while a larger proportion of the control group was in the NICU and CICU (p<0.001). In the treated group, significantly fewer patients were in the inpatient setting (p=0.04) and more patients were admitted from the emergency room (p<0.001). Patients in the treated group also had more hospital visits than the ones in the control group (19 *vs*. 9.4, p<0.001). The diagnostic yield was much higher in the treated group (rWGS 0.56 *vs*. control 0.19, p<0.001) and the length of diagnostic odyssey was significantly lower in the rWGS group than the control group (74 *vs*. 229 days respectively, p<0.001). On average, patients in the treated group had more comorbidities than the control group (45 *vs.* 15, p<0.0016). There were no statistically significant differences between the two comparison groups in other baseline characteristics, including sex, race, ethnicity, mortality, AHRQ and VAN comorbidity scores and hospital length of stay. For more details, see Appendix A, Table 5.

We adjusted our analysis for the significant differences in baseline characteristics between treated and control groups using propensity scores matching (PSM). An inverse probability of treatment weighting (IPTW) was applied to avoid excluding further patients, which is usually the case when traditional PSM approaches are used. In other words, we were able to successfully account for the differences between treated and control, and did not lose any patients in our analysis. The variables used in the PSM were age, race, ethnicity, hospital location (CICU, PICU, etc.), admitting source (e.g. ER transfer), encounter type (inpatient, outpatient), comorbidity score (AHRQ), and time in the health system before genetic test.

IS RAPID WHOLE GENOME SEQUENCING A COST-SAVING INTERVENTION?

We used the incremental cost-effectiveness ratio (ICER) to summarize the cost-effectiveness of the rWGS intervention. ICER is defined by the difference in cost between two possible interventions, divided by the difference in their effect (see Figure 5, above). For this report, only hospital costs were used in the analysis. Cost savings were calculated as the average total cost of the treated group minus the average total cost of the control group, after applying the PSM and IPTW adjustments described above to ensure inclusion of our entire sample for analysis. The difference of total costs per patient between the treated and the control groups is **-$75,285** (SE=23,552, p=.001). This indicates that **using rWGS is cost-saving compared to the standard of care genetic tests** (Figure 6). In other words, for each patient (≤18 years old) moved from standard genetic testing to rWGS, Nicklaus Children's hospital would save $75,285. The estimated cost savings produced by the 50 patients in Project Baby Manatee alone equals

$3,764,250 ($75,285 x 50). Considering that the Florida State Appropriation provided $880,000 in funds to support 50 tests, the estimated return on investment is **$2,884,250**.

In summary, a retrospective analysis of the economic impact of rWGS on total cost has shown significant reductions in the cost of delivering care compared to the current standard of care genetic testing. These, in turn, produced significant savings for the payors.

IS RAPID WHOLE GENOME SEQUENCING A COST-EFFECTIVE INTERVENTION?

rWGS shows effectiveness: Overall survival (OS)

The definition of cost-effectiveness is something that is a good value for the money. In other words, for a good or service to be cost-effective, the benefits and utility derived from it must be worth at least as much as it cost. Here we used overall survival (OS) of patients as one of the outcomes to define the value. The mean OS of the treated (rWGS) population was 65 days less than that of the control group. Some of this is due to parents being able to use rWGS results in making an informed decision not to pursue unnecessary interventions that would only prolong the suffering of babies with severe lethal conditions. The mean cost of the treated population was $75,285 less than the control group. The incremental cost effectiveness ratio (ICER) was $1,167/day and the net monetary benefit (NMB) is $66,445, which indicates that rWGS is cost-effective compared to the control group in terms of OS at a Willingness-to-Pay (WTP) of $137 per patient per day (WTP of $50,000 per patient per year divided by 365 days). In other words, for each additional day survived it would cost $1,167 more to the Nicklaus Children's hospital should standard of care genetic tests be conducted in lieu of rWGS. At a WTP of 137/day, using rWGS instead of standard of care genetic tests would return **$66,445** on the hospital investment per pediatric patient. This estimate accounts for both costs and benefits.

Figure 6: Cost-effectiveness analysis using overall survival as the effectiveness measure

Statistic	Value	Std. Err	t/z	df (large)	t0/z0	p-value
Delta_E	-65	18.87	-3.42	24.00	2.39	0.0022
Delta_C	-75,285	23,552	-3.20	14,969	2.24	0.0014
ICER	1,167					
NMB ($137/day)	66,445	23,334	2.85	14,704	2.24	0.0044

Delta_C, Difference in cost; Delta_E, Difference in effectiveness; df, degrees of freedom; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; Std error, standard error; t, t-test score calculated; t0: critical value for t score based on distribution table.

rWGS shows effectiveness: Diagnostic yield (DY)

Another way to evaluate the effectiveness is to look at the incremental cost effectiveness ratio (ICER) per additional unit of diagnostic yield. After adjusting for differences in baseline characteristics between treated and control group, the mean diagnostic yield (DY) of the treated population was still 16% more than that of the control group (Figure 7). With the mean cost of the treated population $75,285 less than the control group, the incremental cost effectiveness ratio (ICER) was -$465,525 per 1% of diagnostic yield. The negative ICER indicates that rWGS is a dominant strategy when DY is used as the effectiveness measure, In other words, the Nicklaus Children's hospital would save **$465,525** per percent of DY if it moved from standard of care genetic testing to rWGS.

Figure 7: Cost-effectiveness analysis using diagnostic yield as the effectiveness measure

Statistic	Value ($)	Std. Err	t/z	df (large)	t0/z0	p-value
Delta_E	0.16	0.21	0.7748	-	1.96	0.4384
Delta_C	- 75,285.11	23,552.34	-3.20	14,968	2.24	0.0014
ICER_OS	-$465,525					
NMB (137)	75,307.27	23,552.36	3.20	325.00	2.25	0.0015

Delta_C, Difference in cost; Delta_E, Difference in effectiveness; df, degrees of freedom; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; Std error, standard error; t, t-test score calculated; t0: critical value for t score based on distribution table.

HEALTH ECONOMICS ANALYSIS: KEY RESULTS

Nicklaus Children's Hospital has applied highly conservative approach to estimating cost savings. The cost savings in rWGS tested group were lower despite older age, larger number of comorbidities and encounters. At the same time the length of diagnostic odyssey was substantially shorter in the rWGS tested group (74 days vs. 229 days on average). The diagnostic yield was better in treated group and more cost effective. The cost effectiveness on overall survival was also favoring rWGS compared to the standard of care genetic testing.

The implementation of rWGS in Project Baby Manatee led to $3.76 million in healthcare cost savings. These included actual costs that were paid by the payors to Nicklaus Children's Hospital to cover professional and facility fees.

The total cost of supporting rapid precision medicine and sequencing for 50 patients in the Project Baby Manatee was $0.88 million. Therefore, **net cost savings were $2,884,250** ($3.76 million in savings minus $0.88 million in rWGS expenses). In terms of cost-effectiveness on overall

survival and diagnostic yield, the resulting average net monetary benefit of sequencing per patient was between $66,445 and $75,307.

RECOMMENDATIONS: IMPLEMENT RWGS STATEWIDE

Based on the results of Project Baby Manatee, the rapid precision medicine approach not only is cost-saving and cost-effective, but also improves health outcomes and shortens diagnostic odyssey. Going forward, rapid whole genome sequencing (rWGS) is well positioned to be a first-tier diagnostic test for critically ill children with diseases of unknown cause.

Based on the findings of this report, the Project Baby Manatee team:

- Recommends reimbursing rWGS for all critically ill children and infants with diseases of unknown cause and with suspected underlying genetic etiology admitted to NICU, PICU and CICU.
- Recommends employing rapid precision medicine utilizing rWGS as a first-tier test for critically ill children in a multispecialty system that provides an extensive network of support services for both clinicians and families. Hospitals and laboratories that lack these resources will likely fail to achieve similar improvements in the health of children or comparable reductions in the cost of care.
- Cautions against expanding reimbursement to whole genome sequencing that is not rapid as it will prolong diagnostic odyssey and will not have the same benefits.
- Recommends training of clinical personnel in the effective communication of information regarding genomics and genetic testing, both when consenting families and returning test results.
- Recommends providing qualified mental health professionals to address the psychological needs of parents whose children undergo rWGS and other genetic testing. Referring parents for appropriate care can benefit both them and their children, in the time of crisis and in the long term.

rWGS is Ready to be the Standard of Care

Rapid whole genome sequencing is now ready to be the standard of care for critically ill children. It is no longer experimental. This has been endorsed by Blue Shield, which now provides rapid whole genome sequencing as a covered benefit.

Rapid Precision Medicine with rWGS improves lives, and the State of Florida can afford it. It should be accessible to all of Florida's critically ill children as soon as possible.

APPENDIX A:

Table 1: GENETIC DIAGNOSES IN PROJECT BABY MANATEE CHILDREN AND THEIR INCIDENCE

Genetic Diagnoses	Gene	Incidence	Second Genetic Diagnoses	Gene	Incidence
14Q11.2 DELETION	127 genes	1/1,000,000			
ABCC8-RELATED DISORDERS	ABCC8	1/50,000			
ATP1A3-RELATED DISORDERS	ATP1A3	1/1,000,000			
CHROMOSOME 10Q22.3-Q23.2 DELETION SYNDROME	43 Genes	unknown			
CONGENITAL CENTRAL HYPOVENTILATION SYNDROME, WITH OR WITHOUT HIRSCHSPRUNG DISEASE	PHOX2B	1,000 worldwide			
ENCEPHALOPATHY, PROGRESSIVE, EARLY-ONSET, WITH BRAIN EDEMA AND/OR LEUKOENCEPHALOPATHY, 2	CARKD	1/1,000,000	13Q33.1Q34DEL	71 Genes	unknown
EPILEPTIC ENCEPHALOPATHY, CHILDHOOD-ONSET	CHD2	unknown			
GALACTOSE EPIMERASE DEFICIENCY	GALE	1/6,700-7,000			
HEXOSAMINIDASE A DEFICIENCY	HEXA	1/3,600			
KCNT1-RELATED EPILEPSY	KCNT1	88 worldwide			
LEUKOENCEPHALOPATHY WITH BRAINSTEM AND SPINAL CORD INVOLVEMENT AND LACTATE ELEVATION	DARS2	1/1,000,000			
LEUKOENCEPHALOPATHY WITH VANISHING WHITE MATTER	EIF2B2	unknown			
MAGT1-RELATED DISORDERS	MAGT1	<1/10,000			
MICROPHTHALMIA, SYNDROMIC 9	STRA6	1/1,000,000			
MITOCHONDRIAL COMPLEX I DEFICIENCY, NUCLEAR TYPE 12	NDUFA1	1-5/1,000	EPILEPTIC ENCEPHALOPATHY, EARLY INFANTILE, 6	SCN1A	1/15,000-40,000
NEURODEVELOPMENTAL DISORDER	TLK2	1/566			

NEURODEVELOPMENTAL DISORDER WITH SPASTIC DISORDER DIPLEGIA AND VISUAL DEFECTS	CTNNB1	1/1,000,000	BRD4-RELATED DISORDER	BRD4	4-8/100,000
SCN1A SEIZURE DISORDERS	SCN1A	1/20000-1/40000			
SPINOCEREBELLAR ATAXIA, AUTOSOMAL RECESSIVE 17	CWF19L1	1/1,000,000			
VON WILLEBRAND DISEASE	VWF	1/100-1,0000			

Table 2: TYPES OF DISEASES IDENTIFIED IN PROJECT BABY MANATEE

Presenting Symptoms and Signs of Disease	Genetic Diagnoses
Metabolic acidosis; Lactic acidosis; Respiratory distress; Encephalopathy; Abnormal heart morphology	MITOCHONDRIAL COMPLEX I DEFICIENCY, NUCLEAR TYPE 12, EPILEPTIC ENCEPHALOPATHY, EARLY INFANTILE, 6 Susceptibility to Breast and Colorectal Cancer
Seizures; Developmental delay; Autism	EPILEPTIC ENCEPHALOPATHY, CHILDHOOD-ONSET
Chronic constipation, Dependent on ventilator, Gastrostomy in place, Medically complex patient, Myoclonic seizures, intractable, Seizures, Tracheostomy in place	ENCEPHALOPATHY, PROGRESSIVE, EARLY-ONSET, WITH BRAIN EDEMA AND/OR LEUKOENCEPHALOPATHY, 2 Chr 13Q33.1Q34DEL
Microcephaly; Seizures; Patent ductus arteriosus; Pyloric stenosis; Respiratory failure; Micrognathia; Generalized hypotonia	Chr 14Q11.2 DELETION
Thrombocytopenia; Pancytopenia; Abnormal mitral valve physiology	GALACTOSE EPIMERASE DEFICIENCY
Suspected Hirschsprung disease; Constipation; Central hypoventilation	CONGENITAL CENTRAL HYPOVENTILATION SYNDROME, WITH OR WITHOUT HIRSCHSPRUNG DISEASE
Seizure; Global developmental delay; Developmental regression; Encephalopathy	KCNT1-RELATED EPILEPSY
Seizures	SCN1A SEIZURE DISORDERS
Hemiplegia; Dystonia; Seizures; Global developmental delay; Attention deficit hyperactivity disorder	ATP1A3-RELATED DISORDERS
Dystonia; Delayed speech and language development; Global developmental delay; Absence seizure	HEXOSAMINIDASE A DEFICIENCY
Pulmonary artery hypoplasia; Patent ductus arteriosus; Hypoplastic aortic arch; Partial anomalous pulmonary venous return; Anophthalmia	MICROPHTHALMIA, SYNDROMIC 9
Abnormal superior vena cava morphology; Ventricular septal defect; Atrial septal defect; Tachypnea; Abnormal facial shape; Wide intermamillary distance	NEURODEVELOPMENTAL DISORDER
Autism; Delayed speech and language development; Seizures	SPINOCEREBELLAR; ATAXIA, AUTOSOMAL; RECESSIVE 17
Generalized hypotonia; Constipation; Psychomotor deterioration; Lethargy	NEURODEVELOPMENTAL DISORDER WITH SPASTIC DISORDER DIPLEGIA AND VISUAL DEFECTS
	BRD4-RELATED DISORDER
Recurrent infections; Immunodeficiency	GENE OF UNCERTAIN SIGNIFICANCE
Respiratory failure; Hypoxemia; Abnormality of pulmonary circulation; Leukocytosis; Neonatal sepsis; Hypokalemia	MAGT1-RELATED DISORDERS
Developmental regression; Seizures; Leukodystrophy; Encephalopathy; Generalized hypotonia	LEUKOENCEPHALOPATHY WITH VANISHING WHITE MATTER
Hypoglycemia; Hepatic arteriovenous malformation; Encephalomalacia	ABCC8-RELATED DISORDERS

Abnormality of the respiratory system; Abnormality of the liver; Abnormality of hepatobiliary system physiology; Acute kidney injury; Anemia; Sickled erythrocytes; Abnormal circulating metabolite concentration; Sepsis	SICKLE CELL ANEMIA
Left ventricular dysfunction; Reduced ejection fraction; Cardiomyopathy; Intraventricular hemorrhage; Decreased liver function; Anemia; Hypoglycemia; Hypocalcemia; Sepsis	VON WILLEBRAND DISEASE
Ascites; Abnormal heart morphology; Acute kidney injury; Leukocytosis; Immunodeficiency; Respiratory failure; Elevated hepatic transaminase; Lactic acidosis; Abdominal distention; Elevated calcitonin; Sepsis	CHROMOSOME 10Q22.3-Q23.2 DELETION SYNDROME
Encephalocele; Corenal opacity; Coloboma; Agenesis of corpus callosum; Hypertelorism; Hyperbilirubinemia; Elevated serum creatine kinase; Ventricular septal defect; Abnormal mitral valve morphoology	ANEMIA, NONSPHEROCYTIC HEMOLYTIC, DUE TO G6PD DEFICIENCY
Microcephaly; Lissencephaly; Hypoglycemia; Hypernatremia	LEUKOENCEPHALOPATHY WITH BRAINSTEM AND SPINAL CORD INVOLVEMENT AND LACTATE ELEVATION

Table 3: CHANGES IN MANAGEMENT

PARTICIPANT ID	DIAGNOSIS	TYPE OF CHANGE	CHANGE OF MANAGEMENT
31	MITOCHONDRIAL COMPLEX I DEFICIENCY, NUCLEAR TYPE 12	Major change based on genetic diagnoses	Recommended vitamin supplements and surveillance for cancer. Recommended close neurological and cardiology follow up. Also recommended cancer surveillance for mother. In case of developing seizures would have to avoid Carbamazepine, lamotrigine, and vigabatrin, Phenytoin, Rufinamide and Acetaminophen
33	EPILEPTIC ENCEPHALOPATHY, CHILDHOOD-ONSET	Minor change based on genetic diagnoses	Recommended seizure medications that have less hepatic involvement and VEEG monitoring. More accurate prediction outpatient course and may make it less likely that patient will be admitted in the future. Patient will need continued monitoring and treatment for seizures
40	GALACTOSE EPIMERASE DEFICIENCY	Major change based on genetic diagnoses	Indicated change in diet and follow up in metabolic clinic.
44	CONGENITAL CENTRAL HYPOVENTILATION SYNDROME, WITH OR WITHOUT HIRSCHSPRUNG DISEASE	Minor change based on genetic diagnoses	Tracheostomy was performed
45	None	Major change based on negative results	Tested for autoimmune conditions, found to be NMDA AB positive
46	KCNT1-RELATED EPILEPSY	Minor change based on genetic diagnoses	Initiated and continued on ketogenic diet that may reduce seizure frequency
49		Minor change based on genetic diagnoses	Initiated proper ion-channel anti-epileptics treatment
50	ATP1A3-RELATED DISORDERS	Minor change based on genetic diagnoses	Follow-up with neurology treatment
51	HEXOSAMINIDASE A DEFICIENCY	Major change based on genetic diagnoses	Treatment for progressive neurodegenerative genetic condition
52	None	Minor change based on negative results	Performed surgery (fundoplication)
53	MICROPHTHALMIA, SYNDROMIC 9	Major change based on genetic diagnoses	Cardiac surgery avoided. Parents signed an AND.

61	None	Minor change based on negative results	Ruled out genetic diagnoses
64	LEUKOENCEPHALOPATHY WITH VANISHING WHITE MATTER	Minor change based on genetic diagnoses	Patient was placed on respiratory and neurological monitoring with G-tube
65	None	Minor change based on negative results	Moved towards mitochondrial testing
69	SICKLE CELL ANEMIA	Major change based on negative results for additional genetic diagnoses	Avoided more aggressive investigations such as bone marrow aspiration or liver biopsy and more aggressive therapies for HLH.
71	VON WILLEBRAND DISEASE	Minor change based on genetic diagnoses	Discontinued some medications such as carnitine
74	None	Minor change based on negative results	Started IVIG and steroids for suspected autoimmune etiology
75	None	Minor change based on negative results	Repeated MRI brain will be obtained; patient went for tracheostomy based on negative results and abnormal bronchoscopy
76	ANEMIA, NONSPHEROCYTIC HEMOLYTIC, DUE TO G6PD DEFICIENCY	Minor change based on genetic diagnoses	G6PD related medications were avoided

Table 4: INTERVIEW DATA AT THE TIME OF ENROLLMENT (TOE) CODED INTO NINE THEMES

TOE Code	Description	Example
Baby's care and procedures	Concerns about baby's care and procedures including current care, invasive procedures, and stabilizing the baby.	"The blood draws, yeah. You know, with him, you know, getting IVs, and blood samples, and stuff like that, I wanted to really, really mitigate how many times he was poked, you know because it's hard to see after a while." ID 56
Consenting and Understanding	Parents' understanding of the consent process and potential barriers they mention in deciding to enroll their child for genome sequencing.	"Well, I'm under the understanding that it's, um, the idea is to be able to see, if there is – if his problem is something that comes from us, from one of our genetics. Or if it's something that developed." ID 42
Parental Expectations	Parents' expectations of what the rapid whole genome sequencing can tell them such as giving them an answer, a change in their child's medical management, or show that there are no findings from the test.	"No, because, um, I know that the test will give me, um, the – the answers. I mean, I'm always gonna have questions, I'm always gonna have doubts and stuff. But I know that the test will give me answers that – that I need. And even answers that I didn't know that I needed to hear." ID 38
Psychological Responses	Parents' description of how they are responding to the experience such as their anxiety, coping methods, and roller coaster of emotions.	"Um, so I think it's a combination of emotions. So, you sort of feel, um – you know, you feel a little helpless to start with and you're, you know, obviously concerned because the reason why you're doing this is because your baby is not 100% healthy, which is the case with ours. Um, and so, you know, you – you feel upset in that regard. However, you know, because we're getting such good care and such good treatment and we're having all of these options, um, you know, presented to us, it actually gives us a sense of comfort, you know, and confidence

		that we're moving in the right direction and that we're gonna get to the outcome that we need to, which is having a healthy, happy baby boy. ID 70
Knowledge of Genomics	Parents' knowledge of genomics both prior to testing and their description of gaining knowledge through the process.	It's not – it's not something that really interests me, but there's so little public information, of – of the advances, or – or the language is a little complicated for the common person to understand, that one – I didn't know anything. ID 43
Patient-Provider Communication	Parents' reported challenges or successes related to communication with health care providers.	"Yeah. I mean, nurses and doctors are really good. They're very attentive. Um, they're, um – like, they'll answer any questions I have, which is nice, and I have a lot of questions." ID 56
Mother-Father relationship	Parents' report of the mother-father relationship and how this may be impacted by the process.	"Well, I mean I just saw the information I had gathered from the whole stay I've had here, and when she came over, you know, we talked it through as a couple. You know, we pretty much have the same goals for our daughter, so it was easy to make a decision together (to participate), but I didn't want to do it alone. " ID 30
Parental Stressors	Parents' report of stressors including being away from home other children, or future concerns.	"But, it's not awful because the people are not awful. It's not awful because the process is awful. It's just awful because you never want no one in your family, no loved ones in the hospital." ID 35
Social Support	Parents' report of social support provided by family, friends, and peers.	"..Many of my friends have come, thanks to everyone who—I have—I have very good friends who have been here with me because we don't have family here." ID 60

Table 5: BASELINE COHORT CHARACTERISTICS FOR COST SAVINGS AND COST EFFECTIVENESS ANALYSIS

	Treated		Control		Difference	
	Mean/ Proportion	**Std. error**	**Mean/ Proportion**	**Std. error**	**Value**	**p-value**
N	59		268		-	
Age (days)	1166	262	87	31	1079	<0.001
Female	0.39	0.06	0.50	0.03	-0.11	0.14
Race						
Black or African American	0.14	0.04	0.11	0.02	0.02	0.61
White	0.59	0.06	0.65	0.03	-0.06	0.39
Unknown/Other	0.27	0.06	0.24	0.03	0.04	0.56
Ethnicity	0.54	0.06	0.53	0.03	0.01	0.90
Encounter Type						
Inpatient	0.20	0.01	0.23	0.01	-0.03	0.04
Floor						
PICU	0.64	0.01	0.02	0.002	0.62	<0.001
NICU	0.17	0.01	0.36	0.01	-0.18	<0.001
CICU	0.09	0.01	0.63	0.01	-0.54	<0.001
Others (normal floor)	0.10	0.01	0	0	0.10	<0.001
Admitting Source						
Born inside the hospital	0.001	0.001	0.004	0.001	-0.003	0.11
Clinic/physician referral	0.58	0.01	0.70	0.01	-0.13	<0.001
Emergency room	0.21	0.01	0.14	0.01	0.07	<0.001
Transfer from a hospital	0.07	0.01	0.13	0.01	-0.06	<0.001
Non-health care facility	0	0	0.001	0.0004	-0.001	0.38
Telemedicine	0	0	0.01	0.002	-0.01	<0.001
NA/Unknown	0.14	0.01	0.005	0.001	0.13	<0.001
Mortality	0.17	0.05	0.09	0.02	0.08	0.09
Length of the stay	11.9	0.57	11.0	0.34	0.83	0.20
Number of encounters	18.8	4.73	9.41	0.75	11.1	<0.001
Genetic diagnosis rate	0.56	0.07	0.19	0.02	0.37	<0.001
Length of diagnostic odyssey	74.3	15.4	229	14.8	-201	<0.001
Total number of comorbidities	45.2	19.1	14.7	1.48	30.5	0.002
Comorbidity score AHRQ	9.39	1.26	7.28	0.52	2.11	0.09
Comorbidity score VAN	6.24	0.92	5.37	0.39	0.87	0.35

Abbreviations: **AHRQ** - Agency for Healthcare Research and Quality; **CICU** - cardiac intensive care unit; **N** - number; **NA** - not applicable; **NICU** - neonatal intensive care unit; **PICU** - pediatric intensive care unit; **Std** - standard; **VAN** - van Walraven modification to Elixhauser Comorbidity Measures.

APPENDIX B: GLOSSARY OF TERMS AND ACRONYMS

GLOSSARY

Acronym	Definition
AHRQ	Agency for Healthcare Research and Quality
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curves
CI	Confidence Interval
CI LB	Confidence Interval Lower Bound
CI UB	Confidence Interval Upper Bound
CICU	Cardiac Intensive Care Unit
DY	Diagnostic yield
EHR	Electronic health record
HLH	Hemophagocytic lymphohistiocytosis, an aggressive and life-threatening syndrome of excessive immune activation
ICER	Incremental cost-effectiveness ratio
NICU	Neonatal Intensive Care Unit
NMB	Net monetary benefit
OS	Overall survival
PICU	Pediatric Intensive Care Unit
rWGS	rapid Whole genome sequencing
VAN	van Walraven modification to Elixhauser Comorbidity Measures
VUS	Variant of unknown significance
WGS	Whole genome sequencing
WTP	Willingness-to-pay

APPENDIX C: PROJECT TEAM, CONTACT INFORMATION AND ACKNOWLEDGEMENTS

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We are indebted to Dr. Richard K. Moussa, Assistant Professor, Théorie économique, modélisation et applications (ThEMA), Université de Cergy-Pontoise, France and Ecole Nationale Supérieure de Statistiques et d'Economie Appliquée (ENSEA), Côte d'Ivoire, for his assistance in the study design and choice of statistical approaches used in this work.

WHOLE GENOME SEQUENCING

Whole genome sequencing was performed by Rady Children's Institute for Genomic Medicine (RCIGM)