Final Report

Period Covering July 1, 2018 – June 1, 2020

State of California Senate Bill No. 840, effective June 27, 2018
Chapter 29, 4260-001-0001, Provision 8 (pages 372-3)

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Executive Summary

In a pilot study implemented across the State of California, five clinical sites have demonstrated that a rapid precision medicine program for critically ill Medi-Cal babies improves clinical outcomes, improves the experience of care for families and clinicians, and reduces net healthcare expenditures. Over the course of this demonstration pilot ("Project Baby Bear") a single, comprehensive tool historically employed only as a last resort proved it could serve as the standard of care for testing sick babies early in their hospitalizations. Rapid whole genome sequencing (rWGS) yielded vital information that changed the decisions families and clinicians made, and ultimately saved lives and resources.

In short, over a period of 23 months, Project Baby Bear:

- Completed rWGS on 178 babies and families
- Provided diagnoses for 76 babies (43%)
- Led to a change in the management of 55 babies (31%) that resulted in fewer hospital days, fewer procedures or new therapies
- Diagnosed 35 rare conditions that occur in less than one in one million births
- Achieved a three-day turnaround time for provisional results
- Reduced healthcare costs and downstream spending, primarily by empowering doctors to eliminate unnecessary procedures and discharge babies sooner

"I have never seen a diagnostic tool that's made such a huge impact in intensive care medicine in all my years of practice."

—Mario Rojas, MD
NICU Medical Director Valley Children's Hospital

To successfully provide rapid precision medicine for California's most vulnerable children, the program depended on the participation of multidisciplinary teams integrated within each of the five hospital systems. These included medical doctors, genetic counselors, nurses, laboratory personnel, IT personnel and supportive staff. It was this coordinated system of care coupled with a rapid test turnaround time that led to the project's dramatic success. We'd like to recognize and thank the interdisciplinary teams (see pages 26-27) who worked tirelessly to ensure that eligible babies had access to this powerful test.

Through robust stewardship of the funding, these five clinical sites enrolled 78% more babies than expected, nearly doubling the state-mandated genome sequencing requirement of 100 babies in the 2018 Budget Act appropriation of $2 million. The pilot resulted in savings of over $2.5 million, yielding a minimum $750,000 return on investment. In-kind contributions totaling more than $400,000 from the teams at Rady Children's Hospital – San Diego (RCHSD) and the Rady Children's Institute for Genomic Medicine (RCIGM) provided programmatic support and allowed 90% of the $2 million to go directly to supporting the care and management of critically ill babies. The state funds are now fully expended and, as required by legislation, the following summary and analysis serve as the final report to the California Department of Health Care Services.

As NIH Director Dr. Francis Collins has previously noted, DNA sequencing technologies defy one of the time-honored adages of medicine—when it comes to faster, better, cheaper, "you can only get two of the three."[1] When rapid precision medicine is implemented, stakeholders realize that faster and better is actually cheaper.

Respectfully submitted,

Margareta E. Norton
Executive Vice President & Chief Administrative Officer

Project Description

OVERVIEW

Project Baby Bear employed rWGS as part of a precision medicine program to hasten the diagnosis of rare, genetic diseases in critically ill infants and transition from generic treatments for poorly defined diseases of undetermined causes to treatments that target specific conditions with known causes—thus preventing further irreversible harm. In a rapid precision medicine system, clinicians employ genetic and other information to tailor treatments to specific individuals or groups. Project Baby Bear provided rWGS to babies enrolled in the Medi-Cal program who were receiving care at one of five pilot sites.

This report serves as the final written summary for the project. It reports the clinical outcomes for babies in Project Baby Bear and estimates the effects of providing rWGS on healthcare expenditures. Project Baby Bear language in the 2018-19 state budget included the following:

> *(a) Notwithstanding any other law, of the funds appropriated in this item, $2,000,000 shall be available for the Whole Genome Sequencing Pilot Project. The State Department of Health Care Services shall provide this grant to a state nonprofit organization for the execution of a one-time Clinical Whole Genome Sequencing Pilot Project, to investigate the potential clinical and programmatic value of utilizing clinical Whole Genome Sequencing (cWGS) in the Medi-Cal program. The grantee shall complete whole genome sequencings of Medi-Cal neonatal and pediatric intensive care patients from identified Medi-Cal sites statewide with a goal of completing a minimum of 100. The grantee shall report semi-annual updates to the department, and to the fiscal and policy committees of the Legislature through July 1, 2020, or until the funds are fully expended, whichever is sooner. Within 120 days of the final expenditure of all funds appropriated for this purpose, the grantee shall report to the department and to the fiscal and policy committees of the Legislature the results of the pilot project including, but not limited to, the following:*
>
> *1. The number of Medi-Cal genomically informed pediatric cases*
>
> *2. A cost analysis of comparative effectiveness in patient diagnostics and treatment.*
>
> *(b) The award of the grant pursuant to this provision shall be exempt from Part 2 (commencing with Section 10100) of Division 2 of the Public Contract Code.*
>
> *(c) The Department of Finance may authorize the transfer of expenditure authority specified in subparagraph (a) of this provision to Schedule (1) of Item 4260-101-0001.*

For more information on previous state reports and project background, please visit:
https://www.radygenomics.org/our-work/project-baby-bear/

WHAT THE DATA TELL US: KEY RESULTS

Data analyses from Project Baby Bear reveal these key results:

- Rapid whole genome sequencing was provided for 178 Medi-Cal babies and families (Table 1)
- 43% of rapid genome tests resulted in a diagnosis that explained the infant's admission to the hospital
- 31% of babies had changes to their care as a result of rapid genome sequencing
- Median turnaround time for provisional rWGS results was three days
- Of the genetic diagnoses made, 35 had an incidence of less than one in one million births (Appendix A, Table 5)

- Substantial reductions in healthcare spending occurred, largely because rWGS permitted doctors to discharge babies sooner and reduce the number of procedures. These changes led to:
  - 513 fewer days in the hospital (Appendix B, Table 7)
  - 11 fewer major surgeries, including a major reconstructive surgery on the upper airway and a bowel surgery (Appendix C). Given their diagnoses, the children would not have benefited from these surgeries.
  - 16 fewer invasive diagnostic tests (including open muscle, liver and other biopsies under general anesthesia). These tests were no longer necessary because rWGS had identified the causes of their illnesses.
  - $2.5 million in healthcare savings
  - Decreased suffering as a result of more rapid return to health, avoidance of unnecessary surgeries and tests, discontinuation of incorrect therapies and implementation of precision medicine.

TABLE 1. CHANGES IN MANAGEMENT OF BABIES WITH rWGS DIAGNOSES

PILOT SITES	# OF BABIES	BABIES DIAGNOSED	BABIES WHOSE CARE WAS CHANGED*	DAYS TO RESULTS**
CHOC CHILDREN'S HOSPITAL (ORANGE COUNTY)	23	12 (52%)	9 (39%)	2.5
RADY CHILDREN'S HOSPITAL-SAN DIEGO	59	22 (37%)	19 (32%)	3
UC DAVIS CHILDREN'S HOSPITAL *(Sacramento)*	34	12 (35%)	8 (24%)	2
UCSF BENIOFF CHILDREN'S HOSPITAL OAKLAND	24	12 (50%)	9 (38%)	3
VALLEY CHILDREN'S HOSPITAL *(Madera)*	38	18 (47%)	10 (26%)	3
TOTAL PROJECT BABY BEAR CASES	178	76 (43%)	55 (31%)	3

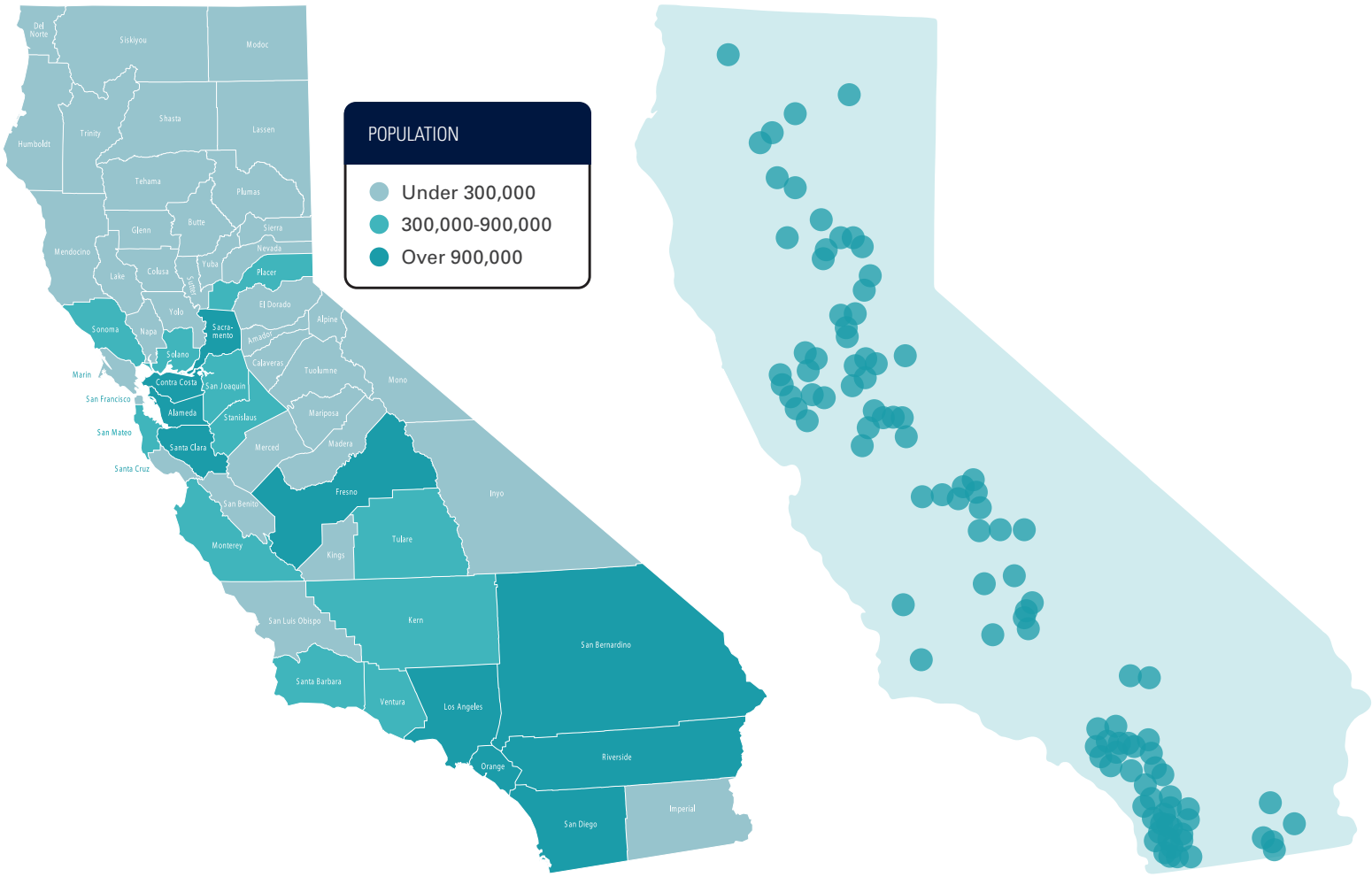
** Results confirmed 21 babies were already receiving appropriate care*
*** Median # days to delivery of provisional positive results*

In Project Baby Bear, 178 babies and their families underwent rapid whole genome sequencing. This table summarizes the results of those tests for each of the five participating hospitals.

Zip Codes Represent Statewide Reach and Underserved Areas

Project Baby Bear provided access to rWGS at five hospitals with California Children's Services accredited regional (Level IV) neonatal and pediatric intensive care units (ICUs). As a result, critically ill Medi-Cal babies had adequate access to rWGS in California from north to south and in regions with the highest population density (Figure 1). Now that Project Baby Bear has ended, our goal is to extend access to all of the approximately 25 California Children's Services accredited regional (Level IV) neonatal and pediatric ICUs and thereby ensure that every California Medi-Cal baby in a neonatal, pediatric or cardiovascular ICU has access to the test.

FIGURE 1. WHERE PROJECT BABY BEAR FAMILIES LIVE



The map on the left shows each of California's 58 counties and its population density. Each dot on the right map represents the zip code of the primary residence of a Project Baby Bear enrollee.

Types of Genetic Diseases Diagnosed

The presentating signs and symptoms of disease in the 178 babies enrolled in Project Baby Bear were extremely varied (Appendix A, Table 4). The most common presentations of illness in which a genetic disease was diagnosed by rWGS were hypotonia or low muscle tone (23% of infants), respiratory failure (17%), seizures (16%), and lactic acidosis, a metabolic upset that inhibits the proper breakdown of food into energy (13%). Furthermore, the clinical presentations of genetic diseases observed among infants in the neonatal intensive care unit (NICU) frequently differed from their classic presentations in older children, making it much more difficult for infants to be diagnosed in the absence of rWGS.

Each genetic disease diagnosed in Project Baby Bear infants is documented in Appendix A, Table 5 alongside the incidence of the disease in the U.S. Thirty-five of the diagnosed genetic diseases have an incidence of less than one in one million births. These conditions are so rare that many treating physicians had never seen them before. Sixty-five of the 71 primary genetic diseases were diagnosed

just once in the Baby Bear population. These findings reinforce earlier results in more than 1,500 children who received rWGS at RCIGM. Many of these disorders are currently underdiagnosed in NICU and pediatric intensive care unit (PICU) infants.

Twenty-six babies (15%) were diagnosed with genetic diseases for which effective treatments are available (Appendix A, Table 6). However, genome screening also led to changes in the management of many other Project Baby Bear infants for whom an effective treatment was not available. In these situations, rWGS results empowered clinicians and parents to quickly make informed decisions that typically altered the course of the baby's hospitalization and led to the initiation or avoidance of a procedure and fewer days in the hospital.

rWGS is Ready to be the New Standard of Care

Among high-risk infants with rare, genetically determined diseases, time-to-treatment is crucial. Project Baby Bear vitally shortened the time needed to accurately diagnose and optimally treat these critically ill children.

The Project refuted the adage that when it comes to faster, better, cheaper, a system can only achieve two out of the three. The results presented in this report demonstrate that earlier clinical decisions informed by rapid diagnoses improved health outcomes, decreased suffering and reduced healthcare costs.

Faster and Better is Actually Cheaper

Caring for severely ill babies entails the use of tremendous resources. This fact was reinforced by the experiences of the Project Baby Bear sites.

However, evidence from the five pilot sites shows that not employing this model is even more expensive, because inconclusive tests, ineffective treatments, lengthy hospitalizations and suboptimal outcomes are costly and time consuming.

Project Baby Bear Demonstrated that rWGS is:

- **FASTER**. rWGS is an extraordinary technology that operates at once-unthinkable speed. It can help doctors diagnose a baby's problem in days. Speedy test results mean babies get the right care sooner. Standard methods of diagnosis for comparable disorders frequently take weeks or months.

- **BETTER**. The project improved the health outcomes of babies, delivering rapid diagnoses that led to valuable changes in clinical management. These changes ranged from prescription of the right medicines sooner to difficult decisions to discontinue futile care. Using the most comprehensive genomic test available, Project Baby Bear provided families with timely diagnostic information that reduced uncertainty and empowered them to make life-altering medical decisions. This led to reduced suffering and better outcomes.

- **CHEAPER**. Because rWGS is accurate and fast, hospitals saved money in useless tests not ordered, futile operations not performed and days of waiting in expensive intensive care units (ICUs) not needed. Rapid precision medicine spends more on the right care and less on care that doesn't help.

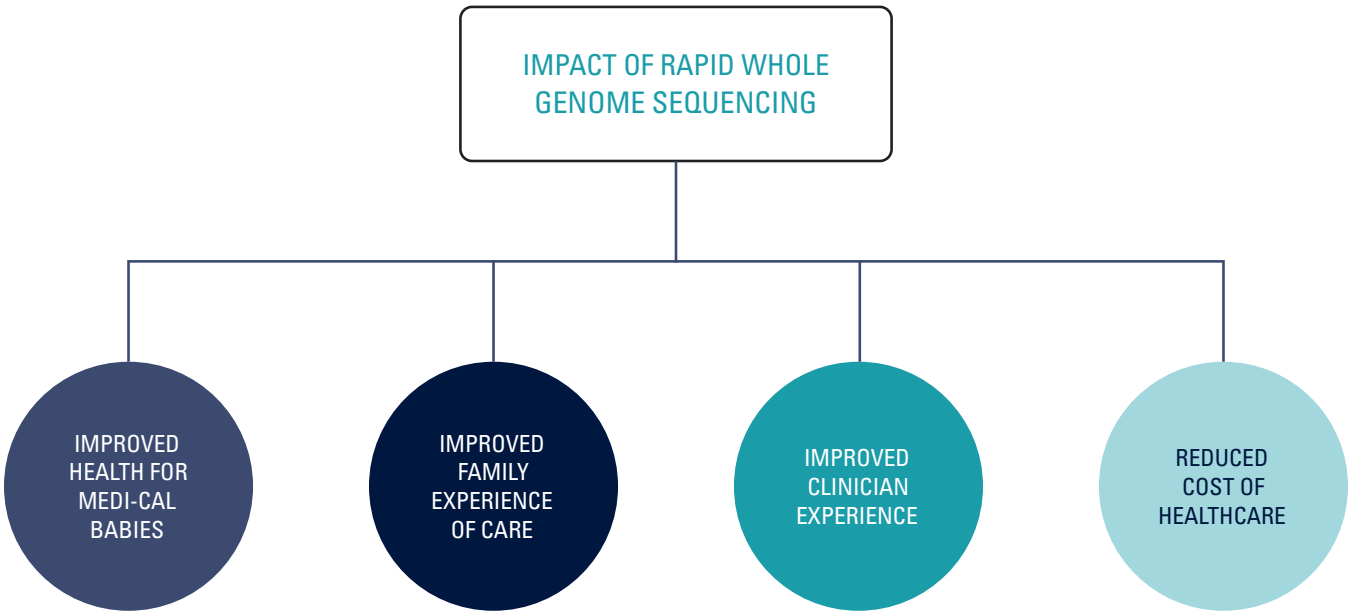
Case Studies Show Impact in Four Dimensions

The introduction of genome sequencing in some of the most vulnerable of babies covered by Medi-Cal had a profound impact on four key dimensions of healthcare (Figure 2). At the pilot sites participating in this project, whole genome sequencing:

1. Improved the health outcomes of babies by providing rapid diagnoses which led to beneficial changes in clinical management.
2. Improved the experience of healthcare for families by providing timely diagnostic and prognostic information, reducing uncertainty and empowering families to make informed medical decisions.
3. Improved the clinicians' experience by bolstering their confidence in treatment decisions, their comfort with the implications of those decisions and their satisfaction by fostering delivery of more effective care in an efficient, collaborative team environment.
4. Lowered the cost of delivering care by reducing unnecessary tests, procedures and time spent in the hospital.

Following are a selection of Project Baby Bear patient stories that highlight the impact of rWGS on each of these dimensions.

FIGURE 2. THE IMPACT OF rWGS IN FOUR DIMENSIONS



IMPROVED HEALTH FOR MEDI-CAL BABIES

Improved Health for Medi-Cal Infants Less than One Year Old

Babies in a NICU face extraordinary medical challenges. By their nature, neonates are very vulnerable. They quickly become ill. Disease progression occurs much faster than in adults. By the time they develop symptoms it may be too late to change the trajectory of their illness. Moreover, their diagnostic workup is challenging and, for many, the results fail to effectively address the root of their illness. In the absence of a definitive diagnosis, medicines, surgeries and other activities intended to be therapeutic may fail to fix the problem or actually be harmful. They expose babies to the risks of anesthesia and to complications from the procedures themselves, without a clear benefit.

Utilizing rWGS provides valuable information about the underlying molecular causes ultimately responsible for the condition. Based on the molecular diagnosis, a care path best suited to the baby's precise situation may be implemented in a timely fashion.

IMPROVED HEALTH FOR MEDI-CAL BABIES

SITE 3, CASE 26

Common Heart Problem… or Something Else?

The mother in Case 26 had an uncomplicated pregnancy and went home with her newborn shortly after delivery. The baby boy was in good health for three months, but then began to fatigue easily, breathe with difficulty and feed and drink less. An echocardiogram showed a severely enlarged left heart with mitral valve regurgitation, a sometimes-benign condition in which a heart valve fails to close completely. The baby's doctor prescribed captopril, a medication to improve the heart's function, and discharged him home.

Within two months the baby returned to the emergency room with a cough and labored breathing. A second echocardiogram showed that his heart function was worsening despite his heart medication. Clinicians suspected his symptoms were linked to an underlying genetic problem and ordered rWGS.

The sequencing identified a genetic change in a gene known to cause cardiomyopathy (a disease that damages the heart muscle and reduces its ability to adequately pump blood and oxygen to the body). Knowing the cardiomyopathy was caused by a genetic disease and not something that would spontaneously improve, clinicians added a full spectrum of heart failure medications to the original captopril prescription.

This more intense approach helped stabilize the baby and prevented further complications. Informed by the known disease trajectory, clinicians were confident that his condition would not improve with medical management alone, allowing the baby to be considered for a heart transplant sooner than would have been the case in the absence of a diagnosis. Informed by the diagnosis, clinicians knew that a heart transplant would be curative.

Informed by the diagnosis, clinicians knew that a heart transplant would be curative.

IMPROVED HEALTH FOR MEDI-CAL BABIES

SITE 3, CASE 29

rWGS Uncovers a Problem No One was Looking for

Even when a diagnosis does not explain a baby's current illness, rWGS can provide life-saving information for the clinicians and family. The baby girl in Case 29 was born with a slow heart rate and severe anatomic and functional heart abnormalities that threatened her life. She was immediately admitted to the NICU following her delivery. (Her diagnoses included heterotaxy, bradycardia, situs inversus and interrupted inferior vena cava.)

Given the baby's symptoms and the potential of an underlying genetic defect, clinicians ordered rWGS. Surprisingly, the results did not explain the baby's symptoms, but they did identify a genetic change that causes a medical problem called malignant hyperthermia that is often fatal—yet treatable if known. A genome sequencing analysis includes incidental findings, genetic changes that are not associated with why the child is sick but that can be extremely helpful in guiding management of the patient now and in the future.

Malignant hyperthermia is a rare but life-threatening condition brought on by general anesthesia. It causes a rapid rise in body temperature and severe muscle contractions. If this condition is not treated promptly by withdrawing the anesthetic medication and administering the muscle relaxer dantrolene, mortality can be greater than 70%.

Unfortunately, because this baby has structural heart defects that threaten her life, heart surgery is inevitable. Thanks to the physicians' actions following the rWGS finding, when she undergoes surgery the anesthesiologist will know to avoid using the specific class of anesthetics that trigger the contractions and spasms and will be prepared to administer the antidote dantrolene, potentially preventing complications or death.

This discovery also has important implications for the family. Genome sequencing of the baby's parents revealed that malignant hyperthermia was inherited from her mother. Doctors will take the same precautions if her mother has surgery. Further testing among extended family members is in progress so that they will be protected if they share susceptibility to this genetic condition.

IMPROVED FAMILY EXPERIENCE OF CARE

Improved Experience of Care for Babies and Families

Conversations with parents demonstrate that rapid genomic medicine improves the experience of care for both babies and their families. Parents of critically ill babies who have no clear explanation for their child's symptoms often feel helpless and uncertain about what to do. They realize their child may be in pain but do not know whether a new test or intervention will help, whether the doctors are missing something or whether they need to seek care at other hospitals. This is often referred to as the diagnostic odyssey for families with undiagnosed disease. Moreover, caring for a sick baby places tremendous stress on a marriage, siblings, work and finances.

Families enrolled in Project Baby Bear said genome sequencing helped them better manage these challenges by explaining in the first week of hospitalization why their baby was sick or that the cause of the illness was unlikely to be genetic. This empowered them to confidently make informed decision about their baby's care.

IMPROVED FAMILY EXPERIENCE OF CARE

SITE 3, CASE 23

Confidence in an Excruciating Decision

The baby in Case 23 was admitted to the NICU with a brain bleed and decreased muscle tone. Among the possible reasons for these symptoms was the difficult birth experience, an infection or a genetic disease.

Rapid whole genome sequencing showed the diagnosis to be a variant in a gene known to cause muscle weakness and decreased muscle tone that can impair a baby's ability to feed and breathe on his own. Babies with this condition frequently require a mechanical ventilator to help them breathe and usually do not survive beyond early childhood.[2]

By coincidence, early clinical trials of a gene therapy drug specifically for this condition had recently reported promising safety and efficacy data. But the drug was not yet approved for use outside closely monitored studies. The patient's clinical team began discussions with the drug's manufacturer for possible compassionate use. They discovered the drug was not currently available, but that the baby could soon be eligible for a clinical trial.

Genome sequencing empowered the baby's parents to make an informed decision with the baby's clinicians. Clinicians educated the parents on the baby's prognosis and the risks and benefits of his treatment options, including the clinical trial. Because of uncertainty about the availability of the gene therapy drug, potential complications from a brain bleed the baby had already suffered and long-term prognosis of the baby's condition, his parents made the decision to shift goals to comfort care and move out of the NICU.

Rapid whole genome sequencing led to an early diagnosis and a timely decision that incorporated the values and wishes of the parents and the knowledge and experience of the baby's clinicians. Eliminating the need for multiple genetic tests and painful surgeries (e.g. a muscle biopsy, a surgery for a breathing tube and a gastrostomy tube for feeding) allowed parents to spend time with their child in the way they found most meaningful.

IMPROVED CLINICIAN EXPERIENCE

Improved Clinician Experience

National studies suggest that at least 50% of physicians are experiencing burnout, driven by factors that include a sense that their efforts are too-often futile and that little they do will make a difference.[3] This sense is often accompanied by frustration with inefficiencies and concerns about their patients' safety and the quality of care they are providing.

The cost to the healthcare system of the resulting physician attrition is estimated to be roughly $500,000-1,000,000 per occurrence.[3]

Project Baby Bear made a tremendous impact on many clinicians who cared for babies receiving rWGS. It provided them with critical diagnoses in three days instead of the four to six weeks standard genetic testing provides.

This bolstered clinicians' confidence in treatment decisions, their comfort with the implications of those decisions and their satisfaction with work. It helped diffuse the uncertainty that hangs over clinicians who wait and wonder if they are doing the right thing for their patients and their distressed parents.

IMPROVED CLINICIAN EXPERIENCE

SITE 5, CASE 10

The Upside of a Fateful Test Result

Case 10 was found unconscious and unresponsive. By the time an ambulance crew arrived, he could not be aroused and on arrival at the hospital he needed machines to take over his breathing.

There are many medical conditions that can cause children to have such problems. Some of these have specific treatments that can change the clinical outcome, while for many more there is no treatment that can reverse the problem. This child underwent rWGS and was diagnosed with a form of spinal muscular atrophy (SMA) for which there is currently no treatment. This type of SMA is very difficult to diagnose. Consistent with the other forms of SMA and amyotrophic lateral sclerosis, when the nerves have died there is no way to restore the nerve and muscle function. Understanding the underlying condition, the doctors knew that the child's current clinical picture was irreversible.

After the doctors discussed the results and their implications with the family, the parents' wishes for their child were clear. The doctors promptly provided the child with permanent breathing and feeding tubes. Knowing that the baby would require assistance to breathe for the rest of his life, they avoided the inevitable failures they would have experienced had they tried to wean the child from the ventilator. Placing the permanent tubes sooner allowed the child to be discharged from the hospital one to two weeks earlier than if he had not undergone rWGS. It also emboldened the team to avoid unnecessary attempts to try to wean the child off a breathing machine.

The rWGS test reassured doctors that they were providing the family with accurate information and care that aligned with the family's wishes. The doctors felt a huge sense of relief knowing this was the right choice for the baby.

REDUCING THE COST OF HEALTHCARE

Reducing the Cost of Healthcare

By reducing the need for tests and procedures and the time babies spent in the hospital, rWGS led to a more efficient use of resources and significant reductions in the cost of delivering care. These in turn produced significant savings for the state Medi-Cal program.

For example, based on information provided from the Project Baby Bear charge data, one day in the intensive care unit (ICU) costs approximately $3000, while one day of extracorporeal membrane oxygenation (ECMO), a machine that provides heart-lung bypass in critically ill children, costs approximately $15,000.

Rapid whole genome sequencing provides clinicians and families with answers quickly, allowing them to promptly choose the best course for each baby. These outcomes often involve fewer interventions and result in lower costs.

REDUCING THE COST OF HEALTHCARE

SITE 1, CASE 10

Precise, Timely Care Avoids Weeks of Unnecessary Treatments

Case 10 was a 6-week-old male who had been admitted for 12 days. His numerous, apparently unrelated medical problems confounded his caregivers and were steadily worsening.

He suffered from multiple structural heart defects, respiratory distress and insufficient weight gain brought on by poor feeding and other problems. He had several infections and copious secretions that clinicians could not explain.

On hospital day 12 providers sent a sample of his blood for whole genome analysis. Three days later, clinicians received a diagnosis. The boy had CHARGE syndrome, a condition that in many children causes heart defects, blockage of the nasal airway (choanal atresia), slowed growth, genital abnormalities, ear abnormalities and a malformation of the eye that can cause vision problems (coloboma).

Interestingly, clinicians at the hospital had cared for another baby with a similar clinical picture two years earlier. That experience would prove invaluable. With the earlier baby, three attempts to remove his breathing tube had failed in 11 days. Those were followed by an operation called a supraglottoplasty that doctors perform to remove a suspected obstruction in the upper airway. When that did not help the baby's breathing, clinicians performed a tracheostomy, surgically creating an opening in the baby's neck to insert a breathing tube.

Unfortunately, in CHARGE syndrome, connective tissue is abnormal, and for most patients with CHARGE syndrome a supraglottoplasty is not effective. By the time clinicians in this first case had ordered rWGS and understood the source of their young patient's problems and why their efforts had been futile, the baby had been in the hospital six weeks.

Now, a second baby lay in a bed sick with CHARGE syndrome, and they approached him differently. They made a minimal number of attempts to remove the breathing tube. They did not consider performing a supraglottoplasty; it would not help clear his airway. Instead, they moved directly to tracheostomy following one trial of extubation. To address the baby's failure to gain weight, clinicians also placed a feeding tube. And they consulted specialists in ophthalmology, genetics and immunology who help babies with this condition.

The baby in Case 10 quickly received care tailored to his rare genetic disease and, compared with the earlier case, avoided suffering from unnecessary and risky surgical procedures. Consequently, he went home about one month sooner, largely as a direct result of the rWGS diagnosis and the system of care built to support it. Fortunately for this child, the parents sought care at a Project Baby Bear pilot site.

Economic Impact of rWGS

OVERVIEW

Phase III of Project Baby Bear included a retrospective analysis of the economic impact of rWGS on the hospitalizations of critically ill infants. By introducing Medi-Cal babies into a coordinated system of care that included physicians trained in identifying babies likely to benefit from whole genome sequencing, lab interpretation scientists, genetic counselors and others, the state of California saved millions of dollars in healthcare expenses due to avoided procedures and shorter hospital stays. Based on this analysis (Appendices B through E), rWGS resulted in:

- 513 fewer days in the hospital
- 11 fewer major surgeries (including a major reconstructive surgery on the upper airway and bowel surgeries)
- 16 fewer invasive diagnostic tests (including open muscle, liver and other biopsies under general anesthesia)

The avoided procedures and reduced hospital time amounted to $2.5 million in cost savings. These cost savings stemmed from changes in the medical management of just 29 babies who received significant benefit from genome sequencing. To determine the extent of the savings, analysts at RCIGM compared the cost of caring for each of these 29 babies with the cost of caring for babies with similar conditions who did not have access to genome sequencing and the system of care that surrounds it. (Appendix B summarizes these savings and includes a brief discussion of each patient.)

Estimating California's Savings from Five Pilot Sites

The RCIGM team employed a highly conservative approach to estimating cost savings (Appendix D). To the extent that these estimates are incorrect, it is likely that savings are underestimated. These analyses considered only the savings that accrued during the hospital stay in which a baby underwent rWGS. It is highly likely that some of the babies who benefited from rWGS will use fewer healthcare resources after they leave the hospital during their first year of life and beyond, but estimating the magnitude of these changes was deemed too speculative. Further, the analysis adopted a conservative approach to estimating the effects of rWGS on length of stay and avoided procedures, requiring unanimous agreement from site-based clinicians and clinicians at RCIGM before concluding that an avoided procedure or shortened hospital stay was indeed a result of genome sequencing.

The RCIGM analytical model incorporated high- and low-cost scenarios to estimate savings. Differences between high and low estimates were primarily due to uncertainty around the reductions in length of stay attributed to rWGS. For example, if a physician team quantified a reduction of between seven and 14 days in length of stay, the financial model resolved this by using the mid-point of these ranges. In aggregate, physicians estimated that between 454 and 573 hospital days were avoided, resulting in a mid-point of 513 hospital days saved. Total Project Baby Bear savings due to the combination of avoided procedures, avoided diagnostic tests, avoided professional fees and the range of avoided hospital days were estimated to be between $2.2 and $2.8 million, with a mid-point of $2.5 million.

To determine the proportion of costs to allocate to professional fees, the analysis used a rate of 17.7% of the reimbursement for facility fees. This is the average reimbursement of professional fees for services covered by Medicaid, according to recently published data[4] (see Appendix D for further explanation).

As a result of employing rWGS, physicians did not order other diagnostic tests such as chromosomal microarrays for more than 50 babies. To estimate cost savings from these avoided tests, pricing information from a variety of sources was used to estimate the cost of purchasing or producing these tests.

Analytic methods are described at length in Appendices D and E. Details about each baby and the impact of rWGS on the cost of caring for them are provided in Appendices B and C.

KEY RESULTS

The implementation of genome sequencing in Project Baby Bear led to $2.5 million in healthcare cost savings. These included facility fees and professional fees.

The total cost of implementing the Project Baby Bear's system of rapid precision medicine and sequencing was $1.73 million. Therefore, net cost savings were $763,000 ($2.5 million in savings minus $1.73 million in rWGS expenses). Distributed over 178 cases, the resulting average net benefit of sequencing per patient was $4,287 ($763,000/178 patients). Of the eliminated costs, approximately 94% resulted from reduced length of stay and 6% from avoided major procedures such as invasive biopsies.

The Economic Value of a Speedy Test

To calculate the benefits that accrue from rapid genome sequencing, RCIGM also estimated the cost savings that would have been produced if the medical team received sequencing results in seven or 14 days rather than the three-day median time achieved in Project Baby Bear. The RCIGM team determined whether a longer turnaround time would have increased inpatient stay for each of the 29 patients who received significant benefit from sequencing— and, if so, whether cost savings associated with sequencing would diminish.

For example, compared to a similar baby who did not have access to whole genome sequencing and who would have proceeded to the same, but delayed, care after undergoing a standard panel of genetic tests with a 17-day turnaround, physicians judged that receiving rWGS results in three days enabled the baby to avoid 14 days in the ICU. A seven-day turnaround meant the baby receiving rWGS avoided 10 days in the ICU. And a 14-day rWGS turnaround saved the baby three days in the ICU. (See Figure 3 and Appendix F for supporting detail.)

FIGURE 3: EFFECTS OF LONGER rWGS TURNAROUND TIME (TAT) ON SAVINGS

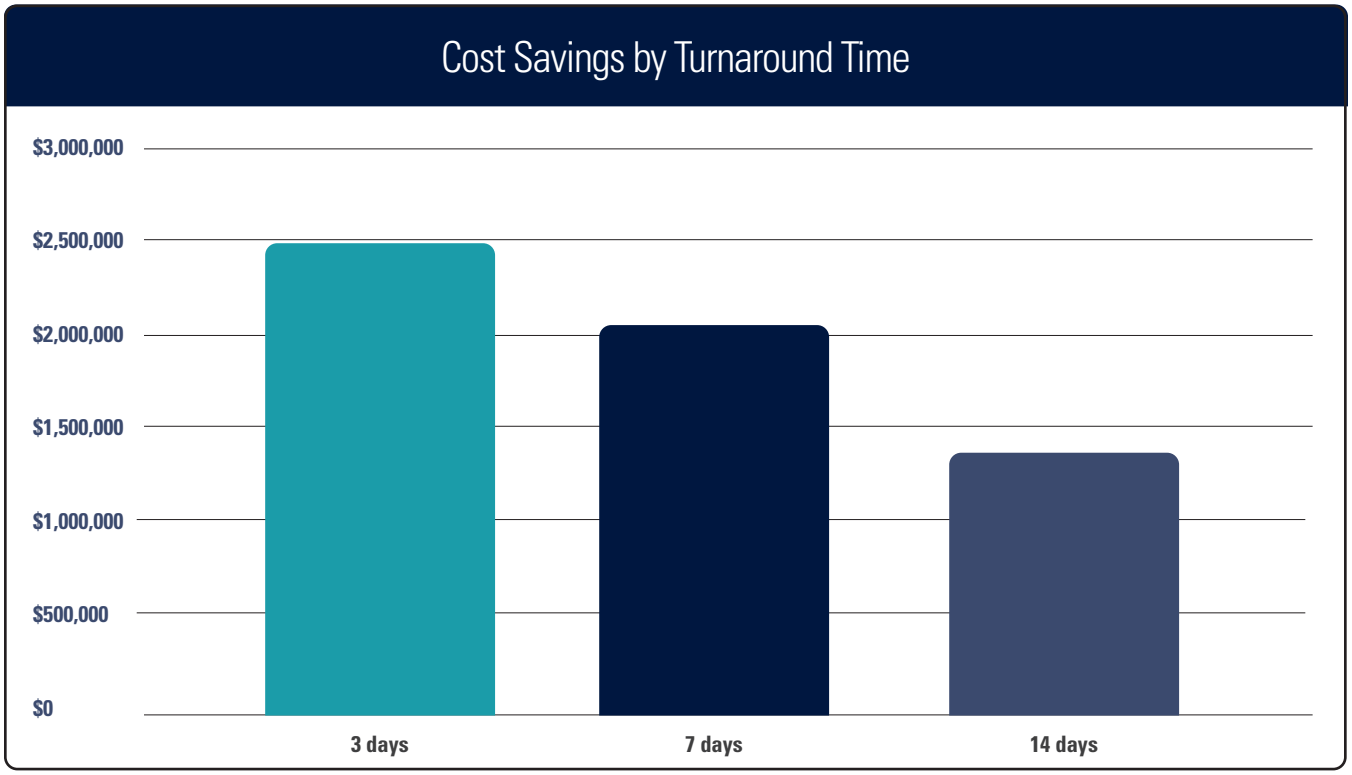


Figure 3 shows the differences in project cost savings if the laboratory returned rWGS results to a clinical team in three days compared to seven days or 14 days. Faster turnaround time (TAT) shortens inpatient days and increases healthcare savings.

Medi-Cal Admissions in Project Baby Bear

Approximately 2,899 babies covered by Medi-Cal were admitted to Level III/IV NICUs at the five hospitals participating in Project Baby Bear during a mean sampling period of approximately 11 months (late 2018 through late 2019). Of these admissions, doctors ordered rWGS for between 3% and 13% of beneficiaries at each site (Table 2).

TABLE 2. NUMBER OF MEDI-CAL ADMISSIONS TO PARTICIPATING LEVEL III/IV NICUs DURING SAMPLE PERIOD

SITE	MEDI-CAL ADMISSIONS *(during sample period)*	PATIENTS ENROLLED IN BABY BEAR *(during sample period)*	PROPORTION OF MEDI-CAL ADMISSIONS ENROLLED
CHOC CHILDREN'S HOSPITAL (ORANGE COUNTY)	667	22	3%
RADY CHILDREN'S HOSPITAL-SAN DIEGO	325	43	13%
UC DAVIS CHILDREN'S HOSPITAL *(Sacramento)*	713	33	5%
UCSF BENIOFF CHILDREN'S HOSPITAL OAKLAND	423	21	5%
VALLEY CHILDREN'S HOSPITAL *(Madera)*	771	35	5%
TOTAL	2,899	154	5%

If rWGS were available to all Medi-Cal babies who met the project's inclusion and exclusion criteria (see Project Baby Bear Second Interim Report, Appendix C), and if the current proportions of sequenced babies (3% to 13%) were applied statewide, it might be expected that between 210 and 910 babies would receive rWGS annually from the five Project Baby Bear sites. As Medi-Cal considers adding rWGS as a covered benefit, it is important to recognize that the number of babies sequenced could change when more clinicians become exposed to this technology. During Project Baby Bear, as physicians became more familiar with the technology, patient identification became more intuitive and ingrained within the care teams. Most of the eligible babies at each site received rWGS, but some did not because of limited enrollment and resources. The variation in the proportion of Medi-Cal babies who received rWGS across sites suggests that local implementation choices will matter, and this should be expected to affect the total number of tests ordered statewide.

Limitations

As with any estimates, there are limitations to the accuracy and comprehensiveness of the data cited in this report. Most importantly, physician judgements about treatment changes are inevitably subjective, although significant care has been taken to be conservative and consistent in those judgments. Additionally, RCIGM's analysis assumed that average charges over the last three inpatient days of a baby's stay represented a reasonable substitute for the charges of an avoided inpatient day. This assumption is reasonable, but certainly introduces some error.

As noted earlier, long-term savings are underestimated because the analysis only considers changes in management during the hospital stay in which rWGS was provided; the analysis did not consider changes in management post-discharge because such changes were considered highly speculative. It should be noted, however, that we anticipate healthcare cost savings to continue to occur through infancy, childhood and the lifetime, and to extend to parents and siblings. Researchers recently reported that children who undergo genome-wide sequencing continue to accrue benefits for 20 years and attributed an incremental cost-effectiveness ratio of $9,910 per quality-adjusted life-year gained from genome-wide sequencing diagnosis.[5]

A final significant limitation of the financial analysis is that it does not account for the possibility that sequencing changed DRG coding. It is possible that the use of rWGS changed the course of care for several patients in such a way that the baby's outcome changed the DRG codes and severity levels assigned to them. This change would likely have an economic impact, as DRG reimbursement rates vary widely. However, this was not addressed in the model as it is too speculative to concretely determine.

Despite these limitations, it should be noted that the methodology used was identical to that published in the peer-reviewed healthcare literature.[6] Furthermore, the magnitude of the cost savings associated with the use of rapid whole genome sequencing herein was similar to that published in the healthcare literature.[6,7,8]

Use of Funds

Budgeting

As of June 1, 2020, $2 million had been expended (Table 3). Genome sequencing has been completed on 178 patients and their families. Through responsible stewardship of the funding, the five clinical sites participating in Project Baby Bear enrolled 78% more babies than projected, nearly doubling the state-mandated genome sequencing requirement of 100 babies in the 2018 Budget Act appropriation of $2 million. Sequencing babies in Project Baby Bear resulted in savings of over $2.5 million, with a minimum $750,000 return on investment. In-kind contributions totaling more than $400,000 from the teams at RCHSD and RCIGM provided programmatic support and allowed 90% of the $2 million in state funds to directly support the care and management of critically ill Medi-Cal babies.

Pricing

Rapid whole genome sequencing pricing is outlined here:

rWGS - Proband Only = rWGS on patient sample and parental samples are included for inheritance or phase testing utilizing Sanger sequencing (orthogonal methodology to rWGS testing)

- Turn around time for rWGS - proband only is ≤ 5 days
- $8,500 per case

Ultra-Rapid Whole Genome Sequencing = Trios are preferred (patient, mother, father) and samples are shipped as soon as possible. All samples receive ultra-rapid whole genome sequencing with additional orthogonal testing as needed based on the results

- Turn around time for ultra-rapid whole genome sequencing is ≤ 3 days
- $12,500 per case

In the Project Baby Bear cohort, 31.5% of the cases were done as ultra-rapid and 68.5% of the cases were done as rapid.

TABLE 3. USE OF FUNDS FROM SEPTEMBER 01, 2018 TO JUNE 01, 2020

PHASE I	SUBTOTAL		
Site Set Up Fees	$45,000		
Site Travel	$12,915		
Site Training	$43,000		
PHASE II			
SITE		**RAPID CASES ($8,500)**	**ULTRA-RAPID CASES ($12,500)**
CHOC Children's Hospital (Orange County)		18	5
Rady Children's Hospital - San Diego		33	26
UC Davis Children's Hospital (Sacramanto)		22	12
UCSF Benioffy Children's Hospital Oakland		21	3
Valley Children's Hospital (Madera)		28	10
Sequencing	$1,737,000	122	56
PHASE III			
RCIGM Project Management and Analytics	$49,400		
Health Economic Consultation Services	$17,250		
Additional Program Management Services	$95,435		
TOTAL			
Total Program Costs		$2,437,204*	
Grant from State of California		$2,000,000	$0
State Funds Expense			$2,000,000

**$437,204 of in-kind donation monies over the $2 million state appropriation were made regarding site time reimbursement, survey time etc.*

Recommendations: Implement rWGS Statewide

Project Baby Bear exceeded virtually all targeted endpoints sooner than anticipated: 78% more babies were enrolled than expected, months ahead of schedule. Rates of diagnosis (43%) and subsequent changes in medical management (31%) exceeded projections. Estimated healthcare savings totaled $2.5 million.

The five pilot sites have demonstrated that this model can be quickly scaled up. The sites were up and running in months, along with the systems to support them. Rapid whole genome sequencing is well positioned to be a first-tier diagnostic test for critically ill babies with diseases of unknown cause.

Based on the findings of this report and others, the Project Baby Bear team:

- Recommends reimbursing rWGS for all babies and infants covered by Medi-Cal in all California Children's Services accredited regional NICUs and PICUs who meet Project Baby Bear inclusion and exclusion criteria (see Project Baby Bear Second Interim Report, Appendix C).
- Recommends employing rapid precision medicine utilizing rWGS as a first-tier test for critically ill infants 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 babies or comparable reductions in the cost of care.
- Cautions against expanding reimbursement to whole genome sequencing that is not rapid (as evidenced above) or whole exome sequencing (because it is neither rapid nor as complete).[9]

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 babies. It is no longer experimental. This has been endorsed by Blue Shield of California, which now provides rapid whole genome sequencing as a covered benefit.[10]

Implementing rWGS statewide would integrate California's technological capability with its clinical and system expertise to achieve "faster, better, and cheaper" care for all California families.

Rapid Precision Medicine with rWGS improves lives, and California can afford it. It should be accessible to all babies covered by Medi-Cal as soon as is possible.

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Appendix A: Patient Presentations, Diagnoses, Disease Incidences & Changes in Management

Following are three tables that describe the infants enrolled in Project Baby Bear, the diseases rWGS helped diagnose in them and the treatments they received.

Table 4 records the wide range of signs and symptoms the 178 enrolled babies presented to clinicians. The most common genetic diseases diagnosed by rWGS were hypotonia or low muscle tone (H, 23% of infants), respiratory failure (RF, 17%), seizures (Sz, 16%), and lactic acidosis, a metabolic upset that inhibits the proper breakdown of food into energy (LA, 13%).

Table 5 documents each genetic disease diagnosed in Project Baby Bear infants as well as the U.S. incidence of the disease. Thirty-five of the diagnosed genetic diseases are rare conditions with an incidence of less than one in one million births. Sixty-five of the 71 primary genetic diseases were diagnosed just once in the Baby Bear population. Five infants had a second diagnosis. One infant had a third diagnosis based on an incidental finding that was unrelated to the signs and symptoms that led to sequencing.

Table 6 catalogs the infants whose medical management changed as a result of an rWGS diagnosis, and describes whether or not the treatments they received were effective.

TABLE 4. TYPES OF DISEASES IDENTIFIED IN PROJECT BABY BEAR

PRESENTING SYMPTOMS AND SIGNS OF DISEASE	GENETIC DIAGNOSIS
INTRACRANIAL CALCIFICATIONS, ABNORMAL NEWBORN SCREEN	Aicardi-Goutieres Syndrome 1
PH, RF	Alveolar capillary dysplasia w. misaligned pulmonary veins
POSTAXIAL HAND & FOOT POLYDACTYLY, RENAL CYSTS, RF	Bardet-Biedl syndrome 10
INTERRUPTED AORTIC ARCH, VSD, ASD, FTT	CHARGE syndrome
PARTIAL APVR, PERSISTENT SUPERIOR VENA CAVA, ASPLENIA, MICROTIA, MICROPTHALMIA	CHARGE syndrome
P, RF, LA, HYPERAMMONEMIA, ABNORMAL CARDIAC VENTRICULAR FUNCTION, PDA, MITRAL REGURGITATION, ASD, LOW SET POSTERIORLY ROTATED EARS, CAMPTODACTYLY, POSTERIORLY PLACED ANUS, ROCKER BOTTOM FOOT, HYPERBILIRUBINEMIA, APNEA, GR	Chr 15q13.1q13.3 deletion
SZ	Chr 16p11.2 deletion syndrome
ASD, PDA, RF, HYPERTELORISM, LOW-SET, POSTERIORLY ROTATED EARS, PROMINENT NASAL BRIDGE, UMBILICAL HERNIA, ABNORMALITY OF CRANIAL SUTURES, PROMINENT FOREHEAD, HYPERTONIA	Chr 16p11.2 duplication syndrome

PRESENTING SYMPTOMS AND SIGNS OF DISEASE	GENETIC DIAGNOSIS
H, HG, HYPERBILIRUBINEMIA, LA, LEFT VENTRICULAR NONCOMPACTION	Chr 1p36 deletion syndrome
RIDGED CRANIAL SUTURES, ABNORMALITY OF ANTERIOR FONTANELLE, HIGH, NARROW PALATE, MICRORETROGNATHIA, MALAR FLATTENING, DOWN SLANTED PALPEBRAL FISSURES, LOW-SET EARS, WIDE INTERMAMMILLARY DISTANCE, SACRAL DIMPLE, ABNORMAL 5TH FINGER MORPHOLOGY, VSD	Chr 4q32.1 deletion
DANDY-WALKER MALFORMATION, HYPOSPADIAS, SACRAL DIMPLE, FLEXION CONTRACTURE, TE, ULNAR DEVIATION OF WRIST, LEUKOCYTOSIS	Congenital disorder of glycosylation type Ig
H, ARTHROGRYPOSIS MULTIPLEX CONGENITA, TE, MACROCEPHALY, MICROGNATHIA, HIGH PALATE, LOW SET EARS, LONG FINGERS, ELEVATED CREATINE KINASE, CEPHALOHEMATOMA, CONGENITAL CATARACT	Congenital muscular dystrophy dystroglycanopathy
FEEDING DIFFICULTIES, RF, PDA, ANEMIA, THROMBOCYTOPENIA, TE, ELBOW FLEXION CONTRACTURE, EEG ABNORMALITY	Congenital Myasthenic Syndrome 18
GR, FTT, ABNORMAL FACIAL SHAPE, SZ	Cutis Laxa 3
FTT, GR, METABOLIC LA, CHOLESTASIS, DIARRHEA, VOMITING, LEUKOCYTOSIS, THROMBOCYTOSIS, MICROCYTIC ANEMIA, P	Diarrhea with Microvillus Atrophy 2
TETRALOGY OF FALLOT, PULMONARY ATRESIA, SZ, ABNORMALITY OF CEREBRAL WHITE MATTER	DiGeorge syndrome
INTERRUPTED AORTIC ARCH, VSD, ABNORMAL LEFT VENTRICULAR OUTFLOW TRACT MORPHOLOGY, ABNORMALITY OF MEDIASTINUM, 2-3 TOE SYNDACTYLY, BULBOUS NOSE, MICROGNATHIA	Digeorge Syndrome
MICROGNATHIA, SHORT RIBS, TE, BILATERAL CLEFT LIP AND PLATE, SHORT FEMUR, HYPOCALCEMIA	Dilated Cardiomyopathy 1
DYSTONIA, H, GROSS MOTOR DELAY	Early onset Parkinson disease 6
HAND & FOOT POLYDACTYLY, TOTAL ANOMALOUS PULMONARY RETURN	Ellis Van Creveld syndrome
SHORT STATURE, SHORT UPPER AND LOWER EXTREMITIES, DYSMORPHIC FACIAL FEATURES, FEEDING DIFFICULTIES, POLYDACTYLY, NATAL TEETH, ACCESSORY FRENULAE, RF, NARROW CHEST	Ellis Van Creveld syndrome
ABNORMAL BLISTERING OF SKIN	Epidermolysis bullosa dystrophica
SZ	Epileptic encephalopathy, early infantile, 11, West syndrome
SZ, ABNORMALITY OF CORPUS CALLOSUM, HG, INFERIOR VERMIS HYPOPLASIA, FEEDING DIFFICULTIES, ABNORMAL RESPIRATORY SYSTEM MORPHOLOGY, APVR, MICROGYRIA	Familial hyperinsulinemic hypoglycemia, type 1
MITRAL REGURGITATION, APICAL HYPERTRABECULATION OF THE LEFT VENTRICLE, CMP	Familial isolated dilated cardiomyopathy

PRESENTING SYMPTOMS AND SIGNS OF DISEASE	GENETIC DIAGNOSIS
MICROTIA, MICROGNATHIA, ANTERIORLY PLACED ANUS, HIGH NARROW PALATE, SHORT PALPEBRAL FISSURE, POOR SUCK, PATELLAR APLASIA, ATRIAL SEPTAL DILATATION, PATENT FORAMEN OVALE, PDA, HYDRONEPHROSIS, TE, HG, RF, MULTIPLE JOINT CONTRACTURES, HYPERBILIRUBINEMIA, ABNORMALITY OF SEPTUM PELLUCIDUM, ABNORMAL EPIPHYSEAL OSSIFICATION	Genitopatellar syndrome
HEMOLYTIC ANEMIA	Glucose-6-phosphate dehydrogenase deficiency
SZ	Glycine encephalopathy
MACROCEPHALY, BIFID RIB, ABNORMALITY OF CEREBRAL VENTRICLES, ENLARGED SYLVIAN CISTERN, LOWER LIMB HYPERTONIA	Gorlin syndrome
AGENESIS OF CORPUS CALLOSUM, OPTIC ATROPHY, UNILATERAL RENAL AGENESIS, LOW-SET EARS, NARROW MOUTH	Helsmoortel-van der Aa Syndrome
SPLENOMEGALY, ANEMIA, CLEFT LIP AND PALATE, HEMOGLOBIN E TRAIT	Hemoglobin E Trait
HIRSCHSPRUNG DISEASE	Hirschsprung Disease
RECURRENT FRACTURES, HYPERTONIA, THORACOLUMBAR KYPHOSIS	Hyaline Fibromatosis Syndrome
VSD, DOUBLE CHAMBERED RIGHT VENTRICLE, ANAL ATRESIA, VASCULAR SKIN ABNORMALITY, ABSENT THUMB, HYPOPLASIA OF ULNA AND RADIUS	Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome
HYPOCALCEMIA, H, SZ	Hypocalcemia 1
H, FTT, FEEDING DIFFICULTIES, ABNORMALITY OF EYE MOVEMENT, PDA, RF, BRAIN IMAGING ABNORMALITY, RECURRENT URINARY TRACT INFECTIONS	Lamb-Shaffer syndrome
DEXTROCARDIA, BRADYCARDIA, INTERRUPTED INFERIOR VENA CAVA WITH AZYGOUS CONTINUATION, PDA, ABDOMINAL SITUS INVERSUS, RIGHT VENTRICULAR DILATION, BILATERAL SUPERIOR VENA CAVA WITH BRIDGING VEIN	Malignant hyperthermia susceptibility
DYSMORPHIC, MICROCEPHALY, CHOANAL ATRESIA, PROXIMAL PLACEMENT OF THUMB, LARGE FEET	Mandibulofacial Dysostosis with Microcephaly
ABNORMAL NEWBORN SCREEN	Maple syrup urine disease
LA, ELEVATED LIVER ENZYMES, FTT	Mitochondrial DNA Depletion Syndrome 6
SZ	Molybdenum cofactor deficiency
CONGENITAL DIAPHRAGMATIC HERNIA, AMBIGUOUS GENITALIA, PULMONARY HYPOPLASIA	N/A
SZ	N/A
HEPATOSPLENOMEGALY, HYPERTROPHIC CMP, THROMBOCYTOSIS, LA, TACHYPNEA, ABNORMALITY OF METABOLISM	N/A

PRESENTING SYMPTOMS AND SIGNS OF DISEASE	GENETIC DIAGNOSIS
MICROGNATHIA, CONTRACTURES OF JOINTS IN UPPER LIMBS, H, INGUINAL HERNIA, LOW SET EARS, SHORT PALPEBRAL FISSURES	N/A
APNEA, RF, LETHARGY, H	N/A
HYPERTONIA, DYSMORPHIC, CYANOTIC EPISODE, CONGENITAL CONTRACTURES, ABNORMAL EEG, LA	N/A
H, ENCEPHALOPATHY, RF, SMOOTH PHILTRUM, LONG FINGERS, SHORT CHIN	Nemaline myopathy 3
THROMBOCYTOPENIA, ANEMIA, PETECHIAE, HYPERBILIRUBINEMIA	Noonan syndrome 1
H, CYSTIC HYGROMA, LYMPHANGIOMA	Polycystic kidney disease 1
H	Prader-Willi syndrome
H, GR, DYSPLASTIC TRICUSPID VALVE	Prader-Willi syndrome
HETEROTAXY, POLYSPLENIA, PH, INTESTINAL MALROTATION, INTERRUPTED INFERIOR VENA CAVA WITH AZYGOUS CONTINUATION	Primary ciliary dyskinesia 7
MICROCEPHALY, VENTRICULOMEGALY, COLPOCEPHALY, ABNORMAL CORTICAL GYRATION, CORTICAL GYRAL SIMPLIFICATION, HYPOPLASIA OF CORPUS CALLOSUM	Primary Microcephaly 5
DIARRHEA, FTT	Prolidase deficiency
EEG ABNORMALITY, APNEIC SPELLS	PURA-related severe neonatal hypotonia-seizures-encephalopathy syndrome
FETAL AKINESIA	Salih myopathy
CUTIS APLASIA, HYPERTELORISM, HYPOSPADIAS	Scalp-Ear-Nipple syndrome
H, ELBOW FLEXION CONTRACTURE, PETECHIAE, RF, PDA, ASD, RIGHT VENTRICULAR HYPERTROPHY	Spinal Muscular Atrophy
H, CARDIAC ARREST, INTERICTAL EPILEPTIFORM ACTIVITY	Spinal Muscular Atrophy with Respiratory Distress type 1
SKELETAL DYSPLASIA, FRACTURES	Spondyloepiphyseal dysplasia congenita
PH, CARDIOMEGALY, ABNORMAL RIGHT ATRIUM MORPHOLOGY, TE, BRUISING SUSCEPTIBILITY, CAMPTODACTYLY, WIDE NASAL BRIDGE, TELECANTHUS, POSTERIORLY ROTATED EARS, HYPERTELORISM	TARP syndrome
SKELETAL DYSPLASIA, FRONTAL BOSSING, MIDFACE HYPOPLASIA, SHORTENED LIMBS	Three M syndrome 1
HYPONATREMIA, HYPERTONIA, HYPERFLEXIA, FTT, SGA, LOW-SET EARS, HIGH PALATE, MICROGNATHIA, SEPSIS, HYPOPLASIA OF CEREBRAL WHITE MATTER	Thyroid dyshormonogenesis 6
ABNORMAL HEART MORPHOLOGY, DILATED CMP, PROLONGED QT INTERVAL, LA	Timothy syndrome

PRESENTING SYMPTOMS AND SIGNS OF DISEASE	GENETIC DIAGNOSIS
SGA, HG, COARCTATION OF AORTA	Turner syndrome
PH, PULMONIC STENOSIS, HYPERTROPHIC CMP, TELECANTHUS, DOWN SLANTING PALPEBRAL FISSURES, WIDE NASAL BRIDGE	Williams syndrome
CONGENITAL ICHTHYOSIFORM ERYTHRODERMA, ABNORMAL HAIR, HIGH NARROW PALATE, P, GR, ECHOGENIC FETAL BOWEL	Xeroderma pigmentosum complementation group D
MYOPATHY, H, INTRAVENTRICULAR HEMORRHAGE	X-linked Myotubular Myopathy
DYSMORPHIC, CORNEAL CLOUDING, POOR FEEDING, H, CRYPTORCHIDISM, JAUNDICE, ABNORMAL BASAL GANGLIA, SZ	Zellweger syndrome

H: Hypotonia (n=15). RF: Respiratory distress or failure (n=11). Sz: Seizures (n=10). LA: lactic acidosis (n=8). PDA: Patent ductus arteriosus (n=7). FTT: Failure to thrive (n=7). GR: Intrauterine growth retardation (n=5). ASD: Atrial septal defect (n=4). VSD: Ventricular septal defect (n=4). PH: pulmonary hypertension (n=4). TE: talipes equinovarus. CMP: cardiomyopathy (n=4). P: premature birth. HG: hypoglycemia (n=4). SGA: small for gestational age (n=2). Anomalous pulmonary venous return (n=2). N/A: not applicable.

TABLE 5. GENETIC DISEASE DIAGNOSES IN PROJECT BABY BEAR INFANTS AND THEIR INCIDENCE IN U.S.

	INFANTS' INITIAL DIAGNOSIS		INFANTS WITH A SECOND DIAGNOSIS		
LOCUS 1	MOLECULAR DIAGNOSIS 1	INCIDENCE 1	LOCUS 2	MOLECULAR DIAGNOSIS 2	INCIDENCE 2
ABCA3	Surfactant dysfunction	<1:1,000,000			
ABCC8	Familial hyperinsulinemic hypoglycemia 1	1:250,000			
ACTA1	Nemaline myopathy 3	<1:1,000,000			
ACTN2	Myopathy, congenital, with structured cores and z-line abnormalities/Cardiomyopathy, dilated 1AA	<1:1,000,000			
ADNP	Helsmoortel-van der Aa Syndrome	<1:1,000,000			
ALDH18A1	Cutis Laxa 3	<1:1,000,000			
ALG12	Congenital disorder of glycosylation type Ig	<1:1,000,000			
AMT	Glycine encephalopathy	1:150,000			
ANTXR2	Hyaline Fibromatosis Syndrome	<1:1,000,000			
ARID1A	Coffin-Siris	<1:1,000,000			
ASPM	Primary Microcephaly 5	<1:1,000,000			
BBS10	Bardet-Biedl syndrome 10	<1:1,000,000			

	INFANTS' INITIAL DIAGNOSIS		INFANTS WITH A SECOND DIAGNOSIS		
BCKDHA	Maple syrup urine disease	1:150,000			
CACNA1C	Timothy syndrome	<1:1,000,000			
CASR	Hypocalcemia 1	<1:1,000,000			
CHD7	CHARGE syndrome	1:12,000			
CHD7	CHARGE syndrome	1:12,000			
Chr 12p12.1 del	Lamb-Shaffer syndrome	<1:1,000,000			
Chr 15q11.2q13.1 del	Prader-Willi syndrome	1:15,000			
Chr 15q13.1q13.3 del	Chr 15q13.1q13.3 deletion	1:40,000			
Chr 15q14-q21.1 del	Prader-Willi syndrome	1:15,000			
Chr 16P11.2 del	Chr 16P11.2 deletion syndrome	1:3,000			
Chr 16p13.3 del	Chr 16p13.3 del	1:2,500	Chr 16P11.2 duplication syndrome	Rubinstein-Taybi syndrome	1:100,000
CPT2	Carnitine palmitoyltransferase II (CPT II) deficiency	<1:1,000,000			
FOXF1 gene enhancer deletion	Alveolar capillary dysplasia with misalignment of pulmonary veins	<1:1,000,000			
Chr 1p36 del	Chr 1p36 deletion syndrome	1:5,000			
Chr 22q11.21 del	DiGeorge syndrome	1:4,000			
Chr 22q11.21 del	Digeorge Syndrome	1:4,000			
Chr 4q32.1 del	Chr 4q32.1 deletion	<1:1,000,000	Chr 11p15.5 dup	Chr 11p15.5 duplication syndrome	<1:1,000,000
Chr 7q11.23 del	Williams syndrome	1:7,500			
Chr X del	Turner syndrome	1:2,500			

	INFANTS' INITIAL DIAGNOSIS		INFANTS WITH A SECOND DIAGNOSIS		
COL2A	Spondyloepiphyseal dysplasia congenita	1:100,000			
COL7A1	Epidermolysis bullosa dystrophica	1:400,000			
CUL7	Three M syndrome 1	<1:1,000,000			
DNAH11	Primary ciliary dyskinesia 7	1:15,000			
DUOX2	Thyroid dyshormonogenesis 6	1:100,000			
EFTUD2	Mandibulofacial Dysostosis with Microcephaly	<1:1,000,000			
ERCC2	Xeroderma pigmentosum group D	1:1,000,000			
EVC2	Ellis Van Creveld syndrome	<1:1,000,000			
EVC2	Ellis Van Creveld syndrome	<1:1,000,000			
G6PD	Glucose-6-phosphate dehydrogenase deficiency	1:50			
G6PD	Glucose-6-phosphate dehydrogenase deficiency	1:50	PIEZO1	VUS	
GMPPB	Congenital muscular dystrophy dystroglycanopathy	<1:1,000,000			
HBB	Hemoglobin E Trait	1:250	ERCC4	VUS	
IGHMBP2	Spinal Muscular Atrophy with Respiratory Distress 1	<1:1,000,000			
KAT6B	Genitopatellar syndrome	<1:100,000	Chr 16p11.2 dup	Chr 16p11.2 duplication syndrome	
KCTD1	Scalp-Ear-Nipple syndrome	<1:1,000,000			
LMNA	Laminopathies	1:100,000			
MOCS1	Molybdenum cofactor deficiency	<1:1,000,000			
MPV17	Mitochondrial DNA Depletion Syndrome 6	<1:1,000,000			
MTM1	X-linked Myotubular Myopathy	1:100,000			
MYBPC3 (I)	Dilated Cardiomyopathy 1	1:2,500			
MYH7	Familial isolated dilated cardiomyopathy	1:10,000			
MYO5B	Diarrhea with Microvillus Atrophy 2	<1:1,000,000	HBB	Sickle cell trait	1:50
MYO9A	Myasthenic syndrome, congenital, 24, presynaptic	<1:1,000,000			
NARS2	Combined oxidative phosphorylation deficiency 24	<1:1,000,000			

	INFANTS' INITIAL DIAGNOSIS		INFANTS WITH A SECOND DIAGNOSIS		
PEPD	Prolidase deficiency	<1:1,000,000			
PEX12	Zellweger syndrome	1:50,000			
PINK1	Early onset Parkinson disease 6	1:5,000			
PKD1	Polycystic kidney disease 1	1:2,000	VUS		
PTCH1	Gorlin syndrome	1:20,000			
PTPN11	Noonan syndrome 1	1:1,000			
PURA	PURA-related severe neonatal hypotonia-seizures-encephalopathy syndrome	<1:1,000,000			
QARS	Microcephaly, progressive, with seizures and cerebral and cerebellar atrophy	<1:1,000,000			
RBM10	TARP syndrome	<1:1,000,000			
RET	Hirschsprung Disease	1:5,000			
RYR1 (I)	Malignant hyperthermia susceptibility	1:100,000			
SCN2A	West syndrome	1:10,000			
SI	Congenital sucrase-isomaltase deficiency	1:5,000			
SLC25A15 (I)	Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome	<1:1,000,000			
SLC4A1	Hereditary spherocytosis/SLC4A1-associated distal renal tubular acidosis	<1:1,000,000			
SMN2	Spinal Muscular Atrophy	1:80,000			
SNAP25	Congenital Myasthenic Syndrome 18	1:500,000			
TREX1	Aicardi-Goutieres Syndrome 1	1:150,000	CHEK2	Hereditary breast and colon cancer susceptibility	1:100,000
TTN	Salih myopathy	<1:1,000,000			
UNC13A	Myasthenic syndrome, congenital	1:100,000			

Chr: Chromosome. Del: deletion. Dup: Duplication. (I): incidental finding (disease causing variants in genes not related to their primary phenotype but considered medically actionable and significant for the patient or family members. VUS: variant of uncertain significance (variants that did not rise to the level of a molecular diagnosis but were considered relevant to the infant's condition)

TABLE 6. GENETIC DISEASE DIAGNOSES THAT CHANGED MANAGEMENT AND EFFECTIVENESS OF TREATMENTS

RWGS DIAGNOSIS 1	RWGS DIAGNOSIS 2	CHANGE OF MANAGEMENT	EFFECTIVE TREATMENT
Aicardi-Goutieres Syndrome 1		Y	1N, 2Y
Alveolar capillary dysplasia with misalignment of pulmonary veins		Y	N
Bardet-Biedl syndrome 10		N	N
CHARGE syndrome		Y	N
CHARGE syndrome		N	N
Chr 15q13.1q13.3 deletion		Y	N
Chr 16P11.2 deletion syndrome		N	N
Chr 16P11.2 duplication syndrome	Rubinstein-Taybi syndrome	N	N
Chr 1p36 deletion syndrome		Y	Y
Chr 4q32.1 deletion	Chr 11P15.5 duplication syndrome	N	N
Congenital disorder of glycosylation type Ig		Y	N
Congenital muscular dystrophy dystroglycanopathy		Y	N
Congenital Myasthenic Syndrome 18		Y	N
Cutis Laxa 3		Y	N
Diarrhea with Microvillus Atrophy 2	Sickle cell trait	Y	Y
DiGeorge syndrome		N	Y
DiGeorge syndrome		N	Y
Dilated Cardiomyopathy 1		Y	Y
Early onset Parkinson disease 6		N	N
Ellis Van Creveld syndrome		Y	Y
Ellis Van Creveld syndrome		N	N
Epidermolysis bullosa dystrophica		N	N
Epileptic encephalopathy, early infantile, 11, West syndrome		Y	Y

Familial hyperinsulinemic hypoglycemia, type 1		N	Y
Familial isolated dilated cardiomyopathy		Y	Y
Genitopatellar syndrome	Chr 16P11.2 duplication syndrome	Y	N
Glucose-6-phosphate dehydrogenase deficiency		Y	Y
Glycine encephalopathy		Y	N
Gorlin syndrome		N	Y
Helsmoortel-van der Aa Syndrome		Y	N
Hemoglobin E Trait		N	Y
Hirschsprung Disease		Y	Y
Hyaline Fibromatosis Syndrome		Y	N
Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome		Y	Y
Hypocalcemia 1		N	Y
Lamb-Shaffer syndrome		Y	N
Malignant hyperthermia susceptibility		Y	Y
Mandibulofacial Dysostosis with Microcephaly		Y	N
Maple syrup urine disease		Y	Y
Mitochondrial DNA Depletion Syndrome 6		Y	N
Molybdenum cofactor deficiency		N	Y
Nemaline myopathy 3		Y	N
Noonan syndrome 1		Y	N
Polycystic kidney disease 1		N	Y
Prader-Willi syndrome		Y	N
Prader-Willi syndrome		N	N
Primary ciliary dyskinesia 7		Y	Y
Primary Microcephaly 5		N	N
Prolidase deficiency		Y	N

Severe neonatal hypotonia-seizures-encephalopathy syndrome		Y	N
Salih myopathy		Y	N
Scalp-Ear-Nipple syndrome		N	N
Spinal Muscular Atrophy		Y	Y
Spinal Muscular Atrophy with Respiratory Distress type 1		Y	N
Spondyloepiphyseal dysplasia congenita		Y	N
TARP syndrome		N	N
Three M syndrome 1		Y	Y
Thyroid dyshormonogenesis 6		N	Y
Timothy syndrome		Y	Y
Turner syndrome		N	N
Williams syndrome		N	N
Xeroderma pigmentosum complementation group D		N	Y
X-linked Myotubular Myopathy		Y	N
Zellweger syndrome		Y	N

Appendix B: Patient Benefit Detail

The following table describes the 29 babies for whom rWGS resulted in significant clinical benefit and quantifies the major economic impact this had on the health system, either through reduced length of stay or avoided major procedures.

TABLE 7. ECONOMIC IMPACT OF REDUCED LENGTH OF STAY AND AVOIDED PROCEDURE

			MEDI-CAL		HOSPITAL	
CASES	AVOIDED PROCEDURES	REDUCED LENGTH OF STAY, DAYS	REDUCED REIMBURSEMENT, LOW ESTIMATE	REDUCED REIMBURSEMENT, HIGH ESTIMATE	COST REDUCTION, LOW ESTIMATE	COST REDUCTION, HIGH ESTIMATE
SITE 1 CASE 2		7-14	$21,950	$48,638	$38,824	$77,649
SITE 1 CASE 10	Supraglottoplasty surgery	30	$100,361	$100,361	$167,287	$167,287
SITE 1 CASE 15		2			$5,294	$5,294
SITE 1 CASE 17		7-14	$11,597	$23,195	$17,990	$35,980
SITE 1 CASE 19	Tracheostomy, g-tube	7-14	$10,793	$23,182	$34,616	$55,268
SITE 1 CASE 33	Exploratory bowel surgery				$11,825	$11,825
SITE 1 CASE 39	Endoscopy	7-14			$23,855	$43,073
SITE 1 CASE 40		21-28	$49,307	$65,743	$82,188	$109,584
SITE 1 CASE 51		5-14	$8,146	$22,808	$13,578	$38,018
SITE 2 CASE 8		14			$47,659	$47,659
SITE 2 CASE 16		2-3			$3,475	$5,212
SITE 2 CASE 18		21	$154,354	$154,354	$327,649	$327,649
SITE 2 CASE 19		7			$11,438	$11,438
SITE 2 CASE 35		14-21	$35,770	$53,654	$59,619	$89,428
SITE 2 CASE 38		6			$15,867	$15,867
SITE 3 CASE 3		7-21	$13,314	$39,941	$22,185	$66,555
SITE 3 CASE 23	Tracheostomy, g-tube	28-56	$45,583	$102,725	$108,920	$200,312
SITE 3 CASE 24	Liver work up including biopsy, magnetic resonance spectroscopy	28	$65,893	$67,500	$109,822	$112,499
SITE 4 CASE 2	G-tube	30	$20,530	$20,530	$73,920	$73,920
SITE 4 CASE 3		60	$76,864	$76,864	$128,102	$128,102
SITE 4 CASE 4	Tracheostomy, g-tube	60	$58,962	$58,962	$168,251	$168,251
SITE 4 CASE 12	Endoscopy, exploratory bowel surgery	30	$37,158	$37,158	$69,032	$69,032
SITE 4 CASE 22		14	$17,720	$17,720	$11,813	$11,813
SITE 5 CASE 3		2	$7,532	$7,532	$12,553	$12,553
SITE 5 CASE 5		14	$21,140	$21,140	$35,232	$35,232
SITE 5 CASE 8	G-tube	7-21	$12,071	$38,554	$29,191	$73,327
SITE 5 CASE 10		7-14	$14,169	$28,338	$23,613	$47,226
SITE 5 CASE 15	Tracheostomy	3-7	$12,487	$20,174	$20,797	$33,622
SITE 5 CASE 19		14	$27,950	$27,950	$46,580	$46,580
AVOIDED COSTS		**454-573**	**$823,640**	**$1,057,022**	**$1,721,173**	**$2,120,255**
AVOIDED COSTS (WITH 17.7% PRO FEES)			**$969,424**	**$1,244,115**	**$2,025,821**	**$2,495,540**
AVOIDED TESTS					**$146,268**	**$310,094**
TOTAL		**454-573**	**$969,424**	**$1,244,115**	**$2,172,089**	**$2,805,634**

Analysts at RCIGM used Medi-Cal's DRG payment calculator to estimate savings that accrued from shorter hospital stays and avoided procedures because of employing rWGS. The following narrative summarizes how sequencing affected each of the individual babies for whom rWGS resulted in a change in medical management. Two of the 29 summaries are longer to provide additional context, examples and clarity.

CASE SUMMARIES USED FOR ECONOMIC MODELING

SITE ONE

Case 02

Case 02 involved a baby who was critically ill and seizing. At day of life three, rWGS was ordered. A negative result was returned six days later. During this waiting period, the baby had failed extubations, and in the absence of a definitive diagnosis physicians were unable to proceed with a specific treatment. If a seizure gene panel had been ordered (current standard of care), the turnaround time for that test would have been four to six weeks. Because the rWGS test was ordered and test results were delivered shortly after admission, the baby's doctors were able to avoid the waiting period for the seizure panel results. Clinicians were able to provide parents with the child's prognosis and start discussions about their options. This allowed the parents to make the informed decision to move the baby to comfort care. Fourteen days of avoided inpatient time were modeled.

Case 10

The baby in Case 10 was diagnosed with CHARGE syndrome (see "Case Studies Show Impact in Four Dimensions—Site 1, Case 10: Precise, Timely Care Avoids Weeks of Futile Treatments"). Without rWGS, the charges and inpatient time likely would have been much higher. A nearly identical patient who did not have access to rWGS was previously treated by the hospital system and had undergone an upper respiratory reconstructive surgery (supraglottoplasty) intended to remove an obstruction believed to be blocking the baby's airway. As a result, supraglottoplasty surgery and 30 days of recovery were modeled.

Case 15

Case 15 was a baby with muscle weakness. Doctors ordered rWGS and found a chromosomal deletion. Initially, the plan was to complete a dysphagia study to discover why the baby had difficulty swallowing. This study would have revealed that the baby was aspirating, and the patient would have been fed through a nasogastric tube for two weeks, after which another dysphagia study would have been performed. Only upon the results of this second test would a gastrostomy tube have been initiated. A chromosomal microarray was ordered before rWGS, but physicians received the results two days after the rWGS result. The rWGS and the chromosomal microarray both indicated that a gastrostomy tube was inevitable, and the family proceeded with the procedure two days earlier than they would have if only the chromosomal microarray had been ordered. Therefore, rWGS saved two days of inpatient time.

Case 17

Case 17 presented with neurological issues. An rWGS and a microarray were ordered to test for genetic problems. The microarray returned a result that explained only some of the symptoms. The rWGS picked up the same finding as the microarray as well as a likely pathogenic variant that initiated a thyroid study. This study showed hypothyroidism; as a result, a hypothyroid medication was started. Unrecognized hypothyroidism can cause developmental delays, which is potentially prevented by detection and initiation of medication. Additionally, a gastrostomy tube was initiated earlier than if the physician team had just waited and observed. The physician team estimated that they would have waited another one to two weeks before placing a gastrostomy tube. One to two weeks of avoided inpatient time were modeled.

Case 19

Case 19 was critically ill, but the underlying problem was unclear. Physicians planned to perform a gastrostomy tube placement, tracheostomy and muscle biopsy in order to stabilize his condition and attempt a diagnosis. An rWGS was sent, and results returned within a couple of days. Simultaneously, clinicians sent a gene panel with a two-week turnaround time. Both tests delivered the same results: a diagnosis of a likely pathogenic variant known for its poor prognosis. However, the rWGS result was returned two weeks before the gene panel. With the rWGS information, the family decided to transition to comfort care. The rWGS precluded a tracheostomy, gastrostomy tube, muscle biopsy and approximately two weeks of inpatient time.

Case 33

Case 33 was experiencing feeding difficulties and respiratory distress. After genome sequencing, the baby was diagnosed with a very rare gene variant that explained the symptoms. The diagnosis meant that an exploratory bowel surgery and muscle biopsy were no longer needed. The baby had a very extended inpatient stay, and no inpatient days were avoided. However, the exploratory bowel surgery and muscle biopsy were included in modeling.

Case 39

Case 39 had a structural heart defect and failed to thrive. The baby's sibling had a variant in a gene, which alerted the clinicians to the possibility that this was a source of her illness. Unfortunately, it did not explain all the symptoms. An rWGS was ordered to identify other potential variants for the unexplained problems. The rWGS identified two variants in the critically ill baby: one was the same variant carried by the sibling and the other was a separate variant in the same gene. Understanding the full picture explained why the patient was not growing and feeding well and allowed clinicians to assign the patient a condition-specific growth curve that followed her current growth patterns. This meant that she was growing appropriately based on what is known about the condition, and the baby was able to leave the hospital early. One to two weeks of inpatient stay and an endoscopy were avoided and modeled.

Case 40

Case 40 was hypotonic and failed to thrive. Usually, NICU teams wait until babies are well past term before they decide on a gastrostomy tube, but it can be done earlier if there is a diagnosis that indicates it will be necessary. This patient was diagnosed with a rare variant that indicated it would be necessary, and the gastrostomy tube was placed soon after rWGS results were returned. The attending physicians estimated that they would have placed the gastrostomy tube three to four weeks later without rWGS. Those days counted as avoided inpatient days.

Case 51

Case 51 was admitted with a suspected brain infection. The rWGS results detected a disease-causing variant that explained his symptoms. In the absence of rWGS it is very likely that the baby would have been hospitalized for weeks to treat the suspected infection (symptoms can sometimes take several weeks to resolve). Only after a few weeks would the team decide that the child's problems might not stem from a brain infection and order a standard panel test with a 10- to 17-day turnaround time. If the panel test was the correct one and it was ordered at the same time as rWGS, the team would receive the results five to14 inpatient days after the rWGS results, significantly delaying a correct diagnosis and the initiation of definitive management. Consequently, at least five to14 avoided inpatient days were modeled.

SITE TWO

Case 8

For case 8, rWGS was sent simultaneously with several other genetic tests. The turnaround for the genetic test that would have yielded the diagnosis was about 14 days slower than rWGS. The rWGS results allowed the physician team to make an informed decision that shortened the baby's discharge time. Fourteen avoided inpatient days were included in the model.

Case 16

Case 16 was in foster care and was having trouble gaining weight. An rWGS discovered a pathogenic gene variant that explained the failure to thrive. The patient was eventually discharged but readmitted shortly after, still with difficulty gaining weight. Because the hospital had the rWGS diagnosis in hand, physicians did not have to spend time attempting to identify the cause of the weight problem, which they stated would have taken two to three days. Two to three avoided days were added to the model.

Case 18: Extended Write-up – Shortened Inpatient Stay

Case 18 demonstrates savings the state incurred by assisting a family with a difficult decision. The patient was critically ill and on extracorporeal membrane oxygenation (ECMO), a machine that circulates and oxygenates blood while providing heart-lung bypass. The physician team was planning to send several genetic tests to assist with the diagnosis, including a microarray and gene panels. Because rWGS was available, they opted for one comprehensive test instead of multiple, separate tests. The physician team received a diagnosis informed by rWGS in two days. The team determined that a conservative alternative time to diagnosis without rWGS would have been three weeks, based on the average turnaround times for the genetic and physiological tests they would have ordered.

The baby had a very poor prognosis. Understanding that, the family made an informed decision to opt out of the ECMO treatment so that their child would not suffer further. The baby died peacefully with the family that same day. Without rWGS, it is likely that this patient would have sustained three additional weeks on ECMO until the alternative testing options delivered the same diagnosis. As a result, the physician team indicated that three weeks of charges were avoided.

Case 18 incurred charges of $696,715 while in the hospital, and was assigned a DRG of 583-4, "Neonate with ECMO," with a severity level of four. The Med-Cal payment for this baby was $482,437, with a negative outlier payment of $154,354 because this case met the catastrophic gain threshold.

Had rWGS not been available, three weeks of additional ECMO would have been added to the original charges. As a rule, throughout the modeling, RCIGM used the patient's three-day average of charges prior to discharge or expiration when extrapolating avoided inpatient charges. This patient's three-day-average of daily charges prior to death was $64,632 per day. Extrapolated across 21 days, the avoided charges were $1,357,285 ($64,632 x 21). By adding this to the actual charges of $697K, the charges would have been $2,054,000. These charges would have warranted a base payment of $482,437, with no outlier payment. The use of rWGS saved the Medi-Cal system $154,354 ($482,437 minus $328,083), as well as three weeks of suffering for the family and baby.

CASE 18: SAVINGS WITH rWGS

	BASE PAYMENT	OUTLIER PAYMENT	TOTAL
WITHOUT rWGS	$482,437	$0	$482,437
WITH rWGS	$482,437	-$154,354	$328,083
			SAVINGS $154,354

Case 19

Case 19 was a baby with multiple fractures and low muscle tone. Based on these signs, a Child Protective Services (CPS) hold was placed on the baby out of concern that he was intentionally being harmed. As a result, he was allowed only supervised visits with his immediate family. Several specialists had seen the baby, but they had not been able to provide an explanation for his clinical picture. An rWGS identified a pathogenic variant, which explained the challenges and laid out a poor prognosis. A palliative care plan was initiated. Moreover, the CPS order was lifted, and the child was reunited with his family. Physicians noted that rWGS helped the clinician team, family and CPS make better decisions, and estimated that it would likely have taken an additional week to come to the same conclusion had rWGS not been available. Seven inpatient days were counted as avoided and modeled.

Case 35

Case 35 was critically ill and seizing. A lumbar puncture was planned but could not be performed due to the patient's condition, and physicians were unable to proceed with a specific treatment. Needing to understand the underlying molecular condition, they ordered rWGS, which yielded a diagnosis that allowed the family and physician team to employ a more targeted treatment. The physician team estimated that knowing the diagnosis allowed the baby to proceed with treatment two to three weeks earlier than expected and shortened the inpatient stay by that amount of time.

Case 38

Case 38 was not breathing and admitted to the PICU (a Sudden Infant Death near miss). Blood tests revealed he had low blood sugar (hypoglycemia) and a worrisome level of lactic acid. The rWGS came back three days later with a negative result; following improvement in symptoms, the patient was discharged home five days after that. Had rWGS not been available, doctors would have ordered a genetic test for hypoglycemia and kept the baby in the hospital until they received the results. Because results of the panel test take two weeks, the child would have remained in the hospital an extra 6 days.

SITE THREE

Case 3

The family of Case 3 was prepared to transition their child to comfort care if the baby received a definitive diagnosis of a known lethal condition. A gene panel and rWGS were ordered at about the same time; the gene panel results were returned two weeks after rWGS with the same diagnosis of a fatal genetic disorder. With the conclusive rWGS report in hand, the family immediately opted for comfort care. Two weeks of inpatient stay were avoided because the family did not need to wait for the gene panel results before making its decision.

Case 23

Case 23 had low muscle tone upon admission and was initially thought to have been injured at birth. Following a decline in respiratory status requiring continuous ventilator support, rWGS delivered a diagnosis. After many family meetings, the parents decided to transition the baby to comfort care. The physician team noted that without this diagnosis, they likely would have performed a gastrostomy tube insertion and tracheostomy in order to keep the infant alive, and the infant would have stayed in the intensive care unit for an additional four to eight weeks before expiring or being discharged. Four to eight weeks of a critical care stay were modeled as well as an avoided gastrostomy tube and tracheostomy.

Case 24

Case 24 presented with liver disease and severe failure to thrive. The physician team ordered rWGS early during the hospitalization. Two days later, the rWGS result revealed a condition known for its poor prognosis. Absent rWGS, the physicians would have ordered a liver transplant workup, including metabolic tests, magnetic resonance imaging, angiography and biopsy, and a series of tests that usually requires about four weeks to complete. Instead, rWGS allowed the clinical team and family to have numerous discussions about the baby's future. The rWGS diagnosis and additional information enabled the family to make an informed decision and opt for comfort care. Four weeks of a critical care stay were modeled.

SITE FOUR

Case 2

Case 2 was born with multiple congenital anomalies. The results of rWGS led to a diagnosis with a very poor prognosis. They also indicated that the baby would likely need a gastrostomy tube. Knowing this, the parents decided to make the most of the time they had with their child and avoid procedures that were futile. Thus, they changed his code status to Do Not Resuscitate and opted to take the baby home so they could enjoy themselves away from the hospital. When the baby became ill again, clinicians admitted him to the medical unit where they made him comfortable. He passed away a few days later. Without the rWGS diagnosis, the baby likely would have been admitted to the PICU, where the clinical team would have subjected him to life-sustaining therapies. A gastrostomy tube and one month of inpatient stay were modeled as likely avoided costs.

Case 3: Extended Write-up – Shortened Inpatient Stay

Case 3 was a baby who showed abnormal brain activity on an electroencephalogram, a test often used to diagnose seizures and sleep problems. The baby also suffered from apneic spells, brief episodes when breathing ceases. An rWGS provided physicians with an explanation for these signs and symptoms. Physicians estimated that without sequencing, this patient would have undergone an extended and uncomfortable diagnostic odyssey, as the diagnosis was rare and difficult to identify.

The infant incurred charges of approximately $1,116,396 over an 85-day inpatient stay. The DRG classification was 860, "Rehabilitation," with the highest severity level of 4, known as a DRG classification of 860-4. For a patient with this classification and charges of $1.12 million, Medi-Cal payment to the hospital is approximately $101,909, split into a base payment of $14,412 and an outlier payment of $87,496.

Without rWGS, the charges and inpatient time would likely have been much higher. In the opinion of the clinician team, rWGS precluded approximately 60 days of inpatient time. The three-day average of daily charges prior to discharge for this patient was $10,972. Extrapolated over 60 days, this patient avoided $658,320 of charges.

As a result, the likely charges for the baby in the absence of rWGS would have been the sum of the actual charges of approximately $1.12 million plus $658,320 for the avoided inpatient time. After entering this into the DRG calculator, Medicaid's payment would have been $178,772, split into a base payment of $14,412 and an outlier payment of $164,360. By sequencing this patient and avoiding the extensive inpatient time, Medi-Cal saved approximately $76,864 of outlier payment to the hospital. (See figure below.)

CASE 3: SAVINGS WITH rWGS

	BASE PAYMENT	OUTLIER PAYMENT	TOTAL
WITHOUT rWGS	$14,412	$164,360	$178,772
WITH rWGS	$14,412	$87,496	$101,908
			SAVINGS $76,864

Case 4

Case 4 had little muscle strength and encephalopathy (a disease in which the brain doesn't work right), resulting in a very long list of potential diagnoses. A little over a week after her admission to the hospital, rWGS identified a diagnosis that explained her symptoms. Physicians noted that making this diagnosis normally takes several months, during which a baby with these problems would assuredly have undergone placement of a gastrostomy tube and tracheostomy surgery. Given the baby's poor prognosis, the family made an informed decision to opt for comfort care. A tracheostomy, gastrostomy tube and 60 avoided inpatient days were modeled.

Case 12

Case 12 suffered from diarrhea and failure to thrive. Confounded by the baby's situation, the physician team expanded to incorporate multiple specialties, including gastroenterology, infectious disease, and genetics teams. The rWGS results yielded a diagnosis and, according to the physician team, precluded what likely would have been another 30 days of diagnostic testing, including an endoscopy and small bowel biopsy. These avoided procedures and inpatient time were added to the results.

Case 22

Shortly after birth, Case 22 started to have seizures. The clinical team received the rWGS results one day after the lab obtained the blood sample. The results identified a disease-causing variant that explained the baby's symptoms. They indicated that the baby would not benefit from a commonly used seizure medication the child was taking, but would likely benefit from a different one. The ineffective seizure medication caused sedation; stopping it enabled the child to breastfeed. Standard testing would have taken more than two weeks, which would delay the diagnosis and postpone weaning the baby off the ineffective medication. With the benefit of rWGS the child went home with appropriate seizure control medication two weeks earlier, and was able to feed on her own.

SITE FIVE

Case 3

Case 3 was a baby with heart and metabolic problems. The physician team ordered rWGS and a microarray, both of which indicated a poor prognosis. Consensus from the critical care doctors was that the rWGS result, which arrived two days before the microarray diagnosis, led to discussion of comfort care about two days earlier in the patient's course. Two days of inpatient stay were avoided.

Case 5

Case 5 failed to thrive and suffered from several hematologic problems. The patient was challenging to manage medically, as the baby would frequently stabilize and relapse. Physicians performed an electron microscopy and received a diagnosis approximately two weeks later. Fortunately, they received rWGS results as that test was ordered, and the diagnosis led

the physicians to change the baby's diet to total parenteral nutrition. The patient improved rapidly and was discharged. Fourteen days of avoided inpatient time were modeled.

Case 8

Case 8 presented with low muscle tone, meager ability to feed and multiple congenital anomalies. An rWGS revealed a pathogenic variant that explained her symptoms. Because clinicians understood the underlying molecular cause of her condition, they prescribed a medication to help with the symptoms. Knowing that her poor feeding might resolve with the new medication, they decided that placement of a gastrostomy tube was no longer necessary. Physicians estimated that the new regimen allowed the patient to be discharged between one and three weeks early and avoid a gastrostomy tube procedure.

Case 10

Case 10 had generalized muscle weakness and a cardiac arrest, prompting the clinical team to quickly send for rWGS. The diagnosis, which explained the symptoms, indicated that the low muscle tone would not improve, and allowed the family and clinical team to confidently move forward with a gastrostomy tube and tracheostomy to help the baby feed and breathe. In the absence of this diagnosis, the clinical team would have made several attempts to remove the baby from artificial ventilation, a process that typically takes one to two weeks to complete. One to two weeks of inpatient time were avoided, as well as the gastrostomy tube and tracheostomy.

Case 15

Case 15 was born with dysmorphic or anatomically abnormal features. Physicians considered mandibular extraction surgery or a tracheostomy as treatments. The results of rWGS allowed the clinical team to confidently move forward with a mandibular distraction operation and avoid unnecessary tracheostomy. The tracheostomy and three to seven avoided inpatient days were modeled.

Case 19

Case 19 presented with a constellation of symptoms, including Dandy-Walker malformation, a congenital defect that can cause developmental delays and other serious problems, as well as hypospadias, a common genital anomaly in newborn boys. An rWGS result diagnosed a variant known to be the most severe form of the condition. The baby's mother clearly communicated to the palliative care team that she did not want the baby to undergo any further invasive procedures. Knowing the diagnosis helped to inform her decision. The physician team noted that the diagnosis and decision likely would have taken two weeks longer if rWGS had not been available.

Appendix C: Comparison Procedures

TABLE 8. AVERAGE CHARGES FOR COMPARISON CASE PROCEDURES

PROCEDURE	NUMBER OF COMPARISON CASES	AVERAGE CHARGES
TRACHEOTOMY AND GASTROSTOMY TUBE *(Simultaneously)*	1	$59,110
GASTROSTOMY TUBE	2	$33,467
TRACHEOSTOMY	1	$52,522
ENDOSCOPY	3	$16,675
EXPLORATORY BOWEL SURGERY	2	$42,522
SUPRAGLOTTOPLASTY SURGERY	1	$99,372

Table 8 lists the number of comparison cases that analysts used to calculate the average amount they would have charged to Medi-Cal for each type of procedure that was avoided as the result of employing rapid whole genome sequencing.

Appendix D: Charge Savings From Reduced Length of Stay and Avoided Procedures

Site and RCIGM physician teams identified the cohort of babies for whom rWGS led to a significant change in medical care that affected clinical outcomes and concomitant charges. Of the 178 babies in Project Baby Bear, clinicians judged that 29 babies avoided a major procedure, had shorter hospital stays or both. For each of these babies, a detailed analysis of the effects of rWGS on hospital charges was performed. Analytic methods are described below.

To estimate avoided charges due to an eliminated major procedure or reduced length of stay, RCIGM used an approach very similar to one previously described by RCIGM investigators.[6]That approach relies on the judgment of clinicians to estimate what would have happened to each baby in the absence or rWGS.

To establish this, the RCIGM team conducted monthly interviews with clinicians at each of the five sites. During these calls, the care of each of the 178 patients was discussed with the teams that treated them, with primary focus on the 29 babies for whom clinicians agreed there was a change in management and cost as a result of rWGS. During these interviews, the physician teams outlined the hypothetical actions they would have taken if they had not had access to whole genome sequencing.These actions were discussed and refined until there was unanimous agreement between the physicians at the site and the RCIGM team that, in the best medical opinion of the two teams, they would have followed the outlined hypothetical course of actions in the absence of rWGS.

As an example, a clinician might say, "If I did not have access to rWGS in this case of a baby with complex, unexplained symptoms, I would have started the process of diagnosis with a gene panel test. However, since this patient's gene variant is not covered by the standard gene panel, I would not have received a diagnosis. So, I would have moved on to testing for toxoplasmosis [a parasite infection]. Since this would not have yielded an answer either, I would have sent a blood sample for a whole exome test, which would have given me the diagnosis."

Length of Stay

For each baby for whom physicians agreed that length of stay was reduced, the average charges per day for the last three days of the hospital stay were calculated. It was assumed that this average charge would have been applied to the additional days of the stay.

Inevitably, there were some babies for whom the hypothetical actions in the absence of rWGS were not clear. For example, clinicians were sometimes sure that length of stay was reduced by rWGS but were not sure by exactly how many days. In these cases, a range of results were used, providing lower and upper limits for the estimates.

Avoided Procedures

For each type of avoided procedure, between one and three non-Project Baby Bear babies were identified who received care at Rady Children's Hospital within the previous year and who had undergone the procedure that was avoided by the baby who received rWGS in Project Baby Bear. For each procedure, the team identified the items on the bill of the non-Project Baby Bear baby that were associated with the procedure and those charges were summed. For example, to estimate charges for a tracheostomy, charges for the operating room, surgery-related materials and anesthesia were aggregated. A full list of comparison procedures, the number of comparison infants that were used in the estimation process and the estimated charge for each avoided procedure is shown in Appendix C.

This approach assumes that the charges per procedure at Rady Children's Hospital are a reasonable estimate of the charges per procedure at other sites as well. Although the charge per procedure will vary somewhat across sites, this approach

provides a reasonable estimate. It should be noted that avoided procedures only account for approximately 6% of the estimated total avoided charges, so the results would not vary significantly due to cross-site variation in charges per procedure.

Avoided Physician Charges

In addition to reduced facility expenditures, rWGS resulted in reduced professional charges because of avoided surgical services and hospital days. The analyses described above were conducted with inpatient bills obtained from each of the five sites. However, analysts did not have access to comparable data on physician services. Peterson and colleagues, using MarketScan claims data in a large, nationwide study of Medicaid patients, found that average reimbursement for professional fees for patients covered by Medicaid was 17.7% of the reimbursement for facility fees.[4] This 17.7% estimate is similar to and more conservative than an estimate from an analysis of professional and facility fee data in a cohort of 42 babies who received rWGS at RCIGM.[6] To estimate total avoided charges, avoided hospital facility expenditures have been increased by 17.7% to account for avoided professional fees. This increase was also used in the Medi-Cal reimbursement calculation.

Appendix E: Effects of rWGS on Medi-Cal Reimbursement

Medi-Cal does not fully reimburse hospitals for their charges, and the effects on Medi-Cal reimbursement are significantly smaller than the effects on charges. This section describes the methods used to estimate the effects of rWGS on Medi-Cal reimbursement.

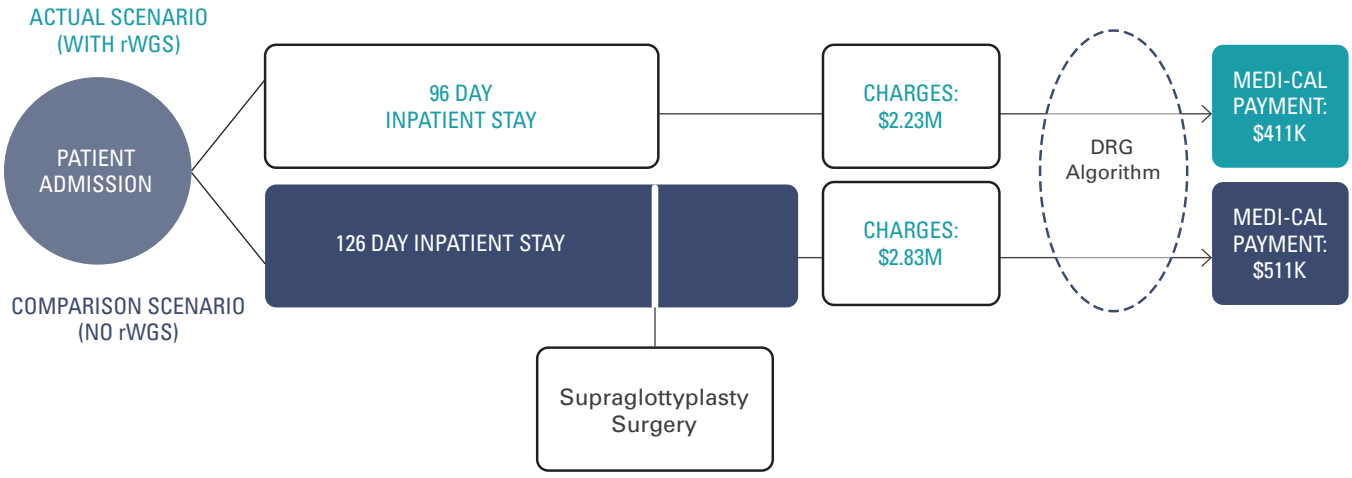
In California, about three quarters of hospitals are paid by Medicaid on a Diagnosis Related Group (DRG) basis. A DRG is a patient classification system that groups similar patients into payment tiers. For example, if a patient has a broken arm, the hospital receives the same "broken arm" payment from the state regardless of how many inpatient days or procedures that patient incurs. There are four possible levels of severity for each DRG so that particularly complex or challenging inpatient stays can be reimbursed appropriately. However, because patients and their treatments are so diverse, DRG reimbursement includes a safety mechanism to ensure that hospitals don't lose significant sums when they care for catastrophic cases. This safety system is achieved through "outlier" payments.

When costs for a patient far exceed the expected costs for a DRG, an outlier payment is added on top of the original DRG payment. The state Medi-Cal program makes available a "DRG estimated payment calculator" which can be used to estimate the amount that Medi-Cal will pay for a patient's DRG (conditional on the hospital) and the total facility charges for that patient.[11]

Accuracy of the DRG calculator was tested with information from babies at Rady Children's Hospital. DRG and total charges were obtained from billing data and entered into the DRG estimated payment calculator. The resulting estimated payment from the calculator was compared with the payment that Rady Children's received from Medi-Cal. For 18 tested babies, estimated payment was within a mean of 2.5% and median of 0.7% of the actual payment received.

As described above, RCIGM and site physician teams assembled an estimate of the additional charges that would have been incurred if the procedure had been performed or the length of stay were longer. Two DRG calculations were then performed—one with the actual data, and one with the data including the increased hypothetical charges. The difference between the two results is the estimated effect of rWGS on Medi-Cal facility reimbursement (Figure 4).

FIGURE 4. COMPARING PATIENTS WITH rWGS VS. NO rWGS



Based on the difference between the two scenarios illustrated (a baby who receives rWGS vs. a similar baby who does not receive rWGS), the RCIGM model would attribute $100,000 of eliminated Medi-Cal payments to the baby who receives rWGS.

Savings for State in Eliminated Medi-Cal Payments

Eliminated aggregated charges of $9.9 million, equivalent to $2.5 million in healthcare costs, resulted in reduced Medi-Cal payments to hospitals of $1.1 million (Figure 5). Under the DRG system, the state of California paid Project Baby Bear sites at a rate of 11.1% of charges (0.11 x $9.9 million = approximately $1.1 million). This rate could change for future cohorts. The remainder of the cost reductions did not directly impact Medi-Cal reimbursement.

FIGURE 5. ESTIMATED ECONOMIC BENEFIT OF rWGS AT FIVE PILOT SITES

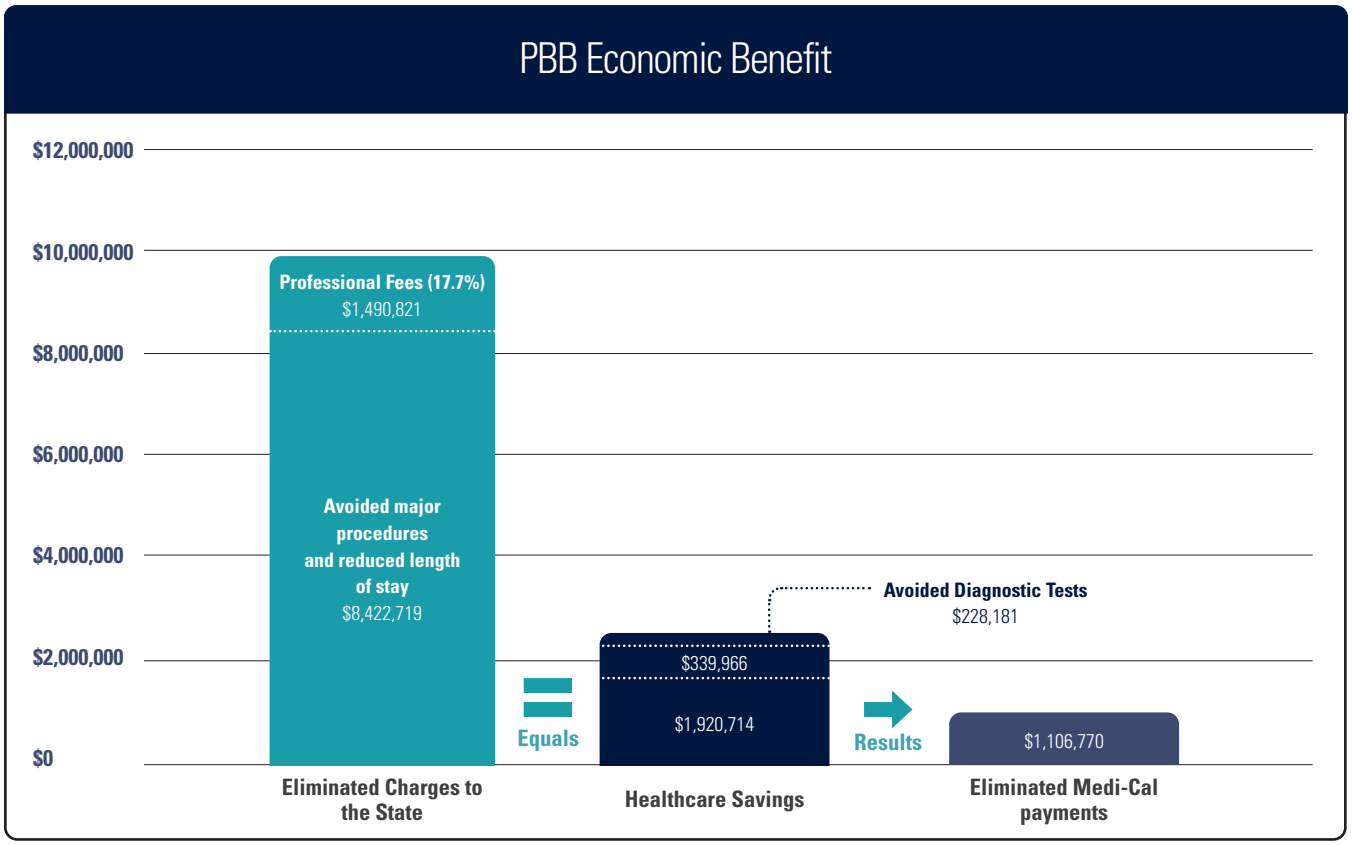


Figure 5 illustrates the aggregated eliminated charges to the state of California (bar on left) and the corresponding decrease in Medi-Cal payments from the state to Project Baby Bear hospitals (bar on right).

Appendix F: Comparing rWGS Turnaround Times

To calculate the benefits that accrue from rapid whole genome sequencing, RCIGM estimated how savings would decrease if the medical team received sequencing results in seven or 14 days rather than the three-day median time achieved in Project Baby Bear (Table 9). To do this, the RCIGM team calculated how a longer turnaround time (TAT) increased inpatient stay for each of the 29 patients who received significant benefit from sequencing.

TABLE 9. FINANCIAL EFFECTS OF LONGER rWGS TURNAROUND TIME (TAT) ON SAVINGS

	3 DAY TAT		7 DAY TAT		14 DAY TAT	
CASES	COST SAVINGS (LOW)	COST SAVINGS (HIGH)	COST SAVINGS (LOW)	COST SAVINGS (HIGH)	COST SAVINGS (LOW)	COST SAVINGS (HIGH)
SITE 1 CASE 2	$45,696	$91,392	$22,437	$74,789		$22,437
SITE 1 CASE 10	$196,896	$196,896	$163,389	$163,389	$104,790	$104,790
SITE 1 CASE 15	$6,231	$6,231				
SITE 1 CASE 17	$21,174	$42,348	$9,750	$32,501	$9,750	
SITE 1 CASE 19	$40,743	$65,050	$28,865	$53,170	$8,090	$32,393
SITE 1 CASE 33	$13,918	$13,918	$13,918	$13,918	$13,918	$13,918
SITE 1 CASE 39	$28,077	$50,697	$15,150	$37,768		$15,150
SITE 1 CASE 40	$96,735	$128,980	$78,301	$110,542	$46,059	$78,301
SITE 1 CASE 51	$15,979	$44,742	$3,196	$31,959		$9,588
SITE 2 CASE 8	$56,095	$56,095	$40,065	$40,065	$12,020	$12,020
SITE 2 CASE16	$4,090	$6,135	$4,090	$6,135	$4,090	$6,135
SITE 2 CASE 18	$385,643	$385,643	$312,174	$312,174	$183,632	$183,632
SITE 2 CASE 19	$13,463	$13,463	$5,770	$5,770		
SITE 2 CASE 35	$70,171	$105,256	$50,120	$85,204	$15,036	$50,120
SITE 2 CASE 38						
SITE 3 CASE 3	$26,112	$78,335	$11,193	$63,426		$37,310
SITE 3 CASE 23	$128,199	$235,767	$108,162	$220,256	$80,933	$193,028
SITE 3 CASE 24	$129,260	$132,412	$112,180	$115,331	$82,289	$85,440
SITE 4 CASE 2	$87,004	$87,004	$76,425	$76,425	$57,912	$57,912
SITE 4 CASE 3	$150,777	$150,777	$140,729	$140,729	$123,138	$123,138
SITE 4 CASE 4	$198,031	$198,031	$185,802	$185,802	$164,394	$164,394
SITE 4 CASE 12	$81,251	$81,251	$72,223	$72,223	$56,429	$56,429
SITE 4 CASE 22	$34,760	$34,760	$24,829	$24,829	$7,449	$7,449
SITE 5 CASE 3	$14,774	$14,774				
SITE 5 CASE 5	$41,468	$41,468	$29,620	$29,620	$8,886	$8,886
SITE 5 CASE 8	$34,357	$86,306	$19,515	$71,466		$45,490
SITE 5 CASE 10	$27,793	$55,585	$11,911	$39,706		$11,911
SITE 5 CASE 15	$24,478	$39,574	$9,382	$24,478		
SITE 5 CASE 19	$54,824	$54,824	$39,162	$39,162	$11,749	$11,749
TOTAL	$2,028,000	$2,497,715	$1,588,358	$2,070,836	$990,562	$1,331,617
TOTAL WITH DIAGNOSTIC TESTS	$2,174,268	$2,807,809	$1,734,626	$2,380,930	$1,136,830	$1,641,711

Table 9 provides the supporting detail to Figure 3, which shows the difference in health system savings for rWGS diagnostic tests with a turnaround time of three, seven, and 14 days. As the time to result lengthens, avoided impatient days are lost and associated cost savings drop in a proportionate manner. The project estimated that 454 to 573 hospital days were avoided. High and low calculations were based on the estimated ranges from providers.

TAT = turnaround time

References

1. Francis Collins. "Whole-Genome Sequencing Plus AI Yields Same-Day Genetic Diagnoses," NIH Director's Blog, May 7, 2019, https://directorsblog.nih.gov/2019/05/07/whole-genome-sequencing-and-ai-yields-same-day-genetic-diagnoses/.

2. "X-linked myotubular myopathy," Genetics Home Reference, National Library of Medicine, published May 26, 2020, https://ghr.nlm.nih.gov/condition/x-linked-myotubular-myopathy.

3. Shanafelt, T., Goh, J., Sinsky, C. The business case for investing in physician well-being. JAMA Intern. Med. 2017;177(12):1826-1832. doi: 10.1001/jamainternmed.2017.4340 https://pubmed.ncbi.nlm.nih.gov/28973070/

4. Peterson C, Xu L, Florence C et al., Professional fee ratios for US hospitals discharge data. Med Care. 2015;53(10):840–849. https://pubmed.ncbi.nlm.nih.gov/26340662

5. Schofield D, Rynehart L, Shresthra R, White SM, Stark Z. Long-term economic impacts of exome sequencing for suspected monogenic disorders: diagnosis, management, and reproductive outcomes. Genet Med. 2019;21(11):2586-2593. doi:10.1038/s41436-019-0534-x https://pubmed.ncbi.nlm.nih.gov/31110331

6. Farnaes L, Hildreth A, Sweeney NM et al., Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization. NPJ Genom Med. 2018;3(10). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5884823/pdf/41525_2018_Article_49.pdf.

7. Stark Z, Schofield D, Alam K, et al. Prospective comparison of the cost-effectiveness of clinical whole-exome sequencing with that of usual care overwhelmingly supports early use and reimbursement. Genet Med. 2017 Aug;19(8):867-874. doi:10.1038/gim.2016.221 https://pubmed.ncbi.nlm.nih.gov/28125081

8. Stark Z, Schofield D, Martyn M, et al. Does genomic sequencing early in the diagnostic trajectory make a difference? A follow-up study of clinical outcomes and cost-effectiveness. Genet Med. 2019;21(1):173-180. doi:10.1038/s41436-018-0006-8 https://pubmed.ncbi.nlm.nih.gov/29765138

9. Kingsmore SF, Cakici JA, Clark MM, et al. A Randomized, Controlled Trial of the Analytic and Diagnostic Performance of Singleton and Trio, Rapid Genome and Exome Sequencing in Ill Infants. Am J Hum Genet. 2019;105(4):719-733. doi:10.1016/j.ajhg.2019.08.009 https://pubmed.ncbi.nlm.nih.gov/31564432

10. "Blue Shield of California Becomes First Health Plan in U.S. to Cover Cost of Rapid Whole Genome Sequencing for Critically Ill Children," Blue Shield of California, March 9, 2020, https://news.blueshieldca.com/2020/03/09/RADY-genomics

11. "DRG pricing resources for SFY 2018/19," California Department of Health Care Services, October 18, 2019, https://www.dhcs.ca.gov/provgovpart/Pages/DRG-Pricing-SFY2018-19.aspx.

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