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project baby bear

Rady Children's Hospital - San Diego

INTERIM REPORT

PERIOD COVERING JULY – DECEMBER 2018

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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GRANT OVERVIEW

BACKGROUND

Research studies have shown that clinical rapid whole genome sequencing (rWGS) is effective for rapid diagnosis and early treatment of genetic diseases in acutely ill infants in intensive care units, and results in improved outcomes and reduced cost of hospitalization in some patients. Currently, rWGS is not a reimbursed test under Medi-Cal, and therefore not available to most Medi-Cal enrolled infants. On June 27, 2018, in support of California's State Department of Health Care Services (4260-001-0001), Provision 8 appropriated $2,000,000 in funding for the Whole Genome Sequencing Pilot Program. The State Department of Health Care Services in turn provided this grant to Rady Children's Hospital – San Diego (RCHSD), a California non-profit organization, in order to execute an rWGS Pilot Program now named "Project Baby Bear".

STRATEGIC OBJECTIVES

Project Baby Bear is a Quality Improvement (QI) project that will implement rWGS in at least 100 acutely ill children enrolled in the Medi-Cal program at a minimum of four neonatal and pediatric intensive care sites in California. Rady Children's Hospital – San Diego in conjunction with Rady Children's Institute for Genomic Medicine will evaluate the extent to which rWGS changes the cost of patient care and patient outcomes within four months of return of results.

At the conclusion of the grant period, Rady Children's Hospital will provide California's State Department of Health Care Services a report of the cost of care and outcomes of children receiving rWGS compared to those not receiving rWGS.

CURRENT STATUS

The following pages summarize the current status of the program through the end of December 2018.

Margareta E. Norton
Executive Vice President & Chief Administrative Officer
January 15, 2019

PROJECT IMPLEMENTATION STATUS

BACKGROUND

Work associated with Project Baby Bear will occur in three phases and follows the Plan, Do, Study, Act cycle recommended by the Institute of Health Improvement to evaluate the implementation of new diagnostic tests. Major tasks for each phase are provided below. See **Appendix A** for a schematic of these tasks and their dependencies.

PHASE DEFINITIONS

Phase 1: Project Design and Site Set-up

Project Design includes identifying the participating sites, describing the intervention (rWGS), determining the inclusion and exclusion criteria of the targeted population (these criteria are shared in **Appendix B**), defining the scope of results to be returned to sites, specifying how and over what period to measure changes in cost of care and outcomes, and developing a plan for statistical analysis of results.

Site Set-Up will include the following activities:

- Visits to individual pilot sites
- Education and training of staff and investigators
- Establish contracts between Rady Children's Hospital San Diego (RCHSD) and Project Baby Bear pilot sites
- Institutional Review Board (IRB) QI determination
- Develop working relationships between staff at RCHSD and pilot sites
- Develop electronic case report forms and physician questionnaires
- Set up electronic database

Phase 2: Rapid whole genome sequencing and genomically informed medical care

Phase 2 will include the following activities:

- Identify patients for whom rWGS is appropriate
- Obtain informed parental consent
- Collect infant or child blood sample and when possible parental samples
- Ship sample to clinical laboratory at RCIGM
- Perform rWGS
- Complete interpretation of rWGS and report findings to referring physician
- Additional tele mentoring with referring physician, genetic counselors or other members of the clinical team as needed.

Phase 3: Analytics & Comparative Effectiveness

Phase 3 will include the following activities:

- Identify control patients
- Establish counterfactual elements such as reduction in length of stay or avoided morbidities compared with similar or previous patients
- Evaluation of outcomes and cost elements

MEDI-CAL PILOT SITES

The four initially selected pilot sites are listed below.

- Valley Children's
- Rady Children's Hospital – San Diego
- UCSF Benioff Children's Hospital Oakland
- UC Davis Medical Center – Sacramento

Site set-up activities (Phase I) are completed at each of these sites. Additional sites are under consideration to ensure the sample volume meets the minimum of 100 patients for the demonstration quality improvement project. Rady Children's Hospital is working closely with Rady Children's Institute of Genomic Medicine on this demonstration project.

PHASE 1 STATUS

The project started in July 2018 and focused on drafting a project map, workflow overview and budget to maximize the number of cases to be completed. Inclusion and exclusion criteria for inpatients across the pilot sites were determined by the clinical teams at Rady Children's Hospital and Rady Children's Institute for Genomic Medicine. The State of California grant was concluded in August and funds were subsequently sent from the state. In August 2018, initial visits were conducted with each pilot site, and included the following activities (1) review of case identification and selection workflows; (2) review of service agreements, and; (3) review of strategy and methods to gather outcome and health economic data elements. Sub-contracts and site agreements were drafted by RCHSD in September and distributed to all prospective sites for clarification and finalization.

PHASE 1 MILESTONES

SITES	TRAINING	IRB WAIVER	CONTRACTS	BETA TESTING
Valley Children's	Aug '18	Oct '18	Oct '18	Oct '18
Rady Children's Hospital – San Diego	Jul '18	Oct '18	Sept '18	n.a.*
UCSF BCHO (Oakland)	Aug '18	Oct '18	Dec '18	Dec '18
UC Davis	Aug '18	Oct '18	Dec '18	Dec '18

* RCHSD has implemented all components of strategy in prior studies

PHASE 2 STATUS

Phase 2 activities began in mid-October, including weekly teleconferences in preparation for beta testing. During beta-testing, every step of the workflow was implemented including shipping an empty sample tube to Rady Children's in San Diego. The teams at Rady Children's and other pilot sites evaluated the findings during beta-testing and changes to optimize workflows were implemented. Approval to send the first sample was given only after both teams finalized and approved the workflows. The initial samples from Rady Children's Hospital & Valley Children's Hospital were received on November 20, 2018. Initial samples from Children's Oakland were received on January 12, 2019 and from UC Davis on January 15, 2019.

PHASE 2 - MEDI-CAL PILOT SITE METRICS

SITES	1ST PATIENT SAMPLE RECEIVED	TOTAL # OF SAMPLES RECEIVED TO DATE
Valley Children's	11/20/18	7
Rady Children's Hospital – San Diego	11/20/18	5
Children's Oakland	1/12/19	1
UC Davis – Sacramento	1/15/19	2
	Total Project Baby Bear Samples to date	**15**

COMPLETED CASES	AVERAGE TIME TO RESULT	DIAGNOSES	CHANGE IN MANAGEMENT
12	3.5 days	5	1

Based on data from previous projects conducted by RCIGM, we expect 30-40% of patients who have rWGS performed will receive a diagnosis, and that among these 30-40% of patients, medical management will be changed for 60% of patients.

To date, Project Baby Bear has completed rWGS on 12 cases, including five patients from Rady Children's Hospital – San Diego and 7 patients from Valley Children's Hospital. Five of the 12 children had the underlying cause for admission determined by rWGS. One of these diagnoses was subsequently identified by standard of care testing that was sent concurrently; the other 4 children received a diagnosis based on results from rWGS. Of these five diagnosed children, a specific treatment was identified based on the results of rWGS for a patient at Rady Children's Hospital. Regrettably, this treatment was not available in the United States. At Valley Children's Hospital, rWGS was performed on an infant diagnosed with near-miss of sudden infant death syndrome. Rapid whole genome sequencing revealed that the infant had a gene variant that led to a diagnosis of congenital myasthenia-like syndrome (CMS). Some children with CMS may be effectively treated with a specific medication. At the time of writing, the long-term benefits of this medication for the infant are still being evaluated. We hope to see improvements in the infant's health over the next 4 months. Similarly, the potential benefits of other changes in care are pending the case conference discussions.

PHASE 3 STATUS

Phase 3 data collection efforts to document outcomes and costs are underway at Rady Children's San Diego and Valley Children's. Physicians at UCSF Benioff Children's Hospital Oakland and UC Davis have reviewed and approved the data collection forms. Physicians and other members of the pilot sites team will complete surveys and supply information at various steps throughout the pilot program.

FINANCIAL UPDATE

BUDGETING

In the table below, planned and actual expenditures by quarter through 12/31/2018 are displayed. The last column reflects how much of the $2M has been used as of 31 December 2018.

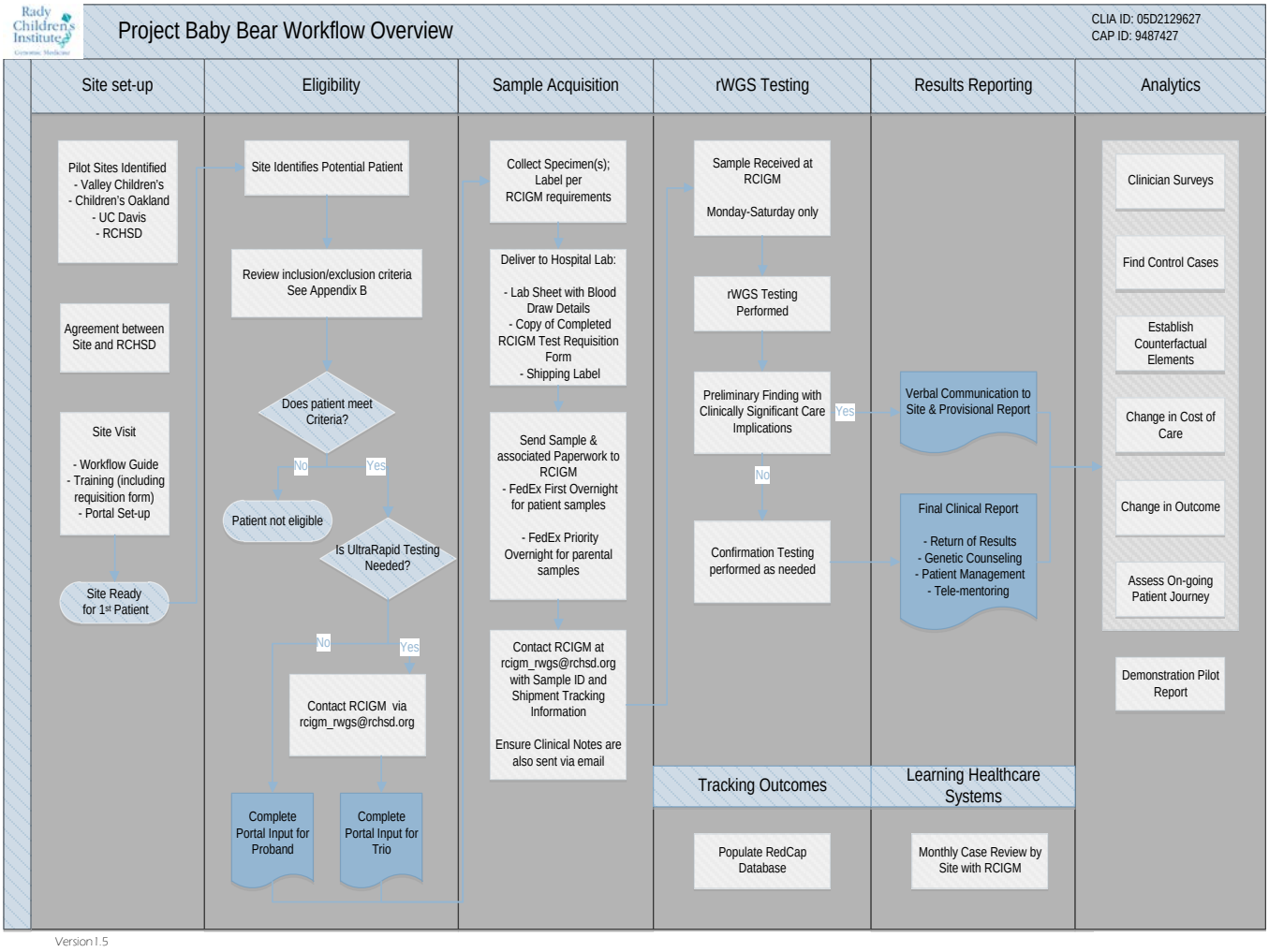
On the following page, we demonstrate how the financial resources made available from the Department for Health Care Services for the Pilot Program have been allocated across each phase to ensure all deliverables are completed on time and the number of patients tested is maximized.

FINANCIALS: PLANNED AND ACTUAL EXPENDITURES (THROUGH 12/31/18)

($000 USD)	3Q:18	4Q:18	1Q:19	2Q:19	3Q:19	4Q:19	Planned ($ M)	Actual ($ M)
Phase1: Site Set-up	$0.05	$0.02					$0.1	$0.07
Phase 2: Genomically Informed Medical Care	$0.02	$0.08					$1.4	$0.10
Phase 3: Analytics & Comparative Effectiveness							$0.5	$0.0
TOTAL							$2.0	$0.17

As of 31 December 2018, a total of $180,038.58 has been spent leaving $1,819,961.42. The project is on track to complete rWGS on a minimum of 100 Medi-Cal babies before the end of 2019.

APPENDIX A: WORKFLOW GUIDE



APPENDIX B: INCLUSION & EXCLUSION CRITERIA

PROJECT BABY BEAR PATIENT IDENTIFICATION

INCLUSION CRITERIA:

- **Acutely ill** inpatient, <1 year Medi-Cal beneficiary, admitted to a project site:
- within 1 week of admission

  or

- within 1 week of development of an abnormal response to standard therapy for an underlying condition

EXCLUSION CRITERIA:

Patients whose clinical course is entirely explained by:

- Infection or sepsis with normal response to therapy
- Isolated prematurity
- Isolated unconjugated hyperbilirubinemia
- Hypoxic Ischemic Encephalopathy with clear precipitating event
- Previously confirmed genetic diagnosis that explains the clinical condition (i.e. have a positive genetic test)
- Isolated Transient Neonatal Tachypnea
- Trauma
- Meconium aspiration

APPENDIX C: QI PROJECT END POINTS

PRIMARY END-POINTS:

1. The primary end-points in infants and children for whom rWGS was performed are as follows:
   - Changes in medical care due to rWGS results
   - Changes in cost of care as a result of rWGS after 4 months, 12 months, and 18 years

   Change in medical care will be documented in electronic medical records and in the health provider questionnaire that will be issued to each provider 10 days after return of rWGS results. Cost data to demonstrate changes in the cost of care at 4 months, 12 months, and 18 years will be through 4 months after return of result. Cost of care will be refined by detailed case review in selected cases through the end of the project. Counterfactual cost of care in the absence of rWGS will be determined by identification of similar historical cases with the same disease and/or literature review followed by consensus expert opinion as previously described (Farnaes et al., 2018). Change in cost of care at 4 months will be extrapolated to 1 year and 18 years of age.

2. In children in whom rWGS results lead to a change in care as documented by the site provider questionnaire (issued 10 days after return of results), change in outcomes through 4 months after return of result. Outcomes will include relevant end-organ function (e.g. heart, liver, kidney, bone marrow, lung, neurodevelopment) and mortality. These outcome measures will be a surrogate for quality of life measurement. Outcomes will be refined by detailed case review in selected cases through the end of the study. Counterfactual outcomes in the absence of rWGS will be determined as in Primary End Point 1. Change in outcome at 4 months will be extrapolated to 1 year and 18 years of age. Two other quality of life surrogates calculated will include change in the number of days as a hospital inpatient and change in the number of invasive procedures through 4 months after return of results.

SECONDARY END-POINTS:

1. Number of diagnoses made with rWGS compared to number of diagnoses made by tests ordered as standard care.
2. Time elapsed from time rWGS ordered by physician to time diagnosis given to ordering physician compared to elapsed time for same time points for tests used in standard care.
3. Clinical utility of rWGS compared to clinical utility of standard of care tests.

CONTACT INFORMATION

If you have any questions or would like more information, please feel free to contact us:

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