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I, Kayleigh A Swaggart Ph.D., hereby submit this original work as part of the requirements for the degree of Master of Science in Genetic Counseling.

It is entitled:

Making a genetic diagnosis in a level IV neonatal intensive care unit population: who, when, how, and at what cost?

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Making a genetic diagnosis in a level IV neonatal intensive care unit population:

who, when, how, and at what cost?

A thesis submitted to the Graduate School
of the University of Cincinnati in partial fulfillment
of the requirements for the degree of

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in the Department of Pediatrics

Of the College of Medicine

by

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ABSTRACT

Purpose: To characterize the genetic testing ordered, diagnoses made, and charges acquired for patients admitted to a level IV Neonatal Intensive Care Unit (NICU) in 2013 and 2014.

Methods: Retrospective chart review of all patients admitted to a single level IV NICU in 2013 and 2014. Demographic, genetic testing, genetic diagnosis, and charge data were collected from the electronic medical record (EMR).

Results: A total of 1327 unique patients were admitted to our level IV NICU during the study period. During the NICU stay and up to two years of age, 478 genetic tests were ordered for 276 (20.8%) patients. Of these, 73.4% (351) were ordered during the initial NICU admission. Most patients had only one test ordered, though this ranged from one to seven tests. The most commonly ordered test in the NICU was a microarray (103, 29.3%), which was the confirmatory test for 12.6% of those patients with a diagnoses. The least commonly ordered test was whole exome sequencing (4, 1.1%). A genetic diagnosis was made in 36.3% of patients who had genetic testing. In total, 128 patients (9.6%) received a genetic diagnosis by two years through genetic testing or other means. These patients were significantly more likely to be either term or late preterm ($p = 0.0025$), and to have normal birth weights ($p = 0.0111$). Inpatient clinical genetics evaluation improved the rate of diagnosis as opposed to performing genetic testing without a clinical genetics evaluation (26.5% vs. 44.5% in patients with a consult). However, a majority of the diagnoses (57.6%) were made after discharge. Of the 265 (20.0% of cohort) patients who received a genetics consult, 83 (31.3%) received a diagnosis. Patients receiving a diagnosis had significantly longer and more costly hospital stays. They had higher genetics charges, as expected. These patients were also more labor intensive than patients without a genetic diagnosis. In total \$851,982 in charges for genetics services were accrued during the two year study window, equaling \$642.04 per patient when averaged across the study cohort.

Conclusions: Our study characterized the genetic evaluation, testing, and diagnoses of a level IV NICU cohort over a two year time period. Nearly 10% of our cohort received a genetic

diagnosis by two years of age. These patients had longer NICU stays, more costly stays, and required more work to care for them than their counterparts without a genetic diagnosis.

Inpatient genetic consultations increased the rate of diagnosis in patients and despite overall more costly stays, genetics charges -- for hospital and physician charges and testing -- were very low relative to the overall cost of their NICU stay across the cohort.

Keywords: neonatal intensive care unit; infants; genetics; genetic testing; hospital charges

Table of Contents

List of Tables and Figures	vi
Introduction	1
Methods	2
Results	5
Discussion	8
References	12
Tables	15
Appendix 1: Data Collection Tools	24

List of Tables and Figures

Table 1. Patient demographics.	15
Table 2. Patient demographics by genetic diagnosis.	16
Table 3. NICU stay data by genetic diagnosis status.	17
Table 4. NICU stay charges and RVUs by genetic diagnosis status.	18
Supplemental Table 1. Automatic Data Collection Fields.	19
Supplemental Table 2. Automatic Data Extraction Validation Cohort.	20
Supplemental Table 3. Manual Data Collection Fields.	21
Supplemental Table 4. Patient genetic diagnoses.	22
Supplemental Table 5. Number of genetic tests ordered per patient.	23
Supplemental Table 6. Ordering and Diagnostic Yield of Testing in the NICU.	23

INTRODUCTION

Genetic conditions and congenital malformations are a leading cause of infant morbidity and mortality, causing over 20% of all US infant deaths in 2013 ¹⁻⁵. Contributing to this, between three and five percent of all newborns have a major birth defect or congenital malformation, of which ten to twenty percent are the result of an identifiable syndrome ⁶. In addition to morbidity and mortality, these syndromes have significant impacts on the hospital care infants require immediately after birth. On average, babies with genetic conditions that require care in a neonatal intensive care unit (NICU) have longer and more costly NICU stays, and require more professional time than babies requiring the same level of care without a genetic diagnosis ⁷⁻⁹.

There are four levels of neonatal care from a level I, where a healthy full term baby might receive care, to level IV where critically ill newborns are provided the highest level of care available. Patients receiving care at a level IV NICU cannot be managed at lower level facilities for various reasons including complicated medical or surgical needs, prematurity, or extremely low birth weight. Infants referred to level IV NICUs often need access to medical and surgical subspecialists as well as high-complexity care, such as extracorporeal membrane oxygenation (ECMO). The needs of patients receiving care at a level IV NICU are often very heterogeneous, unlike those of patients requiring care at a level II or III NICU where prematurity is a common theme ¹⁰.

Some newborns receive genetic diagnoses at or shortly after birth due to the presence of an easily recognizable phenotype, as is often the case for many children with Down syndrome. However, many genetic diagnoses may only have subtle or nonspecific clinical findings in the newborn period, such as hypotonia or feeding difficulties at a gestational age when this should not occur ¹¹. In recent years, there has been growing interest in the use of universal screening programs for infants admitted to the NICU to identify genetic conditions as quickly as possible. These include the trial use of large scale sequencing panels, whole exome sequencing (WES) and whole genome sequencing (WGS) for both ill and well neonates ¹²⁻²⁰.

Before implementing universal screening protocols or testing strategies for neonates, we must first understand what kinds of conditions we are seeing – and missing – in a level IV NICU setting. This includes understanding what testing methodologies would identify the conditions found in this unique population and when genetic assessment is most useful.

Understanding the genetic etiology of disease can improve outcomes and inform care decisions for our sickest newborns, and genetic testing is poised to revolutionize how these patients are cared for by providing a diagnosis rather than a problem list to guide medical decisions ²¹. No systematic reports exist about the rate of genetic evaluation, testing, and subsequent diagnostic yield as well as the economic impact of genetic disease seen within the complex care environment of a level IV NICU. Therefore, we performed a retrospective chart review to characterize the patients treated at a level IV NICU from 2013-2014 in which we evaluated the care they received during their NICU stay as well as all care they received at our institution up until 2 years of age.

METHODS

Study Design and Population

A retrospective chart review was performed to evaluate the incidence of all genetic conditions, utilization of genetic testing, and cost of care in a level IV Neonatal Intensive Care Unit (NICU). All infants admitted to the Cincinnati Children's Hospital Medical Center's (CCHMC) NICU between January 1, 2013 and December 31, 2014 were included in the study, and data was extracted from their electronic medical record (EMR) until each subject turned two years of age. There were no exclusion criteria outside of admission date. This study was approved by the CCHMC Institutional Review Board (Study Number 2017-0665).

Automatic Data Collection

The electronic medical record (Epic Systems) at CCHMC was searched for all patients meeting inclusion criteria. Automatically and manually extracted data were collected and managed using REDCap electronic data capture tools hosted at Cincinnati Children's Hospital Medical Center²². REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Data fields collected automatically are listed in Supplemental Table 1. The following values were automatically calculated from the dates extracted from EPIC: admission length, day of life at first inpatient genetics consult, and day of life at first outpatient genetics consult. For clinical data extraction from the electronic medical record (EMR) system, we utilized the hospital's EMR reporting database. With the help of daily running process, Epic EMR system's data was extracted, transformed and loaded into a relational database, Clarity. The queries used for data extraction and manipulation were developed in Structured Query Language (SQL). For each patient, all gross charges incurred through their first two years of life were collected. These included both hospital and professional charges and were separated by NICU and post-discharge charges. Work and total relative value units (RVUs) were also collected. Work RVU are the Physician Work RVU, which are CPT code based. Total RVU includes not only work RVU but practice expense RVU and malpractice RVU as well.

Validation of Automatic Data Collection

To examine the accuracy of the automatic data collection, all data with the exclusion of charge and RVU data, were abstracted manually from EPIC for a subset of the study population. This

group consisted of 6 neonates admitted during each month of the 24-month study period, for a total of 144 neonates. The 6 admissions per month were selected using a random number generator. This method of creating the validation population aimed to include neonates admitted throughout the study window and account for any changes in how data were collected or stored in EPIC over that time. Results of the validation dataset are shown in Supplemental Table 2. Based on these results, all genetic consult and testing data were extracted manually in addition to the automatic extraction.

Manual Data Collection

Data that could not be extracted automatically with high accuracy based on the validation cohort was collected manually from EPIC, including all genetic consult and testing information. These data fields and genetic testing categorization information are listed in Supplemental Table 3. Day of life at test order and day of life at test result were calculated from the collected data. Genetic tests were classified in more than one category if applicable. Genetic test names and results were recorded according to their associated result report in the medical record. Abnormal test result details were recorded using the nomenclature in the test report; multiple abnormal results were recorded, if applicable.

Classification of Genetic Diagnoses

Genetic diagnoses made for individuals in the study population were identified in two ways: through positive genetic testing results and through examination of patient problem lists and confirmation in the medical record. Diagnostic genetic tests were defined as those that had a positive, disease causing result that explained the phenotype(s) seen in the patient. Not included were variant and negative results. Secondary genetic findings were included as a genetic diagnosis only if the patient had the condition (i.e. was not a carrier). Additional genetic diagnoses were identified through patient problem lists and included diagnoses made prenatally

or at an outside hospital. For example, if a patient problem list included Trisomy 21, but they were not tested for this condition at CCHMC, the diagnosis was confirmed in the medical record and recorded without an accompanying genetic test. A number of patients had diagnoses that were classified as “other” because they had a genetic component and were typically seen by the genetics service, but did not have specific cytogenetic or molecular abnormality identified on genetic testing. Examples of “other” results can be found in the all diagnoses list (Supplemental Table 4).

Data Analysis

De-identified data and reports used for analysis were queried and exported from REDCap. Data analyses were performed using Prism v.7 (GraphPad). Quantitative data were not distributed normally, so non-parametric tests were used as appropriate, including Fisher’s exact, Chi-square, and Mann Whitney rank-sum. Differences between groups were considered statistically significant when $p < 0.05$.

RESULTS

Cohort Demographics

During the study window of January 1, 2013 and December 31, 2014, there were 1374 admissions to the CCHMC NICU representing 1327 unique patients. Of the 44 readmitted patients, 42 were readmitted once, one was readmitted twice, and one was readmitted three times. Demographic information for the full cohort is shown in Table 1.

Genetic Testing

In total, 478 genetic tests were ordered for 276 patients up to two years of age. Of these, 351 (73.4%) were ordered during the NICU stay and 127 (26.6%) were ordered between discharge

and two years of age. Twenty three patients had genetic testing both in the NICU and as an outpatient. The number of genetic tests ordered per patient is listed in Supplemental Table 5. Most patients (159) who had genetic testing ordered had only one test ordered. The highest number of tests ordered for a single patient was seven. The most commonly ordered genetic test in the NICU was a microarray (103, 29.3%) which confirmed a diagnosis for 13 patients, resulting in a diagnostic yield of 12.6%. The second most commonly ordered tests were for a single gene (80, 22.8%), including sequencing and/or deletion duplication or repeat analysis, and lead to a genetic diagnosis in 16 patients for a diagnostic yield of 20.0%. During the study period, the least common test outside of the “other” category was whole exome sequencing (4, 1.1%). However, whole exome sequencing had the highest diagnostic yield of all test types at 50% (2/4). Imprinting/methylation tests had the next highest diagnostic yield, with 42.9% (6/14) positive results. Other test categories, the numbers ordered, and diagnostic yield are shown in Supplemental Table 6.

Genetic Diagnosis

In total, 128 patients (9.6%) received 130 diagnoses. Of the 1195 (90.1%) patients who did not receive a genetic diagnosis, 176 patients underwent genetic testing, accounting for 63.7% of all patients who had genetic testing. Twenty nine (22%) diagnoses were made prenatally or at a referring hospital (12 were Trisomy 21) and eight were made based on clinical criteria or through a research program. Of the diagnoses made at our center, 39 (41.9%) were made during the NICU stay and 54 (58.1%) were made between discharge and two years of age. The average day of life at diagnosis was 125.1 days, the median was 44.5, and the range was 2-624 days. Thirty-four patients (27%) diagnosed at our center received a diagnosis within the neonatal period (≤ 28 days). Genetic diagnoses were significantly more common in patients with later gestational age (>34 weeks; $p = 0.0025$) and were an appropriate weight for gestational age (>2500 grams; $p = 0.0111$). The mortality rate of patients with a genetic diagnosis was

greater than double that of patients who did not receive a genetic diagnosis (14.1% by two years versus 6.2%). An inpatient genetics consult was performed for 83 (64.8%) of the patients with a diagnosis at 2 years of age and occurred on average 2.8 days after admission (median = 1, range = 0-55). Of the 53 diagnoses made after NICU discharge, 85% had no inpatient genetic consult evaluation and 55% had no genetic testing performed during the NICU stay. Patients who underwent genetic testing without a clinical genetics evaluation were less likely to receive a genetic diagnosis (26.5% vs. 44.5%; $p = 0.0025$).

Economics

Age (in days) at admission and discharge are shown in Table 3. There was no difference in when patients with and without a genetic diagnosis were admitted, but those with a diagnosis had a longer length of stay in the NICU (47.9 vs 29.1 days, $p < 0.0001$). Genetic testing was performed for 276 patients (20.8%) admitted to the CCHMC NICU during the study period, and 265 patients (20.0%) had an inpatient genetics consult. Mean, median, and range of total charges for the NICU stay are shown in Table 4. Patients with a genetic diagnosis had significantly higher total charges for their NICU stay with a mean of \$290,754 ($p < 0.0001$) more than those patients without a confirmed diagnosis at 2 years of age. Patients with a genetic diagnosis also had significantly higher professional charges (mean difference: \$37,174, $p < 0.0001$) and hospital charges (mean difference: \$256,951, $p < 0.0001$). Patients with a genetic diagnosis also had higher genetics charges ($p < 0.0001$), as expected, which encompassed both genetic consults and genetic testing. In addition to higher charges, patients who received a genetic diagnosis also had higher RVUs, both total (529.3 vs. 321.1, $p < 0.0001$) and work (354.7 vs. 217.2, $p < 0.0001$), confirming that these patients are more labor intensive despite requiring quaternary care as their counterparts without a genetic diagnosis. In total \$851,982 charges for genetics services were accrued during the two year study window; equaling \$642.04 per patient when averaged across the entire study cohort.

DISCUSSION

The burden of genetic conditions in our quaternary neonatal population was high; of the 1327 patients admitted to our level IV NICU during 2013 and 2014, 9.6% of our population received a genetic diagnosis by two years of age. Within the cohort, 20.8% had an evaluation for a genetic disorder, giving an overall diagnostic yield of 46%. For patients suspected of having a genetic condition, this overall diagnostic yield is higher than almost all of the individual genetic test categories and in line with whole exome sequencing, which had the highest diagnostic yield. Patients with any genetic diagnosis by two years of age were more likely to be born at or close to term than other infants in the same level IV NICU, suggesting that genetic disease is an important driver causing late preterm or term newborns to require quaternary NICU care. Patients with a genetic diagnosis also had longer and more costly NICU stays, in line with previous research ⁷⁻⁹. The mortality rate of patients with a genetic diagnosis was over double that of patients who had not received a diagnosis, also consistent with known epidemiological data ^{1,3}.

Of the 130 genetic diagnoses found in our patient population, 102 were made at our institution following admission to our NICU but before two years of age. Twenty nine (22%) patients were admitted to the NICU with a known genetic diagnosis, made prenatally or at an outside hospital. The diagnoses made prior to NICU admission represented more common or easier to recognize conditions, such as Trisomy 21. The diagnoses made in our cohort were based on clinical criteria, as well as molecular or cytogenetic testing. While the most commonly ordered test was microarray, the test category with the highest diagnostic yield was whole exome sequencing; however, there were only two diagnostic tests in this category. The test category with the next highest diagnostic yield was imprinting/methylation testing, which may be a reflection of suspicion of a specific condition as these tests are typically not ordered for a general suspicion of a genetic condition, but for patients with specific phenotypes matching that of an imprinting disorder.

Patients in our cohort were twice as likely to receive a diagnosis if they underwent a clinical genetics evaluation rather than genetic testing alone. This would suggest that a screening approach to identifying patients with a genetic condition in a quaternary NICU should not be solely about performing a specific genetic test, but also about performing a comprehensive clinical genetics evaluation to guide appropriate selection of testing. The majority of unique diagnoses (48/71, 67%) were seen only one or two times during the two year study period and were made through genetic testing that was not targeted at a specific diagnosis, but with broader genetic testing such as microarray, panel or exome. The rarity of these conditions makes it difficult to recognize a specific phenotype and send targeted testing.

The time to a genetic diagnosis was prolonged, with only 34 diagnoses made during the neonatal period (≤ 28 days), in addition to the patients who were admitted to the NICU with a diagnosis. The remaining five patients were diagnosed later in their NICU stay. This suggests that there is a subset of patients with neonatal presentations of genetic disorders that can be identified earlier than the majority of patients with genetic disorders. Patients who were diagnosed in the neonatal period were discharged home sooner on average than patients diagnosed later, but this difference was not significant. However, the small number of patients with a genetic diagnosis in this study may not have been sufficient to show this important difference in outcome. On average, a diagnosis took 125 days to make (median: 44.5 days of life), though the range was large – from 2 to 624 days – with a significant negative skew. Forty-five patients (35.2%) were found to have a genetic diagnosis after discharge from the NICU while never having any inpatient suspicion for a genetic disorder. While it is difficult to determine why so many neonates were not suspected to have had a genetic condition during their NICU admission, one complicating factor may be that a normal newborn is only expected to perform very basic functions including the ability to eat, breath, and sleep. It may have been that these patients had subtle symptoms but suspicion for an underlying syndrome did not rise until they later failed to meet developmental milestones.

Patients with a genetic condition cost more money and required more work to care for than those without a diagnosis even when that diagnosis is unknown during the NICU admission, as was seen with the majority of our cohort. This is important for both staffing and reimbursement purposes: babies on the same level IV NICU unit with a genetic condition will require more resources than other patients. However, it is important to note that genetics-related costs were not the cause of these differences. Despite the fact that over 60% of all patients that underwent genetic testing ended up with no diagnosis at two years of age, the overall cost of genetic testing and services was a very small proportion of the total health care dollars spent on the cohort. In total, less than \$900,000 was spent on all genetics services for the entire cohort over two years, while some individual patients had NICU stays that cost this much or more. This finding supports the idea of including the genetics service more frequently in the NICU, as their involvement improves diagnostic rate but does not significantly raise costs like other tests and services. Other commonly ordered diagnostic tests in the NICU like complete transthoracic echocardiogram or brain MRI without contrast were charged at \$5,172 and \$4,510 each, respectively, over the study period, but their impact on patient care and outcomes is unclear.

This study utilized a retrospective chart review methodology, which comes with some specific limitations. First, only information in the medical record was available for review. We followed these patients out to their second birthday, but only 886 patients (67%) had any encounter at our institution within 90 days of their second birthday. While we had complete data for all of the patients during their NICU stay we had no information about their current health at two years of age for more than a quarter of our patients. Therefore, our total of 130 confirmed genetic diagnosis is likely an under-representation of the genetic diagnoses in this population. Our mortality rate is also likely an underestimate, as we only have access to death information for patients who continued to receive care at our institution. Additionally, our study period creates important differences in our study cohort compared to current practice. Genetic tests

and testing utilization has evolved significantly over the past decade including over our study period and in the years since. Genetic testing is now more commonly ordered and the kinds of tests being ordered are changing. Perhaps most significant is the increasing use of multi-gene panels and whole exome sequencing as first-line tests.

CONCLUSIONS

Our study is the first to characterized the genetic evaluation, testing, and diagnoses of a level IV NICU cohort up to two years of age. In addition, we showed that caring for patients with a genetic diagnosis in a level IV NICU is more costly even when the care givers are not yet aware of the genetic diagnosis. Despite this higher cost, genetic testing and evaluation did not contribute significantly to that increased cost. Having a genetic diagnosis allows the medical team to better direct and anticipate medical needs, and it also allows families to better understand their child's current and future health care needs.

This study identifies the kinds of genetic conditions seen in a level IV NICU and the time to and cost of diagnosis. While factors like cost and test turnaround time are expected to have changed since the study period, the overall makeup of a level IV NICU cohort likely has not. We have shown that at least 1 in 10 patients in this population has a genetic diagnosis. Because of such high numbers, it may make sense to implement universal screening protocols. Late preterm or term gestation, as well as birth weight, are important predictors of having a genetic diagnosis in this population indicating that these criteria should be used as initial screening criteria for consideration of a genetic disorder. Our results also indicate that a universal screening protocol should involve a clinical genetics evaluation along with appropriate genetic testing as dictated by that evaluation. Our cohort demonstrates, many conditions are only seen once in years and a single testing methodology – like sequencing or microarray – would not identify all patients. A prospective study with a larger study cohort will be needed to fully examine current genetic testing and evaluate protocols and their yield given the rapid evolution

of genetic tests, their utilization and costs and reimbursement. Additional multi-center studies are needed to better define the incidence of genetic disease in level IV NICUs as well as how those diagnoses are made and how caring for these unique patients is different.

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Table 1. Patient demographics.

Total	1327 (%)
Sex	
Male	727 (54.8)
Female	600 (45.2)
Gestational Age (weeks)	
≤27	136 (10.3)
28-31	119 (8.9)
32-33	70 (5.3)
34-36	260 (19.6)
≥37	730 (55.0)
Unknown	12 (0.9)
Birth Weight (grams)	
<1500	238 (17.9)
1500-2500	248 (18.7)
>2500	800 (60.3)
Unknown	41 (3.1)
Race	
White	934 (70.4)
Black	220 (16.6)
Asian	13 (1.0)
American Indian/Alaskan Native	2 (0.1)
Native Hawaiian/Pacific Islander	2 (0.1)
Other	58 (4.4)
Multiracial	48 (3.6)
Unknown	50 (3.8)
Ethnicity	
Hispanic	62 (4.7)
Not Hispanic	1239 (93.4)
Unknown	26 (1.9)
Mortality	
Alive at 2 Years	1232 (92.8)
During NICU Stay	74 (5.6)
Before 2 Years	18 (1.4)
Unknown Age	3 (0.2)
Service Market	
Primary	900 (67.8)
Secondary	202 (15.2)
Regional	183 (13.8)
National	42 (3.2)

Table 2. Patient demographics by genetic diagnosis.

	Genetic Diagnosis*	No Genetic Diagnosis	<i>p-value</i>
Total	128 (9.6)	1199 (90.4)	-
Sex			<i>p = 0.3513</i>
Male	65 (8.9)	662 (91.1)	
Female	63 (10.5)	537 (89.5)	
Gestational Age (weeks)			<i>p = 0.0025</i>
<34	18 (5.5)	307 (94.5)	
≥34	110 (11.1)	880 (88.9)	
Birth Weight (grams)			<i>p = 0.0111</i>
<1500	13 (5.5)	225 (94.5)	
≥1500	114 (10.9)	934 (89.1)	
Mode of Delivery			<i>p = 0.2247</i>
Vaginal	57 (8.7)	601 (91.3)	
Caesarean Section	69 (10.7)	578 (98.3)	
Race			<i>p = 0.1308</i>
White	93 (10.0)	841 (90.0)	
Black	17 (7.7)	203 (92.3)	
Other/Multiracial	18 (14.5)	106 (85.5)	
Mortality During NICU Stay			<i>p = 0.1519</i>
Yes	11 (8.6)	63 (5.3)	
No	117 (91.4)	1133 (94.7)	
Mortality by 2 Years			<i>p = 0.0027</i>
Yes	18 (14.1)	74 (6.2)	
No	110 (85.9)	1122 (93.8)	
Service Market			<i>p = 0.7653</i>
Primary	85 (9.4)	815 (90.6)	
Other	43 (10.1)	384 (89.9)	

*Diagnoses up to two years of age.

Unknown values are not included.

Table 3. NICU stay data by genetic diagnosis status.

		Genetic Diagnosis*	No Genetic Diagnosis	p-value
Admission Day of Life	mean	12.5	13.6	<i>p</i> = 0.8045
	median	2	2	
	range	172 (0-172)	202 (0-202)	
Discharge Day of Life	mean	59.1	42.8	<i>p</i> < 0.0001
	median	31.5	19	
	range	474 (3-477)	654 (0-654)	
Length of Stay (days)	mean	47.9	29.1	<i>p</i> < 0.0001
	median	23.5	10	
	range	438 (0-438)	654 (0-654)	
Genetic Testing	yes	100 (78.1)	176 (14.7)	
	no	28 (21.9)	1023 (85.3)	
Inpatient Genetics Consult	yes	83 (64.8)	182 (15.2)	
	no	45 (35.2)	1017 (84.8)	

*Diagnoses up to 2 years

Table 4. NICU stay charges and RVUs by genetic diagnosis status.

		Genetic Diagnosis*	No Genetic Diagnosis	p-value
Total Charges (dollars)	mean	\$648,204	\$357,450	<i>p < 0.0001</i>
	median	\$265,659	\$113,918	
	range	\$15,421 - 4,099,107	\$3,832 - 7,007,499	
Professional Charges (dollars)	mean	\$95,852	\$58,678	<i>p < 0.0001</i>
	median	\$49,114	\$20,404	
	range	\$1,983 - 541,945	\$67 - 1,046,758	
Hospital Charges (dollars)	mean	\$556,701	\$299,750	<i>p < 0.0001</i>
	median	\$210,235	\$93,617	
	range	\$14,335 - 3,699,489	\$3,832 - 5,960,741	
Total Genetics Charges (dollars)	mean	\$2,336	\$461	<i>p < 0.0001</i>
	median	\$930.50	\$0	
	range	\$0**- 19,132	\$0 - 13,903	
Total RVUs	mean	529.3	321.1	<i>p < 0.0001</i>
	median	258	101	
	range	9 - 3,360	1 - 6,199	
Work RVUs	mean	354.7	217.2	<i>p < 0.0001</i>
	median	165	68	
	range	6 - 2,122	1 - 4,114	

*Diagnoses up to 2 years

**Group includes patients diagnosed before admission.

Supplemental Table 1. Automatic Data Collection Fields

Demographic Data

Medical Record Number (MRN)
Patient Name
Patient Encounter Number
Admission Date(s)
Discharge Dates(s)
Date of Birth
Death of Patient (Yes/No, Date of Death)
Sex
Ethnicity (Hispanic or Not Hispanic)
Race
Zip Code
State

Genetics Data

Inpatient Genetics Consult (Yes/No, Date of First Consult)
Outpatient Genetics Consult (Yes/No, Date of First Consult)
Genetic Testing Ordered (Yes/No)

Charge Data

Hospital Service Market (Primary, Secondary, Regional, National)
Professional Charge Total: NICU Stay
Professional Charge Total: Post-Discharge
Professional Charge Total: Genetics
Hospital Charge Total: NICU Stay
Hospital Charge Total: Post-Discharge
Hospital Charge Total: Genetics
Total RVUs
Total RVUs: Post-Discharge
Work RVUs
Work RVUs: Post-Discharge

Supplemental Table 2. Automatic Data Extraction Validation Cohort

Automatic Extraction Field	Field Performance	Notes
<i>Demographic Data</i>		
Admission Date(s)	99.3 (143/144)	Manual extraction found admission to a different unit.
Discharge Dates(s)	99.3 (143/144)	Manual extraction found admission to a different unit.
Date of Birth	100 (144/144)	-
Sex	100 (144/144)	-
Ethnicity (Hispanic or Not Hispanic)	100 (144/144)	-
Race	100 (144/144)	-
Zip Code	95.1 (137/144)	Incorrect zip codes indicate a move since time of NICU admission.
State	100 (144/144)	-
<i>Genetics Data</i>		
Inpatient Genetics Consult (Yes/No)	100 (144/144)	-
Date of First Consult	97.9 (141/144)	Dates off by one day for unknown reason.
Outpatient Genetics Consult (Yes/No)	98.6 (142/144)	Two multidisciplinary clinics missed.
Date of First Consult	98.6 (142/144)	Dates correspond to above clinic visits.
Genetic Testing Ordered (Yes/No)	94.4 (136/144)	Four missed genetic tests, four non-genetic tests.

Supplemental Table 3. Manual Data Collection Fields

Birth Data

Birth Weight
Mode of Delivery (Vaginal, Cesarean Section, Other
APGAR Scores (One- and Five-Minutes)

Genetic Data

Inpatient Genetics Consult (Yes/No, Date of First Consult)
Outpatient Genetics Consult (Yes/No, Date of First Consult)
Genetic Testing Ordered (Yes/No)
Date of Test Order
Date of Test Result
Type of Test and Results
Fluorescence In Situ Hybridization (FISH)
Normal or Abnormal
Chromosomes
Normal or Abnormal
Microarray
CNV(s) Reported or No CNV Reported
Benign, Pathogenic, VUS
Single Gene Sequencing
Variant(s) Detected or No Variant Detected
Pathogenic, Likely Pathogenic, VUS, Likely Benign, Benign
Single Gene Deletion/Duplication/Repeats
CNV(s) Reported or No CNV Reported
Benign, Pathogenic, VUS
Multi-Gene Panel
CNV(s) Reported or No CNV Reported
Benign, Pathogenic, VUS
Imprinting/Methylation
Normal or Abnormal
Whole Exome Sequencing (WES)
Variant(s) Detected or No Variant Detected
Pathogenic, Likely Pathogenic, VUS, Likely Benign, Benign
Singleton or Trio Testing
Parent of Origin (if Trio)

Other

Supplemental Table 4. Patient genetic diagnoses.

Diagnosis	Patients
Trisomy 21	21
Cystic Fibrosis	6
Prader Willi Syndrome	6
Congenital Adrenal Hyperplasia	5
Myotonic Dystrophy	5
Beckwith-Wiedemann syndrome	3
Mosaic Trisomy 9	3
Osteogenesis Imperfecta (multiple types)	3
18q- syndrome	2
22q11.2 Deletion syndrome	2
22q11.2 Microduplication syndrome	2
Achondroplasia	2
Alagille Syndrome	2
CHARGE syndrome	2
Congenital Central Hypoventilation syndrome	2
Congenital Hypophosphatasia	2
Epidermolysis Bullosa	2
Hemophilia A	2
Isovaleric Acidemia	2
Long QT Syndrome	2
Maternal Uniparental Disomy of Chromosome 16	2
Noonan syndrome	2
Turner syndrome	2
12q15q21.1 deletion syndrome	1
16p12.2 deletion	1
17q21.31	1
1q21.1 Deletion, TAR syndrome	1
21p11.2-q22.3 duplication	1
46,XX,der(6)ins(6;2)(p23;?), 2q23.3q31.2	1
46,XY,t(2;12)(q35;q21.2)	1
4q31.22-q31.3del, AD pseudohypoaldosteronism type 1	1
4q32.3-q35.2 deletion	1
5q33.2-q35.3 duplication	1
7q11.23 Deletion syndrome	1
8p23.1 Deletion syndrome	1
9p21.3 deletion	1
Albinism	1
Balanced Translocation t(4;6)	1
Becker Muscular Dystrophy	1
Blepharo-Cheilo-Dontic syndrome (clinical)	1
Congenital Myasthenic Syndrome	1
Dilated Cardiomyopathy, Familial <i>MYH7</i>	1
Duane retraction syndrome	1
Duarte Galactosemia (Duarte)	1
Emanuel syndrome	1
Factor V Leiden Thrombophilia	1
<i>FLNA</i> -associated disorder	1
<i>FOXG1</i> syndrome	1
G6PD Deficiency	1
Galactosemia	1
Harlequin Ichthyosis	1
Hemophilia B (Factor 9 Deficiency)	1
Hereditary spherocytosis	1
Holoprosencephaly (clinical)	1
Hypertrophic Cardiomyopathy, Familial	1
Joubert Syndrome	1
Leigh Disease	1
Li-Fraumeni syndrome	1
Loeys-Dietz syndrome	1
Malignant Hyperthermia	1
Mandibulofacial Dysostosis Guion-Almeida Type	1
MCAD	1
Mosaic Trisomy 14	1
Mosaic Trisomy 21	1
Mowat-Wilson syndrome	1
<i>MTHFR</i> 677 T/T	1
Netherton Syndrome	1
Nonketotic Hyperglycinemia	1
Opsismodysplasia	1
Pontocerebellar Hypoplasia	1
Prothrombin 20210 G>A	1
Rhizomelic Chondrodysplasia Punctata	1
Russell-Silver syndrome	1
Schaaf-Yang syndrome	1
Sotos syndrome	1
Spinal Muscular Atrophy	1
SPINT2-related diarrhea and choanal atresia	1
Stickler syndrome	1
Treacher Collins syndrome	1
Trichohepatoenteric syndrome 1	1
Trisomy 9p with Monosomy 18q	1
Tuberous Sclerosis	1
Type XI collagenopathy, mosaic	1
von Willebrand disease, type 2b	1
Xq28 duplication	1
Other Diagnoses (counted as "No Diagnosis")	Patients
Pierre Robin Sequence with cleft palate	13
Hirschsprung's disease	7
Pierre Robin Sequence without cleft palate	6
VACTERL association	5
Arthrogryposis	3
Prune Belly syndrome	3
CLOVES syndrome	2
Multiple Congenital Anomalies likely associated with a genetic disorder	2
Disorder of Sexual Development, clinical, unknown etiology	1
Klippel-Trenaunay-Weber syndrome	1
Pierre Robin Sequence, possibly secondary to deformation	1
Wolff-Parkinson-White syndrome	1

Table 5. Number of genetic tests ordered per patient.

Number of Tests Ordered	NICU Stay	All to 2 Years
1	131 (60.4)	159 (57.6)
2	59 (27.2)	68 (24.6)
3	12 (5.5)	27 (9.8)
4	9 (4.1)	12 (4.3)
5	6 (2.8)	7 (2.5)
6	0 (0.0)	2 (0.7)
7	0 (0.0)	1 (0.4)

Table 6. All genetic testing across the study period.

	Ordered (NICU)	Diagnostic (NICU)	Ordered (Post-Discharge)	Diagnostic (Post-Discharge)
FISH	20 (5.7)	4 (20.0)	3 (2.4)	0 (0.0)
Chromosomes	60 (17.1)	10 (16.7)	11 (8.7)	0 (0.0)
Microarray	103 (29.3)	13 (12.6)	17 (13.4)	4 (23.5)
Single Gene¹	80 (22.8)	16 (20.0)	45 (35.4)	15 (33.3)
Multi-Gene Panel	66 (18.8)	15 (22.7)	34 (26.8)	6 (17.6)
Imprinting/Methylation	14 (4.0)	6 (42.9)	4 (3.1)	0 (0.0)
Whole Exome Sequencing	4 (1.1)	2 (50.0)	5 (3.9)	3 (60.0)
Other	4 (1.1)	0 (0.0)	8 (6.3)	1 (12.5)

¹Sequencing and/or Deletion/Duplication or Repeat Analysis

Demographics and NICU Stay

Page 1 of 8

Record ID

---

1. Medical Record Number

---

2. Gestational Age (weeks):

---

3. Birthweight:

---

4. Mode of delivery:

- ☐ Vaginal
☐ Cesarean Section
☐ Unknown

Specify Other:

5a. APGAR at 1 minute:
(99 for unknown)

5b. APGAR at 5 minute:
(99 for unknown)

Demographics and NICU automated

Page 4

1. Medical Record Number:

_____

2. Date of Birth:
(9999/12/31 for missing)

_____

3. Sex:

- ☐ 1 = Male
☐ 2 = Female
☐ 8 = Other
☐ 9 = Unknown

4. Zip Code:
(99999 for unknown)

_____

5. State:

_____

6a. Race (check all that apply):

- ☐ Black
☐ White
☐ American Indian or Alaskan Native
☐ Asian
☐ Native Hawaiian or Other Pacific Islander
☐ Other
☐ Unknown

6b. Ethnicity:

- ☐ Not Hispanic
☐ Hispanic
☐ Unknown

7. NICU admission date:
(9999/12/31 for missing)

_____

DOL at admission

_____

8. NICU discharge date:
(9999/12/31 for missing)

_____

DOL at discharge

_____

9. Inpatient genetic consult:

- ☐ 0 = No
☐ 1 = Yes
☐ 9 = Unknown

9a. Date of inpatient consult:

_____

Day of life at inpatient consult:

_____

10. Outpatient genetic consult:

- ☐ 0 = No
☐ 1 = Yes
☐ 9 = Unknown

10a. Date of outpatient consult:

_____

Day of life at outpatient consult:

_____

Genetic Testing

Page 1

1. Date of Test Order:
(9999/12/31 for unknown)

_____

Day of life at order

_____

2. Date of test result:
(9999/12/31 for unknown)

_____

Day of life at result

_____

3. Genetic Test:

- ☐ FISH
- ☐ Chromosomes
- ☐ Microarray
- ☐ Single gene (Sequencing)
- ☐ Single gene (Del/Dup)
- ☐ Multi-Gene Panel
- ☐ Whole Exome Sequencing
- ☐ Whole Genome Sequencing
- ☐ Imprinting/Methylation
- ☐ Other

FISH:

- ☐ Normal
- ☐ Abnormal

FISH test name:

_____

FISH (text for abnormal result):

_____

Chromosomes:

- ☐ Normal
- ☐ Abnormal

Chromosomes: (free text for location and breakpoints)

_____

Microarray:

- ☐ No CNV Reported
- ☐ CNV Reported

How many CNVs were reported?

_____

Microarray: 1st CNV reported

- ☐ Benign
- ☐ VUS
- ☐ Pathogenic

Microarray: 1st (free text for entry of mutation)

_____

Microarray: 2nd CNV reported

- ☐ Benign
- ☐ VUS
- ☐ Pathogenic

Microarray: 2nd (free text for entry of mutation)

_____

Microarray: 3rd CNV reported

- ☐ Benign
- ☐ VUS
- ☐ Pathogenic

Microarray: 3rd (free text for entry of mutation)

Microarray: 4th CNV reported

- ☐ Benign
- ☐ VUS
- ☐ Pathogenic

Microarray: 4th (free text for entry of mutation)

Microarray: 5th CNV reported

- ☐ Benign
- ☐ VUS
- ☐ Pathogenic

Microarray: 5th (free text for entry of mutation)

Single gene (Sequencing):

- ☐ No variants detected
- ☐ Variant detected

Single gene (Sequencing) Gene/Test Name:

Single gene (Sequencing): If variant detected:

- ☐ Pathogenic
- ☐ Likely Pathogenic
- ☐ Benign
- ☐ Likely Benign
- ☐ Uncertain Significance

Single gene (Sequencing): (free text for entry of mutation)

Single gene (Del/Dup):

- ☐ No CNV Reported
- ☐ CNV Reported

Single gene (Del/Dup) Gene/Test name

Single gene (Del/Dup): If CNV Reported

- ☐ Benign
- ☐ VUS
- ☐ Pathogenic

Single gene (Del/Dup) Repeat Analysis:

- ☐ Normal
- ☐ Abnormal

Single gene (Del/Dup, repeats): (free text for results)

Multi-Gene Panel

- ☐ No variants detected
- ☐ Variant detected

Multi-Gene Panel Test Name

Multi-Gene Panel: Number of Variants:

Multi-Gene Panel: 1st variant:

- ☐ Pathogenic
- ☐ Likely Pathogenic
- ☐ Benign
- ☐ Likely Benign
- ☐ Uncertain Significance

Multi-Gene Panel: 1st variant (free text):

Multi-Gene Panel: 1st CNV:

- ☐ No CNVs detected
- ☐ CNV reported

Multi-Gene Panel: 1st CNV results:

Multi-Gene Panel: 1st CNV reported:

- ☐ Benign
- ☐ VUS
- ☐ Pathogenic

Multi-Gene Panel: 2nd variant:

- ☐ Pathogenic
- ☐ Likely Pathogenic
- ☐ Benign
- ☐ Likely Benign
- ☐ Uncertain Significance

Multi-Gene Panel: 2nd variant (free text):

Multi-Gene Panel: 2nd CNV

- ☐ No CNVs detected
- ☐ CNV reported

Multi-Gene Panel: 2nd CNV results:

Multi-Gene Panel: 2nd CNV reported:

- ☐ Benign
- ☐ VUS
- ☐ Pathogenic

Multi-Gene Panel: 3rd variant:

- ☐ Pathogenic
- ☐ Likely Pathogenic
- ☐ Benign
- ☐ Likely Benign
- ☐ Uncertain Significance

Multi-Gene Panel: 3rd variant (free text):

Multi-Gene Panel: 3rd CNV:

- ☐ No CNVs detected
- ☐ CNV reported

Multi-Gene Panel: 3rd CNV results:

Multi-Gene Panel: 3rd CNV reported:

- ☐ Benign
- ☐ VUS
- ☐ Pathogenic

Multi-Gene Panel: 4th variant:

- ☐ Pathogenic
- ☐ Likely Pathogenic
- ☐ Benign
- ☐ Likely Benign
- ☐ Uncertain Significance

Multi-Gene Panel: 4th variant (free text):

Multi-Gene Panel: 4th CNV:

- ☐ No CNVs detected
- ☐ CNV reported

Multi-Gene Panel: 4th CNV results:

Multi-Gene Panel: 4th CNV reported:

- ☐ Benign
- ☐ VUS
- ☐ Pathogenic

Multi-Gene Panel: 5th variant:

- ☐ Pathogenic
- ☐ Likely Pathogenic
- ☐ Benign
- ☐ Likely Benign
- ☐ Uncertain Significance

Multi-Gene Panel: 5th variant (free text):

Multi-Gene Panel: 5th CNV:

- ☐ No CNVs detected
- ☐ CNV reported

Multi-Gene Panel: 5th CNV results:

Multi-Gene Panel: 5th CNV reported:

- ☐ Benign
- ☐ VUS
- ☐ Pathogenic

Whole Exome Sequencing: Variants:

- ☐ No
- ☐ Yes

Whole Exome Sequencing: (free text for variants)

Whole Exome Sequencing: Trio:

- ☐ No
- ☐ Yes

Whole Exome Sequencing: if Trio is Yes:

- ☐ de novo
- ☐ mother
- ☐ father
- ☐ NA

Whole Genome Sequencing: Variants:

- ☐ No
- ☐ Yes

Whole Genome Sequencing: (free text for variants)

Whole Genome Sequencing: Trio:

- ☐ No
☐ Yes

Whole Genome Sequencing: if Trio is Yes:

- ☐ de novo
☐ mother
☐ father
☐ NA

Imprinting/Methylation:

- ☐ Normal
☐ Abnormal

Name of Imprinting/Methylation test:

_____

Imprinting/Methylation test results:

_____

Other (Test Name):

_____

Other (free text to describe test and result):

_____

Genetic Diagnosis:

- ☐ No
☐ Yes
☐ Other

If Yes, please specify:

_____

If Other, please specify:

_____

CHARGES

Date of NICU admission:

_____

Date of NICU discharge:

_____

Genetic Test:

- ☐ No
☐ Yes

Genetic Diagnosis

- ☐ No
☐ Yes

Initial Stay:

- ☐ Initial
☐ Subsequent

PB charges:

_____

PB charges after DC:

_____

PB Genetics:

_____

HB Charges:

_____

HB charges after DC:

_____

HB Genetics:

_____

Total RVU:

_____

Total RVU after discharge:

Work RVU:

Work RVU after discharge:

Market

☐ Primary

☐ Secondary

☐ Regional

☐ National