

## Supplementary Materials

### Rapid Whole Genome Sequencing Impacts Care and Resource Utilization in Infants with Congenital Heart Disease

Authors: Nathaly M. Sweeney MD, MPH<sup>1,2,3</sup>, Shareef A. Nahas PhD<sup>1</sup>, Shimul Chowdhury PhD<sup>1</sup>, Sergey Batalov MS<sup>1</sup>, Michelle Clark PhD<sup>1</sup>, Sara Caylor BSN<sup>1</sup>, Julie Cakici BSN<sup>1</sup>, John J. Nigro MD<sup>2,4</sup>, Yan Ding MD<sup>1</sup>, Narayanan Veeraraghavan PhD<sup>1</sup>, Charlotte Hobbs, MD PhD<sup>1</sup>, David Dimmock MD<sup>1</sup>, Stephen Kingsmore MB ChB BAO DSc<sup>1</sup>

#### Affiliations:

1. Rady Children's Institute for Genomic Medicine, San Diego, CA, USA;
2. Rady Children's Hospital, San Diego, CA, USA
3. Department of Pediatrics, University of California San Diego, San Diego, CA, USA;
4. Department of Surgery, University of California San Diego, San Diego, CA, USA

**Correspondence:** N. Sweeney (nmsweeney@health.ucsd.edu), (858)966-5818. Rady Children's Institute for Genomic Medicine, Rady Children's Hospital, 3020 Children's Way, San Diego, CA 92123, USA

The RCIGM investigators are Matthew Bainbridge, Jeanne Carroll, Casey Cohenmeyer, Marva Evans, Lauge Farnaes, Jennifer Friedman, Joseph Gleeson, Amber Hildreth, Jose Honold, Amy Kimball, Brian Lane, Crystal Le, Sandra Leibel, Laurel Moyer, Lawrence Prince, Mark Speziale, Charles Sauer, Denise Suttner, Richard Song, Lisa Salz, Kristen Wigby, Audra Wise, Meredith Wright.

## Supplementary Materials

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## Supplementary Data

**Supplementary Table 1: Unit Cost Analysis of rWGS.**

| <b><u>Direct Costs</u></b>                 |                  |                 |                 |                 |
|--------------------------------------------|------------------|-----------------|-----------------|-----------------|
| <b><u>Labor</u></b>                        | Singleton        | Trio            | Duo             | Quad            |
| Enrolment/Intake                           |                  |                 |                 |                 |
| Fellow                                     | \$31             | \$31            | \$31            | \$31            |
| MD                                         | \$154            | \$154           | \$154           | \$154           |
| Genomics Employees                         | \$2,186          | \$3,279         | \$2,733         | \$3,826         |
| Total Labour                               | \$2,371          | \$3,464         | \$2,918         | \$4,011         |
| <b><u>Non-Labor</u></b>                    |                  |                 |                 |                 |
| IT                                         | \$604            | \$1,813         | \$1,208         | \$2,417         |
| Sequencing                                 | \$2,898          | \$8,694         | \$5,796         | \$11,592        |
| Data Analysis                              | \$386            | \$1,159         | \$773           | \$1,546         |
| Reporting                                  | \$150            | \$150           | \$150           | \$150           |
| Total Non-Labour                           | \$4,039          | \$11,816        | \$7,927         | \$15,704        |
| <b><u>Indirect Costs</u></b>               |                  |                 |                 |                 |
| Genomics Non-Lab                           |                  |                 |                 |                 |
| Employees & Professional                   |                  |                 |                 |                 |
| fees                                       | \$892            | \$892           | \$892           | \$892           |
| Supplies                                   | \$42             | \$42            | \$42            | \$42            |
| Purchased services                         | \$298            | \$298           | \$298           | \$298           |
| Leases and rentals                         | \$287            | \$287           | \$287           | \$287           |
| Depreciation                               | \$454            | \$680           | \$567           | \$794           |
| Other expenses                             | \$100            | \$100           | \$100           | \$100           |
| Total Indirect Costs                       | \$2,072          | \$2,299         | \$2,186         | \$2,412         |
| <b><u>Total Cost per Infant</u></b>        | <b>\$8,482</b>   | <b>\$17,579</b> | <b>\$13,031</b> | <b>\$22,128</b> |
| (5 singletons, 16 trios, 2 duos, 1 quad)   | \$42,410         | \$281,264       | \$26,062        | \$22,128        |
| <b>Total Cost for 24 enrolled families</b> | <b>\$371,864</b> |                 |                 |                 |

The full cost of rWGS as a CLIA Laboratory Developed Test, including indirect costs and treatment guidance, was \$8482–\$22,128 (singleton, duo, trio, and quad). The total cost of rWGS in 24 families was \$371,864. Included were consultation for pretest assessment, counseling, result disclosure, precision medicine guidance, and trio Sanger sequencing to validate variants detected by rWGS.

**Supplementary Table 2a: Cost of hospitalization in the rWGS group**

| Patient | Cost (\$)  |           |            |                      |                       |                   |
|---------|------------|-----------|------------|----------------------|-----------------------|-------------------|
|         | Hospital   | Physician | Total      | Daily Hospital (Avg) | Daily Physician (Avg) | Daily total (Avg) |
| 1       | 304,392    | 116,521   | 42,0913    | 3,853.06             | 1,474.95              | 5,328.01          |
| 9       | 863,890    | 331,984   | 1,195,874  | 3,962.80             | 1,522.86              | 5,485.66          |
| *12     | 1,424,903  | 421,070   | 1,845,973  | 5,699.61             | 1,684.28              | 7,383.89          |
| *18     | 505,784    | 123,235   | 629,019    | 4,515.93             | 1,100.31              | 5,616.24          |
| *20     | 1,712,741  | 401,737   | 2,114,478  | 6,414.76             | 1,504.63              | 7,919.39          |
| *24     | 813,837    | 296,545   | 1,110,382  | 4,677.22             | 1,704.28              | 6,381.51          |
| *26     | 27,973     | 8,070     | 36,043     | 2,543.00             | 733.64                | 3,276.64          |
| *30     | 2,380,629  | 667,178   | 3,047,807  | 5,750.31             | 1,611.54              | 7,361.85          |
| 38      | 1,415,016  | 446,997   | 1,862,013  | 4,896.25             | 1,546.70              | 6,442.95          |
| 47      | 1,070,163  | 374,235   | 1,444,398  | 5,096.01             | 1,782.07              | 6,878.09          |
| 49      | 2,077,057  | 684,939   | 2,761,996  | 5,785.67             | 1,907.91              | 7,693.58          |
| 64      | 275,511    | 129,936   | 405,447    | 4,238.63             | 1,999.02              | 6,237.65          |
| 65      | 135,011    | 50,973    | 185,984    | 5,870.04             | 2,216.22              | 8,086.26          |
| 80      | 464,375    | 141,044   | 605,419    | 6,361.30             | 1,932.11              | 8,293.41          |
| *82     | 93,146     | 40,256    | 133,402    | 4,435.52             | 1,916.95              | 6,352.48          |
| 84      | 569,679    | 152,871   | 722,550    | 6,548.03             | 1,757.14              | 8,305.17          |
| 86      | 1,104,726  | 421,232   | 1,525,958  | 4,845.29             | 1,847.51              | 6,692.80          |
| *92     | 582,865    | 178,898   | 761,763    | 3,784.84             | 1,161.68              | 4,946.51          |
| *96     | 449,960    | 146,821   | 596,781    | 4,687.08             | 1,529.39              | 6,216.47          |
| *100    | 108,364    | 49,254    | 157,618    | 4,013.48             | 1,824.22              | 5,837.70          |
| 104     | 57,734     | 17,456    | 75,190     | 3,396.12             | 1,026.82              | 4,422.94          |
| *108    | 22,233     | 10,479    | 32,712     | 3,705.50             | 1,746.50              | 5,452.00          |
| ^112    | 10,699     | 4,189     | 14,888     | 10,699.00            | 4,189.00              | 14,888.00         |
| 114     | 494,115    | 135,659   | 629,774    | 5,551.85             | 1,524.26              | 7,076.11          |
| SUM     | 16,964,803 | 5,351,579 | 2,2316,382 | 121,331.33           | 41,243.98             | 162,575.32        |
| AVG     | 706,866.79 | 222,982   | 929,849.25 | 5,055.47             | 1,718.50              | 6,773.97          |

There was no statistically significant difference between average daily hospital cost (mean difference diagnostic vs non-diagnostic rWGS: -903.4 (-2176.0, 369.1);p=0.19), average daily physician cost (mean difference diagnostic vs non-diagnostic rWGS: -400.5 (-893.2, 92.3);p=0.12) or average daily total cost of hospitalization (mean difference diagnostic vs non-diagnostic: -1303.9 (-2999.6, 391.8);p=0.14) between diagnostic and non-diagnostic rWGS. ^Patient died on hospital day 1. \*Diagnostic rWGS. P-values calculated using Wilcoxon rank sum test due to deviations from normality. Avg=Average

**Supplementary Table 2b: Average daily total cost of hospitalization in the rWGS group by time period**

| Patient | Cost (\$)              |                        |                        |
|---------|------------------------|------------------------|------------------------|
|         | Period 1<br>(DOA-DOBC) | Period 2<br>(DOBC-DOR) | Period 3<br>(DOR-DODC) |
| 1       | 5,347.29               | 3,206.00               | 639.00                 |
| 9       | 5,221.47               | 9,693.96               | 4,242.34               |
| *12     | 7,103.56               | 8,982.15               | 5,067.00               |
| *18     | 8,602.00               | 4,649.96               | 4,132.00               |
| *20     | 13,862.00              | 9,777.00               | 7,721.00               |
| *24     | 6,466.49               | 7,559.14               | 5,017.24               |
| *26     | 2,344.00               | 4,115.00               | 2,402.00               |
| *30     | 7,673.37               | 7,379.23               | 7,075.50               |
| 38      | 6,930.00               | 7,437.52               | 5,689.00               |
| 47      | 6,459.00               | 6,655.00               | 7,009.00               |
| 49      | 8,044.05               | 9,586.00               | 6,863.97               |
| 64      | 5,198.00               | 10,084.00              | 5,721.00               |
| 80      | 9,789.00               | 6,983.00               | 3,032.00               |
| 84      | 12,294.00              | 8,813.00               | 7,795.00               |
| 86      | 4,726.00               | 6,867.00               | 6,512.00               |
| *92     | 5,336.00               | 6,003.20               | 4,512.00               |
| *96     | 8,875.00               | 4,756.30               | 5,217.12               |
| 100     | 5,017.00               | 4,611.00               | 6,134.00               |
| 104     | 5,343.00               | 3,522.00               | 294.00                 |
| 114     | 12,626.00              | 9,591.00               | 6,855.00               |
| AVG     | 7,362.86               | 7,013.57               | 5,096.51               |

Spending trend surrounding the rWGS process for the patients with complete data during the time periods of healthcare trend evaluation. There is a significant association between time period and cost ( $p=.01$ ; repeated measures ANOVA). Specifically, there is a significant difference in cost between periods 1 and 3 (Mean Difference 2266.4; 95% CI 1035.6 - 3497.1;  $p=0.001$ ; paired t-test) and periods 2 and 3 (Mean Difference 1917.1; 95% CI 1077.2 - 2756.9;  $p=0.0001$ ; paired t-test). There is not a significant difference in cost between the nondiagnostic and diagnostic groups by time period ( $p=0.70$ ; repeated measures ANOVA). \*Diagnostic rWGS.

**Supplementary Table 2c: Average daily total cost of hospitalization in the rWGS group with complete cost data by equal terciles**

| Patient | Cost (\$) |           |           |
|---------|-----------|-----------|-----------|
|         | Tercile 1 | Tercile 2 | Tercile 3 |
| 1       | 5,327.65  | 4,846.65  | 5,791.48  |
| 9       | 5,897.62  | 4,633.95  | 5,931.53  |
| *12     | 5,099.07  | 6,305.09  | 5,694.73  |
| *18     | 8,118.68  | 4,576.77  | 4,191.77  |
| *20     | 6,463.37  | 6,645.42  | 10,649.39 |
| *24     | 6,001.93  | 4,786.45  | 8,356.14  |
| *26     | 3,796.75  | 3,584.25  | 1,537.00  |
| *30     | 7,799.10  | 7,120.60  | 7,166.00  |
| 38      | 6,868.28  | 7,570.71  | 4,882.22  |
| 47      | 6,805.93  | 8,065.13  | 5,768.77  |
| 49      | 8,581.53  | 8,418.66  | 6,107.22  |
| 64      | 6,260.76  | 8,517.72  | 4,134.79  |
| 80      | 7,296.79  | 7,639.58  | 4,236.08  |
| 84      | 9,344.24  | 8,762.58  | 6,808.72  |
| 86      | 7,238.03  | 6,013.65  | 7,125.59  |
| *92     | 4,804.73  | 6,180.22  | 3,875.60  |
| 96      | 8,342.68  | 6,415.35  | 4,003.29  |
| *100    | 5,245.78  | 8,455.67  | 3,811.67  |
| 104     | 6,450.34  | 4,370.33  | 2,053.20  |
| 114     | 9,108.69  | 8,378.79  | 3,956.07  |
| AVG     | 6,742.60  | 6,564.38  | 5,304.06  |

Total Hospital cost divided in three equal parts and the average daily hospital costs calculated. There is a significant association between time period and cost ( $p=.047$ ; repeated measures ANOVA). There was statistically significant decrease in average daily hospital cost from the first third of the hospitalization compared to the last third ( $p=0.036$ , Mean Difference 1438.53, SE 518.81, 95% CI 76.60-2800.47), but there was no statistically significant decrease when comparing the 1st third of the hospitalization with the 2nd third ( $p=1$ , Mean Difference 178.22, SE 352.18, 95% CI -746.30-1102.73) or the 2nd third with the last 3rd ( $p=0.1$ , Mean Difference 1260.32, SE 551.59, 95% CI -187.66-2708.30; repeated measures ANOVA with Bonferroni correction). \*Diagnostic rWGS.

**Supplementary Table 3: Metrics of rapid whole genome sequencing for twenty-four proband inpatient infants**

| Family ID      | Raw sequence (GB) | % reads mapped | % duplicates | Yield (GB) | Mean Insert size (nt) | Average coverage | MIM genes with <10X coverage at 100% CD nt | MIM genes with ≥10X coverage at 100% of CD nt | Nt variant calls | Passing nt variant calls | CD nt variants | SNVs    | Indels  | Nt variant Hom /Het ratio | Ti/Tv ratio (in CD) |
|----------------|-------------------|----------------|--------------|------------|-----------------------|------------------|--------------------------------------------|-----------------------------------------------|------------------|--------------------------|----------------|---------|---------|---------------------------|---------------------|
| 1              | 190.6             | 99.00%         | 11.80%       | 166.5      | 332.2                 | 50.0             | 276                                        | 98.00%                                        | 5060268          | 4881770                  | 27452          | 4050165 | 889492  | 0.56                      | 2.03                |
| 9              | 163.1             | 98.70%         | 10.40%       | 144.8      | 341.8                 | 43.0             | 316                                        | 97.80%                                        | 4788941          | 4702331                  | 26445          | 3934041 | 854900  | 0.57                      | 2.04                |
| 12             | 195.5             | 98.80%         | 10.00%       | 174.1      | 369.3                 | 52.0             | 254                                        | 98.20%                                        | 4945287          | 4867107                  | 27343          | 4059083 | 886204  | 0.53                      | 2.04                |
| 18             | 197.8             | 98.60%         | 10.00%       | 179.5      | 392.4                 | 49.3             | 285                                        | 98.00%                                        | 5083464          | 4975587                  | 25953          | 4088583 | 887004  | 0.49                      | 1.98                |
| 20             | 144.9             | 98.40%         | 4.10%        | 137.5      | 407.6                 | 42.0             | 520                                        | 96.30%                                        | 4787333          | 4685966                  | 26064          | 3913210 | 874123  | 0.67                      | 2.03                |
| 24             | 217.8             | 98.80%         | 14.90%       | 183.5      | 358.3                 | 47.6             | 315                                        | 97.80%                                        | 4974795          | 4862566                  | 26778          | 3996325 | 866241  | 0.55                      | 1.98                |
| 26             | 135.1             | 98.60%         | 2.90%        | 129.9      | 390.6                 | 40.6             | 215                                        | 98.50%                                        | 4763155          | 4720511                  | 26645          | 3940960 | 876245  | 0.63                      | 2.03                |
| 30             | 275.0             | 98.90%         | 25.70%       | 202.0      | 351.9                 | 45.8             | 268                                        | 98.10%                                        | 4932826          | 4820090                  | 26800          | 3956885 | 863205  | 0.68                      | 1.96                |
| 38             | 177.6             | 98.90%         | 9.10%        | 175.7      | 339.4                 | 48.7             | 337                                        | 97.60%                                        | 4909747          | 4794272                  | 26569          | 3938653 | 855619  | 0.57                      | 1.96                |
| 47             | 169.0             | 98.20%         | 14.40%       | 156.0      | 417.0                 | 43.0             | 325                                        | 97.70%                                        | 5111922          | 5026580                  | 27903          | 4127940 | 898640  | 0.58                      | 1.96                |
| 49             | 155.7             | 98.80%         | 7.60%        | 153.8      | 395.8                 | 42.1             | 445                                        | 96.80%                                        | 4975793          | 4885594                  | 27524          | 4030736 | 854858  | 0.58                      | 1.94                |
| 64             | 202.7             | 98.90%         | 8.20%        | 200.6      | 411.5                 | 56.1             | 239                                        | 98.30%                                        | 5017220          | 4876361                  | 27611          | 4034132 | 842229  | 0.64                      | 1.91                |
| 65             | 164.5             | 98.90%         | 8.60%        | 162.6      | 414.7                 | 45.2             | 348                                        | 97.50%                                        | 4966944          | 4829817                  | 27275          | 4011528 | 818289  | 0.56                      | 1.94                |
| 80             | 243.2             | 73.90%**       | 13.60%       | 179.6      | 417.3                 | 62.4             | 235                                        | 98.34%                                        | 5654509          | 5512543                  | 28372          | 4561483 | 951060  | 0.39                      | 1.93                |
| 82             | 162.8             | 98.40%         | 3.00%        | 160.2      | 365.3                 | 47.3             | 394                                        | 97.21%                                        | 5018475          | 4911886                  | 24758          | 4010946 | 900940  | 0.56                      | 1.95                |
| 84             | 131.2             | 98.70%         | 2.70%        | 129.5      | 389.0                 | 38.4             | 669                                        | 95.26%                                        | 5559549          | 5463776                  | 27962          | 4482940 | 980836  | 0.43                      | 1.96                |
| 86             | 167.6             | 98.80%         | 9.90%        | 165.6      | 450.5                 | 40.9             | 476                                        | 96.63%                                        | 5026704          | 4920452                  | 25952          | 4077211 | 843241  | 0.55                      | 1.93                |
| 92             | 249.2             | 99.00%         | 8.50%        | 246.6      | 413.8                 | 62.7             | 230                                        | 98.37%                                        | 5021492          | 4893226                  | 24837          | 4041753 | 851473  | 0.57                      | 1.92                |
| 96             | 146.0             | 98.60%         | 2.60%        | 144.1      | 403.3                 | 41.8             | 586                                        | 95.85%                                        | 5853946          | 5753090                  | 29361          | 4719925 | 1033165 | 0.47                      | 1.96                |
| 100            | 154.5             | 98.50%         | 2.70%        | 152.3      | 426.7                 | 44.1             | 533                                        | 96.23%                                        | 4922578          | 4821402                  | 24904          | 3937729 | 883673  | 0.59                      | 1.95                |
| 104            | 234.4             | 99.00%         | 13.70%       | 232.0      | 395.6                 | 52.6             | 247                                        | 98.25%                                        | 5594682          | 5455289                  | 27937          | 4517661 | 937628  | 0.43                      | 1.92                |
| 108            | 151.5             | 98.80%         | 8.40%        | 149.8      | 418.5                 | 38.1             | 523                                        | 96.30%                                        | 4977806          | 4877602                  | 24928          | 4060905 | 816697  | 0.58                      | 1.92                |
| 112            | 190.8             | 98.80%         | 14.60%       | 188.6      | 393.5                 | 41.6             | 379                                        | 97.32%                                        | 5020358          | 4904266                  | 25010          | 4067012 | 837254  | 0.59                      | 1.92                |
| 114            | 200.0             | 98.90%         | 10.80%       | 197.8      | 419.9                 | 48.0             | 245                                        | 98.26%                                        | 4978561          | 4838703                  | 24457          | 3999455 | 839248  | 0.55                      | 1.90                |
| <b>Average</b> | 184.2             | 97.70%         | 9.51%        | 171.4      | 392.3                 | 46.8             | 361                                        | 97.44%                                        | 5081098          | 4970033                  | 26618          | 4106636 | 880928  | 0.56                      | 1.96                |
| <b>Minimum</b> | 131.2             | 73.90%         | 2.60%        | 129.5      | 332.2                 | 38.1             | 215                                        | 95.26%                                        | 4763155          | 4685966                  | 24457          | 3913210 | 816697  | 0.39                      | 1.90                |
| <b>Maximum</b> | 275.0             | 99.00%         | 25.70%       | 246.6      | 450.5                 | 62.7             | 669                                        | 98.50%                                        | 5853946          | 5753090                  | 29361          | 4719925 | 1033165 | 0.68                      | 2.04                |
| <b>Median</b>  | 173.3             | 98.80%         | 9.50%        | 166.1      | 395.7                 | 45.5             | 321                                        | 97.75%                                        | 4997891          | 4879686                  | 26712          | 4037943 | 870182  | 0.565                     | 1.96                |

DNA was extracted and sequenced using an Illumina HiSeq X with paired 150 nucleotide reads. The average library insert size was 392.3 nt for proband. Sequencing was completed 7 days after consent. rWGS was performed to an average depth of coverage of 47-fold (minimum 38-fold; Table S3). Completeness of rWGS was assessed by the proportion of 15,643 genes in Mendelian Inheritance in Man with ≥10-fold coverage of all coding domain nucleotides (median 97.8%)<sup>1</sup>. Rapid alignment and nucleotide variant calling was performed using the Dragen (Edico Genome) hardware and software<sup>2</sup>. Yield was 171.4 Gb for the proband with an average coverage of 46.8x resulting in 4,970,033 distinct variant calls (4,106,636 single nucleotide variants (SNV), 880,928 small insertion deletion variants (indels), 26618 coding domain (CD) variants, with a Ti/Tv ratio of 1.96 (1.90-2.04)). Variants were automatically annotated and analyzed in Opal Clinical (Omicia, Oakland, CA)<sup>3</sup>. Initially, variants were filtered to retain those with allele frequencies of <1% in the Exome Variant Server, 1000 Genomes Samples, and Exome Aggregation Consortium database<sup>4,5</sup>. A differential diagnostic gene list was built in Phenolyzer using the HPO (and SNOMED-CT) codes<sup>6-8</sup>. Yielding a list of potential genes. Variants were further filtered to retain those mapping to the list of potential genes, yielding a small number of variants of interest. Likely pathogenic and pathogenic mutations were curated manually following ACMG criteria<sup>9</sup>. Abbreviations. GB: gigabase; nt: nucleotides; MIM: Mendelian inheritance in Man; CD: coding domain; indels: insertion-deletion nucleotide variants; SNVs: single nucleotide variants; Hom: homozygous; Het: heterozygous; Ti: nucleotide transition; Tv: nucleotide transversion; \*\*Exception pass genome per laboratory director discretion.

**Supplementary Table 4: Human Phenotype Ontology (HPO) terms for clinical features, Online Mendelian Inheritance in Man (OMIM)# for diagnoses and type of rWGS test in the twenty-four proband inpatient infants**

| Patient ID | HPO #      | Human Phenotype Ontology Term              | Causative Gene | OMIM   | rWGS Test |
|------------|------------|--------------------------------------------|----------------|--------|-----------|
| 01         | HP:0001684 | Atrial septal defect                       |                | N/A    | Solo      |
|            | HP:0001331 | Absence cavum septum pellucidum, complete  |                |        |           |
|            | HP:0030283 | Absence cavum septum pellucidum, partial   |                |        |           |
|            | HP:0007370 | Corpus callosum hypoplasia/partial absence |                |        |           |
|            | HP:0001338 | Callosal agenesis or severe hypogenesis    |                |        |           |
|            | HP:0011451 | Congenital microcephaly                    |                |        |           |
|            | HP:0001276 | Hypertonia                                 |                |        |           |
|            | HP:0006895 | Hypertonia, lower limbs                    |                |        |           |
|            | HP:0200049 | Hypertonia, upper limbs                    |                |        |           |
|            | HP:0100490 | Campylodactyly                             |                |        |           |
|            | HP:0008619 | Bilateral hearing loss, sensorineural      |                |        |           |
|            | HP:0008513 | Bilateral hearing loss, conductive         |                |        |           |
|            | HP:0000486 | Strabismus                                 |                |        |           |
|            | HP:0000487 | Congenital strabismus                      |                |        |           |
|            | HP:0004626 | Scoliosis                                  |                |        |           |
|            | HP:0002944 | Thoracolumbar scoliosis                    |                |        |           |
|            | HP:0004626 | Lumbar scoliosis                           |                |        |           |
|            | HP:0000921 | Missing ribs                               |                |        |           |
|            | HP:0001385 | Bilateral hip dysplasia, congenital        |                |        |           |
|            | HP:0005407 | Low CD4+ T cell subset                     |                |        |           |
|            | HP:0001511 | In utero growth restriction                |                |        |           |
|            | HP:0000519 | Congenital cataracts                       |                |        |           |
| 09         | HP:0001511 | In utero growth restriction                |                | N/A    | Solo      |
|            | HP:0005160 | Total anomalous pulmonary venous return    |                |        |           |
|            | HP:0011682 | Perimembranous ventricular septal defect   |                |        |           |
|            | HP:0001684 | Moderate atrial septal defect              |                |        |           |
|            | HP:0001171 | Ectrodactyly of the right hand             |                |        |           |
|            | HP:0006101 | Syndactyly                                 |                |        |           |
|            | HP:0000308 | Microretrognathia                          |                |        |           |
|            | HP:0000347 | Micrognathia                               |                |        |           |
|            | HP:0000219 | Thin protruding upper lip                  |                |        |           |
|            | HP:0008583 | Under folded superior helices              |                |        |           |
|            | HP:0001894 | Thrombocytosis                             |                |        |           |
|            | HP:0012408 | Medullary nephrocalcinosis                 |                |        |           |
| 12         | HP:0001511 | Small for gestational age                  | <i>ARID1B</i>  | 135900 | Solo      |
|            | HP:000776  | Congenital diaphragmatic hernia            |                |        |           |
|            | HP:0030680 | Congenital heart disease                   |                |        |           |
|            | HP:0002079 | Hypoplasia of corpus callosum              |                |        |           |
|            | HP:0001999 | Abnormal face shape                        |                |        |           |
|            | HP:0002205 | Recurrent respiratory infections           |                |        |           |
|            | HP:0002194 | Delayed gross motor development            |                |        |           |
| 18         | HP:0001657 | Prolonged QT syndrome                      | <i>POLR1C</i>  | 616494 | Trio      |
|            | HP:0005184 | Prolonged QTc syndrome                     |                |        |           |
|            | HP:0002092 | Pulmonary hypertension                     |                |        |           |
|            | HP:0001385 | Hip dysplasia                              |                |        |           |
|            | HP:0011451 | Congenital microcephaly                    |                |        |           |
|            | HP:0011968 | Feeding difficulties                       |                |        |           |
|            | HP:0002835 | Aspiration                                 |                |        |           |
|            | HP:0001508 | Failure to Thrive                          |                |        |           |
| 20         | HP:0001789 | Hydrops fetalis                            | <i>TPM1</i>    | 611878 | Solo      |
|            | HP:0001791 | Foetal ascites                             |                |        |           |
|            | HP:0001698 | Pericardial effusion                       |                |        |           |
|            | HP:0001711 | Left ventricular abnormality               |                |        |           |
|            | HP:0030682 | Left ventricular noncompaction             |                |        |           |
|            | HP:0001646 | Abnormal aortic valve                      |                |        |           |
|            | HP:0012304 | Hypoplastic aortic arch                    |                |        |           |

|    |            |                                                |                            |        |      |
|----|------------|------------------------------------------------|----------------------------|--------|------|
|    | HP:0011649 | Patent ductus arteriosus after premature birth |                            |        |      |
|    | HP:0001708 | Right ventricular failure                      |                            |        |      |
|    | HP:0009937 | Facial hirsutism                               |                            |        |      |
|    | HP:0000494 | Down slanting palpebral fissures               |                            |        |      |
|    | HP:0011247 | Prominent antihelix, crimped superiorly        |                            |        |      |
|    | HP:0010946 | Dilation of the renal pelvis                   |                            |        |      |
|    | HP:0004719 | Hyperechogenic kidneys                         |                            |        |      |
|    | HP:0001873 | Thrombocytopenia                               |                            |        |      |
|    | HP:0001942 | Metabolic acidosis                             |                            |        |      |
| 24 | HP:0001680 | Coarctation of the aorta                       | <i>PHEX</i>                | 307800 | Trio |
|    | HP:0012304 | Hypoplastic aortic arch                        |                            |        |      |
|    | HP:0011682 | Peri-membranous VSD                            |                            |        |      |
|    | HP:0011670 | Left superior vena cava to coronary sinus      |                            |        |      |
|    | HP:0011668 | Bilateral superior vena cava                   |                            |        |      |
|    | HP:0001655 | Patent foramen ovale                           |                            |        |      |
|    | HP:0000062 | Ambiguous external genitalia at birth          |                            |        |      |
|    | HP:0000033 | Ambiguous genitalia, male                      |                            |        |      |
|    | HP:0000808 | Penoscrotal hypospadias                        |                            |        |      |
|    | HP:0000041 | Chordee                                        |                            |        |      |
|    | HP:0000960 | Sacral dimple                                  |                            |        |      |
|    | HP:0003468 | Abnormality of the vertebrae                   |                            |        |      |
|    | HP:0006380 | Knee flexion contractures                      |                            |        |      |
|    | HP:0001511 | In utero growth restriction                    |                            |        |      |
|    | HP:0000347 | Mild micrognathia                              |                            |        |      |
|    | HP:0001873 | Thrombocytopenia                               |                            |        |      |
|    | HP:0001905 | Congenital thrombocytopenia                    |                            |        |      |
| 26 | HP:0002908 | Conjugated hyperbilirubinemia                  | <i>JAG1 (3Mb deletion)</i> | 118450 | Trio |
|    | HP:0001396 | Cholestasis                                    |                            |        |      |
|    | HP:0004971 | Pulmonary artery hypoplasia                    |                            |        |      |
|    | HP:0001643 | Patent ductus arteriosus                       |                            |        |      |
|    | HP:0001942 | Metabolic acidosis                             |                            |        |      |
|    | HP:0001947 | Renal tubular acidosis                         |                            |        |      |
|    | HP:0001508 | Failure to thrive                              |                            |        |      |
| 30 | HP:0030680 | Congenital heart disease                       | <i>NF1</i>                 | 162200 | Trio |
|    | HP:0004935 | Pulmonary valve atresia                        | <i>MYBPC3</i>              | 615396 |      |
|    | HP:0000967 | Petechiae                                      |                            |        |      |
|    | HP:0000938 | Osteopenia                                     |                            |        |      |
|    | HP:0002788 | Recurrent upper respiratory infections         |                            |        |      |
|    | HP:0002742 | Recurrent Klebsiella infections                |                            |        |      |
|    | HP:0002726 | Recurrent Staphylococcus infections            |                            |        |      |
| 38 | HP:0011863 | Sternal ossification center anomalies          |                            | N/A    | Trio |
|    | HP:0001539 | Omphalocele                                    |                            |        |      |
|    | HP:0011623 | Moderate/large mid muscular VSD                |                            |        |      |
|    | HP:0001684 | Moderate/large secundum atrial septal defect   |                            |        |      |
|    | HP:0004927 | Dilated main pulmonary artery                  |                            |        |      |
|    | HP:0000776 | Left posterior congenital diaphragmatic hernia |                            |        |      |
|    | HP:0002092 | Pulmonary hypertension                         |                            |        |      |
|    | HP:0002089 | Pulmonary hypoplasia                           |                            |        |      |
|    | HP:0002878 | Respiratory failure                            |                            |        |      |
|    | HP:0001334 | Communicating hydrocephalus                    |                            |        |      |
|    | HP:0007165 | Periventricular heterotopia                    |                            |        |      |
|    | HP:0010946 | Renal pelviectasis                             |                            |        |      |
| 47 | HP:0005298 | AVC with right ventricle aorta and pulmonary   |                            | N/A    | Trio |
|    | HP:0011579 | atresia                                        |                            |        |      |
|    | HP:0004935 | Unbalanced AV canal defect                     |                            |        |      |
|    | HP:0011563 | Pulmonary atresia                              |                            |        |      |
|    | HP:0011670 | Ventriculoarterial discordance                 |                            |        |      |
|    | HP:0011649 | Left superior vena cava to coronary sinus      |                            |        |      |
|    | HP:0011701 | PDA after premature birth                      |                            |        |      |
|    | HP:0002104 | Atrial tachycardia                             |                            |        |      |
|    | HP:0006528 | Apnea                                          |                            |        |      |

|    |            |                                                                                        |     |      |
|----|------------|----------------------------------------------------------------------------------------|-----|------|
|    | HP:0005100 | Chronic lung disease                                                                   |     |      |
|    | HP:0001508 | Premature birth following PROM                                                         |     |      |
|    | HP:0008872 | Failure to thrive                                                                      |     |      |
|    |            | Feeding difficulties in infancy                                                        |     |      |
| 49 | HP:0010882 | Pulmonary valve atresia                                                                | N/A | Trio |
|    | HP:0011612 | Type A interruption of the pulmonary artery                                            |     |      |
|    | HP:0011604 | Large aorto-pulmonary window                                                           |     |      |
|    | HP:0001643 | Large patent ductus arteriosus                                                         |     |      |
|    | HP:0001707 | Abnormality of the right ventricle                                                     |     |      |
|    | HP:0001714 | Ventricular hypertrophy                                                                |     |      |
|    | HP:0004762 | Severe right ventricular hypoplasia                                                    |     |      |
|    | HP:0006704 | Right ventricular sinusoids                                                            |     |      |
|    | HP:0001647 | Bicuspid aortic valve                                                                  |     |      |
|    | HP:0011726 | Persistent fetal circulation                                                           |     |      |
|    | HP:0008757 | Unilateral vocal cord paralysis                                                        |     |      |
|    | HP:0012821 | Unilateral vocal cord paresis                                                          |     |      |
|    | HP:0001601 | Laryngomalacia with redundant arytenoids prolapsing into airway                        |     |      |
|    | HP:0002625 | Deep venous thrombosis                                                                 |     |      |
|    | HP:0001511 | In utero growth restriction                                                            |     |      |
|    | HP:0001508 | Poor weight gain                                                                       |     |      |
|    | HP:0002718 | Multiple bacterial infections                                                          |     |      |
|    | HP:0005420 | Multiple bacterial infections with gram negative organisms                             |     |      |
|    | HP:0000260 | Large anterior fontanel                                                                |     |      |
|    | HP:0005556 | Delayed metopic suture closure                                                         |     |      |
|    | HP:0005280 | Very depressed nasal bridge                                                            |     |      |
|    | HP:0002056 | Furrows in glabellar region with flat vascular malformation                            |     |      |
|    | HP:0001076 | Glabellar capillary hemangioma                                                         |     |      |
|    | HP:0000463 | Anteverted nares                                                                       |     |      |
| 64 | HP:0030853 | Heterotaxy syndrome                                                                    | N/A | Duo  |
|    | HP:0001748 | Polysplenia                                                                            |     |      |
|    | HP:0011578 | Atrioventricular canal, transitional                                                   |     |      |
|    | HP:0010445 | Large primum atrial septal defect                                                      |     |      |
|    | HP:0001680 | Coarctation                                                                            |     |      |
|    | HP:0001659 | Mild aortic valve regurgitation                                                        |     |      |
|    | HP:0011103 | Abnormality of the left ventricular outflow tract                                      |     |      |
|    | HP:0011589 | Left aortic arch with common brachiocephalic trunk                                     |     |      |
|    | HP:0011671 | Interrupted inferior vena cava with azygous connection to the right superior vena cava |     |      |
|    | HP:0011669 | Let superior vena cava directly joins left atrium                                      |     |      |
|    | HP:0004794 | Small bowel malrotation                                                                |     |      |
|    | HP:0000121 | Nephrocalcinosis                                                                       |     |      |
| 65 | HP:0001680 | Severe coarctation of the aorta                                                        | N/A | Duo  |
|    | HP:0011622 | Large inlet ventricular septal defect                                                  |     |      |
|    | HP:0011625 | Multiple muscular ventricular septal defects                                           |     |      |
|    | HP:0001643 | Large patent ductus arteriosus                                                         |     |      |
|    | HP:0011667 | Bilateral superior vena cava with small bridging vein                                  |     |      |
|    | HP:0001274 | Agensis of the corpus callosum                                                         |     |      |
|    | HP:0012762 | Cerebral white matter atrophy                                                          |     |      |
|    | HP:0030048 | Colpocephaly                                                                           |     |      |
|    | HP:0002418 | Abnormality of midbrain morphology                                                     |     |      |
|    | HP:0001321 | Hypoplastic cerebellar hemispheres                                                     |     |      |
|    | HP:0001320 | Hypoplastic cerebellar vermis                                                          |     |      |
|    | HP:0006951 | Prominent retrocerebellar cyst                                                         |     |      |
|    | HP:0000175 | Cleft palate                                                                           |     |      |
|    | HP:0000126 | Hydronephrosis                                                                         |     |      |
|    | HP:0012435 | Ventral shortening of foreskin                                                         |     |      |

|    |                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |              |        |      |
|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|--------|------|
| 80 | HP:0001674<br>HP:0001635<br>HP:0009775<br>HP:0001873<br>HP:0002580<br>HP:0005214<br>HP:0100584<br>HP:0004887                                                                                                                                           | Complete, balanced atrioventricular canal<br>Congestive heart failure<br>Amniotic band syndrome<br>Thrombocytopenia<br>Volvulus<br>Small bowel obstruction<br>Endocarditis<br>Respiratory failure, post-operative                                                                                                                                                                                                                                                               |              |        | Trio |
| 82 | HP:0005164<br>HP:0001642<br>HP:0030732<br>HP:0001667<br>HP:0011648<br>HP:0000470<br>HP:0005989<br>HP:0000278<br>HP:0001873<br>HP:0000836                                                                                                               | Dysplastic pulmonary valve<br>Pulmonary valve stenosis<br>Dysplastic tricuspid valve<br>Right ventricular hypertrophy<br>Patent ductus arteriosus after term birth<br>Short neck<br>redundant skin in nuchal area<br>Mild retrognathia<br>Thrombocytopenia<br>Hyperthyroidism<br>Neonatal Graves' Disease                                                                                                                                                                       | <i>KMT2D</i> | 147920 | Quad |
| 84 | HP:0001719<br>HP:0001629<br>HP:0001643<br><br>HP:0012304<br>HP:0011611<br>HP:0001680<br><br>HP:0001647<br>HP:0000400<br>HP:0000448<br>HP:0001176<br>HP:0001833<br>HP:0001541<br>HP:0002202<br>HP:0001688<br><br>HP:0002637<br>HP:0001250<br>HP:0003128 | Double outlet right ventricle<br>Large VSD<br>Large PDA<br>Shone's complex<br>Hypoplastic aortic arch<br>Transverse arch hypoplasia<br>Focal coarctation<br>Dysplastic/hypoplastic mitral valve<br>Mild LV hypoplasia<br>Bicuspid aortic valve<br>Large ears with uplifted lobes<br>Prominent, large nose<br>Large hands<br>Large feet<br>Ascites<br>Pleural effusions<br>Sinus Bradycardia<br>Hypoxic Ischemic Encephalopathy<br>Brain ischemia<br>Seizures<br>Lactic Acidosis |              | N/A    | Trio |
| 86 | HP:0001627<br>HP:0001629<br>HP:0002623<br>HP:0001684<br>HP:0001642<br>HP:0011670<br>HP:0002575<br>HP:0002032<br>HP:0002023<br>HP:0010479<br>HP:0000076<br><br>HP:0000795                                                                               | VACTERL association<br>Congenital heart defects<br>Moderate-large VSD<br>Aortic valve override<br>Moderate secundum ASD<br>Mild pulmonary stenosis<br>Left SVC to coronary sinus<br>Tracheoesophageal fistula<br>Esophageal atresia<br>Imperforate Anus<br>Patent Urachus<br>Vesicoureteral reflux<br>grade 5 bilaterally<br>Duplicated urethra<br>Abnormality of urethra                                                                                                       |              |        | Trio |

|     |            |                                              |              |        |      |
|-----|------------|----------------------------------------------|--------------|--------|------|
|     | HP:0000028 | Undescended testes                           |              |        |      |
|     | HP:0003316 | Butterfly Vertebrae                          |              |        |      |
|     |            | Limb anomalies                               |              |        |      |
|     | HP:0001776 | Club feet                                    |              |        |      |
|     | HP:0003974 | Right upper extremity missing radial bone    |              |        |      |
|     | HP:0000843 | Elevated Parathyroid hormone                 |              |        |      |
|     | HP:0000083 | Renal failure                                |              |        |      |
|     | HP:0000822 | Hypertension                                 |              |        |      |
|     | HP:0009894 | Abnormal ears, thickened                     |              |        |      |
| 92  | HP:0010775 | Vascular Ring of Aorta                       | <i>CHD7</i>  | 214800 | Trio |
|     | HP:0010296 | Ankyloglossia                                |              |        |      |
|     | HP:0002835 | Aspiration, Silent Aspiration                |              |        |      |
|     | HP:0001601 | Laryngomalacia                               |              |        |      |
|     | HP:0001607 | Subglottic stenosis                          |              |        |      |
|     | HP:0000126 | Pelviectasis , hydronephrosis                |              |        |      |
| 96  | HP:0011726 | Persistent Pulmonary Hypertension of the     | <i>FOXF1</i> | 265380 | Solo |
|     | HP:0010773 | Newborn (PPHN), Persistent Fetal Circulation |              |        |      |
|     |            | Partial Anomalous Pulmonary Venous Return    |              |        |      |
| 100 | HP:0002251 | Aganglionic megacolon                        | <i>ZEB2</i>  | 235730 | Trio |
|     | HP:0001290 | Generalized Hypotonia                        |              |        |      |
|     | HP:0008743 | Coronal Hypospadias                          |              |        |      |
|     | HP:0001273 | Abnormality of corpus callosum               |              |        |      |
|     | HP:0001642 | Pulmonic stenosis                            |              |        |      |
|     | HP:0001629 | Ventricular septal defect                    |              |        |      |
|     | HP:0000288 | Abnormality of philtrum                      |              |        |      |
| 104 | HP:0001642 | Pulmonary Stenosis                           |              | N/A    | Trio |
|     | HP:0010773 | Partial anomalous pulmonary venous return to |              |        |      |
|     | HP:0011625 | SVC                                          |              |        |      |
|     | HP:0011664 | Ventricular septal defects, multiple         |              |        |      |
|     | HP:0001716 | Left Ventricular Non-compaction              |              |        |      |
|     | HP:0010296 | cardiomyopathy                               |              |        |      |
|     |            | Wolff-Parkinson-White                        |              |        |      |
|     |            | Ankyloglossia                                |              |        |      |
| 108 | HP:0009729 | Cardiac Rhabdomyoma                          | <i>TSC2</i>  | 613254 | Trio |
|     | HP:0010568 | Hamartoma of the eye                         |              |        |      |
|     | HP:0009731 | Cerebral hamartomas                          |              |        |      |
| 112 | HP:0001511 | In Utero Growth Restriction                  |              |        | Trio |
|     | HP:0000776 | Congenital Diaphragmatic Hernia              |              |        |      |
|     | HP:0002575 | Tracheoesophageal Fistula                    |              |        |      |
|     | HP:0001561 | Polyhydramnios                               |              |        |      |
|     | HP:0008386 | Hypoplastic nail beds                        |              |        |      |
|     | HP:0000122 | Single kidney (unilateral renal agenesis)    |              |        |      |
|     | HP:0012304 | Aortic arch hypoplasia                       |              |        |      |
|     | HP:0000175 | Cleft palate                                 |              |        |      |
|     | HP:0008551 | Microtia                                     |              |        |      |
|     | HP:0004209 | 5 <sup>th</sup> Finger Clinodactyly          |              |        |      |
|     | HP:0002119 | Ventriculomegaly                             |              |        |      |
|     |            | Wide spaced nipples                          |              |        |      |
| 114 | HP:0000776 | Congenital diaphragmatic hernia              |              | N/A    | Trio |
|     | HP:0011611 | Interrupted aortic arch                      |              |        |      |
|     | HP:0001269 | Ventricular septal defect                    |              |        |      |
|     | HP:0004383 | Hypoplastic left heart                       |              |        |      |
|     | HP:0002092 | Pulmonary Hypertension                       |              |        |      |
|     |            | Mitral valve hypoplasia                      |              |        |      |

**Supplementary Table 5: Cardiac defects, rWGS and Clinical Genetic tests metrics**

| ID | Cardiac Dx                                                                                                                                                | Age at Consent (days) | rWGS Test | rWGS result | Turn Around Time | Diagnosis                                                 | Microarray                                                   | Targeted Gene Panel                                                                                                                     |
|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|-----------|-------------|------------------|-----------------------------------------------------------|--------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| 01 | Moderate atrial septal defect (ASD)                                                                                                                       | 120                   | Solo      | N           | 4                | N/A                                                       | Normal                                                       |                                                                                                                                         |
| 09 | Total anomalous pulmonary venous return, Peri-membranous ventricular septal defect (VSD), Moderate ASD, Patent Ductus Arteriosus (PDA)                    | 145                   | Solo      | N           | 22               | N/A                                                       | Normal                                                       |                                                                                                                                         |
| 12 | Shone's Complex, Bicuspid aortic valve, Coarctation, Peri-membranous VSD, PDA                                                                             | 231                   | Solo      | LP          | 15               | Coffin-Siris Syndrome (OMIM# 135900)                      | Normal                                                       |                                                                                                                                         |
| 18 | Bicuspid Aortic valve, ASD, Cardiomegaly                                                                                                                  | 29                    | Trio      | LP          | 31               | leukodystrophy, hypomyelinating (OMIM# 616494)            | Normal                                                       | Long QT Panel: negative (AKAP9, ANK2, CACNA1C, CALM1, CALM3, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ5, KCNQ1, SCN4B, SCN5A, SNTA1, TRDN) |
| 20 | Non-apex forming left ventricle (LV), Suspect LV Non-Compaction, PDA, Cardiac Failure                                                                     | 5                     | Solo      | LP          | 26               | Left Ventricular Noncompaction Syndrome (OMIM# 611878)    | N/A                                                          | Rasopathy Panel: negative (A2ML1, BRAF, HRAS, KRAS, MAP2K1, MAP2K2, NF1, NRAS, PTPN11, RAF1, RASA1, RIT1, SHOC2, SOS1, SPRED1)          |
| 24 | Coarctation of the aorta, transverse arch hypoplasia, Perimembranous VSD, Left Superior Vena Cava (LSVC) to Coronary Sinus (CS), Congestive heart failure | 137                   | Trio      | LP          | 14               | X-linked Hypophosphatemic Rickets Syndrome (OMIM# 307800) | Normal                                                       |                                                                                                                                         |
| 26 | Significant LPA hypoplasia with proximal stenosis. Mild RPA hypoplasia. Tortuous PDA. Aberrant Right subclavian artery.                                   | 80                    | Trio      | P           | 5                | Alagille Syndrome (OMIM# 118450)                          | Pathogenic: 3.0Mb deletion of 20p12.2p12.1-Alagille Syndrome |                                                                                                                                         |
| 30 | Pulmonary Atresia/Intact Ventricular Septum (PA/IVS) with coronary sinusoids communicating to                                                             | 227                   | Trio      | LP/ LP      | 13               | Neurofibromatosis Type 1 OMIM# 162200) Cardiomyopathy     | Normal                                                       |                                                                                                                                         |

|     |                                                                                                                                                                                                                                                                                                                                                 |     |      |    |    |                                                                                            |                           |                                                           |
|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|------|----|----|--------------------------------------------------------------------------------------------|---------------------------|-----------------------------------------------------------|
|     | bilateral coronary arterial vasculature                                                                                                                                                                                                                                                                                                         |     |      |    |    | (OMIM# 615396)                                                                             |                           |                                                           |
| 38  | Pentalogy of Cantrell: Large mid-muscular VSD, Moderate ASD, LSVC to CS, Aberrant Right Subclavian                                                                                                                                                                                                                                              | 131 | Trio | N  | 21 | N/A                                                                                        | Normal                    |                                                           |
| 47  | Unbalanced Atrioventricular canal (AVC), PA, ventriculoarterial discordance                                                                                                                                                                                                                                                                     | 58  | Trio | N  | 17 | N/A                                                                                        | Normal                    |                                                           |
| 49  | PA/IVS, Interrupted Aortic Arch, Bicuspid Aortic Valve                                                                                                                                                                                                                                                                                          | 168 | Trio | N  | 34 | N/A                                                                                        | Normal                    |                                                           |
| 64  | Heterotaxy Syndrome, AVC, Coarctation                                                                                                                                                                                                                                                                                                           | 83  | Duo  | N  | 14 | N/A                                                                                        | Normal                    |                                                           |
| 65  | Coarctation of the Aorta, Multiple VSDs, Bilateral SVCs                                                                                                                                                                                                                                                                                         | 16  | Duo  | N  | 20 | N/A                                                                                        | Normal                    |                                                           |
| 80  | Complete balanced AVC, Congestive Heart Failure                                                                                                                                                                                                                                                                                                 | 125 | Trio | N  | 15 | N/A                                                                                        | Normal                    |                                                           |
| 82  | Pulmonary valve stenosis, dysplastic pulmonary valve, Right Ventricular hypertrophy                                                                                                                                                                                                                                                             | 15  | Quad | LP | 11 | Kabuki Syndrome (OMIM# 147920)                                                             | Normal                    |                                                           |
| 84  | Double Outlet Right Ventricle, Shone's Complex, large VSD                                                                                                                                                                                                                                                                                       | 22  | Trio | N  | 29 | N/A                                                                                        | VUS: 31Kb deletion 9p24.3 |                                                           |
| 86  | Large VSD, Overriding Aorta, LSVC to CS                                                                                                                                                                                                                                                                                                         | 54  | Trio | N  | 15 | N/A                                                                                        | Normal                    |                                                           |
| 92  | Vascular Ring: right sided Aortic Arch with anomalous Left Subclavian Artery, Mildly hypoplastic/bicuspid Aortic Valve, Abnormal Mitral valve, Moderate mitral stenosis                                                                                                                                                                         | 59  | Trio | P  | 10 | CHARGE Syndrome (OMIM# 214800)                                                             | N/A                       |                                                           |
| 96  | Partial Anomalous Pulmonary Venous Return (PAPVR), Right atrial enlargement. Severe right ventricular hypertension. Left aortic arch with common brachiocephalic trunk. LPA borderline hypoplastic. Small anterior muscular and tiny mid muscular type VSD. Doming and thickened pulmonic valve with moderate to severe pulmonary stenosis, PDA | 37  | Solo | LP | 10 | Alveolar Capillary Dysplasia with misalignment of pulmonary veins (Dx 5/18) (OMIM# 265380) | N/A                       | Surfactant Panel: VUS FOXF1 c.188G>T p.Ser63Ile, Het, AD. |
| 100 | Small anterior muscular and tiny mid muscular type VSD. Doming and thickened pulmonic valve with moderate to severe pulmonary stenosis, PDA                                                                                                                                                                                                     | 9   | Trio | P  | 8  | Mowat-Wilson Syndrome (OMIM# 235730)                                                       | Normal                    |                                                           |
| 104 | Swiss cheese apical muscular VSDs. PAPVR to SVC. Thickened and doming pulmonic valve.                                                                                                                                                                                                                                                           | 79  | Trio | N  | 12 | N/A                                                                                        | N/A                       |                                                           |

|     |                                                                                                                                                                                                                                                                                                                                                                                                                                           |   |      |   |    |                                   |        |
|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|------|---|----|-----------------------------------|--------|
|     | Moderate RA dilation, mildly dilated left atrium. Papillary muscles slightly asymmetric. Posterior leaflet of the mitral valve is shorter. LV appears non-compacted and mildly hypertrophied. Diminished LV function.                                                                                                                                                                                                                     |   |      |   |    |                                   |        |
| 108 | Multiple rhabdomyomas. Very large mass associated with the RV free wall. Multiple small masses in the LV free wall and near the anterolateral papillary muscle. Large PDA                                                                                                                                                                                                                                                                 | 3 | Trio | P | 13 | Tuberous Sclerosis (OMIM# 613254) | N/A    |
| 112 | Hypoplastic transverse arch with concern for critical arch obstruction, mild hypoplasia of the ascending aorta. Large PDA, LPA hypoplasia. Rightward displaced heart. Interrupted aortic arch type B with aberrant right subclavian, moderate-large cono-ventricular type VSD. Moderately hypoplastic mitral valve. Hypoplastic aortic valve, bicuspid. Moderate hypoplasia of the ascending aorta. Large PDA, LPA is mildly hypoplastic. | 1 | Trio | N | 26 | N/A                               | Normal |
| 114 |                                                                                                                                                                                                                                                                                                                                                                                                                                           | 6 | Trio | N | 12 | N/A                               | Normal |

Proband's age of consent ranged from DOL1 to DOL23. There was varied cardiac diagnosis ranging from moderate atrial septal defect to more complex diagnosis like Pulmonary Atresia Intact Ventricular septum. Sixteen of the 24 families (67%) received trio sequencing (proband and parents), 5 (21%) solo (proband only), 2 (8%) duo (proband and mother), and 1 (4%) quad (proband, parents and an affected sibling). All but one had only 1 affected family member (the proband). The family that underwent quad rWGS had two affected children and one affected parent. Twenty-one of 24 probands had clinical genetic testing in the form of microarray and/or targeted gene panels. Three children had no additional genetic testing. Molecular diagnoses ranged from syndromes affecting multiple organ systems to disorders limited to the cardiovascular system. ASD=Atrial Septal Defect, VSD=Ventricular Septal Defect, PDA=Patent Ductus Arteriosus, LV= Left Ventricle, LSVC= Left Superior Vena Cava, CS= Coronary Sinus, LPA=Left Pulmonary Artery, RPA=Right Pulmonary Artery, PA/IVS=Pulmonary Atresia/Intact Ventricular Septum, AVC=Atrioventricular Canal, PA=Pulmonary Atresia, SVC=Superior Vena Cava, PAPVR= Partial Anomalous Pulmonary Venous Return, OMIM= Online Mendelian Inheritance in Man, AKAP9=A-kinase anchor protein 9, ANK2=Ankyrin 2, CACNA1C=Calcium Voltage-Gated Channel Subunit Alpha1 C, CALM1=Calmodulin 1, CALM3=Calmodulin 3, CAV3=Caveolin-3, KCNE1=Potassium Voltage-Gated Channel Subfamily E member 1, KCNE2= Potassium Voltage-Gated Channel Subfamily E member 2, KCNH2= Potassium Voltage-Gated Channel Subfamily H Member 2, KCNJ2= Potassium Inwardly Rectifying Channel Subfamily J Member 2, KCNJ5= Potassium Inwardly Rectifying Channel Subfamily J Member 5, KCNQ1= Potassium Voltage-Gated Channel Subfamily Q Member 1, SCN4B= Sodium channel  $\beta$ -subunit 4, SCN5A= Sodium Voltage-Gated Channel Alpha Subunit 5, SNTA1= Syntrophin Alpha 1, TRDN=Triadin, A2ML1= alpha-2-macroglobulin like 1, BRAF= B-Raf Proto-Oncogene, Serine/Threonine Kinase, HRAS= HRas Proto-Oncogene, GTPase, KRAS= KRAS Proto-Oncogene, MAP2K1= Dual specificity mitogen-activated protein kinase 1, MAP2K2= Dual specificity mitogen-activated protein kinase 2, NF1= Neurofibromatosis type 1, NRAS= NRas Proto-Oncogene, PTPN11= Protein Tyrosine Phosphatase Non-Receptor Type 11, RAF1= Raf-1 Proto-Oncogene, Serine/Threonine Kinase, RASA1= RAS p21 protein activator 1, RIT1= Ras-Like Without CAAX Protein 1, SHOC2= Leucine-Rich Repeat Protein SHOC-2, SOS1= Son of sevenless homolog 1, SPRED1= Sprouty Related EVH1 Domain Containing 1, FOXF1= Forkhead Box F1, N=Negative, P=Pathogenic, LP=Likely Pathogenic, N/A= Not Applicable, VUS= Variant of Unknown Significance.

**Supplementary Table 6: Neurodevelopmental/ Infectious/ Immunological and Endocrinological implications of rWGS diagnosis**

| Patient ID | Disease Associations                                                     | Effect on Management                      | Neurodevelopmental Associations                                                                                                                                                                         | Infectious/Immunological/Endocrinological Associations                                              |
|------------|--------------------------------------------------------------------------|-------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| 12         | Coffin-Siris Syndrome (OMIM# 135900)                                     | Palliative Care                           | Feeding problems (90%), Hypotonia (75%), Seizures (50%)<br>Hearing impairment (45%), Visual Impairment (~40%), Developmental delay, Intellectual disability, Behavioral abnormalities                   | Frequent Infections, mostly upper respiratory infections                                            |
| 18         | Hypomyelinating leukodystrophy (OMIM# 616494)                            | Enlistment of additional subspecialists   | Delayed psychomotor development, loss/lack of independent ambulation, abnormal cognition, tremor, ataxia, spasticity, cerebellar signs                                                                  | Hypogonadotropic hypogonadism                                                                       |
| 20         | Left Ventricular (LV) Noncompaction (OMIM# 611878)                       | Listing for Cardiac Transplantation       |                                                                                                                                                                                                         |                                                                                                     |
| 24         | X-linked hereditary hypophosphatemic rickets (XLHR) (OMIM# 307800)       | Enlistment of additional subspecialists   | Deafness appearing in adulthood (rare)                                                                                                                                                                  | Reduction in renal phosphate reabsorption per glomerular filtration rate to ~50% of normal          |
| 26         | Alagille Syndrome (OMIM# 118450)                                         | Avoidance of Intraoperative Cholangiogram | Absent deep tendon reflexes, poor school performance                                                                                                                                                    | Growth retardation unresponsive to growth hormone therapy (may benefit from IGF1 treatment instead) |
| 30         | Neurofibromatosis (OMIM# 162200)                                         | Enlistment of additional subspecialists   | Macrocephaly/ short stature, Vision loss due to optic gliomas in ~47% of patients by 4 year of age, Cognitive deficits in language and reading abilities, impaired visual spatial and neuromotor skills |                                                                                                     |
|            | Hypertrophic and Dilated Cardiomyopathy, LV Noncompaction (OMIM# 615396) | Medication Change                         |                                                                                                                                                                                                         |                                                                                                     |
| 82         | Kabuki Syndrome (OMIM# 147920)                                           | Enlistment of additional subspecialists   | Mild to moderate mental retardation, Post-natal growth deficiency                                                                                                                                       | Recurrent otitis media, congenital hypothyroidism, Hypogammaglobulinemia (low IgA, IgG)             |
| 92         | CHARGE syndrome (OMIM# 214800)                                           | Enlistment of additional subspecialists   | Developmental delay, growth retardation                                                                                                                                                                 | T cell abnormalities                                                                                |

|     |                                                                                  |                                                                      |                                                                       |
|-----|----------------------------------------------------------------------------------|----------------------------------------------------------------------|-----------------------------------------------------------------------|
| 96  | Alveolar Capillary Dysplasia with misalignment of Pulmonary Veins (OMIM# 265380) | Avoidance of lung biopsy.<br>Transfer to Pulmonary transplant center |                                                                       |
| 100 | Mowat-Wilson Syndrome (OMIM# 235730)                                             | Enlistment of additional subspecialists                              | Mental retardation, microcephaly (sometimes), short stature, epilepsy |
| 108 | Tuberous Sclerosis type 2 (OMIM# 613254)                                         | Targeted Genetic Counseling (TSC2 more severe phenotype than TSC1)   | Epilepsy, learning difficulties, behavioral problems                  |

rWGS diagnosis had implications for neurodevelopment in 82% (9/11) of the probands and had endocrinologic, immunologic and/or infectious concerns that could impact short and long-term outcome in 52% (6/11). LV= Left Ventricle, IGF1= Insulin Like Growth Factor 1, IgA=Immunoglobulin A, IgG=Immunoglobulin G, TSC2=Tuberous Sclerosis 2, TSC1=Tuberous Sclerosis 1, OMIM= Online Mendelian Inheritance in Man.

**Supplementary Table 7. Cardiac defects, surgical interventions/procedures, Costs trends around rWGS**

| ID | Cardiac Dx                                                                                                                             | Age at Consent (days) | rWGS results |                              | DOA-DOBC                                                                                                                      |                                                              | DOBC to DOR                                                                                           |                         | DOR to DODC                                            |                                                 |
|----|----------------------------------------------------------------------------------------------------------------------------------------|-----------------------|--------------|------------------------------|-------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-------------------------|--------------------------------------------------------|-------------------------------------------------|
| 01 | Moderate atrial septal defect (ASD)                                                                                                    | 120                   | N            | Avg Daily Hospital Cost (\$) | 5,347.29                                                                                                                      |                                                              | 3,206.00                                                                                              |                         | 639.00                                                 |                                                 |
|    |                                                                                                                                        |                       |              |                              | Surgical Interventions Laparoscopic fundoplication with gastrostomy<br>None                                                   | Intubations/ Procedures Skin Biopsy                          | Surgical Interventions                                                                                | Intubations/ Procedures | Surgical Interventions                                 | Intubations/ Procedures                         |
| 09 | Total anomalous pulmonary venous return, Peri-membranous ventricular septal defect (VSD), Moderate ASD, Patent Ductus Arteriosus (PDA) | 145                   | N            | Avg Daily Hospital Cost (\$) | 5,221.47                                                                                                                      |                                                              | 9,693.96                                                                                              |                         | 4,242.34                                               |                                                 |
|    |                                                                                                                                        |                       |              |                              | Surgical Interventions                                                                                                        | Intubations/ Procedures                                      | Surgical Interventions Repair TAPVR, VSD closure, removal PA band and patch reconstruction of the MPA | Intubations/ Procedures | Surgical Interventions Fundoplication with gastrostomy | Intubations/ Procedures                         |
| 12 | Shone's Complex, Bicuspid aortic valve, Coarctation, Peri-membranous VSD, PDA                                                          | 231                   | LP           | Avg Daily Hospital Cost (\$) | 7,103.56                                                                                                                      |                                                              | 8,982.15                                                                                              |                         | 5,067.00                                               |                                                 |
|    |                                                                                                                                        |                       |              |                              | Surgical Interventions Arch repair with patch homograft, VSD/ASD closure<br><br>ECMO delayed sternal closure<br>G-tube Nissen | Intubations/ Procedures Bronchoscopy and direct laryngoscopy | Surgical Interventions                                                                                | Intubations/ Procedures | Surgical Interventions                                 | Intubations/ Procedures Oscillatory Ventilation |

|    |                                                                                                                                                           |     |    |                              |                                                                       |                                                           |  |                                                  |                                         |                                                       |                            |
|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----|------------------------------|-----------------------------------------------------------------------|-----------------------------------------------------------|--|--------------------------------------------------|-----------------------------------------|-------------------------------------------------------|----------------------------|
|    |                                                                                                                                                           |     |    |                              | Exploratory<br>Laparotomy                                             |                                                           |  |                                                  |                                         |                                                       |                            |
|    |                                                                                                                                                           |     |    |                              | Tracheostomy                                                          |                                                           |  |                                                  |                                         |                                                       |                            |
| 18 | Bicuspid Aortic valve, ASD, Cardiomegaly                                                                                                                  | 29  | LP | Avg Daily Hospital Cost (\$) | 8,602.00                                                              |                                                           |  | 4,649.96                                         |                                         | 4,132.00                                              |                            |
|    |                                                                                                                                                           |     |    |                              | Surgical Interventions<br>Left thoracotomy for temporary pacing wires | Intubations/<br>Procedures                                |  | Surgical Interventions<br>Pacemaker implantation | Intubations/<br>Procedures              | Surgical Interventions                                | Intubations/<br>Procedures |
| 20 | Non-apex forming left ventricle (LV), Suspect LV Non-Compaction, PDA, Cardiac Failure                                                                     | 5   | LP | Avg Daily Hospital Cost (\$) | 13,862.00                                                             |                                                           |  | 9,777.00                                         |                                         | 7,721.00                                              |                            |
|    |                                                                                                                                                           |     |    |                              | Surgical Interventions                                                | Intubations/<br>Procedures                                |  | Surgical Interventions<br>Bilateral PA Bands     | Intubations/<br>Procedures<br>Brain MRI | Surgical Interventions<br>Orthotopic Heart Transplant | Intubations/<br>Procedures |
|    |                                                                                                                                                           |     |    |                              |                                                                       |                                                           |  | Delayed Sternal Closure                          |                                         | Fundoplication and G-tube                             |                            |
|    |                                                                                                                                                           |     |    |                              |                                                                       |                                                           |  | PDA stent                                        |                                         |                                                       |                            |
| 24 | Coarctation of the aorta, transverse arch hypoplasia, Perimembranous VSD, Left Superior Vena Cava (LSVC) to Coronary Sinus (CS), Congestive heart failure | 137 | LP | Avg Daily Hospital Cost (\$) | 6,466.49                                                              |                                                           |  | 7,559.14                                         |                                         | 5,017.24                                              |                            |
|    |                                                                                                                                                           |     |    |                              | Surgical Interventions<br>PA banding                                  | Intubations/<br>Procedures<br>Direct laryngo-bronchoscopy |  | Surgical Interventions                           | Intubations/<br>Procedures              | Surgical Interventions                                | Intubations/<br>Procedures |
|    |                                                                                                                                                           |     |    |                              | DSC<br>Repair aortic arch, VSD, ASD                                   | MRI-Spine                                                 |  |                                                  |                                         |                                                       |                            |
|    |                                                                                                                                                           |     |    |                              | DSC                                                                   |                                                           |  |                                                  |                                         |                                                       |                            |
|    |                                                                                                                                                           |     |    |                              | L diaphragm plication                                                 |                                                           |  |                                                  |                                         |                                                       |                            |

G-tube  
Fundoplication

|    |                                                                                                                                       |     |        |                              |                                                                          |                                                  |                                 |                         |                                                   |                         |
|----|---------------------------------------------------------------------------------------------------------------------------------------|-----|--------|------------------------------|--------------------------------------------------------------------------|--------------------------------------------------|---------------------------------|-------------------------|---------------------------------------------------|-------------------------|
| 26 | Significant LPA hypoplasia with proximal stenosis. Mild RPA hypoplasia. Tortuous PDA. Aberrant Right subclavian artery.               | 80  | P      | Avg Daily Hospital Cost (\$) | 2,344.00                                                                 |                                                  | 4,115.00                        |                         | 2,402.00                                          |                         |
|    |                                                                                                                                       |     |        |                              | Surgical Interventions                                                   | Intubations/ Procedures Fluoroscopy              | Surgical Interventions          | Intubations/ Procedures | Surgical Interventions                            | Intubations/ Procedures |
|    |                                                                                                                                       |     |        |                              |                                                                          | Cardiac CT                                       |                                 |                         |                                                   |                         |
| 30 | Pulmonary Atresia/Intact Ventricular Septum (PA/IVS) with coronary sinusoids communicating to bilateral coronary arterial vasculature | 227 | LP/ LP | Avg Daily Hospital Cost (\$) | 7,673.37                                                                 |                                                  | 7,379.23                        |                         | 7,075.50                                          |                         |
|    |                                                                                                                                       |     |        |                              | Surgical Interventions Atrial septectomy, PDA ligation, Central AP shunt | Intubations/ Procedures DLB                      | Surgical Interventions          | Intubations/ Procedures | Surgical Interventions Hickman Catheter insertion | Intubations/ Procedures |
|    |                                                                                                                                       |     |        |                              | DSC                                                                      |                                                  |                                 |                         |                                                   |                         |
|    |                                                                                                                                       |     |        |                              | Bilateral PA banding                                                     |                                                  |                                 |                         |                                                   |                         |
|    |                                                                                                                                       |     |        |                              | Tracheostomy                                                             |                                                  |                                 |                         |                                                   |                         |
|    |                                                                                                                                       |     |        |                              | G-tube/Fundo                                                             |                                                  |                                 |                         |                                                   |                         |
| 38 | Pentalogy of Cantrell: Large mid-muscular VSD, Moderate ASD, LSVC to CS, Aberrant Right Subclavian                                    | 131 | N      | Avg Daily Hospital Cost (\$) | 6,930.00                                                                 |                                                  | 7,437.52                        |                         | 5,689.00                                          |                         |
|    |                                                                                                                                       |     |        |                              | Surgical Interventions left diaphragmatic hernia repair                  | Intubations/ Procedures Laryngoscopy/ bronchospy | Surgical Interventions VP Shunt | Intubations/ Procedures | Surgical Interventions                            | Intubations/ Procedures |
|    |                                                                                                                                       |     |        |                              | Diaphragm revision                                                       | Cardiac Cath                                     |                                 |                         |                                                   |                         |
|    |                                                                                                                                       |     |        |                              | Tracheostomy                                                             |                                                  |                                 |                         |                                                   |                         |

Circumcision

Etv (endoscopic  
third  
ventriculostomy)

|    |                                                                                            |     |   |                                    |                           |                                             |                                                                                                                                                                         |                                           |                                                                                                     |                            |
|----|--------------------------------------------------------------------------------------------|-----|---|------------------------------------|---------------------------|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|-----------------------------------------------------------------------------------------------------|----------------------------|
| 47 | Unbalanced<br>Atrioventricular<br>canal (AVC),<br>PA,<br>ventriculoarterial<br>discordance | 58  | N | Avg Daily<br>Hospital<br>Cost (\$) | 6,459.00                  |                                             | 6,655.00                                                                                                                                                                |                                           | 7,009.00                                                                                            |                            |
|    |                                                                                            |     |   |                                    | Surgical<br>Interventions | Intubations/<br>Procedures<br>Re-intubation | Surgical<br>Interventions                                                                                                                                               | Intubations/<br>Procedures<br>Fluoroscopy | Surgical<br>Interventions<br>PDA ligation,<br>bidirectional<br>shunt<br>placement and<br>LPA plasty | Intubations/<br>Procedures |
| 49 | PA/IVS,<br>Interrupted<br>Aortic Arch,<br>Bicuspid Aortic<br>Valve                         | 168 | N | Avg Daily<br>Hospital<br>Cost (\$) | 8,044.05                  |                                             | 9,586.00                                                                                                                                                                |                                           | DSC<br>6,863.97                                                                                     |                            |
|    |                                                                                            |     |   |                                    | Surgical<br>Interventions | Intubations/<br>Procedures                  | Surgical<br>Interventions<br>reconstruction<br>of ascending<br>Aorta/<br>Aortoplasty,<br>Bilateral PA<br>plasty, BT<br>shunt removal,<br>central AP<br>Shunt<br>(3.5mm) | Intubations/<br>Procedures                | Surgical<br>Interventions                                                                           | Intubations/<br>Procedures |
| 64 | Heterotaxy<br>Syndrome, AVC,<br>Coarctation                                                | 83  | N | Avg Daily<br>Hospital<br>Cost (\$) | 5,198.00                  |                                             | 10,084.00                                                                                                                                                               |                                           | 5,721.00                                                                                            |                            |
|    |                                                                                            |     |   |                                    | Surgical<br>Interventions | Intubations/<br>Procedures                  | Surgical<br>Interventions<br>Transitional<br>AV canal                                                                                                                   | Intubations/<br>Procedures                | Surgical<br>Interventions                                                                           | Intubations/<br>Procedures |

|    |                                                                                                       |     |    |                                    |           |                                                          |                                                                     |                                                      |                                   |                           |                            |
|----|-------------------------------------------------------------------------------------------------------|-----|----|------------------------------------|-----------|----------------------------------------------------------|---------------------------------------------------------------------|------------------------------------------------------|-----------------------------------|---------------------------|----------------------------|
|    |                                                                                                       |     |    |                                    |           |                                                          | repair, LSVC<br>baffle to RA,<br>Closure<br>primum ASD              |                                                      |                                   |                           |                            |
|    |                                                                                                       |     |    |                                    |           |                                                          | Delayed<br>Sternal<br>Closure                                       |                                                      |                                   |                           |                            |
| 65 | Coarctation of<br>the Aorta,<br>Multiple VSDs,<br>Bilateral SVCs                                      | 16  | N  | Avg Daily<br>Hospital<br>Cost (\$) | N/A       |                                                          | N/A                                                                 |                                                      |                                   | N/A                       |                            |
|    |                                                                                                       |     |    |                                    |           | Surgical<br>Interventions                                | Intubations/<br>Procedures                                          | Surgical<br>Interventions                            | Intubations/<br>Procedures        | Surgical<br>Interventions | Intubations/<br>Procedures |
|    |                                                                                                       |     |    |                                    |           | PA Band                                                  |                                                                     | DSC                                                  |                                   |                           |                            |
| 80 | Complete<br>balanced AVC,<br>Congestive<br>Heart Failure                                              | 125 | N  | Avg Daily<br>Hospital<br>Cost (\$) | 9,789.00  |                                                          |                                                                     | 6,983.00                                             |                                   | 3,032.00                  |                            |
|    |                                                                                                       |     |    |                                    |           | Surgical<br>Interventions<br>Complete AV<br>canal repair | Intubations/<br>Procedures                                          | Surgical<br>Interventions                            | Intubations/<br>Procedures        | Surgical<br>Interventions | Intubations/<br>Procedures |
| 82 | Pulmonary valve<br>stenosis,<br>dysplastic<br>pulmonary<br>valve, Right<br>Ventricular<br>hypertrophy | 15  | LP | Avg Daily<br>Hospital<br>Cost (\$) | N/A       |                                                          |                                                                     | N/A                                                  |                                   | N/A                       |                            |
|    |                                                                                                       |     |    |                                    |           | Surgical<br>Interventions                                | Intubations/<br>Procedures<br>Pulmonary<br>Balloon<br>Valvuloplasty | Surgical<br>Interventions                            | Intubations/<br>Procedures        | Surgical<br>Interventions | Intubations/<br>Procedures |
| 84 | Double Outlet<br>Right Ventricle,<br>Shone's<br>Complex, large<br>VSD                                 | 22  | N  | Avg Daily<br>Hospital<br>Cost (\$) | 12,294.00 |                                                          |                                                                     | 8,813.00                                             |                                   | 7,795.00                  |                            |
|    |                                                                                                       |     |    |                                    |           | Surgical<br>Interventions                                | Intubations/<br>Procedures                                          | Surgical<br>Interventions<br>PD drain                | Intubations/<br>Procedures<br>MRI | Surgical<br>Interventions | Intubations/<br>Procedures |
|    |                                                                                                       |     |    |                                    |           |                                                          |                                                                     | Exploratory<br>laparotomy,<br>ileostomy<br>Decreased | Abdominal<br>CT                   |                           |                            |
| 86 | Large VSD,<br>Overriding                                                                              | 54  | N  | Avg Daily<br>Hospital<br>Cost (\$) | 4,726.00  |                                                          |                                                                     | 6,867.00                                             |                                   | 6,512.00                  |                            |

| Aorta, LSVC to CS |                                                                                                                                                                                                     |    |    |                              | Surgical Interventions | Intubations/ Procedures                   | Surgical Interventions PD drain placement and excision of umbilical polyp/ granuloma Increased | Intubations/ Procedures                       | Surgical Interventions Repair VSD                | Intubations/ Procedures               |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|----|------------------------------|------------------------|-------------------------------------------|------------------------------------------------------------------------------------------------|-----------------------------------------------|--------------------------------------------------|---------------------------------------|
| 92                | Vascular Ring: right sided Aortic Arch with anomalous Left Subclavian Artery, Mildly hypoplastic/bicuspid Aortic Valve, Abnormal Mitral valve, Moderate mitral stenosis                             | 59 | P  | Avg Daily Hospital Cost (\$) | 5,336.00               |                                           | 6,003.20                                                                                       |                                               | 4,512.00                                         |                                       |
|                   |                                                                                                                                                                                                     |    |    |                              | Surgical Interventions | Intubations/ Procedures Re-intubations X2 | Surgical Interventions Laryngo-tracheal reconstruction<br>Vascular Ring division               | Intubations/ Procedures                       | Surgical Interventions DLB and Supraglottoplasty | Intubations/ Procedures Re-intubation |
| 96                | Partial Anomalous Pulmonary Venous Return (PAPVR), Right atrial enlargement. Severe right ventricular hypertension. Left aortic arch with common brachiocephalic trunk. LPA borderline hypoplastic. | 37 | LP | Avg Daily Hospital Cost (\$) | 8,875.00               |                                           | 4,756.30                                                                                       |                                               | 5,217.12                                         |                                       |
|                   |                                                                                                                                                                                                     |    |    |                              | Surgical Interventions | Intubations/ Procedures                   | Surgical Interventions                                                                         | Intubations/ Procedures                       | Surgical Interventions                           | Intubations/ Procedures               |
| 100               | Small anterior muscular and tiny mid muscular type VSD. Doming and thickened pulmonic valve with moderate to                                                                                        | 9  | P  | Avg Daily Hospital Cost (\$) | 5,017.00               |                                           | 4,611.00                                                                                       |                                               | 6,134.00                                         |                                       |
|                   |                                                                                                                                                                                                     |    |    |                              | Surgical Interventions | Intubations/ Procedures                   | Surgical Interventions                                                                         | Intubations/ Procedures Rectal suction Biopsy | Surgical Interventions laparoscopic SOAVE pull-  | Intubations/ Procedures               |

|     |                                                                                                                                                                                                                                                                                                             |    |   |                              |          |                        |                                      |                        |                         |                        |                         |
|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|---|------------------------------|----------|------------------------|--------------------------------------|------------------------|-------------------------|------------------------|-------------------------|
|     | severe pulmonary stenosis, PDA                                                                                                                                                                                                                                                                              |    |   |                              |          |                        |                                      | PICC line              |                         | through surgery        |                         |
| 104 | Swiss cheese apical muscular VSDs. PAPVR to SVC. Thickened and doming pulmonic valve. Moderate RA dilation, mildly dilated left atrium. Papillary muscles slightly asymmetric. Posterior leaflet of the mitral valve is shorter. LV appears non-compacted and mildly hypertrophied. Diminished LV function. | 79 | N | Avg Daily Hospital Cost (\$) | 5,343.00 |                        |                                      | 3,522.00               |                         | 294.00                 |                         |
|     |                                                                                                                                                                                                                                                                                                             |    |   |                              |          | Surgical Interventions | Intubations/ Procedures              | Surgical Interventions | Intubations/ Procedures | Surgical Interventions | Intubations/ Procedures |
| 108 | Multiple rhabdomyomas. Very large mass associated with the RV free wall. Multiple small masses in the LV free wall and near the anterolateral papillary muscle. Large PDA                                                                                                                                   | 3  | P | Avg Daily Hospital Cost (\$) | N/A      |                        |                                      | N/A                    |                         | N/A                    |                         |
|     |                                                                                                                                                                                                                                                                                                             |    |   |                              |          | Surgical Interventions | Intubations/ Procedures<br>Brain MRI | Surgical Interventions | Intubations/ Procedures | Surgical Interventions | Intubations/ Procedures |
| 112 | Hypoplastic transverse arch with concern for critical arch obstruction, mild hypoplasia of the ascending aorta. Large                                                                                                                                                                                       | 1  | N | Avg Daily Hospital Cost (\$) | N/A      |                        |                                      | N/A                    |                         | N/A                    |                         |
|     |                                                                                                                                                                                                                                                                                                             |    |   |                              |          | Surgical Interventions | Intubations/ Procedures              | Surgical Interventions | Intubations/ Procedures | Surgical Interventions | Intubations/ Procedures |

|     |                                                                                                                                                                                                                                                                                                                        |   |   |                              |                                                                  |                            |                        |                            |                                                                                           |                            |
|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|---|------------------------------|------------------------------------------------------------------|----------------------------|------------------------|----------------------------|-------------------------------------------------------------------------------------------|----------------------------|
| 114 | PDA, LPA hypoplasia.<br>Rightward displaced heart. Interrupted aortic arch type B with aberrant right subclavian, moderate-large cono-ventricular type VSD. Moderately hypoplastic mitral valve. Hypoplastic aortic valve, bicuspid. Moderate hypoplasia of the ascending aorta. Large PDA, LPA is mildly hypoplastic. | 6 | N | Avg Daily Hospital Cost (\$) | 12,626.00                                                        |                            | 9,591.00               |                            | 6,855.00                                                                                  |                            |
|     |                                                                                                                                                                                                                                                                                                                        |   |   |                              | Surgical Interventions<br>Congenital Diaphragmatic Hernia repair | Intubations/<br>Procedures | Surgical Interventions | Intubations/<br>Procedures | Surgical Interventions<br>Repair IAA, VSD<br><br>DSC<br><br>LADDs/Nissen Gastrostomy tube | Intubations/<br>Procedures |

Spending in period 2 (DOBC to DOR) was dichotomous: 50% (n=10) of the cohort had increased cost relative to period 1, while 50% (n=10) had decreased cost. One explanation for this finding is the higher frequency of major surgical procedures, cardiac and other, in patients with increased cost during this period (60%) compared with the group with decreased cost (30%); however, this difference did not reach statistical significance likely due to sample size. There was no difference in the number of patients who underwent expected cardiac surgical procedures in the two groups. ASD=Atrial Septal Defect, VSD=Ventricular Septal Defect, PDA=Patent Ductus Arteriosus, LV= Left Ventricle, LSVC= Left Superior Vena Cava, CS= Coronary Sinus, LPA=Left Pulmonary Artery, RPA=Right Pulmonary Artery, PA/IVS=Pulmonary Atresia/Intact Ventricular Septum, AVC=Atrioventricular Canal, PA=Pulmonary Atresia, SVC=Superior Vena Cava, PAPVR= Partial Anomalous Pulmonary Venous Return, MPA=Main Pulmonary Artery, ECMO=Extracorporeal Membrane Oxygenation, OHT=Orthotopic Heart Transplant, DSC=Delayed Sternal Closure, AP=Aortopulmonary Shunt, BT=Blalock-Taussig, AV=Atrioventricular, IAA=Interrupted Aortic Arch, DLB: Direct Laryngo-bronchoscopy N=Negative, P=Pathogenic, LP=Likely Pathogenic, N/A= Not Applicable, Avg=Average.

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