

**The Hospital for Sick Children  
Technology Assessment at SickKids (TASK)**

**TECHNICAL APPENDIX**

**UPDATED**

**A MICROCOSTING AND COST-CONSEQUENCE ANALYSIS OF GENOMIC TESTING  
STRATEGIES IN AUTISM SPECTRUM DISORDER**

Authors:

Kate Tsiplova, MSc

Research Project Manager, Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto,  
Canada

Richard M. Zur, PhD

Research Project Manager, Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto,  
Canada

Wendy J. Ungar, MSc, PhD

Senior Scientist, Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, Canada  
Professor, Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada

**Report No. 2016-02.2**

**Date: September 21, 2016**

Co-investigators:

Christian R. Marshall, PhD

Associate Director, Genome Diagnostics, Department of Paediatric Laboratory Medicine, The Hospital for Sick Children, Toronto, Canada

Assistant Professor, Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada

Dimitri J. Stavropoulos, PhD

Co-Director, Cytogenetics, Department of Paediatric Laboratory Medicine, The Hospital for Sick Children, Toronto, Canada

Assistant Professor, Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada

Sergio Pereira, PhD

Manager, The Centre for Applied Genomics, Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, Canada

Daniele Merico, PhD

Facility Manager, The Centre for Applied Genomics, Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, Canada

Ted Young, PhD

Laboratory Specialist, Cytogenetics, Department of Paediatric Laboratory Medicine, The Hospital for Sick Children, Toronto, Canada

Wilson W.L. Sung, MSc

Bioinformatics Analyst, The Centre for Applied Genomics, Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, Canada

Stephen W. Scherer, PhD

Director, The Centre for Applied Genomics, Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, Canada

Professor of Medicine, Department of Molecular Genetics, University of Toronto, Toronto, Canada

**Acknowledgements:**

This research was supported by a Large-Scale Applied Research Project grant from Genome Canada and the Ontario Genomics Institute. We thank the following individuals who provided assistance with obtaining re and price data: Team Lead with the Cytogenetics, The Department of Paediatric Laboratory Medicine, Mary Shago, Co-Director with the Cytogenetics, The Department of Paediatric Laboratory Medicine and Manager, Decision Support at The Hospital for Sick Children and Kelly Hogan at the Canadian Institute for Health Information. We thank Pooyeh Graili for reviewing the microcosting models. We also wish to thank Dr. Robin Hayeems, PhD, The Hospital for Sick Children, for valuable feedback.

**Appendix 1. Resource use and unit prices for CMA inputs**

| Cost Items  | Quantity of Use per Sample |              |   | Price (CAD/unit) |              |   |
|---|----------------------------|--------------|---|------------------|--------------|---|
|   | Estimate                   | Range        | Source  | Estimate         | Range        | Source  |
| <b>Labour</b>   |                            |              |   |                  |              |   |
| <b>Specimen Preparation (Units: minutes)</b>  |                            |              |   |                  |              |   |
| 10120 Pediatric venipuncture  | 7.6                        | Not assigned | MIS Standards 2012-2013   | Confidential     | -21% to +28% | SickKids wage information, 2013                   |
| 11090 Packaging with testing documentation  | 1.0                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential     | -21% to +28% | SickKids wage information, 2013                   |
| 11500 Service recipient primary registration  | 1.8                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential     | -10% to +9%  | Lab staff survey, SickKids wage information, 2013 |
| 10360 Printing and sorting of specimen labels (per label)   | 0.4                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential     | -10% to +9%  | Lab Staff survey, SickKids wage information, 2013 |
| 88550 Creation of family/service recipient folder (add sample to existing family folder, assign a new number and retrieve or make a new folder) (once per folder) | 5.0                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential     | -10% to +9%  | Lab staff survey, SickKids wage information, 2013 |
| 11090 Packaging with testing documentation  | 1.0                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential     | -10% to +9%  | Lab staff survey, SickKids wage information, 2013 |
| 11500 Service recipient limited registration  | 1.8                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential     | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| <b>DNA Extraction (Units: minutes)</b>  |                            |              |   |                  |              |   |
| 85340 Extraction using an automated kit (once per specimen)   | 2.0                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential     | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| 85360 Manual nucleic acid quantitation (once per specimen)  | 5.0                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential     | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |

| Cost Items   | Quantity of Use per Sample |              |   | Price (CAD/unit) |              |   |
|--|----------------------------|--------------|---|------------------|--------------|---|
|  | Estimate                   | Range        | Source  | Estimate         | Range        | Source  |
| 84510 Freezing of cells/tissue without cryopreservation  | 9.0                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential     | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| 85370 Nucleic acid quantitation using spectrophotometer with sample retention tech (once per specimen) | 1.0                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential     | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| <b>Microarray sample processing (Unites: minutes)</b>  |                            |              |   |                  |              |   |
| 85500 Assay preparation - manual worksheet prep (3 units for each assay and 1 per specimen)            | 2.0                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential     | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| 83440 Fluorochrome labelling without dye swap  | 4.0                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential     | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| 85560 Dilution of specimens (at the assay stage only, once per specimen)                               | 2.0                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential     | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| DNA Fragmentation, by Restriction Enzyme Digestion   | 2.3                        | Not assigned | Cytogenetics lab specialist                                     | Confidential     | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| Ligation   | 1.5                        | Not assigned | Cytogenetics lab specialist                                     | Confidential     | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| PCR amplification  | 2.3                        | Not assigned | Cytogenetics lab specialist                                     | Confidential     | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| PCR purification by magnetic beads (once per sample)   | 12.4                       | Not assigned | Cytogenetics lab specialist                                     | Confidential     | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| DNA Fragmentation-by Restriction Enzyme Digestion  | 2.3                        | Not assigned | Cytogenetics lab specialist                                     | Confidential     | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| Fluorochrome labelling without dye swap.   | 1.1                        | Not assigned | Cytogenetics lab specialist                                     | Confidential     | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |

| Cost Items  | Quantity of Use per Sample |              |   | Price (CAD/unit) |              |   |
|---|----------------------------|--------------|---|------------------|--------------|---|
|   | Estimate                   | Range        | Source  | Estimate         | Range        | Source  |
| Microarray Slide Hybridization  | 4.1                        | Not assigned | Cytogenetics lab specialist                           | Confidential     | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| Microarray Slide Washing and Drying - Automated   | 8.0                        | Not assigned | Cytogenetics lab specialist                           | Confidential     | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| Microarray slide scanning - Affymetrix scanner (once per slide)   | 10.0                       | Not assigned | Cytogenetics lab specialist                           | Confidential     | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| <b>Analysis (Units: minutes)</b>  |                            |              |   |                  |              |   |
| Data preparation (includes transfer of data images)   | 8.0                        | Not assigned | Cytogenetics lab specialist                           | Confidential     | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| 83550 Data analysis (includes review and analysis of each chromosome, prep prelim report, once per service recipient) | 12.0                       | Not assigned | Lab technician  | Confidential     | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| <b>Clinical interpretation and report writing (Units: minutes)</b>  |                            |              |   |                  |              |   |
| 87760 Collation and write up on molecular genetic analysis - simple (60% of cases)                                    | 2.0                        | Not assigned | MIS Standards 2012-2013 and Cytogenetics lab director | Confidential     | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| 87760 Collation and write up on molecular genetic analysis - intermediate (20% of cases)                              | 10.0                       | Not assigned | MIS Standards 2012-2013 and Cytogenetics lab director | Confidential     | -23% to +28% | Lab director, 2014                                |
| 87760 Collation and write up on molecular genetic analysis - complex (20% of cases)                                   | 50.0                       | Not assigned | MIS Standards 2012-2013 and Cytogenetics lab director | Confidential     | -23% to +28% | Lab director, 2014                                |
| 87770 Technical checking/reporting of molecular genetic interpretation (30% of cases)                                 | 5.0                        | Not assigned | Cytogenetics lab director                             | Confidential     | -30% to +15% | Informatics facility manager, 2014                |
| <b>Clinical interpretation (Units: minutes)</b>   |                            |              |   |                  |              |   |
| 87780 Clinical interpretation and professional signoff (80% of cases,   | 8.0                        | Not assigned | Cytogenetics lab director                             | Confidential     | -20% to +20% | Public sector disclosure 2012                     |

| Cost Items   | Quantity of Use per Sample |                |                           | Price (CAD/unit) |               |   |
|--|----------------------------|----------------|---------------------------|------------------|---------------|---|
|  | Estimate                   | Range          | Source                    | Estimate         | Range         | Source  |
| 10 minutes per case)   |                            |                |                           |                  |               |   |
| 87780 Clinical interpretation and professional signoff (15% of cases, 20 minutes per case) | 3.0                        | Not assigned   | Cytogenetics lab director | Confidential     | -20% to +20%  | Public sector disclosure 2012   |
| 87780 Clinical interpretation and professional signoff (5% of cases, 60 minutes per case)  | 3.0                        | Not assigned   | Cytogenetics lab director | Confidential     | -20% to +20%  | Public sector disclosure 2012   |
| <b>Large Equipment</b>   |                            |                |                           |                  |               |   |
| Affymetrix 1 GeneChip 3000Dx, 2 Fluidics stations, 1 hybridization oven                    | 2/all tests                | Not applicable | Lab manager               | 250000           | 225000-275000 | Affymetrix sales representative, 2014                                 |
| 1-year service contract  | 1/all tests                | Not applicable | Affymetrix representative | 25000            | 22500-27500   | Affymetrix sales representative, 2015                                 |
| <b>Supplies</b>  |                            |                |                           |                  |               |   |
| Shipping & Handling  | 1                          | Not assigned   | FedEx                     | 51.52            | 46.37-56.67   | FedEx, 2013   |
| Microarray Slide & Reagents per patient  | 1                          | Not assigned   | Cytogeneticist            | Confidential     | -10% to +10%  | Affymetrix sales representative, 2015                                 |
| <b>Follow-up (proportion of cases)</b>   |                            |                |                           |                  |               |   |
| Note: Price for FISH and qPCR tests includes three tests, proband and two parents          |                            |                |                           |                  |               |   |
| FISH followup (proband and two parents)  | 0.1                        | Not assigned   | Cytogeneticist            | 655.00           | 578.04-720.50 | SickKids molecular genetics costing/BC laboratory reimbursement, 2013 |
| qPCR followup (proband and two parents)  | 0.05                       | Not assigned   | Cytogeneticist            | 671.71           | 604.54-738.88 | Expert opinion, 2013  |

Abbreviations: CMA, Chromosomal Microarray Analysis; PCR, Polymerase chain reaction; MIS, Management Information Systems; qPCR, Real-time polymerase chain reaction; FISH, Fluorescence in situ hybridization

**Appendix 2. Resource use and unit prices for WES inputs, High throughput flow cell**

| Cost Items  | Quantity of Use per Sample |              |   | Price (CDN \$/unit) |              |   |
|---|----------------------------|--------------|---|---------------------|--------------|---|
|   | Estimate                   | Range        | Source  | Estimate            | Range        | Source  |
| <b>Labour</b>   |                            |              |   |                     |              |   |
| <b>Specimen Preparation (Units: minutes)</b>  |                            |              |   |                     |              |   |
| 10120 Pediatric venipuncture  | 7.6                        | Not assigned | MIS Standards 2012-2013   | Confidential        | -21% to +28% | SickKids wage information, 2013                   |
| 11090 Packaging with testing documentation  | 1.0                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential        | -21% to +28% | SickKids wage information, 2013                   |
| 11500 Service recipient primary registration  | 1.8                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential        | -10% to +9%  | Lab staff survey, SickKids wage information, 2013 |
| 10360 Printing and sorting of specimen labels (per label)   | 0.4                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential        | -10%to +9%   | Lab Staff survey, SickKids wage information, 2013 |
| 88550 Creation of family/service recipient folder (add sample to existing family folder, assign a new number and retrieve or make a new folder) (once per folder) | 5.0                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential        | -10% to +9%  | Lab staff survey, SickKids wage information, 2013 |
| 11090 Packaging with testing documentation  | 1.0                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential        | -10% to +9%  | Lab staff survey, SickKids wage information, 2013 |
| 11500 Service recipient limited registration  | 1.8                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential        | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| <b>Library preparation (Units: minutes)</b>   |                            |              |   |                     |              |   |
| Note: Total time per task was divided by the number of samples per batch. Resource use estimate was based on 8 samples per batch.                                 |                            |              |   |                     |              |   |
| DNA quantification (20 min)   | 2.5                        | Not assigned | TCAG lab manager  | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Pre-prep reagents (20 min)  | 2.5                        | Not assigned | TCAG lab manager  | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Shearing (20 min)   | 2.5                        | Not assigned | TCAG lab manager  | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Purification (40 min)   | 5.0                        | Not assigned | TCAG lab manager  | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| End repair (40 min)   | 5.0                        | Not assigned | TCAG lab manager  | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| A-tailing (40 min)  | 5.0                        | Not assigned | TCAG lab manager  | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Adapter ligation (45 min)   | 5.6                        | Not assigned | TCAG lab manager  | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |

| Cost Items   | Quantity of Use per Sample |               |   | Price (CDN \$/unit) |              |   |
|--|----------------------------|---------------|---|---------------------|--------------|---|
|  | Estimate                   | Range         | Source                                  | Estimate            | Range        | Source  |
| Pre-hybridization PCR (45 min)   | 5.6                        | Not assigned  | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Pre-hybridization QC (60 min)  | 7.5                        | Not assigned  | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Lyophilization (20 min)  | 2.5                        | Not assigned  | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Hybridization (30 min)   | 3.8                        | Not assigned  | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Hybridization washes (150 min)   | 18.8                       | Not assigned  | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Post-Hybridization PCR (40 min)  | 5.0                        | Not assigned  | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Post Hybridization QC (120 min)  | 15.0                       | Not assigned  | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| <b>Sequencing (Units: minutes)</b>   |                            |               |   |                     |              |   |
| Note: Total time per task was divided by the number of samples per lane. Resource use estimate was based on 8 samples per lane.  |                            |               |   |                     |              |   |
| HiSeq wash (30 min)  | 3.8                        | Not assigned  | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Sequencing prep (30 min)   | 3.8                        | Not assigned  | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| HiSeq post-run wash (45 min)   | 5.6                        | Not assigned  | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Run quality control (15 min)   | 1.9                        | Not assigned  | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| cBot (30 min)  | 3.8                        | Not assigned  | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| <b>Bioinformatics (Units: minutes)</b>   |                            |               |   |                     |              |   |
| Note: Resource use estimate was based on the instrument's capacity, 87.5 tests a month. The lower bound was based on 100 tests and the upper bound was based on to 75 tests.   |                            |               |   |                     |              |   |
| Variant calling (1 FTE hour for 75-100 tests a month)  | 96.0                       | 84.0-112.0    | TCAG Bioinformatics manager             | Confidential        | -20% to +20% | TCAG Bioinformatics manager, 2014                 |
| Annotation (0.25 FTE hour for 75-100 tests a month)  | 24.0                       | 21.0-28.0     | TCAG Bioinformatics manager             | Confidential        | -20% to +20% | TCAG Bioinformatics manager, 2014                 |
| <b>Bioinformatics Maintenance (Units: minutes)</b>   |                            |               |   |                     |              |   |
| Note: One full time equivalent (FTE) hour to support one node per year was assumed. Resource use in minutes was calculated by multiplying the time to complete a job by the time needed to support the required number of nodes per job. For example, if a job required 0.5 hours and 3 nodes, then the resource use for the job is calculated as follows: 60 FTE minutes in an hour per year/(365*24 hours in a year)*3 hours to support 3 nodes*0.5 hours (i.e. number of minutes per year to support a 30 minute job on 3 nodes). The lower bound of resource use was based on 75% of the computation time and the upper bound was based on 125% of computation time. |                            |               |   |                     |              |   |
| Alignment<br>0.5 hours (range: 0.4-0.6) 3 nodes  | 0.010                      | 0.008-0.012   | TCAG Bioinformatics manager, Brown 2003 | Confidential        | -16% to +10% | Lab staff survey, SickKids wage information, 2015 |
| Remove Duplicates - Genome Analysis Toolkit (GATK)<br>1 hour (range: 0.75-1.25) 0.5 nodes  | 0.0034                     | 0.0026-0.0043 | TCAG Bioinformatics manager, Brown 2003 | Confidential        | -16% to +10% | Lab staff survey, SickKids wage information, 2015 |
| Recalibration  | 0.017                      | 0.014-0.021   | TCAG Bioinformatics manager, Brown 2003 | Confidential        | -16% to +10% | Lab staff survey, SickKids wage information, 2015 |



| Cost Items  | Quantity of Use per Sample |                |   | Price (CDN \$/unit) |               |   |
|---|----------------------------|----------------|---|---------------------|---------------|---|
|   | Estimate                   | Range          | Source                                    | Estimate            | Range         | Source  |
| 5 hours (range: 4-6) 0.5 nodes  |                            |                |   |                     |               |   |
| SNV/indel variant calling - Genome Analysis Toolkit (GATK haplotype caller)<br>6.25 hours (range: 5-7.5) 0.2 nodes  | 0.009                      | 0.007-0.010    | TCAG Bioinformatics manager, Brown 2003   | Confidential        | -16% to +10%  | Lab staff survey, SickKids wage information, 2015 |
| Annotation (ANNOVAR)<br>1.25 hours (range: 1-1.5) 0.2 nodes   | 0.009                      | 0.007-0.010    | TCAG Bioinformatics manager, Brown 2003   | Confidential        | -16% to +10%  | Lab staff survey, SickKids wage information, 2015 |
| <b>Clinical Interpretation (Units: minutes)</b>   |                            |                |   |                     |               |   |
| Clinical classification of primary variants<br><br>15 minutes if no variants are found, otherwise 30 minutes per variant. On average, 2 variants are found (range: 0-4) | 60                         | 15-120         | DPLM Associate director, Genomic Analysis | Confidential        | -20% to +20%  | Expert opinion, 2015                              |
| Clinical classification of secondary variants<br><br>30 minutes per case (range: 20-40), found in 4% of cases (range: 3-5%)   | 1.2                        | 0.6-2.0        | DPLM Associate director, Genomic Analysis | Confidential        | -20% to +20%  | Expert opinion, 2015                              |
| <b>Report Writing (Units: minutes)</b>  |                            |                |   |                     |               |   |
| Addressing primary variants<br><br>15 minutes base plus 15 minutes per variant. On average, 2 variants are found (range: 0-4)   | 45                         | 15-75          | DPLM Associate director, Genomic Analysis | Confidential        | -20% to +20%  | Expert opinion, 2015                              |
| Addressing secondary variants<br><br>30 minutes per case (range: 20-40), found in 4% of cases (range: 3-5%)   | 1.2                        | 0.6-2.0        | DPLM Associate director, Genomic Analysis | Confidential        | -20% to +20%  | Expert opinion, 2015                              |
| <b>Large Equipment</b>  |                            |                |   |                     |               |   |
| Illumina HiSeq 2500   | 1/all tests                | Not applicable | TCAG lab manager                          | 750000              | 700000-800000 | TCAG lab manager, 2014                            |

| Cost Items   | Quantity of Use per Sample |                |  | Price (CDN \$/unit) |               |   |
|--|----------------------------|----------------|--|---------------------|---------------|---|
|  | Estimate                   | Range          | Source                                       | Estimate            | Range         | Source  |
| 1-year service contract  | 1/all tests                | Not applicable | TCAG lab manager                             | 75000               | 50000-82500   | TCAG lab manager, 2014                            |
| Agilent BioAnalyzer/Tape station   | 1/all tests                | Not applicable | Agilent representative                       | 38500               | 34000-43000   | Agilent representative/<br>TCAG Lab Manager, 2015 |
| <b>Small Equipment</b>   |                            |                |  |                     |               |   |
| Tube microcentrifuge   | 1/all tests                | Not applicable | TCAG lab manager                             | 2250                | 2000-2500     | TCAG lab manager, 2014                            |
| Plate microcentrifuge  | 1/all tests                | Not applicable | TCAG lab manager                             | 5000                | 4500-5500     | TCAG lab manager, 2014                            |
| Thermomixer  | 1/all tests                | Not applicable | TCAG lab manager                             | 5000                | 4500-5500     | TCAG lab manager, 2014                            |
| Vortex   | 1/all tests                | Not applicable | TCAG lab manager                             | 450                 | 400-500       | TCAG lab manager, 2014                            |
| Pipette sets   | 2/all tests                | Not applicable | TCAG lab manager                             | 1600                | 1400-2000     | TCAG lab manager, 2014                            |
| Magnet particle concentrator for tubes   | 1/all tests                | Not applicable | TCAG lab manager                             | 700                 | 630-770       | TCAG lab manager, 2014                            |
| Thermocyclers  | 2/all tests                | Not applicable | TCAG lab manager                             | 3000                | 2700-3300     | TCAG lab manager, 2014                            |
| <b>Supplies</b>  |                            |                |  |                     |               |   |
| Shipping & Handling  | 1                          | Not assigned   | TCAG Lab Manager                             | 51.5                | 46.37-56.67   | FedEx, 2013                                       |
| SureSelect Baits (96 reactions)  | 1                          | Not assigned   | TCAG lab manager                             | 242.2               | 239.43-292.64 | TCAG lab manager, 2015                            |
| SureSelect Library prep (96 reactions)   | 1                          | Not assigned   | TCAG lab manager                             | 58.5                | 57.92-70.80   | TCAG lab manager, 2015                            |
| Other library prep consumables   | 1                          | Not assigned   | TCAG lab manager                             | 50.0                | 45.00-55.00   | TCAG lab manager, 2014                            |
| Sequencing reagents (8 samples per lane)   | 1                          | Not assigned   | TCAG lab manager                             | 274.4               | 540.00-660.00 | TCAG lab manager 2015                             |
| <b>Follow-up (proportion of cases)</b>   |                            |                |  |                     |               |   |
| Sanger sequencing (two tests per person, proband and two parents)  | 0.5                        | Not assigned   | DPLM Associate Director,<br>Genomic Analysis | 37.77               | 35.31-40.24   | Blons et al. 2013                                 |
| <b>Bioinformatics</b>  |                            |                |  |                     |               |   |
| <b>Bioinformatics File Storage (Units: GB per year)</b>  |                            |                |  |                     |               |   |
| Notes: 1. Resource use volume was calculated by multiplied the file size by the storage time (in years). |                            |                |  |                     |               |   |
| 2. Price was given in dollars per GB per year.   |                            |                |  |                     |               |   |
| trimmed fastq<br>file size: 9 GB; storage time: 9 months (range: 6-12)                                   | 6.8                        | 4.5-9.0        | TCAG Bioinformatics manager                  | 0.4                 | 0.36-0.45     | TCAG Bioinformatics manager, 2014                 |
| temporary BAM files<br>file size: 30 GB; storage time: 1   | 2.5                        | Not assigned   | TCAG Bioinformatics manager                  | 0.4                 | 0.36-0.45     | TCAG Bioinformatics manager, 2014                 |

| Cost Items  | Quantity of Use per Sample |           |                             | Price (CDN \$/unit) |             |                                   |
|---|----------------------------|-----------|-----------------------------|---------------------|-------------|-----------------------------------|
|   | Estimate                   | Range     | Source                      | Estimate            | Range       | Source                            |
| month   |                            |           |                             |                     |             |                                   |
| final rem-dup, recalibrated, locally re-aligned BAM file<br>file size: 9 GB; storage time: 9 months (range: 6-12)   | 4.5                        | 3.0-6.0   | TCAG Bioinformatics manager | 0.4                 | 0.36-0.45   | TCAG Bioinformatics manager, 2014 |
| <b>Bioinformatics Computation Use (Units: CPU time per hour)</b>  |                            |           |                             |                     |             |                                   |
| Notes: 1. Resource use volume use was calculated by multiplying the number of jobs by the number of cores per job and time (hours) required to complete a job. 25% (range 0 to 50%) was added to account for additional processing time to avoid operating at full capacity.<br>2. Scalar Decisions, Inc. quote of \$9560 per node (20 cores) or \$478 per core was used. A straight line depreciation method over 5 years was applied and the price per CPU per year was calculated to be \$95.6. This price was converted to price per CPU per hour by dividing \$95.6 by (365*24). |                            |           |                             |                     |             |                                   |
| Alignment<br>36 jobs, 4 cores per job, 0.5 hours to complete  | 90.0                       | 72.0-108  | TCAG Bioinformatics manager | 0.011               | 0.010-0.012 | Scalar quote, 2014                |
| Remove Duplicates - Genome Analysis Toolkit (GATK)<br>1 job, 1 core per job, 1 hour to complete   | 1.3                        | 1.0-1.5   | TCAG Bioinformatics manager | 0.011               | 0.010-0.012 | Scalar quote, 2014                |
| Recalibration<br>1 job, 1 core per job, 4 hours to complete   | 5.0                        | 4.0-6.0   | TCAG Bioinformatics manager | 0.011               | 0.010-0.012 | Scalar quote, 2014                |
| SNV/indel variant calling - Genome Analysis Toolkit (GATK haplotype caller)<br>1 job, 1 core per job, 5 hours to complete   | 6.3                        | 5.0-7.5   | TCAG Bioinformatics manager | 0.011               | 0.010-0.012 | Scalar quote, 2014                |
| Annotation (ANNOVAR)<br>1 jobs, 16 cores per job, 1 hour to complete  | 20.0                       | 16.0-24.0 | TCAG Bioinformatics manager | 0.011               | 0.010-0.012 | Scalar quote, 2014                |

Abbreviations: WES, Whole Exome Sequencing; TCAG, The Centre for Applied Genomics ; DPLM, The Department of Paediatric Laboratory Medicine; FTE, Full-time equivalent; MIS, Management Information Systems; GATK, Genome Analysis Toolkit; SNV, Single nucleotide variant.

**Appendix 3.** Resource use and unit prices for WGS inputs, Illumina HiSeq® 2500

| Cost Items   | Quantity of Use per Sample |              |   | Price (CDN \$/unit) |              |   |
|--|----------------------------|--------------|---|---------------------|--------------|---|
|  | Estimate                   | Range        | Source  | Estimate            | Range        | Source  |
| <b>Labour</b>  |                            |              |   |                     |              |   |
| <b>Specimen Preparation (Units: minutes)</b>   |                            |              |   |                     |              |   |
| 10120 Pediatric venipuncture   | 7.6                        | Not assigned | MIS Standards 2012-2013   | Confidential        | -21%to +28%  | SickKids wage information, 2013                   |
| 11090 Packaging with testing documentation   | 1.0                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential        | -21% to +28% | SickKids wage information, 2013                   |
| 11500 Service recipient primary registration   | 1.8                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential        | -10% to +9%  | Lab staff survey, SickKids wage information, 2013 |
| 10360 Printing and sorting of specimen labels (per label)  | 0.4                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential        | -10% to +9%  | Lab Staff survey, SickKids wage information, 2013 |
| 88550 Creation of family/service recipient folder (add sample to existing family folder, assign a new number and retrieve or make a new folder) (once per folder)  | 5.0                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential        | -10% to +9%  | Lab staff survey, SickKids wage information, 2013 |
| 11090 Packaging with testing documentation   | 1.0                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential        | -10% to +9%  | Lab staff survey, SickKids wage information, 2013 |
| 11500 Service recipient limited registration   | 1.8                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential        | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| <b>Library preparation (Units: minutes)</b>  |                            |              |   |                     |              |   |
| Note: Total time per task was divided by the number of samples per batch. The number of samples per batch was assumed to vary between 8 and 16. The resource use estimate was based on 12 samples (average of 8 and 16). The upper bound was based on 8 samples and the lower bound was based on 16 samples. |                            |              |   |                     |              |   |
| DNA quantification (20 min)  | 1.7                        | 1.3-2.5      | TCAG lab manager  | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Pre-prep reagents (20 min)   | 1.7                        | 1.3-2.5      | TCAG lab manager  | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Shearing (20 min)  | 1.7                        | 1.3-2.5      | TCAG lab manager  | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Purification (40 min)  | 3.3                        | 2.5-5.0      | TCAG lab manager  | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| End repair (40 min)  | 3.3                        | 2.5-5.0      | TCAG lab manager  | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| A-tailing (40 min)   | 3.3                        | 2.5-5.0      | TCAG lab manager  | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Adapter ligation (45 min)  | 3.8                        | 2.8-5.6      | TCAG lab manager  | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |

| Cost Items   | Quantity of Use per Sample |             |   | Price (CDN \$/unit) |              |   |
|--|----------------------------|-------------|---|---------------------|--------------|---|
|  | Estimate                   | Range       | Source                                  | Estimate            | Range        | Source  |
| <b>Sequencing (Units: minutes)</b>   |                            |             |   |                     |              |   |
| Note: Total time per task was divided by the number of samples per lane. The number of samples per lane ranged from 4 to 8. The resource use estimate was based on 6 samples (average of 4 and 8). The resource use lower bound was based on 8 samples per lane and the upper bound was based on 4 samples per lane.   |                            |             |   |                     |              |   |
| HiSeq wash (30 min)  | 5.0                        | 3.8-7.5     | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Sequencing prep (30 min)   | 5.0                        | 3.8-7.5     | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| HiSeq post-run wash (45 min)   | 7.5                        | 5.6-11.3    | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Run quality control (15 min)   | 2.5                        | 1.9-3.8     | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| cBot (30 min)  | 5.0                        | 3.8-7.5     | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| <b>Bioinformatics (Units: minutes)</b>   |                            |             |   |                     |              |   |
| Note: resource use estimate is based on the instrument's capacity, 22.5 tests a month. The lower bound corresponds to 20 tests a month and the upper bound corresponds to 25 tests per month.  |                            |             |   |                     |              |   |
| Variant calling (1 FTE hour for 20-25 tests a month)   | 373.3                      | 336.0-420.0 | TCAG Bioinformatics manager             | Confidential        | -20% to +20% | TCAG Bioinformatics manager, 2014                 |
| Annotation (0.25 FTE hour for 20-25 tests a month)   | 93.3                       | 84.0-105.0  | TCAG Bioinformatics manager             | Confidential        | -20% to +20% | TCAG Bioinformatics manager, 2014                 |
| <b>Bioinformatics Maintenance (Units: minutes)</b>   |                            |             |   |                     |              |   |
| Note: One full time equivalent (FTE) hour to support one node per year was assumed. Resource use in minutes was calculated by multiplying the time to complete a job by the time needed to support the required number of nodes per job. For example, if a job required 1.5 hours and 55 nodes, then the resource use for the job is calculated as follows: 60 FTE minutes in an hour per year/(365*24 hours in a year)*55 hours to support 55 nodes*1.5 hours (i.e. number of minutes per year to support a 90 minute job on 55 nodes). The lower bound of resource use was based on 75% of the computation time and the upper bound was based on 125% of computation time. |                            |             |   |                     |              |   |
| Alignment<br>1.5 hours (range: 1.13-1.88), 55 nodes  | 0.565                      | 0.424-0.706 | TCAG Bioinformatics manager, Brown 2003 | Confidential        | -16% to +10% | Lab staff survey, SickKids wage information, 2015 |
| Remove Duplicates - Genome Analysis Toolkit (GATK)<br>14 hours (range: 10.5-17.5), 1 node  | 0.096                      | 0.072-0.120 | TCAG Bioinformatics manager, Brown 2003 | Confidential        | -16% to +10% | Lab staff survey, SickKids wage information, 2015 |
| Recalibration<br>7 hours (range: 5.3-8.8) 12 nodes   | 0.575                      | 0.432-0.719 | TCAG Bioinformatics manager, Brown 2003 | Confidential        | -16% to +10% | Lab staff survey, SickKids wage information, 2015 |
| Post-recalibration merge-Genome<br>3.5 hours (range: 2.6-4.4), 12 nodes  | 0.288                      | 0.216-0.360 | TCAG Bioinformatics manager, Brown 2003 | Confidential        | -16% to +10% | Lab staff survey, SickKids wage information, 2015 |

| Cost Items  | Quantity of Use per Sample |                |   | Price (CDN \$/unit) |               |   |
|---|----------------------------|----------------|---|---------------------|---------------|---|
|   | Estimate                   | Range          | Source                                    | Estimate            | Range         | Source  |
| SNV/indel variant calling - Genome Analysis Toolkit (GATK haplotype caller)<br>4 hours (range: 3-5), 32 nodes                                 | 0.877                      | 0.658-1.096    | TCAG Bioinformatics manager, Brown 2003   | Confidential        | -16% to +10%  | Lab staff survey, SickKids wage information, 2015 |
| Annotation (ANNOVAR)<br>3 hours (range: 2.3-3.8), 1 node  | 0.021                      | 0.015-0.026    | TCAG Bioinformatics manager, Brown 2003   | Confidential        | -16% to +10%  | Lab staff survey, SickKids wage information, 2015 |
| <b>Clinical Interpretation (Units: minutes)</b>   |                            |                |   |                     |               |   |
| Clinical classification of primary variants<br><br>15 minutes base plus 30 minutes per variant. On average, 2 variants are found (range: 0-4) | 75                         | 15-135         | DPLM Associate Director, Genomic Analysis | Confidential        | -20% to +20%  | Expert opinion, 2015                              |
| Clinical classification of secondary variants<br><br>30 minutes per case (range: 20-40), found in 4% of cases (range: 3-5%)                   | 1.2                        | 0.6-2.0        | DPLM Associate Director, Genomic Analysis | Confidential        | -20% to +20%  | Expert opinion, 2015                              |
| <b>Report Writing (Units: minutes)</b>  |                            |                |   |                     |               |   |
| Addressing primary variants<br><br>15 minutes base plus 15 minutes per variant. On average, 2 variants are found (range: 0-4)                 | 45                         | 15-75          | DPLM Associate Director, Genomic Analysis | Confidential        | -20% to +20%  | Expert opinion, 2015                              |
| Addressing secondary variants<br><br>30 minutes per case (range: 20-40), found in 4% of cases (range: 3-5%)                                   | 1.2                        | 0.6-2.0        | DPLM Associate Director, Genomic Analysis | Confidential        | -20% to +20%  | Expert opinion, 2015                              |
| <b>Large Equipment</b>  |                            |                |   |                     |               |   |
| Illumina HiSeq 2500   | 1/all tests                | Not applicable | TCAG Lab manager                          | 750000              | 700000-800000 | TCAG Lab Manager, 2015                            |
| 1-year service contract   | 1/all tests                | Not applicable | TCAG Lab Manager                          | 75000               | 50000-82500   | TCAG Lab Manager, 2015                            |
| Agilent BioAnalyzer/Tape station  | 1/all tests                | Not applicable | Agilent representative                    | 38500               | 34000-43000   | Agilent representative/TCAG Lab Manager, 2015     |

| Cost Items   | Quantity of Use per Sample |                |   | Price (CDN \$/unit) |               |                                   |
|--|----------------------------|----------------|---|---------------------|---------------|-----------------------------------|
|  | Estimate                   | Range          | Source                                    | Estimate            | Range         | Source                            |
| <b>Small Equipment</b>   |                            |                |   |                     |               |                                   |
| Tube microcentrifuge   | 1/all tests                | Not applicable | TCAG lab manager                          | 2250                | 2000-2500     | TCAG lab manager, 2014            |
| Plate microcentrifuge  | 1/all tests                | Not applicable | TCAG lab manager                          | 5000                | 4500-5500     | TCAG lab manager, 2014            |
| Thermomixer  | 1/all tests                | Not applicable | TCAG lab manager                          | 5000                | 4500-5500     | TCAG lab manager, 2014            |
| Vortex   | 1/all tests                | Not applicable | TCAG lab manager                          | 450                 | 400-500       | TCAG lab manager, 2014            |
| Pipette sets   | 2/all tests                | Not applicable | TCAG lab manager                          | 1600                | 1400-2000     | TCAG lab manager, 2014            |
| Magnet particle concentrator for tubes   | 1/all tests                | Not applicable | TCAG lab manager                          | 700                 | 630-770       | TCAG lab manager, 2014            |
| Thermocyclers  | 2/all tests                | Not applicable | TCAG lab manager                          | 3000                | 2700-3300     | TCAG lab manager, 2014            |
| <b>Supplies</b>  |                            |                |   |                     |               |                                   |
| Shipping & Handling  | 1                          | Not assigned   | TCAG lab manager                          | 51.5                | 46.37-56.67   | FedEx, 2013                       |
| Illumina Nano DNA library prep   | 1                          | Not assigned   | TCAG lab manager                          | 30.0                | 27.0-33.0     | TCAG lab manager, 2015            |
| Other library prep consumables per sample  | 1                          | Not assigned   | TCAG lab manager                          | 50.0                | 45.00-55.00   | TCAG lab manager, 2015            |
| Sequencing reagents (2 lanes per sample)   | 1                          | Not assigned   | TCAG lab manager                          | 4055.0              | 3649.5-4460.5 | TCAG lab manager, 2015            |
| <b>Follow-up (proportion of cases)</b>   |                            |                |   |                     |               |                                   |
| Note: Price for qPCR test included three tests, proband and two parents  |                            |                |   |                     |               |                                   |
| Sanger sequencing (two tests per person, proband and two parents)  | 0.5                        | Not assigned   | DPLM Associate Director, Genomic Analysis | 37.77               | 35.31-40.24   | Blons et al. 2013                 |
| qPCR followup (proband and two parents)  | 0.1                        | Not assigned   | Team Leader, Molecular Genetics           | 671.71              | 604.54-738.88 | Expert opinion, 2013              |
| <b>Bioinformatics</b>  |                            |                |   |                     |               |                                   |
| <b>Bioinformatics File Storage (Units: GB/year)</b>  |                            |                |   |                     |               |                                   |
| Notes: 1. Resource use volume was calculated by multiplied the file size by the storage time (in years).<br>2. Price was given in dollars per GB per year. |                            |                |   |                     |               |                                   |
| trimmed fastq<br>file size: 100 GB; average storage time: 9 months (range: 6-12)   | 75                         | 50-100         | TCAG Bioinformatics manager               | 0.4                 | 0.36-0.45     | TCAG Bioinformatics manager, 2014 |
| temporary BAM files<br>file size: 150 GB; storage time: 1 month  | 12.5                       | Not assigned   | TCAG Bioinformatics manager               | 0.4                 | 0.36-0.45     | TCAG Bioinformatics manager, 2014 |

| Cost Items  | Quantity of Use per Sample |           |                             | Price (CDN \$/unit) |             |                                   |
|---|----------------------------|-----------|-----------------------------|---------------------|-------------|-----------------------------------|
|   | Estimate                   | Range     | Source                      | Estimate            | Range       | Source                            |
| final rem-dup, recalibrated, locally re-aligned BAM file<br>file size: 200 GB; average storage time: 9 months (range: 6-12)   | 150                        | 100-200   | TCAG Bioinformatics manager | 0.4                 | 0.36-0.45   | TCAG Bioinformatics manager, 2014 |
| <b>Bioinformatics Computation Use (Units: CPU time per hour)</b>  |                            |           |                             |                     |             |                                   |
| Notes: 1. Resource use volume use was calculated by multiplying the number of jobs by the number of cores per job and time (hours) required to complete a job. 25% (range 0 to 50%) was added to account for additional processing time to avoid operating at full capacity.<br>2. Scalar Decisions, Inc. quote of \$9560 per node (20 cores) or \$478 per core was used. A straight line depreciation method over 5 years was applied and the price per CPU per year was calculated to be \$95.6. This price was converted to price per CPU per hour by dividing \$95.6 by (365*24). |                            |           |                             |                     |             |                                   |
| Alignment<br>400 jobs, 1 core per job, 1.5 hours to complete  | 750                        | 600-900   | TCAG Bioinformatics manager | 0.011               | 0.010-0.012 | Scalar quote, 2014                |
| Remove Duplicates - Genome Analysis Toolkit (GATK)<br>1 job, 1 core per job, 14 hours to complete   | 17.5                       | 14.0-21.0 | TCAG Bioinformatics manager | 0.011               | 0.010-0.012 | Scalar quote, 2014                |
| Recalibration<br>86 jobs, 1 core per job, 7 hours to complete   | 752.5                      | 602-903   | TCAG Bioinformatics manager | 0.011               | 0.010-0.012 | Scalar quote, 2014                |
| Post-recalibration merge - Genome Analysis Toolkit (GATK)<br>1 job, 1 core per job, 3.5 hours to complete   | 4.4                        | 3.5-5.3   | TCAG Bioinformatics manager | 0.011               | 0.010-0.012 | Scalar quote, 2014                |
| SNV/indel variant calling - Genome Analysis Toolkit (GATK haplotype caller)<br>240 jobs, 1 core per job, 4 hours to complete  | 1200                       | 960-1440  | TCAG Bioinformatics manager | 0.011               | 0.010-0.012 | Scalar quote, 2014                |
| Annotation (ANNOVAR)<br>1 jobs, 16 cores per job, 3 hours to complete   | 60                         | 48-72     | TCAG Bioinformatics manager | 0.011               | 0.010-0.012 | Scalar quote, 2014                |

Abbreviations: WGS, Whole Genome Sequencing; TCAG, The Centre for Applied Genomics ; DPLM, The Department of Paediatric Laboratory Medicine; FTE, Full-time equivalent; qPCR, Real-time polymerase chain reaction; MIS, Management Information Systems; GATK, Genome Analysis Toolkit; SNV, Single nucleotide variant.



**Appendix 4.** Resource use and unit prices for WGS inputs, Illumina HiSeq X™

| Cost Items  | Quantity of Use per Sample |              |   | Price (CDN \$/unit) |              |   |
|---|----------------------------|--------------|---|---------------------|--------------|---|
|   | Estimate                   | Range        | Source  | Estimate            | Range        | Source  |
| <b>Labour</b>   |                            |              |   |                     |              |   |
| <b>Specimen Preparation (Units: minutes)</b>  |                            |              |   |                     |              |   |
| 10120 Pediatric venipuncture  | 7.6                        | Not assigned | MIS Standards 2012-2013   | Confidential        | -21%to +28%  | SickKids wage information, 2013                   |
| 11090 Packaging with testing documentation  | 1.0                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential        | -21% to +28% | SickKids wage information, 2013                   |
| 11500 Service recipient primary registration  | 1.8                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential        | -10% to +9%  | Lab staff survey, SickKids wage information, 2013 |
| 10360 Printing and sorting of specimen labels (per label)   | 0.4                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential        | -10% to +9%  | Lab Staff survey, SickKids wage information, 2013 |
| 88550 Creation of family/service recipient folder (add sample to existing family folder, assign a new number and retrieve or make a new folder) (once per folder) | 5.0                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential        | -10% to +9%  | Lab staff survey, SickKids wage information, 2013 |
| 11090 Packaging with testing documentation  | 1.0                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential        | -10% to +9%  | Lab staff survey, SickKids wage information, 2013 |
| 11500 Service recipient limited registration  | 1.8                        | Not assigned | MIS Standards 2010-2011/2012-2013 and Cytogenetics lab director | Confidential        | -16% to +10% | Lab staff survey, SickKids wage information, 2013 |
| <b>Library preparation (Units: minutes)</b>   |                            |              |   |                     |              |   |
| Note: Total time per task was divided by the number of samples per batch. The number of samples per batch was assumed to be 48.                                   |                            |              |   |                     |              |   |
| DNA quantification (20 min total)   | 0.4                        | Not assigned | TCAG lab manager  | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Pre-prep reagents (20 min total)  | 0.4                        | Not assigned | TCAG lab manager  | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Shearing (20 min total)   | 0.4                        | Not assigned | TCAG lab manager  | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Purification (40 min total)   | 0.8                        | Not assigned | TCAG lab manager  | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| End repair (40 min total)   | 0.8                        | Not assigned | TCAG lab manager  | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |

| Cost Items   | Quantity of Use per Sample |              |   | Price (CDN \$/unit) |              |   |
|--|----------------------------|--------------|---|---------------------|--------------|---|
|  | Estimate                   | Range        | Source                                  | Estimate            | Range        | Source  |
| A-tailing (40 min total)   | 0.8                        | Not assigned | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Adapter ligation (45 min total)  | 0.9                        | Not assigned | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| <b>Sequencing (Units: minutes)</b>   |                            |              |   |                     |              |   |
| Note: Total time per task was divided by the number of samples per lane. The number of samples per lane was assumed to be 16.  |                            |              |   |                     |              |   |
| HiSeq wash (30 min total)  | 1.9                        | Not assigned | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Sequencing prep (30 min total)   | 1.9                        | Not assigned | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| HiSeq post-run wash (45 min total)   | 2.8                        | Not assigned | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| Run quality control (15 min total)   | 0.9                        | Not assigned | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| cBot (30 min total)  | 1.9                        | Not assigned | TCAG lab manager                        | Confidential        | -7% to +7%   | TCAG lab manager, 2014                            |
| <b>Bioinformatics (Units: minutes)*</b>  |                            |              |   |                     |              |   |
| Note: resource use estimate is based on the instrument's capacity, 150 tests a month. The range corresponds to 10% variation.  |                            |              |   |                     |              |   |
| Data processing (1.5 FTE hour for 150 tests a month)   | 84.0                       | 75.6-92.4    | TCAG Bioinformatics manager             | Confidential        | -20% to +20% | TCAG Bioinformatics manager, 2014                 |
| <b>Bioinformatics Maintenance (Units: minutes)*</b>  |                            |              |   |                     |              |   |
| Note: One full time equivalent (FTE) hour to support one node per year was assumed. Resource use in minutes was calculated by multiplying the time to complete a job by the time needed to support the required number of nodes per job. For example, if a job required 3.2 hours and 1 nodes, then the resource use for the job is calculated as follows: 60 FTE minutes in an hour per year/(365*24 hours in a year)*1 hour to support 1 node*3.2 hours (i.e. number of minutes per year to support a 192 minute job on 1 node). The lower bound of resource use was based on 75% of the computation time and the upper bound was based on 125% of computation time. |                            |              |   |                     |              |   |
| Alignment/Remove Duplicates/Re-alignment – HiSeq Analysis Software (HAS)<br>3.2 hours (range: 2.4-4.0) 1 node  | 0.022                      | 0.016-0.027  | TCAG Bioinformatics analyst, Brown 2003 | Confidential        | -16% to +10% | Lab staff survey, SickKids wage information, 2015 |
| SNV/indel variant calling – HiSeq Analysis Software (HAS)<br>0.7 hours (range: 0.53-0.88) 1 node   | 0.005                      | 0.004-0.006  | TCAG Bioinformatics analyst, Brown 2003 | Confidential        | -16% to +10% | Lab staff survey, SickKids wage information, 2015 |
| CNV/SV calling – HAS<br>0.6 hours (range: 0.45-0.75) 1 node  | 0.004                      | 0.003-0.005  | TCAG Bioinformatics analyst, Brown 2003 | Confidential        | -16% to +10% | Lab staff survey, SickKids wage information, 2015 |
| Statistics – HAS<br>0.5 hours (range: 0.38-0.63) 1 node  | 0.003                      | 0.003-0.004  | TCAG Bioinformatics analyst, Brown 2003 | Confidential        | -16% to +10% | Lab staff survey, SickKids wage information, 2015 |
| Annotation (ANNOVAR)<br>3 hours (range: 2.3-3.8) 1 node  | 0.021                      | 0.015-0.026  | TCAG Bioinformatics analyst, Brown 2003 | Confidential        | -16% to +10% | Lab staff survey, SickKids wage information, 2015 |

| Cost Items  | Quantity of Use per Sample |                |   | Price (CDN \$/unit) |                 |   |
|---|----------------------------|----------------|---|---------------------|-----------------|---|
|   | Estimate                   | Range          | Source                                    | Estimate            | Range           | Source  |
| <b>Clinical Interpretation (Units: minutes)</b>   |                            |                |   |                     |                 |   |
| Clinical classification of primary variants<br><br>15 minutes base plus 30 minutes per variant. On average, 2 variants are found (range: 0-4) | 75                         | 15-135         | DPLM Associate Director, Genomic Analysis | Confidential        | -20% to +20%    | Expert opinion, 2015                          |
| Clinical classification of secondary variants<br><br>30 minutes per case (range: 20-40), found in 4% of cases (range: 3-5%)                   | 1.2                        | 0.6-2.0        | DPLM Associate Director, Genomic Analysis | Confidential        | -20% to +20%    | Expert opinion, 2015                          |
| <b>Report Writing (Units: minutes)</b>  |                            |                |   |                     |                 |   |
| Addressing primary variants<br><br>15 minutes base plus 15 minutes per variant. On average, 2 variants are found (range: 0-4)                 | 45                         | 15-75          | DPLM Associate Director, Genomic Analysis | Confidential        | -20% to +20%    | Expert opinion, 2015                          |
| Addressing secondary variants<br><br>30 minutes per case (range: 20-40), found in 4% of cases (range: 3-5%)                                   | 1.2                        | 0.6-2.0        | DPLM Associate Director, Genomic Analysis | Confidential        | -20% to +20%    | Expert opinion, 2015                          |
| <b>Large Equipment</b>  |                            |                |   |                     |                 |   |
| Illumina HiSeq X  | 1/all tests                | Not applicable | TCAG Lab manager                          | 1150000             | 1035000-1265000 | TCAG Lab Manager, 2015                        |
| 1-year service contract   | 1/all tests                | Not applicable | TCAG Lab Manager                          | 75000               | 107123-130928   | TCAG Lab Manager, 2015                        |
| Agilent BioAnalyzer/Tape station  | 1/all tests                | Not applicable | Agilent representative                    | 38500               | 34000-43000     | Agilent representative/TCAG Lab Manager, 2015 |
| <b>Small Equipment</b>  |                            |                |   |                     |                 |   |
| Tube microcentrifuge  | 1/all tests                | Not applicable | TCAG lab manager                          | 2250                | 2000-2500       | TCAG lab manager, 2014                        |
| Plate microcentrifuge   | 1/all tests                | Not applicable | TCAG lab manager                          | 5000                | 4500-5500       | TCAG lab manager, 2014                        |
| Thermomixer   | 1/all tests                | Not applicable | TCAG lab manager                          | 5000                | 4500-5500       | TCAG lab manager, 2014                        |
| Vortex  | 1/all tests                | Not applicable | TCAG lab manager                          | 450                 | 400-500         | TCAG lab manager, 2014                        |
| Pipette sets  | 2/all tests                | Not applicable | TCAG lab manager                          | 1600                | 1400-2000       | TCAG lab manager, 2014                        |

| Cost Items  | Quantity of Use per Sample |                |   | Price (CDN \$/unit) |               |                                   |
|---|----------------------------|----------------|---|---------------------|---------------|-----------------------------------|
|   | Estimate                   | Range          | Source                                    | Estimate            | Range         | Source                            |
| Magnet particle concentrator for tubes  | 1/all tests                | Not applicable | TCAG lab manager                          | 700                 | 630-770       | TCAG lab manager, 2014            |
| Thermocyclers   | 2/all tests                | Not applicable | TCAG lab manager                          | 3000                | 2700-3300     | TCAG lab manager, 2014            |
| <b>Supplies</b>   |                            |                |   |                     |               |                                   |
| Shipping & Handling   | 1                          | Not assigned   | TCAG lab manager                          | 51.5                | 46.37-56.67   | FedEx, 2013                       |
| Illumina Nano DNA library prep  | 1                          | Not assigned   | TCAG lab manager                          | 30.0                | 27.0-33.0     | TCAG lab manager, 2015            |
| Other library prep consumables per sample   | 1                          | Not assigned   | TCAG lab manager                          | 50.0                | 45.00-55.00   | TCAG lab manager, 2015            |
| Sequencing reagents (1 lane per sample)   | 1                          | Not assigned   | TCAG lab manager                          | 1290.0              | 1161.0-1419.0 | TCAG lab manager, 2015            |
| <b>Follow-up (proportion of cases)</b>  |                            |                |   |                     |               |                                   |
| Note: Price for qPCR test included three tests, proband and two parents   |                            |                |   |                     |               |                                   |
| Sanger sequencing (two tests per person, proband and two parents)   | 0.5                        | Not assigned   | DPLM Associate Director, Genomic Analysis | 37.77               | 35.31-40.24   | Blons et al. 2013                 |
| qPCR followup (proband and two parents)   | 0.1                        | Not assigned   | Team Leader, Molecular Genetics           | 671.71              | 604.54-738.88 | Expert opinion, 2013              |
| <b>Bioinformatics*</b>  |                            |                |   |                     |               |                                   |
| <b>Bioinformatics File Storage (Units: GB/year)</b>   |                            |                |   |                     |               |                                   |
| Notes: 1. Resource use volume was calculated by multiplied the file size by the storage time (in years).<br>2. Price was given in dollars per GB per year.  |                            |                |   |                     |               |                                   |
| trimmed fastq<br>file size: 120 GB; average storage time: 9 months (range: 6-12)  | 90                         | 60-120         | TCAG Bioinformatics analyst               | 0.4                 | 0.36-0.45     | TCAG Bioinformatics manager, 2014 |
| final rem-dup, recalibrated, locally re-aligned BAM file<br>file size: 80 GB; average storage time: 9 months (range: 6-12)  | 60                         | 40-80          | TCAG Bioinformatics analyst               | 0.4                 | 0.36-0.45     | TCAG Bioinformatics manager, 2014 |
| <b>Bioinformatics Computation Use (Units: CPU time per hour)</b>  |                            |                |   |                     |               |                                   |
| Notes: 1. Resource use volume use was calculated by multiplying the number of jobs by the number of cores per job and time (hours) required to complete a job. 25% (range 0 to 50%) was added to account for additional processing time to avoid operating at full capacity.<br>2. The cost of each compute node to TCAGE was \$26804, including warranty. A straight line depreciation method over 5 years was applied and the price per CPU per year was calculated to be \$5,360.80. This price was converted to price per CPU per hour by dividing \$5360.80 by (365*24). An exception was Annotation, to which a Scalar price (see Appendix 3) was applied |                            |                |   |                     |               |                                   |

| Cost Items   | Quantity of Use per Sample |         |                             | Price (CDN \$/unit) |             |                                   |
|--|----------------------------|---------|-----------------------------|---------------------|-------------|-----------------------------------|
|  | Estimate                   | Range   | Source                      | Estimate            | Range       | Source                            |
| Alignment/Remove Duplicates/Re-alignment – HiSeq Analysis Software (HAS)<br>1 job, 40 cores per job, 3.2 hours to complete | 160                        | 128-192 | TCAG Bioinformatics analyst | 0.612               | 0.551-0.673 | TCAG Bioinformatics analyst, 2016 |
| SNV/indel variant calling – HAS<br>1 job, 40 cores per job, 0.7 hours to complete  | 35                         | 28-42   | TCAG Bioinformatics analyst | 0.612               | 0.551-0.673 | TCAG Bioinformatics analyst, 2016 |
| CNV/SV calling –HAS<br>1 job, 40 cores per job, 0.6 hours to complete  | 30                         | 24-36   | TCAG Bioinformatics analyst | 0.612               | 0.551-0.673 | TCAG Bioinformatics analyst, 2016 |
| Statistics – HAS<br>1 job, 40 cores per job, 0.5 hours to complete   | 25                         | 20-30   | TCAG Bioinformatics analyst | 0.612               | 0.551-0.673 | TCAG Bioinformatics analyst, 2016 |
| Annotation (ANNOVAR)<br>1 job, 16 cores per job, 3 hours to complete   | 60                         | 48-72   | TCAG Bioinformatics analyst | 0.011               | 0.010-0.012 | Scalar quote, 2014                |

Abbreviations: WGS, Whole Genome Sequencing; TCAG, The Centre for Applied Genomics ; DPLM, The Department of Paediatric Laboratory Medicine; FTE, Full-time equivalent; qPCR, Real-time polymerase chain reaction; MIS, Management Information Systems; GATK, Genome Analysis Toolkit; SNV, Single nucleotide variant.