

**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**

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Report No. 2016-02.2

Date: September 21, 2016

Available at: <https://lab.research.sickkids.ca/task/reports-theses/>

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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
Labour						
Specimen Preparation (Units: minutes)						
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
DNA Extraction (Units: minutes)						
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
Microarray sample processing (Unites: minutes)						
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
Analysis (Units: minutes)						
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
Clinical interpretation and report writing (Units: minutes)						
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
Clinical interpretation (Units: minutes)						
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
Large Equipment						
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
Supplies						
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
Follow-up (proportion of cases)						
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
Labour						
Specimen Preparation (Units: minutes)						
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
Library preparation (Units: minutes)						
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
Sequencing (Units: minutes)						
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
Bioinformatics (Units: minutes)						
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
Bioinformatics Maintenance (Units: minutes)						
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 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) 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) 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) 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
Clinical Interpretation (Units: minutes)						
Clinical classification of primary variants 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 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
Report Writing (Units: minutes)						
Addressing primary variants 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 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
Large Equipment						
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/ TCAG Lab Manager, 2015
Small Equipment						
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
Supplies						
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
Follow-up (proportion of cases)						
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
Bioinformatics						
Bioinformatics File Storage (Units: GB per year)						
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 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 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 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
Bioinformatics Computation Use (Units: CPU time per hour)						
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. 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 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) 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 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) 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) 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
Labour						
Specimen Preparation (Units: minutes)						
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
Library preparation (Units: minutes)						
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
Sequencing (Units: minutes)						
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
Bioinformatics (Units: minutes)						
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
Bioinformatics Maintenance (Units: minutes)						
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 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) 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 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 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) 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) 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
Clinical Interpretation (Units: minutes)						
Clinical classification of primary variants 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 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
Report Writing (Units: minutes)						
Addressing primary variants 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 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
Large Equipment						
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
Small Equipment						
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
Supplies						
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
Follow-up (proportion of cases)						
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
Bioinformatics						
Bioinformatics File Storage (Units: GB/year)						
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 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 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 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
Bioinformatics Computation Use (Units: CPU time per hour)						
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. 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 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) 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 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) 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) 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) 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
Labour						
Specimen Preparation (Units: minutes)						
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
Library preparation (Units: minutes)						
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
Sequencing (Units: minutes)						
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
Bioinformatics (Units: minutes)*						
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
Bioinformatics Maintenance (Units: minutes)*						
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) 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) 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 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 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) 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
Clinical Interpretation (Units: minutes)						
Clinical classification of primary variants 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 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
Report Writing (Units: minutes)						
Addressing primary variants 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 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
Large Equipment						
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
Small Equipment						
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
Supplies						
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
Follow-up (proportion of cases)						
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
Bioinformatics*						
Bioinformatics File Storage (Units: GB/year)						
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 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 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
Bioinformatics Computation Use (Units: CPU time per hour)						
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. 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) 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 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 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 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) 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.