Table 1 Inclusion and exclusion criteria for rWES study

Inclusion criteria	Exclusion criteria
Pediatric patient (0–18 years)	Copy-number variant responsible for phenotype
Likely monogenic disorder	Previous genetic sequencing test (completed)
Complexity	Single-gene disorder unlikely, e.g., isolated congenital heart disease
• Multiple organ systems involved and/or	Secure clinical diagnosis of a monogenic disorder, e.g. Apert syndrome, CHARGE syndrome
• Severe condition with high morbidity and mortality and/or	
• Severe limitations on function and activities of daily living	
High acuity:	
• Inpatient in an intensive-care unit or	
• Other medical indication (e.g., awaiting transplantation or acute neurological deterioration)	

rWES, rapid singleton whole-exome sequencing.

Table 2 Demographics, indications for testing, referral sources, diagnostic and clinical utility, and performance metrics for rWES cohort compared with previously published sWES infant cohort[1]

Characteristic	sWES infant cohort (2014–2015) N = 80	rWES cohort (2016–2017) N = 40	P value
Sex			NS
Male	50 (62.5%)	22 (55%)	
Female	30 (37.5%)	18 (45%)	
Age at enrollment			
0–6 m	37 (46%)	30 (75%) P o 0.001	P o 0.001
6 m	43 (54%)	10 (25%)	
Median (IQR)	271 (77–409)	28 (12–204)	
Parental consanguinity	17 (21%)	8 (20%)	NS
Symptoms present at birth	77 (96%)	28 (70%)	P o 0.001
Principal phenotypic feature			
Congenital abnormalities and dysmorphic features	43 (54%)	9 (22%)	P = 0.00
Neurometabolic disorder	19 (24%)	17 (43%)	5
Other (e.g., gastrointestinal, renal)	18 (22%)	14 (35%)	
Referral source			
Inpatient consultation	44 (55%)	36 (90%)	P o 0.001
• **NICU**	33 (41%)	21 (53%)	
• **PICU**	4 (5%)	10 (25%)	
• **Other inpatient consultation**	7 (8%)	5 (12%)	
Outpatient consultation	36 (45%)	4 (10%)	
Genomic testing initiated during first hospital admission	8 of 44 inpatient referrals (18%)	34 of 36 inpatient referrals (94%)	P o 0.001
Time to ascertainment (tertiary hospital presentation to enrollment), median (IQR)	149 days (13–909)	12 days (2–209)	P o 0.001
Time to result (enrollment to report), median (IQR)	136 days (71–277)	16 days (9–109)	P o 0.001

Result returned during first hospital admission	0 of 44 inpatient referrals	28 of 36 inpatient referrals (78%)	P o 0.001
Diagnostic yield	58%	52.5%	
Change in patient management	16 (20%)	14 (35%)	ND
• **Medication started/adjusted**	7	4	
• **Medication stopped**	1	1	
• **Surveillance initiated**	9	7	
• **Surveillance stopped**	1	0	
• **Avoidance of tissue biopsy**	3	3	
• **Redirection to palliative care**	0	2	
Mortality	9 (11%)	9 (23%)	ND
Symptom resolution/diagnosis of nonmonogenic disorder on follow-up	7 (8.75%)	6 (15%)	ND

IQR, interquartile range; ND, not determined (insufficient power); NICU, neonatal intensive-care unit; NS, not significant; PICU, pediatric intensive-care unit; rWES, rapid singleton whole-exome sequencing; sWES, whole-exome sequencing with standard turnaround times.

Table 3 Summary of costs (in AU$) associated with diagnostic assessments and investigations in patients receiving rWES compared with our previously published infant cohort receiving sWES[15]

	sWES infant cohort 2014–2015 Usual care + conventional sequencing tests, AU$ n=40	sWES infant cohort 2014–2015 Usual care + sWES, AU$ n=40	rWES cohort 2016–2017 AU$ n=40
Clinical assessments			
Clinical geneticist	22,239.24	32,452.97	6,681.54
Genetic counselor	0	14,914.07	1,527.60
Subspecialist (OP)	9,187.73	9,187.73	240.00
Pathology			
Anatomical pathology	14,409.32	14,409.32	3,277.81
Basic biochemistry	4,289.12	4,289.12	2,204.81
Complex biochemistry	9,437.04	9,437.04	17,767.52
Serology/immunology	1,520.72	1,520.72	2,145.41
Imaging	50,165.45	50,165.45	35,198.15
Electrophysiology	22,027.97	22,027.97	20,886.90
Genetic tests			
SNP microarray	23,880.00		23,880.00 23,880.00
Nonsequencing tests (e.g., methylation)	2,663.40	3,863.40	6,403.20
Single-gene and panel sequencing	22,488.39	0	0
WES	0	80,000.00	157,960.00
Other			
Medical photography	809.62	809.62	0
DNA extraction/ sample shipping	2,541.00	440.00	1,710.00
OT/anesthesia costs	3,693.53	3,693.53	1,260.00
Total cost	189,352.53	271,090.94	281,142.94
Patients diagnosed	7	25	21
Cost per diagnosis 95% CI	27,050.36 (15,365.51–68,529.77)	10,843.60 (7,487.62–14,090.02)	13,387.76 (9,268.68–17,506,84

CI, confidence interval; OP, outpatient; OT, operating theater; rWES, rapid singleton whole-exome sequencing; SNP, single-nucleotide polymorphism; sWES, wholeexome sequencing with standard turnaround times.

Figure 1 Chronological case-by-case time to report, demonstrating relative contribution of the steps in the rWES laboratory pathway to turnaround times. A timeline for the study is provided on the X-axis, demonstrating the increase in throughput over time, and the principal interventions implemented to reduce time to report