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Feasibility of Ultra-Rapid Exome Sequencing in Critically Ill Infants and Children With Suspected Monogenic Conditions in the Australian Public Health Care System

Australian Genomics Health Alliance Acute Care Flagship

IMPORTANCE Widespread adoption of rapid genomic testing in pediatric critical care requires robust clinical and laboratory pathways that provide equitable and consistent service across health care systems.

OBJECTIVE To prospectively evaluate the performance of a multicenter network for ultra-rapid genomic diagnosis in a public health care system.

DESIGN, SETTING, AND PARTICIPANTS Descriptive feasibility study of critically ill pediatric patients with suspected monogenic conditions treated at 12 Australian hospitals between March 2018 and February 2019, with data collected to May 2019. A formal implementation strategy emphasizing communication and feedback, standardized processes, coordination, distributed leadership, and collective learning was used to facilitate adoption.

EXPOSURES Ultra-rapid exome sequencing.

MAIN OUTCOMES AND MEASURES The primary outcome was time from sample receipt to ultra-rapid exome sequencing report. The secondary outcomes were the molecular diagnostic yield, the change in clinical management after the ultra-rapid exome sequencing report, the time from hospital admission to the laboratory report, and the proportion of laboratory reports returned prior to death or hospital discharge.

RESULTS The study population included 108 patients with a median age of 28 days (range, 0 days to 17 years); 34% were female; and 57% were from neonatal intensive care units, 33% were from pediatric intensive care units, and 9% were from other hospital wards. The mean time from sample receipt to ultra-rapid exome sequencing report was 3.3 days (95% CI, 3.2-3.5 days) and the median time was 3 days (range, 2-7 days). The mean time from hospital admission to ultra-rapid exome sequencing report was 17.5 days (95% CI, 14.6-21.1 days) and 93 reports (86%) were issued prior to death or hospital discharge. A molecular diagnosis was established in 55 patients (51%). Eleven diagnoses (20%) resulted from using the following approaches to augment standard exome sequencing analysis: mitochondrial genome sequencing analysis, exome sequencing–based copy number analysis, use of international databases to identify novel gene–disease associations, and additional phenotyping and RNA analysis. In 42 of 55 patients (76%) with a molecular diagnosis and 6 of 53 patients (11%) without a molecular diagnosis, the ultra-rapid exome sequencing result was considered as having influenced clinical management. Targeted treatments were initiated in 12 patients (11%), treatment was redirected toward palliative care in 14 patients (13%), and surveillance for specific complications was initiated in 19 patients (18%).

CONCLUSIONS AND RELEVANCE This study suggests feasibility of ultra-rapid genomic testing in critically ill pediatric patients with suspected monogenic conditions in the Australian public health care system. However, further research is needed to understand the clinical value of such testing, and the generalizability of the findings to other health care settings.

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Supplemental content

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Group Information: The authors/members of the Australian Genomics Health Alliance Acute Care Flagship are listed at the end of the article.

Corresponding Author: Zornitza Stark, DM, Victorian Clinical Genetics Services, Murdoch Children's Research Institute, 50 Flemington Rd, Parkville, VIC 3052, Australia (zornitza.stark@vcgs.org.au).

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More than 10 single-center studies including more than 600 critically ill neonatal and pediatric patients with suspected genetic conditions have demonstrated genomic testing has a high diagnostic yield and influences clinical management.[1-9] In the critical care setting, genomic testing results need to be delivered rapidly to be useful and the mean turnaround times achieved by nascent rapid testing programs have ranged from 7 to 23 days. Although studies of rapid genomic testing have primarily included infants in neonatal intensive care units (NICUs),[1,3-5,9] a minority of studies have included other critically ill children such as those in pediatric intensive care units (PICUs).[2,6-8] These early results from multiple centers have created momentum for broader implementation of rapid genomic sequencing in critically ill neonatal and pediatric patients worldwide.

Translating the experience of academic single-center studies into implementation across health care systems requires the development of robust clinical and laboratory pathways to deliver rapid genomic testing reliably and consistently. Furthermore, the successful spread and scaling up of innovations in health care systems is complex, and necessitates both structure and adaptability to the local context, benefitting from a participatory culture, distributed leadership, transparent assessment of outcomes, collective learning, and adaptation.[10] Developing purposeful implementation strategies that recognize the iterative, nonlinear, and multicomponent nature of change has the potential to streamline the process of scaling up rapid diagnostic programs across health care systems, preventing costly trial and error at multiple sites.[11]

The objective of this study was to examine the feasibility of providing ultra-rapid genomic testing for critically ill neonatal and pediatric patients with suspected monogenic conditions across multiple centers in Australia.

Key Points

Question Can ultra-rapid genomic testing be performed for critically ill pediatric patients in a public health care system?

Findings This multisite descriptive feasibility study included 12 Australian hospitals and 2 laboratories. Among the 108 critically ill infants and children with suspected monogenic conditions who had ultra-rapid genomic testing, the mean time to genomic test report was 3.3 days and the molecular diagnostic yield was 51%.

Meaning This study suggests feasibility of ultra-rapid genomic testing in a public setting for critically ill pediatric patients. However, further research is needed to understand its clinical value.

Methods

The Australian Genomics Acute Care study received human research ethics committee approval from Melbourne Health (HREC/16/MH251). Parents provided written informed consent for participation in the study.

Study Design and Participants

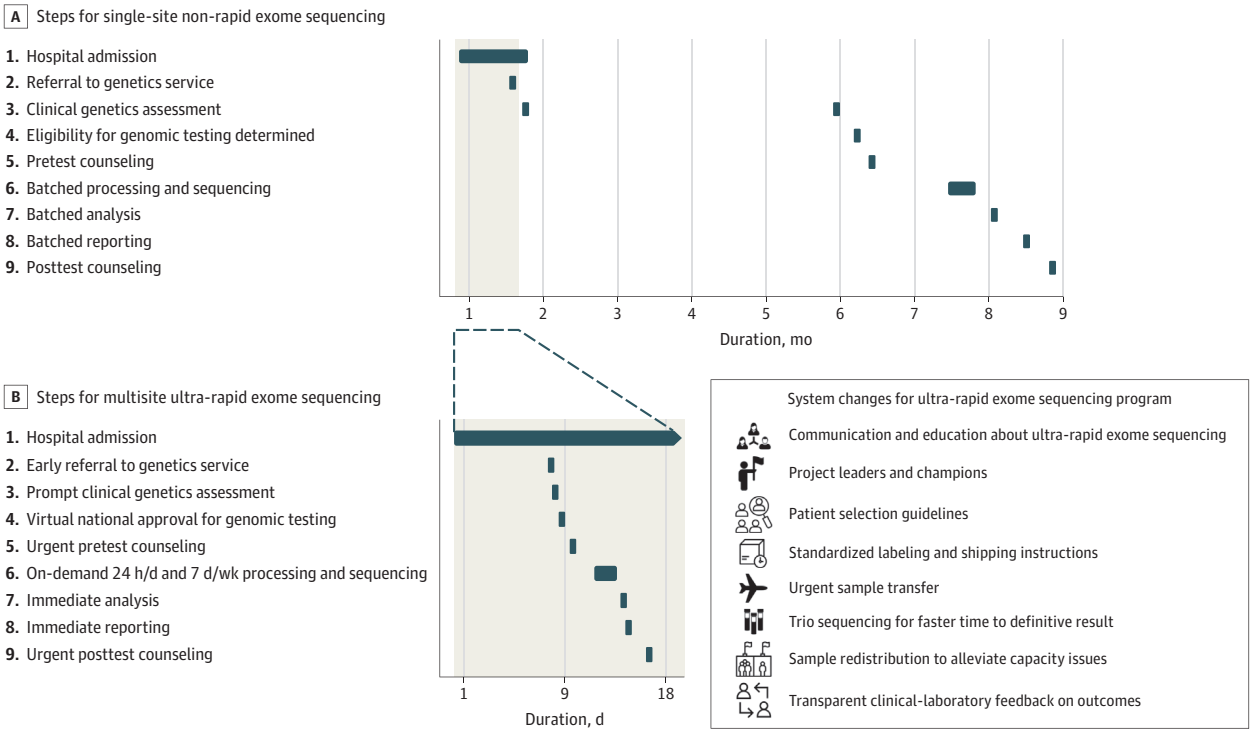
The study adopted a hybrid implementation-effectiveness study design, with simultaneous evaluation of processes and outcomes.[12] An implementation strategy was developed based on prior experience with rapid exome sequencing (target results in <21 days) implementation at 2 Australian centers[8] and using the Consolidated Framework for Implementation Research,[13] which is a theory-informed set of constructs associated with effective implementation. Twelve participating hospitals and 2 laboratories formed a network aiming to deliver genomic results within 5 days. Professionals at the participating sites were surveyed to determine the preferred clinical service delivery model and implementation readiness.[14]

A multidisciplinary working group developed the patient selection criteria and the clinical and laboratory pathways. Clinical geneticists acted as formal implementation leaders at each site. Process communication was addressed through the development of standard operating procedures for patient recruitment, test ordering, sample labeling, tracking, and transportation. Structured electronic communication procedures were implemented to facilitate the timely exchange of information between the clinical and laboratory teams. The ultra-rapid exome sequencing report and the turnaround time for each case were distributed to the study leadership group, and the summary statistics were provided bimonthly to the entire working group. Components of the implementation strategy were mapped to the Consolidated Framework for Implementation Research[13] (eTable 1 in the Supplement).

Recruitment occurred prospectively between March 2018 and February 2019, with data collected to May 2019. The 12 tertiary hospitals included 5 women's hospitals, 3 women's and children's hospitals, and 4 children's hospitals. Of the latter, 2 were quaternary hospitals caring for complex patients from throughout Australia and overseas. The total number of NICU beds was 451 and the total number of PICU beds was 135. Patients were eligible if admitted to a participating NICU or PICU and had been referred to the clinical genetics service for a suspected monogenic condition. Other hospitalized patients were considered for inclusion if a rapid result was likely to alter clinical management (eg, organ transplant decisions). Patients were ineligible if (1) a monogenic etiology was considered unlikely (eg, isolated congenital diaphragmatic hernia); (2) a secure clinical diagnosis (such as Apert syndrome) was made; or (3) death or hospital discharge were imminent.

An expert panel of study investigators (S.L., M.W., C.P., C.P.B., J.P., M.F.B., T.R., J.C., and Z.S.) discussed referrals electronically to determine study eligibility. Other clinicians participated on an as-needed basis (S.A.S., D.M., E.P.K., K.B.H., and S.M.W.). When panel members disagreed about eligibility, recruitment proceeded with majority approval. A core clinical data set was collected at recruitment (including Human Phenotype Ontology terms) and was managed using REDCap, which is a secure, web-based application designed to support data capture for research studies.[15] Chromosomal microarray was performed prior to enrollment if the likelihood of a chromosomal condition was considered high by the referring teams (eg, in patients with multiple congenital abnormalities) and concurrently with ultra-rapid

Figure 1. Steps for Non-Rapid Genomic Testing Compared With Ultra-Rapid Genomic Testing



exome sequencing when the pretest probability was considered low. If a mitochondrial condition was suspected, rapid mitochondrial genome sequencing was performed concurrently with ultra-rapid exome sequencing after obtaining specific approval from the panel. The steps for the diagnostic ultra-rapid exome sequencing pathway appear in **Figure 1** and are compared with non-rapid testing.

Exome Sequencing, Data Analysis, and Interpretation

Ultra-rapid exome sequencing was performed in both the parents and the child (trio) when possible at 2 laboratories accredited by the National Association of Testing Authorities. The sequencing and bioinformatics analyses are described in eMethods 1 in the Supplement. Variants relevant to patient phenotype were classified based on the standards of the American College of Medical Genetics and Genomics.[16] All pathogenic and likely pathogenic variants identified in this study have been deposited in ClinVar (submission IDs: SUB6379721, SCV000929966, and SCV000929967; SUB7027998 and SUB7195751 are still under review).

Outcome Measures

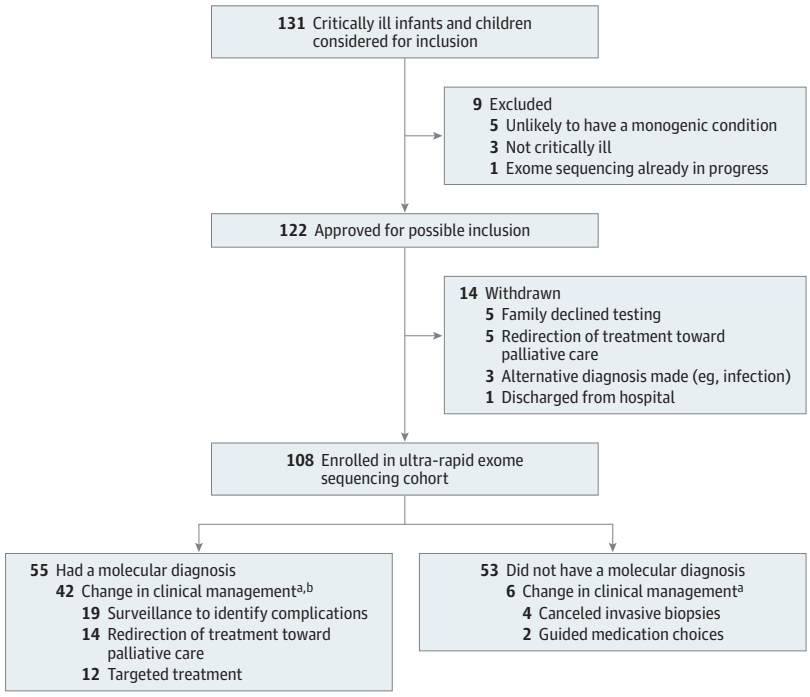
The primary outcome was time from sample receipt to ultra-rapid exome sequencing report. The secondary outcomes were the molecular diagnostic yield, the change in clinical management after the ultra-rapid exome sequencing report, the time from hospital admission to the laboratory report, and the proportion of laboratory reports returned prior to death or hospital discharge. The time from hospital admission to laboratory report was measured in calendar days and included the following time points: referral to clinical genetics service, clinical genetics assessment, patient proposal for ultra-rapid exome sequencing, approval by the expert panel, consent, transportation, and laboratory report issue.

The changes in clinical management were collected from the medical records by the clinical geneticist site leaders (M.W., C.P., C.P.B., J.P., S.A.S., E.I.K., M.E., A.V., and Z.S.) 3 months after the laboratory report using a structured data collection instrument (eMethods 2 in the Supplement). These changes in clinical management were grouped into 3 main categories: targeted treatments, redirection of treatment toward palliative care, and targeted surveillance (investigations and subspecialist referrals aimed at known complications). Referring clinical geneticists subjectively rated the usefulness of ultra-rapid exome sequencing using a 5-point scale ranging from "very useful" to "not useful at all."

Statistical Analysis

Descriptive statistics were used for participant characteristics, referral source, the duration of the clinical and laboratory components of the diagnostic trajectory, the molecular diagnostic yield, and the changes in clinical management after the ultra-rapid exome sequencing report. The 95% CIs for the means of the nonnormally distributed quantitative results (the normality of the data was assessed using the Shapiro-Wilk test) were calculated using bias-corrected, accelerated bootstrapping from the boot package version 1.3-24 in R version 3.6.2 (R Foundation for Statistical Computing) with a 0.95 confidence limit and 10 000 iterations. No patients were lost to follow-up and all data collection was complete.

Figure 2. Recruitment and Summary of Ultra-Rapid Exome Sequencing Cohort



[a] Occurred 3 months after the ultra-rapid exome sequencing report and was considered by clinicians to have been influenced by the genomic report.

[b] Some patients had changes in management from more than 1 category.

Results

Participant Demographics and Indications for Testing

The program considered 131 patients over 11 months. Of these 131 patients, the expert panel excluded 9 (7%) because they did not meet the study criteria, and 14 (11%) were approved and subsequently withdrawn by the referring teams (**Figure 2**). Of the 108 patients approved for ultra-rapid exome sequencing, panel members disagreed regarding the likelihood of a monogenic condition in 15 patients (14%).

The median age of participants was 28 days (range, 0 days-17 years); 34% were female; 62 patients (57%) were admitted to NICUs, 36 patients (33%) were admitted to PICUs, and 10 patients (9%) were from other hospital wards. The most common clinical indication for ultra-rapid exome sequencing was neurological signs and symptoms (33%) such as hypotonia or seizures (**Table 1**). Seventy-five patients (69%) originated from 3 pediatric hospitals. In 105 cases (97%), patients were analyzed together with both parents (trio); in 3 cases, patients were analyzed together with only 1 parent (duo) due to the unavailability of the other parent.

Mitochondrial genome testing occurred concurrently with ultra-rapid exome sequencing in 7 patients (6%). The mean number of clinical geneticist inpatient consultations was 2.8 (range, 1-7 consultations). Genetic counselors were involved with 95 families (88%), and the mean number of consultations was 2.0 (range, 1-6 consultations).

Patient characteristics, the indications for testing, the molecular diagnostic yield, the changes in clinical management after the ultra-rapid exome sequencing report, and the time from hospital admission to the ultra-rapid exome sequencing report appear in Table 1 and are compared against the previously published Australian rapid exome sequencing study,[8] which aimed to deliver results within 21 days at 2 pediatric hospitals.

Primary End Point: Time From Sample Receipt to Ultra-Rapid Exome Sequencing Report

One hundred and two reports (94%) were issued within the performance target of 5 calendar days. The mean time from sample receipt to ultra-rapid exome sequencing report was 3.3 days (95% CI, 3.2-3.5 days) and the median time was 3 days (range, 2-7 days). The mean time from hospital admission to ultra-rapid exome sequencing report was 17.5 days (95% CI, 14.6-21.1 days). The longest component was time from hospital admission to clinical genetics referral, which had a mean time of 8.1 days (95% CI, 6.0-10.8 days). The mean sample transportation time was 1.6 days (95% CI, 1.4-1.9 days) despite the furthest hospital being 1600 km away from the laboratory site. Laboratory 1 performed 94 tests and laboratory 2 performed 14 tests. Data on time from hospital admission to ultra-rapid exome sequencing report, broken down per patient and per referral site, appear in eTable 2 in the Supplement.

Secondary End Points

Molecular Diagnostic Yield

A total of 56 molecular diagnoses were made for 55 patients (51%) (Table 1 and **Table 2**). Routine ultra-rapid exome sequencing trio analyses resulted in 45 molecular diagnoses, with an additional 11 molecular diagnoses made through

Table 1. Comparison of Multisite Ultra-Rapid Exome Sequencing Cohort vs Rapid Exome Sequencing Cohort From Prior Study[8]

	Participants by Speed of Exome Sequencing[a]	
	Ultra-Rapid Cohort (2018-2019; n = 108)	Rapid Cohort[8] (2016-2017; n = 40)
Cohort characteristics[b]		
Sex		
Male	71 (66)	22 (55)
Female	37 (34)	18 (45)
Referral source		
NICU	62 (57)	21 (53)
PICU	36 (33)	10 (25)
Other hospital wards	10 (9)	5 (12)
Outpatient	0	4 (10)
Age group, mo		
0-6	87 (81)	30 (75)
>6	21 (19)	10 (25)
Age, median (range)	28 d (0 d-17 y)	28 d (3 d-4 y)
Parental consanguinity	18 (17)	8 (20)
Symptoms present at birth	87 (81)	28 (70)
Test indications		
Neurological	36 (33)	14 (35)
Syndromic	28 (26)	11 (27.5)
Metabolic	13 (12)	2 (5)
Cardiovascular	9 (8)	3 (7.5)
Respiratory	5 (5)	1 (2.5)
Renal	5 (5)	1 (2.5)
Other single system	10 (9)	8 (20)
Outcomes		
Time to initiation of test, mean (95% CI), d	12.7 (10.0-16.2)	34.0 (22.4-53.6)
Time from sample receipt to report, mean (95% CI), d	3.3 (3.2-3.5)	24.7 (19.2-34.4)
Time from hospital admission to report, mean (95% CI), d	17.5 (14.6-21.1)	57.8 (44.1-78.0)
Report returned prior to hospital discharge or death	93 (86)	28 (78)[c]
Molecular diagnosis made[d]	55 (51)	21 (52.5)
Clinical management changed after genomic report[e]	48 (44)	14 (35)
Report formed part of palliative care decision, No./total No. (%)	12/21 (57)	2/9 (22)
Died	21 (19)	9 (23)

Abbreviations: NICU, neonatal intensive care unit; PICU, pediatric intensive care unit.

[a] Data are expressed as No. (%) unless otherwise indicated. Percentages within categories may not sum to 100 due to rounding.

[b] Race/ethnicity data were collected using nonstandard US categories; most families identified as Australian.

[c] Of 36 patients in the cohort who had testing initiated during hospital stay.

[d] Established by identifying pathogenic or likely pathogenic variants in the genomic data.

[e] Measured after 3 months.

extended approaches. Of these 11 molecular diagnoses, 7 were made as part of the original analysis, including 3 through hypothesis-driven identification of copy number variants affecting single genes from the exome sequencing data (10-kb homozygous deletion of *NEU1* causing sialidosis type 1, 12-kb deletion in *ABCC6* in *trans* with pathogenic variant causing arterial calcification of infancy, and 12-kb hemizygous deletion in *ATP7A* causing Menkes disease). Two molecular diagnoses of Pearson syndrome due to mitochondrial deletions were achieved through concurrent mitochondrial genome sequencing.[17]

Two further molecular diagnoses were made by submitting novel gene candidates to GeneMatcher[18] (an international data sharing platform) and matching to multiple other cases in real time, enabling establishment of novel gene-disease associations and diagnostic reporting.[19] Four diagnoses were initially reported as variants of uncertain significance but upgraded with additional data, including publication of another novel gene, *IREB2*, 6 months later.[20,21] Rapid RNA studies confirmed the pathogenicity of a homozygous splice-site *ASNS* variant in 10 days, and 2 other variants of uncertain significance were reclassified as likely pathogenic after further phenotyping during a period of 6 months.[22] One patient with pontocerebellar hypoplasia was found to have an unbalanced translocation on concurrent chromosomal microarray, and was not included in the ultra-rapid exome sequencing diagnostic yield.

Among 35 of the 62 patients enrolled from the NICU, the molecular diagnostic yield was 56.0% (95% CI, 41.9%-66.1%). Among 17 of the 36 patients enrolled from the PICU, the molecular diagnostic yield was 47.0% (95% CI, 27.8%-66.1%). Among 3 of the 10 patients enrolled from other hospi-

Table 2. Presenting Clinical Features, Ultra-Rapid Exome Sequencing Results, and Subsequent Clinical Course in a Representative Selection of Patients

Presenting clinical features of patients[a]	Findings from the ultra-rapid exome sequencing report	Subsequent clinical course
Infant aged 6 mo admitted to PICU with anuric renal failure. Ultrasonography revealed increased renal echogenicity.	Primary hyperoxaluria type 1, OMIM #259900, caused by homozygous pathogenic variant in *AGXT* NM_000030.2: c.364C>T, p. (Arg122*)	Switched from peritoneal dialysis to hemodialysis to prevent oxalate deposition in bones, eyes, heart, and peripheral nerves. Listed for combined liver and renal transplant. Screened at-risk relatives.
Infant aged 85 d admitted to PICU with high-output congestive heart failure.	Arterial calcification 2, generalized, of infancy, OMIM #614473, caused by pathogenic variants in *ABCC6* NM_001171.5: c.3421C>T, p.(Arg1141*) and chr16p13.11(16,48,791-16,260,443)x1	Clinical diagnosis made through imaging prior to ultra-rapid exome sequencing report and treatment with etidronate started. Molecular diagnosis not considered to have contributed to clinical management.
Term neonate admitted to NICU for ventilatory support. Had severe hydrops and subtle joint contractures.	Lethal congenital contracture syndrome 11, OMIM #617194, caused by homozygous pathogenic variant in *GLDN* NM_181789.4: c.980_981delCT, p.(Ser327Cysfs*2)	Clinical management redirected toward palliative care within 24 h of ultra-rapid exome sequencing report disclosure.
Term neonate admitted to NICU for ventilatory support with extensive interstitial pulmonary abnormalities, but without evidence of sepsis or meconium aspiration.	No pathogenic or likely pathogenic variants identified	Canceled planned lung biopsy because probability of underlying monogenic condition lowered. Improved condition with supportive clinical management.
Child aged 4 y admitted to PICU with severe acute rhabdomyolysis on background of episodic ataxia and mild global developmental delay.	Metabolic encephalomyopathic crises, recurrent, with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration, OMIM #616878, caused by homozygous pathogenic variant in *TANGO2* NM_152906.6: c.94C>T, p.(Arg32*)	Commenced vitamin supplementation and metabolic clinical management plan put in place to prevent further crises. Referral to cardiology service for arrhythmia surveillance.
Term neonate admitted to NICU with cardiomyopathy, seizures, hearing impairment, bull's eye maculopathy, and bulbar palsy.	No pathogenic or likely pathogenic variants identified	Probability of underlying monogenic condition remained high and symptomatic clinical management was continued.

Abbreviations: NICU, neonatal intensive care unit; OMIM, Online Mendelian Inheritance in Man; PICU, pediatric intensive care unit.

[a] Data on the full cohort are available in eTable 3 in the Supplement.

tal wards, the molecular diagnostic yield was 30% (95% CI, 0%-50%). Among 4 of the 15 patients about whom there was disagreement among the expert panel members, the molecular diagnostic yield was 27.0% (95% CI, 6.7%-46.7%). Among 51 of the 93 patients approved by all the expert panel members, the molecular diagnostic yield was 57.0% (95% CI, 43.0%-63.4%).

Changes in Clinical Management After the Ultra-Rapid Exome Sequencing Report and Perceived Utility

After the ultra-rapid exome sequencing report, changes in clinical management were identified by clinicians for 48 of 108 patients (44%). Among the 55 patients receiving a molecular diagnosis, 42 (76%) were considered as having had a subsequent change in clinical management, including targeted surveillance to identify complications of the condition in 19 patients (18%). The ultra-rapid exome sequencing result formed part of the palliative care discussions in 14 patients (13%). The molecular diagnosis was considered to have contributed to targeted treatment in 12 patients (11%).

Among the 53 patients who did not receive a molecular diagnosis through ultra-rapid exome sequencing, 6 (11%) were considered as having had a change in clinical management (eg, cancellation of planned tissue biopsies and cessation of medications) as a result of nongenetic diagnoses being thought to be more likely. Changes in clinical management were considered as having occurred in 35 of 62 patients (56%) from the NICU and in 17 of 36 patients (47%) from the PICU. Illustrative examples appear in Table 2 and the full data appear in eTable 3 in the Supplement.

Ultra-rapid sequencing reports establishing a molecular diagnosis were perceived as "very useful" or "useful" by referring clinical geneticists in 52 of 55 cases (95%) and were perceived as "neutral" in 3 of 55 cases (5%). Ultra-rapid exome sequencing reports that did not establish a molecular diagnosis were perceived as "very useful" or "useful" in 31 of 53 cases (58%), were perceived as "neutral" in 20 of 53 cases (38%), and were perceived as "not useful" in 2 of 53 cases (4%).

Discussion

This prospective study of 108 critically ill infants and children from multiple sites across Australia demonstrates the feasibility of a national, highly coordinated clinical and laboratory ultra-rapid genomic diagnosis program in a public health care system, with a 3-fold reduction in the mean time from hospital admission to molecular diagnosis compared with the prior Australian rapid exome sequencing study[8] conducted in 2016-2017 at 2 centers. A greater proportion of reports were returned prior to hospital discharge or death and the reports formed part of the palliative care decisions in a greater proportion of the patients who died. The ultra-rapid exome sequencing report was perceived as contributing to the clinical management of the patients regardless of whether a molecular diagnosis was made.

Twenty percent of the molecular diagnoses were made using approaches that extend usual clinical exome sequencing diagnostic practice, including mitochondrial genome sequencing, identification of single-gene copy number variants

from exome sequencing data, real-time use of international databases to establish novel gene-disease associations, RNA studies, and additional phenotyping. There is a need to integrate these ancillary approaches into the diagnostic process, and to develop pathways for rapid turnaround times. Genome sequencing is likely to be the preferred modality for rapid diagnostics in the future[4] because in addition to shortening processing times, it confers the capacity to simultaneously evaluate mitochondrial DNA, structural genomic variants, and repeat expansions. Consolidation of diagnostic approaches to multiple variant types into a single assay may shorten time to test initiation and thus overall time to molecular diagnosis.

A partially centralized model of laboratory service delivery was adopted during this feasibility study, with one laboratory processing the majority of samples and providing redundancy for a second laboratory. The 2 laboratories together were able to provide consistent service based on clinical demand, with 94% of tests reported before the target time of 5 calendar days. The logistical challenges in coordinating an ultra-rapid diagnosis program involving multiple clinical and laboratory sites were considerable, and specifically designed procedures for sample identification, shipping, and tracking were invaluable in preventing delays.

The lack of health care funding, the underpreparedness of the pediatric workforce, and the resource-intensive nature of rapid testing represent significant barriers to widespread adoption.[8,14,23] The potential role for automated phenotyping and interpretation in the scaling up of whole genome sequencing was recently highlighted in a largely retrospective cohort[23] with a mean time saving of 22 hours. However, rapid genomic testing challenges all the components of the clinical and laboratory pathway, necessitating timely patient identification, skilled assessment, appropriate counseling, and a high degree of communication and coordination in emotionally charged and rapidly evolving clinical situations.[8]

Health care is a complex adaptive system and the successful adoption of innovations such as rapid genomic testing relies not only on the scalability of the laboratory testing, but on the multidisciplinary teams of intensive care physicians, medical subspecialists, clinical geneticists, genetic counselors, laboratory scientists, and bioinformaticians simultaneously changing practices across multiple sites to provide consistent service. The creation of a collaborative learning community was used to accelerate implementation and promote a unified approach across different professional groups and multiple sites in Australia through shared decision-making, regular feedback regarding process and molecular diagnostic outcomes, opportunities for reflection, and the sharing of expertise. The creation of the network was greatly facilitated by the Australian Genomics Health Alliance, a government-funded national genomic medicine initiative, which provided governance, research infrastructure, and operational support.[24]

In addition to the substantial reduction in the mean time to molecular diagnosis achieved by the program, there was little variability in the duration of each step of the diagnostic pathway, indicative of a high degree of consistency. However, there was marked variation in the rates of recruitment between sites, which may be partly explained by the uneven distribution of the Australian population and the transfer of complex patients to specialist pediatric hospitals. It may also partly represent different levels of clinician engagement, prior experience, and perceptions of utility at different sites. The longest component of the diagnostic pathway remained time from hospital admission to test initiation, suggesting that further efforts to shorten the diagnostic trajectory need to focus on changing clinician practice as much as they do on shortening laboratory turnaround times.

Limitations

This study has several limitations. First, all clinical and laboratory services participated on a voluntary basis, and expressed high levels of implementation readiness prior to study commencement.[14]

Second, all participating hospitals had clinical genetics services on site, and the service delivery model implemented was led by the clinical genetics service as per participating center preferences.[14] The program leveraged interdisciplinary expertise in patient selection and data interpretation and therefore outcomes such as molecular diagnostic yield may not be generalizable to other health care systems or service delivery models.

Third, there is no consensus on how to evaluate rapid testing programs or what evidentiary threshold should be used for health care system funding.[25,26] The optimal study design to assess the utility of rapid (and non-rapid) genomic testing for rare diseases remains an unresolved question, and a blinded randomized clinical trial[9] of rapid genome sequencing vs standard care was terminated prematurely due to loss of equipoise. This current study, and many others,[1-3,5-8] have opted for a descriptive approach, acknowledging this has the potential for biased reporting of outcomes, in particular in drawing a causal link between ultra-rapid exome sequencing results and subsequent changes in clinical management.

Fourth, this study was not designed or powered to measure differences in major clinical outcomes like morbidity and mortality against those that result from standard care of critically ill pediatric patients. There is a need to develop robust frameworks to measure the long-term clinical outcomes and performance of rapid diagnosis programs to assist with international benchmarking, service planning, funding, and iterative program development. Best practices in pretest and posttest counseling need to be informed by exploration of family experiences and preferences, and further analysis is required to establish cost-effectiveness.

Conclusions

This study suggests feasibility of ultra-rapid genomic testing in critically ill pediatric patients with suspected monogenic conditions in the Australian public health care system. However, further research is needed to understand the clinical value of such testing, and the generalizability of the findings to other health care settings.

ARTICLE INFORMATION

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Authors/Members of the Australian Genomics Health Alliance Acute Care Flagship: Sebastian Lunke, PhD; Stefanie Eggers, PhD; Meredith Wilson, MBBS; Chirag Patel, MD; Christopher P. Barnett, MBBS; Jason Pinner, MBBS; Sarah A. Sandaradura, PhD; Michael F. Buckley, PhD; Emma I. Krzesinski, MBChB; Michelle G. de Silva, PhD; Gemma R. Brett, MGenCouns; Kirsten Boggs, MGenCouns; David Mowat, MBBS; Edwin P. Kirk, PhD; Lesley C. Adès, MBBS; Lauren S. Akesson, PhD; David J. Amor, PhD; Samantha Ayres, MGenCouns; Anne Baxendale, GradDipGenetCounsel; Sarah Borrie, MGenCouns; Alessandra Bray, PhD; Natasha J. Brown, PhD; Cheng Yee Chan, MBChB; Belinda Chong, PhD; Corrina Cliffe, BSc, Biomed; Martin B. Delatycki, PhD; Matthew Edwards, MD; George Elakis, BSc; Michael C. Fahey, PhD; Andrew Fennell, MBBChBAO; Lindsay Fowles, PhD; Lyndon Gallacher, MGenCouns; Megan Higgins, MBBS; Katherine B. Howell, PhD; Lauren Hunt, MSc; Matthew F. Hunter, MBChB; Kristi J. Jones, PhD; Sarah King, PhD; Smitha Kumble, MBBS; Sarah Lang, PhD; Maelle Le Moing, MSc; Alan Ma, MBBS; Dean Phelan, PhD; Michael C. J. Quinn, PhD; Anna Richards, MSc; Christopher M. Richmond, MBBS; Jessica Riseley, BSc; Jonathan Rodgers, MBBS; Rani Sachdev, MBBS; Simon Sadedin, PhD; Luregn J. Schlapbach, MD; Janine Smith, MBBS; Amanda Springer, MGenCouns; Natalie B. Tan, MBBS; Tiong Y. Tan, PhD; Suzanna L. Temple, PhD; Christiane Theda, MD; Anand Vasudevan, MBBS; Susan M. White, MBBS; Alison Yeung, MBBS; Ying Zhu, PhD; Melissa Martyn, PhD; Stephanie Best, PhD; Tony Roscioli, PhD; John Christodoulou, PhD; Zornitza Stark, DM.

Affiliations of Authors/Members of the Australian Genomics Health Alliance Acute Care Flagship: Australian Genomics Health Alliance, Parkville, Australia (Lunke, de Silva, Boggs, Ayres, Bray, King, Best, Christodoulou, Stark); Victorian Clinical Genetics Services, Murdoch Children's Research Institute, Melbourne, Australia (Lunke, Eggers, de Silva, Brett, Akesson, Ayres, Brown, Chong, Delatycki, Gallacher, Kumble, Le Moing, Phelan, Richmond, Riseley, Sadedin, N. B. Tan, T. Y. Tan, White, Yeung, Christodoulou, Stark); University of Melbourne, Melbourne, Australia (Lunke, de Silva, Brett, Akesson, Amor, Brown, Delatycki, Gallacher, Howell, T. Y. Tan, Theda, White, Christodoulou, Stark); Sydney Children's Hospitals Network-Westmead, Sydney, Australia (Wilson, Sandaradura, Boggs, Adès, Bray, Jones, Ma, Smith); University of Sydney, Sydney, Australia (Wilson, Sandaradura, Adès, Jones, Ma, Smith, Christodoulou); Genetic Health Queensland, Royal Brisbane and Women's Hospital, Brisbane, Australia (Patel, Fowles, Higgins, Hunt, Quinn, Rodgers); Women's and Children's Hospital, North Adelaide, Australia (Barnett, Baxendale, Borrie); Sydney Children's Hospitals Network-Randwick, Sydney, Australia (Pinner, Boggs, Mowat, Kirk, Bray, Sachdev); University of New South Wales, Sydney, Australia (Pinner, Mowat, Kirk, Roscioli); NSW Health Pathology Randwick Genomics Laboratory, Sydney, Australia (Buckley, Kirk, Chan, Cliffe, Elakis, Lang, Richards, Temple, Zhu, Roscioli); Monash Genetics, Monash Health, Melbourne, Australia (Krzesinski, Akesson, Fahey, Fennell, Hunter, Springer, Yeung); Department of Paediatrics, Monash University, Melbourne, Australia (Krzesinski, Fahey, Fennell, Hunter, Springer); Royal Children's Hospital, Melbourne, Australia (Amor, Howell); Murdoch Children's Research Institute, Melbourne, Australia (Amor, Howell, Theda, Martyn, Best); Neuroscience Research Australia, University of New South Wales, Sydney, Australia (Chan, Roscioli); Hunter Genetics, Newcastle, Australia (Edwards); Department of Paediatrics, School of Medicine, University of Western Sydney, Sydney, Australia (Edwards); University of Queensland, Brisbane, Australia (Higgins, Hunt); Centre for Cancer Biology, SA Pathology and University of South Australia, Adelaide (King); Paediatric Critical Care Research Group, Child Health Research Centre, the University of Queensland and Queensland Children's Hospital, Brisbane, Australia (Schlapbach); Royal Women's Hospital, Melbourne, Australia (Theda, Vasudevan); Melbourne Genomics Health Alliance, Melbourne, Australia (Martyn); Australian Institute of Health Innovation, Macquarie University, Sydney (Best).

Author Contributions: Drs Lunke and Stark had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Lunke, Eggers, Barnett, Brett, Hunter, Theda, Martyn, Best, Roscioli, Christodoulou, Stark.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Lunke, Barnett, Brett, Amor, Ayres, Fahey, Schlapbach, White, Martyn, Best, Stark.
Critical revision of the manuscript for important intellectual content: Lunke, Eggers, Wilson, Patel, Barnett, Pinner, Sandaradura, Buckley, Krzesinski, de Silva, Brett, Boggs, Mowat, Kirk, Ades, Akesson, Amor, Baxendale, Schenscher, Bray, Brown, Chan, Chong, Cliffe, Delatycki, Edwards, Elakis, Fahey, Fennell, Fowles, Gallacher, Higgins, Howell, Hunt, Hunter, Jones, King, Kumble, Lang, Le Moing, Ma, Phelan, Quinn, Richards, Richmond, Riseley, Rodgers, Sachdev, Sadedin, Schlapbach, Smith, Springer, N. Tan, T. Tan, Temple, Theda, Vasudevan, White, Yeung, Zhu, Best, Roscioli, Christodoulou, Stark.
Statistical analysis: Lunke, Martyn.
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Supervision: Lunke, Wilson, Barnett, Pinner, Buckley, Boggs, Brown, Hunter, Sachdev, T. Tan, Martyn, Best, Roscioli, Christodoulou, Stark.

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