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A cost-effectiveness analysis of genomic sequencing in a prospective versus historical cohort of complex pediatric patients

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Purpose: Cost-effectiveness evaluations of first-line genomic sequencing (GS) in the diagnosis of children with genetic conditions are limited by the lack of well-defined comparative cohorts. We sought to evaluate the cost-effectiveness of early GS in pediatric patients with complex monogenic conditions compared with a matched historical cohort.

Methods: Data, including investigation costs, were collected in a prospective cohort of 92 pediatric patients undergoing singleton GS over an 18-month period (2016–2017) with two of the following: a condition with high mortality, multisystem disease involving three or more organs, or severe limitation of daily function. Comparative data were collected in a matched historical cohort who underwent traditional investigations in the years 2012–2013.

Results: GS yielded a diagnosis in 42% while traditional investigations yielded a diagnosis in 23% ($p = 0.003$). A change in management was experienced by 74% of patients diagnosed following GS, compared with 32% diagnosed following traditional investigations. Singleton GS at a cost of AU$3100 resulted in a mean saving per person of AU$3602 (95% confidence interval [CI] AU$2520–4685). Cost savings occurred across all investigation subtypes and were only minimally offset by clinical management costs.

Conclusion: GS in complex pediatric patients saves significant costs and doubles the diagnostic yield of traditional approaches.

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Key words: genomic sequencing; exome sequencing; pediatric; monogenic; cost-effectiveness

INTRODUCTION

Complex pediatric patients with multisystem disease and high morbidity traditionally undergo more extensive investigation on the pathway to diagnosis than patients with single-system disorders. They also place a high economic burden on health-care systems necessitating more frequent admissions, acute intervention, and outpatient specialist appointments compared with patients with single-system disorders who often can be managed in the community.[1,2] These complex patients have not been represented in previously published clinical utility and cost-effectiveness studies of genomic sequencing (GS) that focus on single-system diseases such as epilepsy or intellectual disability, or include broader pediatric populations with less complex genetic disorders. We sought to provide evidence for the utility and cost-effectiveness of GS in this complex group of patients, recognizing that, in this population more than any other, establishing an early molecular diagnosis is likely to alter acute management, mitigate further costly investigations, and provide timely prognostic information.

The utility of GS as a diagnostic test in pediatric patients with suspected monogenic disorders has been established by a number of studies demonstrating diagnostic yields of 20–50%.[3–17] There are relatively few prospective studies evaluating the cost-effectiveness of GS, largely due to the

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Table 1 Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Pediatric patient (0–18 years)	Investigated for more than two years since tertiary presentation
Likely monogenic disorder	Copy-number variant responsible for phenotype
Complex condition as defined by two or more of	Previous genetic sequencing (single-gene or multigene panel) or enrollment in other GS study
• multisystem disorder with three or more organ systems involved	Single-gene disorder unlikely
• severe condition with high morbidity and mortality	Novel syndrome, i.e., phenotype-driven candidate gene panel cannot be generated
• severe limitations on function and activities of daily living	Secure clinical diagnosis of a monogenic disorder, e.g., achondroplasia, CHARGE syndrome

GS genome sequencing.

lack of well-defined, comparative cohorts.[18,19] This has meant all studies to date have relied on performing cost-effectiveness analyses within a single cohort of patients receiving both GS and traditional investigations. Two early cost-effectiveness studies compared the cost of GS in undiagnosed patients with the cost of investigations performed up to the time of their genomic test.[20,21] This approach is limited in its inability to take into account patients who would have been diagnosed using traditional investigations alone and may, therefore, overestimate the cost-effectiveness of GS. Our group has conducted previous cost-effectiveness studies in children with undiagnosed syndromes by performing GS in parallel with standard investigations within the same cohort,[9,15,22,23] an approach that is no longer feasible given the established evidence for first-line use of GS in this population. Indeed, the demonstrable diagnostic superiority of GS was the reason for the loss of equipoise in a recent cost-effectiveness study of neonatal intensive care patients randomized to receive rapid GS or standard testing.[24] The early termination of this study suggests that randomized control studies are not well suited to the purpose of evaluating the health economics of GS.

We developed a study design to evaluate the health economics of GS and address the limitations of previous studies. We identified two matched cohorts of complex pediatric patients for comparison—a "historical cohort" retrospectively ascertained from a period prior to the availability of clinical GS and a second, prospectively recruited cohort in whom singleton exome sequencing was performed. This allowed us to directly compare the effectiveness and cost of GS to that of traditional investigations without the imperative to perform these investigations in parallel or risk the loss of equipoise by randomizing patients to separate intervention arms. This approach also allowed us to capture the proportion of patients diagnosed with traditional investigations alone and more accurately compare diagnostic yield and clinical management changes between the two investigation pathways.

MATERIALS AND METHODS

Ethics statement

The study was part of the Complex Care flagship of the Melbourne Genomics Health Alliance project[25] (http://www.melbournegenomics.org.au) and received ethics approval through the Melbourne Health Research Ethics Committee (approval number 13/MH/326). Parents of participants provided written consent for GS following genetic counseling.

Study design and participants

Pediatric patients were prospectively recruited for singleton exome sequencing following a clinical genetics assessment at the Royal Children's Hospital, Austin Health or Monash Medical Centre in Melbourne, Australia within the 18-month period from March 2016 to September 2017. Eligibility for recruitment required fulfillment of the inclusion criteria (Table 1), discussion and approval by a panel of clinical geneticists, as well as a nondiagnostic microarray. To determine the utility of GS applied early in the diagnostic trajectory, we excluded patients who had been investigated for more than two years and those who had undergone previous sequencing.

For comparison, a historical cohort of patients meeting the inclusion criteria and who had undergone traditional diagnostic investigations was ascertained from a medical record review of all patients who received a clinical genetics assessment at the Royal Children's Hospital during the period January 2012 to December 2013.

Exome sequencing, variant filtration, and interpretation

Prospectively recruited patients meeting the inclusion criteria underwent singleton whole exome sequencing, variant detection and filtering in a National Association of Testing Authorities (NATA)-accredited laboratory in Melbourne, Victorian Clinical Genetics Services (VCGS) Pathology, as described previously.[9,26] Variants were assessed using the Melbourne Genomics variant curation database, a modification of the Leiden Open Variation Database.[27] Variants were prioritized based on a phenotype-driven gene panel supplied by the referring clinician at the time of recruitment and based on predicted effect (Variant Prioritization Index). Variants were classified based on principles outlined by the American College of Medical Genetics and Genomics (ACMG) standards for interpretation of sequence variants.[28] Variant classifications were reviewed in a multidisciplinary team

meeting attended by clinical geneticists, medical subspecialists, genetic counselors, laboratory genomics scientists, and bioinformaticians. Parental segregation studies were performed at the discretion of the referring clinical geneticist where clarification of variant inheritance or phase was likely to aid in variant classification. Variant classifications were reviewed in a multidisciplinary team meeting when parental segregation results were available with all reported variants uploaded to the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/).

Data collection and statistical analyses

Demographic data were collected in REDCap[29] while phenotypic data using standardized Human Phenotype Ontology terms were entered into PhenoTips[30] at the time of recruitment. All investigations, hospital admissions, and specialist appointments performed for the purpose of delineating the patient's underlying diagnosis were extracted from medical records by a clinical geneticist. These included investigations or specialist reviews for the purpose of defining structural malformations, a biochemical abnormality or neurological deficit, or to rule out an acquired cause of the patient's presentation, for example, viral serological studies. We did not include procedures required for the treatment of a patient's medical illness, for example, microbiological tests for an infective organism or chest X-ray for suspected pneumonia. Diagnostic procedures and their associated costs were recorded from the time of first tertiary hospital presentation to one year after the patient's first genetics appointment.

We compared diagnostic yield and changes with management between the two cohorts by collecting information from medical records detailing the clinical trajectory of patients from their first tertiary hospital presentation to the end of the first year following their genetics assessment. Information collected from medical records included changes to clinical management, established reproductive risk, and cascade testing in family members. Costing data related to diagnostic investigations were obtained from the Clinical Costings Department of the Royal Children's Hospital, Australian or overseas laboratories, and the Australian Medicare Benefits Schedule (http://www.mbsonline.gov.au). We anticipated that there would be a difference in the cost of investigations given the time between ascertainment of the two cohorts. We sought to obtain accurate costings for both time periods by comparing the 2012 Australian Medicare Benefits Schedule for the most common investigations used in our patients with the 2016 schedule. There was, however, no observed increase in the Medicare benefits for these investigations over this time and the same costs were used in our analysis of both cohorts.

We sought to obtain information on the sensitivity of gene panel selection for patients diagnosed by GS. To do this we denoted whether a patient's diagnosis was made from prioritization of a gene within their preselected gene panel, or whether the patient required expansion of analysis to a wider list of 3856 Mendelian genes, the so-called Mendeliome.

We determined the difference in costs between the two cohorts using nonparametric bootstrapping with generalized linear regression models. A gamma distribution was used for costs, and models were adjusted for baseline imbalances in the phenotypic composition of the two cohorts.

Investigation costs were broken down by subtype (e.g., simple biochemistry, anatomical pathology, serology, etc.) to determine whether cost differences between the two cohorts were observed across all types of investigations or only certain subtypes.

The cost of investigation in the prospective cohort included both the cost of singleton exome sequencing, currently AU $3100 at VCGS Pathology in the state of Victoria, as well as the additional cost of variant segregation (AU$250 per variant) where required to determine the phase of a variant or confirm inheritance.

We also performed a separate analysis to include the cost of trio exome sequencing in Australia, currently AU$3500 at South Eastern Area Laboratory Services (SEALS) in the state of New South Wales, to determine whether cost savings would still be seen if trio sequencing had been performed in place of singleton sequencing.

Finally, we captured the resource use, such as additional specialist appointments and surveillance investigations associated with a change in clinical management in patients who received a molecular diagnosis for both cohorts. In the historical cohort, we obtained this information from the medical record, recording resource use over a period of three years following diagnosis. For the prospective cohort, we recorded the anticipated resource use by reviewing published management guidelines for each specific diagnosis. Where published guidelines were not available, expert opinion from the patient's geneticist was sought to determine an appropriate management plan. This allowed us to determine the recommended frequency and duration of treatment or surveillance measures for individual conditions and assign costs for these measures. These costs were projected for a period of three years to allow capture of both one-off costs and recurring costs, and six years in a sensitivity analysis.

Additional matching methods on the phenotypic group composition were explored using propensity score matching and inverse probability weighting to ensure the robustness of the study findings. All statistical analyses were performed in Stata Statistical Software: Release 15 (StataCorp, College Station, TX).

RESULTS

Patient demographics and phenotype

Ninety-one patients meeting the eligibility criteria were retrospectively ascertained for the historical control cohort.

One hundred fifty-six patients were considered for enrollment into the prospective sequencing cohort. Of these, 53 patients were excluded. Twenty-two did not meet the complexity criteria, 11 had been investigated for more than two years, 3 achieved a diagnosis of copy-number variant (CNV) on microarray, 2 were deemed to have a

multifactorial etiology, 5 had undergone previous sequencing, 2 exhibited features for which a candidate gene panel could not be derived, 5 were over 18 years at the time of recruitment, 2 had secure clinical diagnoses, and 1 patient was already enrolled in another sequencing project. Of the 103 patients who met inclusion criteria, 8 declined enrollment or were unavailable for consent and 3 patients died prior to recruitment, leaving 92 patients for singleton exome sequencing.

The two cohorts were well-matched across some, but not all, parameters. The mean age at presentation (13.0 months in the historical cohort) was slightly younger than the age at presentation of the prospective cohort (19.8 months). The mean interval to genetics assessment in the prospective cohort (133 days) was similar to controls (106 days). The median number of specialists involved in the care of the historical cohort patients was higher (seven) that the number of specialists involved in the GS patients (five); the median number of admissions for investigative purposes was two for both cohorts and the median number of organ systems involved was three for both cohorts.

Patients were categorized into four different phenotypic groups on the basis of their presenting features with most patients falling into the multiple congenital malformations or neurodevelopmental categories. There were notably more patients in the multiple congenital malformations group recruited to the prospective cohort compared with the historical cohort (33 patients versus 16 patients, $p = 0.005$). Conversely, fewer patients with neurodevelopmental phenotypes were recruited to the prospective cohort than were ascertained for the historical cohort (69 patients versus 49 patients, $p = 0.001$).

A small number of patients with single-system disorders and high acuity included acutely unwell patients awaiting transplants, redirection of care, or other therapeutic interventions that might be influenced by a genetic diagnosis. The patient characteristics for each cohort are summarized in Table 2.

Table 2 Patient demographics, measures of complexity, and phenotypic groupings.

Characteristic	Historical cohort $N = 91$	Prospective cohort $N = 92$	*P* value
Female (%)	48 (52)	43 (47)	0.5
Male (%)	43 (47)	49 (53)	0.5
Mean age at presentation for tertiary investigation in months (range)	13 (0–187)	19.8 (0–210)	0.16
Mean interval to genetics assessment in days (range)	106 (0–902)	133 (0–825)	0.34
Median number of specialists involved (range)	5 (2–8)	5 (2–9)	0.7
Median number of organs involved (range)	3 (1–7)	3 (1–9)	0.2
Median number of hospital admissions for investigation per child (range)	2 (0–11)	2 (0–8)	0.2
Phenotypic group: multiple congenital malformation	16	32	**0.005**
Phenotypic group: neurodevelopmental	63	49	**0.001**
Phenotypic group: multisystem disorder	6	8	0.55
Phenotypic group: high acuity, single system	6	3	0.19

p values in bold are statistically significant (<0.05).

Diagnostic yield and changes to management

Twenty-one of 91 patients (23%) received a diagnosis using traditional investigations in the historical cohort compared with 39 of 92 patients (42%) who underwent exome sequencing ($p = 0.003$). Those who received a molecular diagnosis in the historical cohort did so after initiation of a single-gene sequencing test or a multigene panel. There were no diagnoses made from nongenetic investigations in either cohort. The diagnostic yield and management changes in both cohorts are summarized in Table 3.

Twenty-eight of the 39 (72%) diagnoses made in the prospective sequencing cohort were in genes within the preselected gene panel specified by the patient's clinician. The remaining 11 diagnoses (28%) involved genes outside of preselected panels requiring analysis of a larger panel of Mendelian disease genes. Twenty-two parents underwent segregation testing for a variant to clarify phase or confirm inheritance. This resulted in the reclassification of 11 variants: 7 from a classification of variant of unknown significance (VUS) to likely pathogenic and 4 variants from likely pathogenic to pathogenic. One variant, found to be paternally inherited, was changed from a classification of likely pathogenic to VUS.

Seven of the 21 diagnosed patients (33%) in the historical cohort (8% of the total cohort) underwent a change in management as a result of their molecular diagnosis. This included one patient with neonatal Marfan syndrome in whom β-blocker therapy was instituted, and two patients in whom a diagnosis guided the decision for palliative care.

Meanwhile, 29 of the 39 diagnosed patients (74%) who received a diagnosis from GS (32% of the total cohort) experienced a change in management. Examples of treatment changes included the commencement of a cholinesterase inhibitor in a patient with congenital myasthenic syndrome due to *RAPSN* variants and the revision of seizure medications in a child with *SCN8A*-related epilepsy to include the institution of trihexyphenidyl and cessation of phenytoin (known to exacerbate symptoms in this disorder). Patient diagnoses and subsequent changes to management are summarized in Supplementary Tables S1 and S2.

Diagnosis from the finding of de novo variants established a low recurrence risk in 14 families from the historical cohort

Table 3 Diagnostic yield and changes to management following diagnosis.

	Historical cohort $N = 91$	Prospective cohort $N = 92$	P value
Molecular diagnosis confirmed (%)	**21 (23%)**	**39 (42%)**	**0.003**
Mean days to diagnosis (from date of tertiary presentation to date of genetic test report issue)	**1046**	**423**	**<0.0001**
Total patients experiencing management change	**7 (8% of total cohort, 33% of diagnosed patients)**	**29 (32% of total cohort, 74% of diagnosed patients)**	**<0.001**
Treatment started	1	4	
Treatment ceased	0	1	
Redirection to palliative care	2	1	
Surveillance commenced	4	21	
Surveillance ceased	0	2	
Low recurrence risk established	14	28	
High (25% or 50%) recurrence risk established	7	12	
Cascade testing in family member	0	5	
Invasive investigations	**134**	**31**	
MRI under GA	37	0	
Tissue biopsy under GA	21	9	
Tissue biopsy no GA	10	1	
Bone marrow biopsy	8	0	
Lumbar puncture	21	15	
EMG	3	0	
NCS	9	3	
ERG	5	0	
EUA	12	2	
Endoscopy	4	1	
Postmortem examination	4	0	

EMG electromyography, *ERG* electroretinography, *EUA* examination under anesthetic, *GA* general anesthetic, *NCS* nerve conduction study.
p values in bold are statisctically significant (<0.05). The bold text in table 3 represent major categories and total values. The regular text represents the sub-categories and subtotal values applicable to the total values specified above in bold.

(15%) and 27 families in the prospective cohort (29%). A high recurrence risk (25% or 50%) was established in seven families from the historical cohort (8%) compared with 12 families who underwent GS (13%). Following the diagnosis of two patients who underwent GS, a mildly affected parent was unexpectedly diagnosed. One parent had somatic mosaicism for the familial variant.

Patients who underwent GS had four times fewer invasive tests performed compared with those undergoing traditional investigations (31 invasive investigations compared with 134 in the historical cohort). All of the 31 invasive investigations performed in the prospective cohort were initiated in the period prior to genetics review with no invasive investigations recorded in the one-year period following GS.

Table 4 Cost differences between cohorts: total cost, mean cost per patient, and cost savings from GS.

Cohort and investigation method	Total cost ($AU)	Mean cost per person ($AU) and SD	Mean cost saving per person from GS ($AU)
Historical cohort	796,667.93	8755 SD 5298	–
Prospective cohort (investigations excluding GS)	265,540.70	–	–
Prospective cohort (including singleton GS at AU$3100 and segregation costs)	556,240.70	5205 SD 1680	3602 95% CI 2520–4685
Prospective cohort (including trio GS at AU $3500)	587,540.70	6305 SD 1680	2446 95% CI 1380–3515

CI confidence interval, *GS* genome sequencing.

Cost evaluation

The total cost of investigations, admissions, and ambulatory care was significantly greater in the historical cohort, at AU $796,667.93 compared with the total cost in the prospective cohort of AU$556,240.70. The mean cost per patient undergoing singleton GS (at AU$3100 per test) was AU $5205, two-thirds the mean cost per patient undergoing traditional investigations at AU$8755. The mean cost saving per patient from singleton GS was AU$3602 (95% confidence interval [CI] AU$2520–4685). Had trio GS been applied this cost saving per patient would have been AU $2446 (95% CI AU$1380–3515). Table 4 summarizes the cost differences between the two cohorts. See Supplementary Table S3 for costs by patient in the historical cohort and Supplementary Table S4 for costs by patient in the prospective cohort.

Analysis of cost differences by subtype of investigation revealed cost savings from exome sequencing across all investigation categories (Table 5). The greatest savings were seen in the cost of anatomical pathology (with a mean cost saving per patient of AU$1892), electrophysiology (with a mean cost saving per patient of AU$1632), imaging (with a mean saving per patient of AU$1566), and complex biochemical investigations (with a mean saving per patient of AU$1051).

Table 5 Cost difference between cohorts by investigation subtype and comparison of clinical management-related costs over a three-year period in diagnosed patients.

	Historical ($AU)		Prospective ($AU)		Cost difference ($AUD)	Normal-based 95% confidence interval	
Investigation subtype	Mean	SD	Mean	SD			
Appointments	1230	694.7	459.2	140.7	−771.0	−911.8	−630.2
Simple chemistry	182	110	88	43	−93	−122	−64
Complex chemistry	1305	1252	254	360	−1051	−1357	−746
Serology/immunology	602	974	19	119	−583	−919	−246
Anatomical pathology	1924	3292	32	122	−1892	−3044	−739
Imaging	2324	2098	758	502	−1566	−2004	−1127
Electrophysiology	2249	1864	616	1116	−1632	−2153	−1111
Genetic testing (excluding exome)	1560	1306	645	236	−915	−1187	−643
Clinical management-related costs over a three-year period in diagnosed patients	238	193	319	72	358	177	461

The three-year projected cost of additional resource use following GS, including surveillance investigations and specialist appointments, was AU$358 per person. When offset against the mean cost saving of singleton GS (AU$3602) there was still a significant cost saving of AU$3244 from this diagnostic pathway.

DISCUSSION

The availability of well-defined comparative data has been lacking in other cost-effectiveness studies of GS and has limited the current health economic evidence base to support the integration of GS into health care. Our study took the approach of ascertaining a clinically matched control cohort of patients undergoing traditional investigations for comparison with a cohort of patients undergoing GS. Moreover, we chose to include only pediatric patients with high morbidity and multisystem disease to provide evidence lacking in the current literature that GS in this more complex population provides clinical benefit.

We have demonstrated that singleton GS doubles the diagnostic rate of patients with complex genetic conditions compared with traditional investigations. This is achieved with an average cost per patient that is two-thirds that of traditional investigation costs and represents a mean cost saving of AU$3602 per patient. The clinical utility of GS was also made evident in this study with a molecular diagnosis resulting in direct changes to management in 74% of diagnosed patients (32% of the entire cohort) who underwent GS compared with 33% of diagnosed patients (8% of the entire cohort) who underwent traditional investigations. Meanwhile our study demonstrated that the mean time to diagnosis from tertiary presentation to genetic test reporting was 2.5 times faster with GS (1046 days in the historical cohort versus 423 days in the prospective cohort). The faster turnaround time of genetic test results in the prospective cohort may, in part, have been skewed by the recruitment method, which was conditional on receiving a genomic test. Nevertheless, the greater clinical impact of GS may be a reflection of patients receiving a diagnosis early enough in their disease trajectory to allow new treatments or surveillance measures to be instituted prior to the onset of irreversible complications or disease progression.

There was also some observed discordance between the two cohorts despite our attempts to match prospective and historical patients by applying the same strict inclusion and exclusion criteria. Notably, the prospective cohort patients were slightly older, had seen fewer specialists prior to genetics assessment, and had a greater likelihood of having multiple congenital malformations. A possible reason for this discordance may be the method of recruitment into the prospective cohort and subsequent selection bias, for example, patients with congenital malformations were more likely to be referred because of a perceived higher yield from genomic testing; the availability of genomic testing bypassed the need for referral to a greater number of specialists; and a slightly older cohort of patients were recruited for the prospective cohort because their phenotypes had become more differentiated over time and therefore more readily fulfilled the inclusion criteria.

We took into account the resource-use implications of altered clinical management following GS by anticipating costs related to surveillance investigations and specialist appointments over a time horizon of three years, a period that allowed us to capture one-off costs and recurring costs. This demonstrated that the additional cost of resource use after a GS diagnosis (AU$358 per patient) minimally offsets the much larger diagnostic cost savings of GS. A sensitivity analysis using a six-year horizon further supported the limited effect of additional resource use on cost savings.

We have also demonstrated that the patients having traditional investigations underwent four times more invasive investigations than patients in the GS cohort. No invasive investigations were performed after GS was initiated. This suggests that even in those patients who do not receive a

diagnosis by GS, the test itself appears to have an end-of-odyssey effect by putting an end to further invasive investigations and ultimately saving costs. There are several possible reasons for this effect, including the assurance for specialists that an uninformative GS result has "ruled out" the diagnoses they would have considered likely. There is also likely to be the perception by the patient and the referring clinician that genomic sequencing is "the best test available" and further tests are unlikely to yield a diagnosis. It is unclear from this study whether the reduction in ongoing testing will be sustained over time, given the limited one-year timeframe of follow-up. Exploring the attitudes of referring clinicians and their patients to further testing following an uninformative genomic test is an interesting area for future study.

Contrary to expectation, the time to genetics referral was not greatly altered by the availability of GS in the prospective cohort. Moreover, a number of invasive investigations in our prospective cohort had already been initiated prior to referral for genetics assessment. The number of costly and invasive investigations would be reduced by changing the clinical practice of nonspecialist clinicians, and emphasizes a need to raise their awareness of the benefits first-line genomic sequencing can provide.

The diagnostic yield of GS in the prospective cohort of 42% was similar to previous studies performed by our research group that included patients with less complex, single-organ conditions.[9,15] There is, however, likely to be a higher proportion of undiagnosed patients in the current complex group who have a novel genetic condition due to a variant in a gene that was not included in their genomic analysis, or an unrecognized presentation of a known condition where the causative variant was not identified during analysis. The undiagnosed patients from this exome sequencing cohort are therefore ideal candidates for future gene discovery studies.

Our group has previously demonstrated the improved diagnostic yield from utilizing an expanded panel of Mendelian disease genes or Mendeliome in the analysis of complex phenotypes compared with an approach that restricts analysis to genes within a preselected panel.[31] In this study 11/39 (28%) of diagnoses made by GS were in genes outside of preselected gene panels demonstrating that an analysis restricted to a preselected panel of genes would have missed 28% of diagnoses in this complex pediatric cohort.

We have also recently published on the efficiencies gained from a trio sequencing approach over singleton sequencing in complex pediatric cohorts.[32] Our current study further demonstrates that the implementation of trio sequencing in place of singleton sequencing involves only a small increase in mean costs yet still yields significant cost savings when compared with traditional investigations.

There are likely to have been technological advancements in nongenetic investigation methods in the time interval between the ascertainment of the two cohorts, most notably affecting the accuracy of biochemical assays and resolution of medical imaging, as well as new microscopy and staining techniques for anatomical specimens. By enrolling patients on the condition that they undergo genomic sequencing we bypassed these investigations for many patients and have therefore not accounted for the diagnoses that might have been made using modern nongenetic approaches in the prospective cohort. To evaluate this, however, we would have had to perform these investigations in parallel with genomic sequencing, which was not a feasible undertaking in this study.

One major advantage of GS over a panel or single-gene testing approach is the opportunity it affords for reanalysis of sequencing data. We did not perform or factor in the costs of systematic reanalysis in undiagnosed patients at the conclusion of the one-year follow-up period; had we done so, we may have found additional diagnoses at relatively low cost. There is growing evidence that reanalysis of genomic data is a cost-effective strategy for enhancing diagnostic yield[33–36] and sustainable health-care funding of genomic testing should include this additional cost.

The costs of GS are unlikely to remain static over time and while this study provides a snapshot of current costs, there will be a need for more up-to-date cost evaluations as well as reassessments of funding provided to health services for genomic testing. Moreover, while the findings of this study are applicable in the Australian context, they may not be reproducible in other countries where the funding model and costs of health care may differ.

While the significant personal utility effects of GS were not explicitly taken into consideration, this study design lends itself to future long-term follow-up of both cohorts beyond the one-year period we have reported. The inclusion of patient experience data, reproductive data, and quality of life measures highlighting the personal utility effects of GS are likely to yield further evidence supporting its cost-effectiveness.

Conclusion

We have demonstrated that early GS in children with complex conditions doubles the diagnostic yield of traditional approaches at two-thirds the mean cost per patient. A diagnosis from GS in our cohort impacted on the management of one in three patients tested and resulted in four times fewer invasive investigations compared with traditional diagnostic approaches. This evidence strongly supports the early implementation of GS in complex pediatric patients.

SUPPLEMENTARY INFORMATION

The online version of this article (https://doi.org/10.1038/s41436-020-0929-8) contains supplementary material, which is available to authorized users.

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DISCLOSURE

The authors declare no conflicts of interest.

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