Abstract

The study characterised differences in costs associated with raising a child between four rare disorders and examined the associations between these costs with clinical severity. Caregivers of 108 individuals with Prader Willi, Angelman (AS), Chromosome 15 duplication, and fragile X (FXS) syndromes completed a modified Client Services Receipt Inventory and participants completed intellectual/developmental functioning and autism assessments. AS incurred the highest yearly costs per individual ($AUD96,994), while FXS had the lowest costs ($AUD33,221). Intellectual functioning negatively predicted total costs, after controlling for diagnosis. The effect of intellectual functioning on total costs for those with AS was significantly different to the other syndromes. The study highlights the significant costs associated with these syndromes, particularly AS, linked with severity of intellectual functioning.

Key words: Fragile X syndrome, Angelman syndrome, Prader-Willi syndrome, Chromosome 15 Duplication syndrome, Health Economics

The Cost of Raising Individuals with Fragile X or a Chromosome 15 Imprinting Disorder in Australia

Fragile X syndrome (FXS) and chromosome 15 (C15) imprinting disorders, including Angelman (AS), Prader-Willi (PWS) and Chromosome 15q duplication (Dup15q) syndromes are characterised by varying degrees of intellectual disability (ID), autism spectrum disorder (ASD) features, and challenging behaviours (Kalsner & Chamberlain, 2015; Raspa et al., 2017). Approximately 135 individuals are born with one of these syndromes each year in Australia. Most infants with AS, FXS, and Dup15q syndrome are not diagnosed within the first year of life (Supplemental Table S1 for summary of each syndrome). For PWS, diagnosis in infancy allows early initiation of growth hormone treatment (Kimonis et al., 2019). Such early *targeted* interventions are reliant on early diagnosis (e.g., communication/speech, physical, and behaviour therapies). Early diagnoses may now be possible through inclusion of each of these syndromes in population wide newborn screening (NBS) using a methylation-based screening method that has recently been developed called Methylation Specific Quantitative Melt Analysis (MS-QMA; Inaba et al., 2014; Kraan et al., 2020). MS-QMA can be used to screen for the four syndromes simultaneously based on the levels of DNA methylation, at a reagent cost consistent with the costs of other conditions currently included in state sponsored NBS programs. However, in addition to having a validated screening test, inclusion of these and other conditions in NBS panels requires further, specific criteria to be met.. These include the benefits to the infants and to society (e.g., economic benefits) outweighing the risks and burdens of screening and treatment (Department of Health., 2018; Therrell et al., 2015).

In Australia, the inclusion of new tests and/or new conditions for existing newborn screening panels for public subsidy is considered by the Medical Services Advisory Committee (MSAC). MSAC appraises new medical services proposed for public funding and provides advice to Government on whether a new medical service should be publicly funded on an

assessment of its comparative safety, clinical effectiveness, cost-effectiveness, and total cost, using the best available evidence.

This study aims to understand the costs associated with these conditions and to help identify the cost savings that might result from earlier diagnosis and interventions targeting these conditions. This information will assist in the assessment of combined screening for FXS, PWS, AS and Dup15q syndrome for public subsidy. For these conditions to be included in publicly subsidised programs in Australia, and in many other countries with Health Technology Assessment systems (e.g., Canada, UK, Scotland, Japan), the costs and health outcomes of the test must be considered, usually using cost-utility analyses (CUA) or cost effectiveness analyses (CEA). CUAs and CEAs allow the intervention (the test) to be compared to the status quo by estimating the cost per gain in a unit of health outcome. Therefore, an understanding of the costs associated with each condition is imperative in assessing the relative benefit/cost ratio of any intervention targeting that condition. These analyses will also help with understanding how new therapies, currently being trialled for these disorders (https://clinicaltrials.gov/), may reduce the costs associated with these disorders.

While there is some literature exploring medical or resource utilisation in AS and PWS (Khan et al., 2019; Shoffstall et al., 2016), there is no literature, to our knowledge, comparing overall costs associated with caring for individuals with PWS, AS or Dup15q syndrome, internationally or in the Australian context. The clinical and medical presentations of each of these syndromes will likely result in increased health care resource utilisation. For example, severe seizures occur in more than 80% of individuals with AS (Bindels-de Heus et al., 2020) and Dup15q syndrome (isodicentric subtype; Conant et al., 2014) and require ongoing monitoring and treatment throughout the lifespan (Khan et al., 2019; Thomson et al., 2006). Larson and colleagues (2015) found that the frequency and severity of seizures increased in adults with AS aged over 25 years compared to young persons with AS aged 16-20 years. For

PWS, overweight and obesity is reported in 40% of children and adolescents (Diene et al., 2010), and up to 98% of adults with the syndrome (Grugni et al., 2008), which significantly increases the risk for morbidity if not externally supported (Butler et al., 2017).

Autistic features are also commonly observed in each of these syndromes. owever, the prevalence of individuals meeting Diagnostic and Statistical Manual (DSM) criteria for ASD varies between research studies for each syndrome, given varying methodologies and assessments are often used to define ASD. Approximately 30% of individuals with FXS (Richards et al., 2015), 26.7% with PWS (Bennett, Germani, Haqq, & Zwaigenbaum, 2015), and 34% with AS (Richards et al., 2015) are reported to meet diagnostic criteria for ASD. Compared to other copy number variants known to cause ASD, Dup15q syndrome confers the greatest risk (Moreno-De-Luca et al., 2013), and as such most individuals with Dup15q syndrome meet diagnostic criteria for ASD (DiStefano et al., 2020). Nonetheless, across all four syndromes autistic features are common, regardless of whether these symptoms meet diagnostic thresholds.

Understanding the magnitude and pattern of costs associated with these disorders can assist in the prioritisation and cost-effective provision of screening programs, health care, and early intervention services for FXS, AS, PWS and Dup15q, with broader implications for other rare syndromes where ID and ASD are significant comorbidities. Thus, this study explores the similarities and differences in the costs associated with caring for individuals affected with these syndromes in the Australian setting, aiming to characterise costs based on comorbidities, behavioural challenges, and age of diagnosis. It was hypothesised that costs would differ between groups linked to the specific comorbidities experienced by each syndrome, with ID and ASD severity providing a major contribution to these costs.

Method

Participants

This study included 108 individuals, aged between 8 months and 45 years, with a diagnosis of FXS, PWS, AS, or Dup15q syndrome. Participants were recruited between November 2016 and March 2019 via <removed for blinded peer review>, and Australian disorder specific support groups and organisations. Participants were included in the study based on a molecular diagnosis of the respective syndrome (confirmed with diagnostic reports). For males with FXS, 36% were *FMR1* CGG size mosaic. That is, they were mosaic for *FMR1* alleles termed premutation (PM: 55–199 CGG repeats) in combination with methylated full mutation (FM: ≥ 200 CGG repeats) *FMR1* alleles that cause FXS. All females with FXS and remaining males were FM only. The genetic molecular classes of the C15 imprinting disorder groups are presented in Supplemental Table S2. Study exclusion criteria included any other genetic conditions, the presence of significant medical or neurological condition(s) including stroke, malignancies, severe head trauma, liver or renal failure, and inadequate control of seizures.

Materials

Parents/caregivers completed a modified version of the Client Service Receipt Inventory (CSRI; Supplemental Material Appendix A). Modification of the CSRI was undertaken in consultation with stakeholders, family support organisations (Prader-Willi Syndrome Association of Australia, Foundation for Angelman Syndrome Therapeutics; Dup15q Australia Ltd) and clinical specialists to include disorder specific information. The original CSRI was developed for patients with psychiatric disorders (Beecham & Knapp, 1992) but has also been used in studies of patients with ID (Doran et al., 2012). The CSRI collects data on service utilisation, household composition, income, and care arrangements (Beecham & Knapp, 1992). Parents/caregivers also completed a developmental and medical history questionnaire which included questions regarding lifetime presence of seizures.

Parents/caregivers also completed the Aberrant Behaviour Checklist-Community (ABC-C; Aman et al., 1985) to assess behavioural problems. For the FXS group the fragile X specific version of the ABC-C was used (Sansone et al., 2012), while for the C15 imprinting syndromes, the original ABC-C scoring was used. Kerr and colleagues (2015) developed a utility index (UI) from the ABC-C, in order to estimate health-related quality of life impact for economic evaluation. Briefly, the ABC-UI was developed to enable reporting of health state utility scores in children, adolescents, and adults with FXS, based on responses to the ABC-C. Nine key health items to determine health related quality of life impacts in FXS were selected via statistical analyses and clinical experts (Kerr et al., 2015). We applied this algorithm to all participants' ABC-C questionnaires.

Participants aged >12 months who were at a minimum cruising/walking were assessed with the Autism Diagnostic Observation Schedule-2nd edition (ADOS-2; Lord et al., 2012), a semi-structured assessment of autism symptoms in the domains of social affect and restricted and repetitive behaviours. The ADOS-2 also provides categorical classifications: Autism, Autism Spectrum and Non-Spectrum. In this study, participants were classified with ASD if they met the ADOS-2 cut-off for 'Autism' or 'Autism Spectrum' and non ASD if they met the 'Non-Spectrum' cut-off.

The Mullen Scales of Early Learning (Mullen, 1995) was used to assess intellectual functioning in FXS and PWS children aged 8 months to 2 years and 11 months and all individuals with AS. An age-appropriate Wechsler intelligence scale (Wechsler, 2003, 2004, 2008) was used for the remaining FXS and PWS individuals . Given the propensity for many individuals with FXS and C15 imprinting disorders to fall at the floor on standardised intellectual functioning assessments, we used corrected full-scale intelligence quotient scores (cFSIQ; see Arpone et al., 2018 for a description of this method). Depending on the developmental level observed during the ADOS-2 the individual with Dup15q syndrome,

completed either the MSEL or an age-appropriate Wechsler scale. Thus, the MSEL was used beyond its normative age range in some individuals with AS and Dup15q, with IQ scores calculated, as previously described <removed for blinded peer review>.

Data Analysis/Empirical Approach

Costs were estimated using individual data (bottom-up approach). The CSRI asked caregivers to recall resource and service utilisation across varying time periods (1 month to 1 year) depending on the resource/service category. In this study costs were standardised to reflect the costs incurred in the previous one-year period. Costs are reported per resource use category and by syndrome. Where participants had a diagnosis of FXS further sub-group analyses were conducted, analysing cost by sex, combining participants with a full mutation (FM) and mosaicism for premutation and full mutation (PM/FM) alleles.

Resource utilisation, service use, and government benefits are reported as costs incurred in the previous year. A societal perspective was adopted, reporting costs incurred by the healthcare system but also costs incurred by individuals and families. 'Whether the cost was incurred by the individual or by government was determined by assuming that all costs relating to that resource use category were incurred by the most likely payer in the Australian health care context. For example, in Australia most prescription medicines are publicly funded and as such the analysis assumed that these costs were incurred by government. The questionnaire asked individuals to report resource and service utilisation that related to their disability.

Resource utilisation (including equipment, medications, and transportation) service use (including out of home care, hospital admissions, outpatient visits, special education, group home/residential care), lost employment, informal care and government benefits received for each individual were collected via the modified CSRI (Supplemental Table S3 for costs and their sources). Examples of equipment used by participants included but were not limited to wheelchairs, toilet aids, hoists, walkers, special car seats and supportive clothing. Medications

included prescription medications and over-the-counter medications. Transport costs were those costs reported by the caregiver to be a result of the child's disability. Participants were asked to self-report how much they spent on transport as a result of the medical condition, for example taxi journeys and payments for special school buses. Out of home care included social, short-term, overnight or day respite. Hospital admissions included inpatient visits or emergency department visits and outpatient visits included visits to general practitioners, medical specialists, or other allied health practitioners. Informal care refers to unpaid care provided by people such as grandparents, aunts, uncles, other family and friends. While informal care is unpaid it carries an opportunity cost, whereby the care provided represents a cost to the family and society, in terms of hours in paid employment and leisure hours forgone. The opportunity cost of informal care was valued using the average hourly wage. Costs relating to informal care provided by the primary caregiver were not included.

Previous year costs relating to special education for individuals aged under five years and 18 years and over were assumed to be zero since they reported not being in any education. Costs relating to unemployment relate to the number of weeks the affected individuals aged over 18 years old were not in paid employment. The total cost of unemployment was calculated by multiplying the number of weeks in unemployment by the average Australian weekly income (Australian Bureau of Statistics, 2019). This total cost of unemployment was then split into cost to government and cost to individual, according to the average taxation rate.

Source data for the costs applied included the Schooling Resource Standard (Australian Government Department of Education, 2020), National Disability Insurance Scheme (NDIS) Price Guide and Support Catalogue (Australian Government., 2019), Australian Bureau of Statistics (Australian Bureau of Statistics., 2018, 2019), Medicare Benefits Schedule (Australian Government Department of Health., 2019), Pharmaceutical Benefits Scheme (Australian Government Department of Health., 2020), FXS and AS equipment survey

(Supplemental Note S1). All costs were inflated to 2019/2020 prices using inflation rates derived using the average service price inflation (Australian Bureau of Statistics, 2019).

Multiple regression analyses were conducted to measure whether the participant's diagnosis, experience of seizures, and presence of ASD and behavioural problems were associated with increased total costs. Regression analyses used FXS as the base, as there is currently a greater understanding of the economic cost of FXS and the sample of FXS was larger than the C15 imprinting disorder groups. All analyses controlled for the following variables: participant age, participant sex, country of birth, and primary language. Three regression analyses were conducted to analyse the effect of participant's diagnosis and comorbidities on total costs, as detailed in the Supplemental Note S2. In the first regression model the effect of diagnostic category on total cost was estimated. In the second regression model total cost was regressed on diagnostic category, seizures, age of diagnosis and behaviour. In the third regression model diagnostic category was interacted with FSIQ. Participants with a missing response for any of the covariates controlled for within the models were removed via listwise deletion in STATA.

Given FXS is an X linked condition where females are usually less severely affected, another set of multiple regression analyses were used to assess whether participant's sex influenced costs in FXS. Consistent with the previous regression analyses experience of seizures, and presence of ASD and behavioural problems were also included in these models. All analyses controlled for participant age, country of birth, and primary language (see Supplemental Note S3 for details).

Results

Table 1 shows the sample characteristics and Supplemental Figure S1 provides the distribution of age for participants affected with each syndrome. Table 2 shows the costs associated with each syndrome. AS incurred the highest mean cost per person ($AUD 96,988).

The cost per individual in the previous year was $AUD 57,576 for PWS, $AUD 52,130 for Dup15q syndrome and $AUD 33,219 for FXS. Of participants with FXS (FM and PM/FM), males had a higher cost than females ($AUD 38,569 compared to $AUD 24,164; Supplementary Table S3). The resource use categories with the largest costs were incurred by the government, including government benefits paid to individuals/families, and costs associated with unemployment of the affected individual, group home/residential care living, and informal care.

The AS group had significantly greater total costs compared to the FXS group, after controlling for participant age, country of birth, and primary language (Table 3).

Determing impact of comorbidities on costings

Total yearly costs were reduced by a mean of $AUD 734, after controlling for diagnostic category, for every one point increase in cFSIQ (Table 4). Regression analysis that interacted cFSIQ and diagnostic category revealed that the relationship between FSIQ on costs differed depending on the diagnositc category (Table 4). Marginal effects analysis showed that for those with AS, total cost significantly decreased by $5,102 per year per point increase in FSIQ (Table 5). Post-hoc testing revealed that the difference in the effect of FSIQ on total costs for those with AS was significantly different to those with FXS, PWS or Dup15q. When the sub-scales of the ABC-C were included in the analysis (Supplemental Table S5) results were consistent with those reported in Table 4.

Comparison between Males and Females with FXS

Females with FXS did not incur significantly different total costs compared to males with FXS after controlling for participant age and country of birth (Supplemental Table S6). However, females with FXS did have significantly lower costs relating to government benefits compared to FXS males (Supplemental Table S6). Presence of seizures and behavioural issues were not significantly associated with total costs for those with FXS (Supplemental Table S7).

Discussion

This study demonstrates the considerable economic impact of FXS, PWS, AS and Dup15q syndrome, with the majority of costs incurred by the Australian government (benefits paid to families, unemployment, out of home care). Of the syndromes included in this analysis AS was associated with the highest costs, with a mean annual cost of $AUD 96,988, while FXS was associated with the lowest costs per individual ($AUD 33,219). The estimate for FXS is somewhat lower than has been reported in previous literature (Chevreul et al., 2016) with the exception of a study in Hungary which estimated the incremental annual per person cost for FXS to be Euro 4,951 (~$AUD 8,380) (Chevreul et al., 2016). However, a study from Sweden (Chevreul et al., 2016) estimated the incremental annual per person cost of FXS to be Euro 58,862 (~$AUD 99,630), while another from the US estimated $USD 33,409 (~$AUD 52,260) (Nazareth et al., 2016). Differences in estimates are likely due to availability and access to services within each country, the varying healthcare systems, and the aetiology of each cohort studied such as proportion of PM/FM mosaic individuals, who usually have better intellectual functioning than their FM only FXS counterparts (Baker et al., 2020; Pretto et al., 2018).

Previous research has found that the lost opportunity cost of time spent caring by primary caregivers represents the greatest proportion of the cost burden relating to ID (Doran et al., 2012). In a recent Australian study of children with ID aged 2-10 years (Arora et al., 2020), it was estimated that care because of the child's disability cost the individual/family $AUD 5033.69 per month (2018-2019 prices). Moreover, the opportunity cost of lost time spent caring comprised the greatest proportion of the cost burden of childhood ID, which was estimated at $AUD12.501 billion per year based on prevalence estimates of childhood ID in Australia. Thus, our estimates of the economic burden are likely underestimated, given the significant lost opportunity costs that have been attributed to ID more generally. Future

research examining the costs associated with these four syndromes should include the lost opportunity cost in the data collection and analyses.

Cost implications for early diagnosis and targeted intervention

Our findings have implications for the diagnostic and clinical care of these syndromes. Our findings showed reductions in total yearly costs were related to better intellectual functioning. Specifically, for every one-point increase in cFSIQ, total yearly costs were reduced by $AUD734. Further analyses demonstrated that the effect of cFSIQ on total costs for those with AS was significantly different to the other three syndromes. This suggests that the severe ID associated with AS (usually more severe than the other three syndromes) is a significant contributor to the financial burden of AS. The findings provide support for interventions that target intellectual/cognitive functioning in these disorders, particularly AS. Even small improvements in intellectual functioning may result in significant cost reductions. However, further research in larger samples of individuals with each condition is required to better understand these relationships.

The significant ID in these syndromes may also result in lost employment, as usually one parent is required to take on a full-time caring role. Ouyang and colleagues (2010) found that approximately 40% of parents of children with FXS reported quitting employment because of their child's condition. Moreover, multivariate analyses stratified by age and controlling for co-occurring conditions and functional difficulties demonstrated that the odds ratio for the FXS group (aged 12-17 years) was significantly elevated for financial burden, quitting employment, and reducing work hours, relative to children with ASD only. In an Italian study of parents of children with PWS (Ragusa et al., 2020), 62% of family caregivers reported changing their job after the birth of their child with PWS. More specifically, over one-third left their current work, 8% reported changing jobs to assist the child, 8% requested part-time work, and 3% gave up the perspective of a career. For AS and Dup15q syndrome there is limited data on lost

employment. Nonetheless, a recent qualitative study acknowledged reduced caregiver capacity to work as an important factor in a patient centred model of care (Willgoss, 2020). There are now a number of active clinical trials aiming to improve cognitive functioning in FXS, with one recent study (Hessl et al., 2019) of 100 children and adolescents with FXS demonstrating modest improvements in working memory (WM) and executive functioning skills after undergoing intensive WM training using Cogmed (https://www.cogmed.com/). Similarly, there is some evidence for improvement in intellectual functioning with growth hormone use in PWS (Dykens et al., 2017), with early treatment (before 12 months of age) demonstrating better effects than those treated later (1 to 5 years of age; Dykens et al., 2017). Based on research demonstrating that the neural circuits in a child's brain are most adaptable in the first three years of life (Goode et al., 2011) interventions, particularly those targeting cognitive functioning may be most effective when implemented during this early developmental phase. Thus, if future additional targeted interventions became available that demonstrate efficacy in improving intellectual functioning in each syndrome, and the individuals are diagnosed as early as possible (in the 1st year of life) through newborn screening, this may result in significant cost savings to both the government and families.

Differences in Cost Utilisation

The study also demonstrated differences in cost utilisation across syndromes. In particular individuals with PWS had greater costs related to pharmaceutical use compared to those with FXS, AS or Dup15q syndrome. Higher medication costs in PWS are likely due to the specific comorbid issues experienced by these individuals including obesity and low muscle tone (treated with growth hormone) and hypothyroidism (treated with thyroxine). This finding is consistent with a large study from the USA demonstrating synthetic hormones, predominantly recombinant human growth hormone (rhGH) was a leading driver of medication costs in PWS, particularly for those aged between 5 and 17 years (Shoffstall et al., 2016).

Taken together these findings, have implications for funding schemes related to ID more generally (e.g., NDIS in Australia). Providing recommendations regarding allocation of funding based on the specific syndrome and their base set of needs and the specific comorbidities, may assist in informing these government funding schemes and significantly reduce government costs.

Strengths and Limitations

This study used a modified version of the CSRI that was adapted for the Australian setting but also to include items that were specific to each of the syndromes included in the study. This modified CSRI appears to have been successful in capturing disorder-specific resource utilisation and may be useful for health economic research in other rare disorders. A strength of this study is the detailed cost information reported across a wide range of resource use categories coupled with formal assessments of intellectual functioning and behavioural symptoms in a relatively large sample size for these syndromes.

A limitation of this study is that without a control group, estimates reported in this study may be overestimated as some medications and visits to health professionals may not be related to the disability itself. Nevertheless, care was taken to collect costs relating only to the disability where possible and costs potentially not related to the disability are likely to represent a small proportion of total costs. Conversely, the costs reported here are more likely to be a significant underestimation of costs incurred by families, as the time spent caring for the participant by primary caregivers was not reported in this study. Moreover, the psychological caregiver burden (e.g., stress, depression) associated with caring for children with these syndromes (Ouyang et al., 2010; Wulffaert et al., 2010), represents a potential source of underestimated lost opportunity cost (income) as well as high resource utilisation in the parents themselves (Ouyang et al., 2010). Further costs relevant under a societal perspective that were not able to be incorporated in the study included those associated with travel and time costs for medical

appointments, private health insurance, and early intervention programs and should also be considered in future health economic evaluations.

Additionally, the small sample sizes with wide age ranges likely influenced costing data. Specifically, special education and group home/residential care living costs were lower than expected for the AS and PWS groups, respectively. This is likely attributed to the AS group having a greater number of adult participants (not in education) and the PWS group having a small number of adults who may be more likely to be in residential care/group homes. Thus, while this study has provided initial costings related to raising and caring for children with these four rare syndromes in Australia, future research in larger independent samples is required. Addressing the limitations of this current study by collecting more specific disorder related data for medication and health professional visits as well as costings of lost employment and mental health service use of the carers would be highly beneficial. Another limitation of the current study is that data could not be analysed separately for the specific genetic sub-types of FXS, AS, PWS, and Dup15q syndrome, each with specific co-morbidities, due to the small number of individuals within each molecular class for these disorders.

Conclusions

The costs associated with raising and caring for individuals with FXS, PWS, AS and Dup15q syndrome are significant and experienced over a wide range of resource use categories including costs associated with out of home care, special education, group home/residential care living, government benefits, lost employment, medications, and visits to health professionals and hospitals. Significant reductions in total yearly costs were related to intellectual functioning across these syndromes, suggesting that the economic burden across these syndromes can be reduced by earlier diagnosis and targeted interventions.

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Table 1: Sample characteristics of FXS, PWS, AS and Dup15q syndrome

	FXS		PWS		AS		Dup15q syndrome	
	n	*M* (*SD*)	*n*	*M* (*SD*)	*n*	*M* (*SD*)	*n*	*M* (*SD*)
Age at assessment (yrs)	35	9.44 (9.24)	32	10.32 (10.40)	27	11.63 (9.75)	14	9.84 (7.18)
Age at diagnosis (mths)	34	29.71 (3.94)	32	18.50 (58.08)	27	52.85 (87.01)	13	30.81 (26.72)
cFSIQ	35	51.71 (22.74)	31	59.77 (15.95)	26	22.04 (12.93)	13	33.77 (26.09)
ABC UI	35	0.764 (0.148)	28	0.758 (0.181)	27	0.757 (0.111)	13	0.581 (0.200))
Irritability	35	8.40 (7.13)	28	9.36 (9.64)	27	7.19 (5.39)	13	13.77 (10.22)
Lethargy	35	4.43 (4.17)	28	6.25 (5.35)	27	3.63 (3.59)	13	11.31 (10.28)
Stereotypy	35	3.17 (3.16)	28	2.11 (3.00)	27	4.04 (4.01)	13	8.08 (5.68)
Hyperactivity	35	8.63 (7.73)	28	8.82 (9.03)	27	16.11 (10.43)	13	24.62 (15.77)
Inappropriate Speech	35	2.29 (3.11)	28	3.43 (3.21)	27	0.41 (0.93)	13	4.31 (3.92)
Social Avoidance	35	2.11 (2.70)	-	-	-	-	-	-
	n	%	*n*	%	*n*	%	*n*	%
% male	35	62.9%	32	46.9%	27	59.3%	14	57.1%
Children/Adolescents (< 18 yrs)	35	91.4%	32	81.1%	27	66.7%	14	92.9%
Children (< 5 yrs)	35	28.6%	32	37.5%	27	33.3%	14	28.6%
% seizures	35	11.4%	31	12.9%	27	74.1%	14	57.1%
Country of Birth								
Australia	34	97.1%	32	96.8%	27	96.3%	14	92.9%
Other	34	2.9%	32	3.1%	27	3.7%	14	7.1%
Primary Language								
English	33	97.0%	32	90.6%	27	100.0%	14	100.0%
Other	33	3.0%	32	9.4%	-	-	-	-
ASD (ADOS-2)	35	82.9%	27	70.4%	25	44.4%	11	100%

Abbreviations: ABC UI – Aberrant Behavior Checklist Utility Index; ADOS-2 – Autism Diagnostic Observation Schedule-2nd edition; AS – Angelman syndrome; ASD – autism spectrum disorder; cFSIQ – corrected full scale IQ; Dup15q – Chromosome 15q duplication syndrome; FXS – Fragile X syndrome; M – mean; PWS – Prader-Willi syndrome; SD – standard deviation.

Table 2: Mean costs relating to the participant's disability in the previous year by syndrome

Cost category	**FXS Total cost ($) (95%CI) N=35**	**PWS Total cost ($) (95%CI) N=32**	**AS Total cost ($) (95%CI) N=27**	**Dup15q Total cost ($) (95%CI) N=14**
Out of home care	5,332 (694 to 9971)	1,926 (358 to 3,494)	15,738 (1,921 to 29,553)	6,414 (-2,153 to 14,981)
Cost of purchasing and renting equipment	149 (44-253)	321 (82-560)	430 (276-584)	488 (175-802)
Government benefits	6,752 (2,651-10,583)	10,020 (4,905-15,134)	9,149 (3,668-14,631)	7,637 (724-14,549)
Inpatient and ED hospital admissions	NR	2,586 (-462-5,632)	4,794 (-360-9,947)	5,910 (-3,119-14,938)
Outpatient visits	5,469 (3,504-7,434)	6,303 (4,095-8,511)	5,181 (2,901-7,462)	8,386 (4,420-12,353)
Cost of medications	300 (100-500)	7,714 (4,909-10,520)	587 (364-810)	542 (-43-1127)
Special education	7,483 (3,500-12,186)	4,047 (1,489-6,645)	5,288 (868-9,707)	15,997 (7,979-24,014)
Group home/residential care living	NR	8,001 (-7,831-23,833)	28,449 (-2,775-59,674)	NR
Lost employment / employment taxation	3,735 (-1,553-9,024)	12,256 (3,189-21,322)	19,367 (7,785-30,949)	4,669 (-4,569-13,907)
Informal care (excl. primary caregivers)	4,534 (254-8,815)	5,909 (508-11,310)	8,320 (1,524-15,116)	2,674 (-1,533-6,881)
Transportation	1,869 (-701-4,440)	1,182 (567-1,797)	1,502 (687-2,317)	1,110 (69-2,150)

Total cost to government	**25,485 (16,068-34,092)**	**42,481 (25,844-78,086)**	**72,870 (39,554-106,187)**	**45,031 (31,472-58,591)**
Total cost to individual/family	**7,733 (2,747-12,719)**	**15,095 (7,249-22,941)**	**24,118 (14,346-33,889)**	**7,099 (-964-15,162)**
Total cost	**33,219 (23,653-42,784)**	**57,576 (37,030-78,123)**	**96,988 (59,025-134,951)**	**52,130 (36,091-68,169)**

Abbreviations: AS = Angelman syndrome; CI = confidence interval; Dup15q = Chromosome 15q duplication syndrome; ED = emergency department; FXS = Fragile X syndrome; PWS = Prader-Willi syndrome; NR = none reported.

Table 3: Regression analyses regressing total cost on diagnosis

Cost category	Total cost Coefficient N=106
Diagnosis (base FXS)	
PWS	19,731
AS	**53,892****
Dup15q	16,990
Sex (base male)	-10,882
Constant	27,630
R-squared	0.40

Note. Costings are relative to FXS, positive numbers indicate greater cost than FXS while negative costs indicate less than FXS. All models control for participant age, country of birth and primary language

Abbreviations: AS – Angelman syndrome; Dup15q – Chromosome Duplicate 15q syndrome; FXS – Fragile X syndrome; PWS – Prader-Willi syndrome;

***,**,* = Significant at the <0.001, 0.01 and 0.05 levels respectively

Table 4: Regression analyses (main effects only and interaction of diagnosis with FSIQ) regressing total cost on diagnosis, seizures, age of diagnosis, intellectual functioning, and behavioural problems

Cost category	Total cost Coefficient N=93	Interaction model (Diagnosis with FSIQ) N=93
Diagnosis (base FXS)		
PWS	21,874	74,312
AS	29,401	**151,951*** **
Dup15q	-10,435	3,184
FSIQ (cFSIQ)	**-734***	-351
Diagnosis (base FXS) x cFSIQ		
PWS	-	-928
AS	-	**-4,751*** **
Dup15q	-	107
Seizures	7,440	-8,919
ASD (ADOS-2)	2,841	-11,418
ABC-C UI	-87,946	-117,786
Age of diagnosis (mths)	129	37
Sex (base male)	-5,369	-11,291
Constant	115,378	**153,326***
R-squared	0.51	0.63

Note. Costings are relative to FXS, positive numbers indicate greater costs than FXS, while negative numbers indicate less costs than FXS. All models control for participant age, country of birth and primary language

Abbreviations: ABC-C UI – Aberrant Behavior Checklist-Community Utility Index ADOS-2 – Autism Diagnostic Observation Schedule-2nd edition; AS – Angelman syndrome; ASD – autism spectrum disorder; cFSIQ – corrected Full Scale IQ; Dup15q – Chromosome Duplication 15q syndrome; FXS – Fragile X syndrome; PWS – Prader-Willi syndrome.

***,**,* = Significant at the <0.001, 0.01 and 0.05 levels respectively.

Table 5: Marginal effect of FSIQ on total cost by diagnosis category

Cost category	Marginal effect ($)
Diagnosis	
FXS	-351
PWS	-1,278
AS	**-5,102*** **
Dup15q	-244

Abbreviations: AS – Angelman syndrome; Dup15q – Chromosome Duplication 15q syndrome; FXS – Fragile X syndrome; PWS – Prader-Willi syndrome.
***,**,* = Significant at the <0.001, 0.01 and 0.05 levels respectively.