ORIGINAL RESEARCH

Impacts of genomics on the health and social costs of intellectual disability

Brett Doble ,[1,2] Deborah Schofield,[1,3] Carey-Anne Evans,[4] Tudor Groza,[5] John S Mattick,[1,6] Mike Field,[7] Tony Roscioli[4,8]

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jmedgenet-2019-106445).

[1]Garvan Institute of Medical Research, Darlinghurst, New South Wales, Australia
[2]Programme in Health Services and Systems Research, Duke-NUS Medical School, Singapore, Singapore
[3]GenImpact, School of Economics, Faculty of Business and Economics, Macquarie University, Sydney, New South Wales, Australia
[4]Neuroscience Research Australia, Prince of Wales Clinical School, University of New South Wales, Randwick, New South Wales, Australia
[5]Pryzm Health, Gold Coast, Queensland, Australia
[6]St Vincent's Clinical School, University of New South Wales, Sydney, New South Wales, Australia
[7]The Genetics of Learning Disability Service, Waratah, New South Wales, Australia
[8]NSW Health Pathology East Laboratory, Prince of Wales Private Hospital, Randwick, New South Wales, Australia

Correspondence to
Dr Brett Doble, Garvan Institute of Medical Research, Darlinghurst, NSW 2010, Australia;
brett.doble@duke-nus.edu.sg

Received 16 July 2019
Revised 17 December 2019
Accepted 3 January 2020
Published Online First 24 January 2020

Check for updates

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To cite: Doble B, Schofield D, Evans C-A, *et al*. *J Med Genet* 2020;**57**:479–486.

ABSTRACT

Background This study provides an integrated assessment of the economic and social impacts of genomic sequencing for the detection of monogenic disorders resulting in intellectual disability (ID).

Methods Multiple knowledge bases were cross-referenced and analysed to compile a reference list of monogenic disorders associated with ID. Multiple literature searches were used to quantify the health and social costs for the care of people with ID. Health and social expenditures and the current cost of whole-exome sequencing and whole-genome sequencing were quantified in relation to the more common causes of ID and their impact on lifespan.

Results On average, individuals with ID incur annual costs in terms of health costs, disability support, lost income and other social costs of US$172 000, accumulating to many millions of dollars over a lifetime.

Conclusion The diagnosis of monogenic disorders through genomic testing provides the opportunity to improve the diagnosis and management, and to reduce the costs of ID through informed reproductive decisions, reductions in unproductive diagnostic tests and increasingly targeted therapies.

INTRODUCTION

Intellectual disability (ID) may be non-syndromic or syndromic, with various other body systems affected. Syndromic forms of ID may include those associated with epilepsy, inborn errors of metabolism and malformations of the central nervous system or other organs. Additional inherited conditions, such as cardiac and gastrointestinal syndromes associated with ID, may also occur, which in total result in almost 2000 disorders associated with ID. High-penetrance, single-gene disorders, many of which are not inherited and occur de novo,[1] account for approximately 20% of infant mortality[2] and 10% of paediatric hospitalisations,[3] with significant costs to the healthcare system and to families. Many children with a genetic disorder remain undiagnosed,[4] leading to poorly optimised management, recurrence estimates limited to empiric risks and a failure to address psychosocial morbidity.[5] Expensive and unproductive diagnostic odysseys have occurred frequently in the pregenomic era as a result of pursuing serial single-gene tests and invasive investigations, resulting in a low diagnostic yield for ID of ~20%.[6 7] Genomic testing has radically altered the rate of molecular diagnosis in individuals with monogenic disorders to approximately 50%.[1 8–10]

Along with the decreasing cost of sequencing, these improvements have facilitated the transition of genomic testing from a research endeavour to clinical diagnosis. There is limited economic evidence supporting this transition.[6 11–16] The available studies that attempt to determine the cost-effectiveness of genomic testing[1 12 17 18] do not employ standard methods for the economic evaluation of health technologies,[19] relying on simplified assumptions to estimate cost-effectiveness, largely due to lack of data to populate the models.[20 21]

We have focused specifically on monogenic forms of ID, which are common and often also associated with physical disability. Four knowledge bases, Deciphering Developmental Disorders (DDD) UK (https://decipher.sanger.ac.uk/genes), PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), Online Mendelian Inheritance in Man (OMIM) (https://www.omim.org) and Orphanet (https://www.orpha.net/consor/cgi-bin/index.php), were cross-referenced and analysed to compile a reference list of monogenic disorders associated with ID. The health and social expenditures as a result of both ID and physical disability were also estimated and contrasted with the current costs of genomic testing. The results provide the first integrated assessment of the potential economic impacts of genomic testing for ID and offer a foundation for additional economic evaluations of the comprehensive detection of monogenic disorders that result in significant disability.

MATERIALS AND METHODS

Information sources and search

The DDD UK, OMIM,[22] PubMed and Orphanet knowledge bases were integrated and cross-referenced to compile a comprehensive list of monogenic diseases associated with ID (online supplementary figure S1). Additional PubMed literature searches were carried out by clinical geneticists and senior scientists (TR, MF and C-AE) on genes and disorders that were present in two or fewer databases to assess that they were in fact ID-confirmed genes by confirming that likely pathogenic or pathogenic variants had been identified in more than one unrelated individual and in more than one family. Genes and disorders not fulfilling these criteria were excluded from online supplementary table S1. While this study summarises the top 100 genes as determined by the numbers of pathogenic alleles reported in DDD UK, there are approximately 2000 genes recognised where ID is part of

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the phenotype, all with significant impacts on morbidity and mortality.

Data items and synthesis of results

Diseases identified were categorised based on affected body system with data items extracted, when available, from the databases for each individual gene and associated syndromes. The choice of body system in syndromic ID was based on whether a predominant organ system was involved. Items included disease reference information (OMIM reference), the associated gene, the body system affected, and items that may influence the economic and social benefits of determining the genetic aetiology, such as inheritance pattern and impact of disease on longevity (coded as 1=less than 2 years of life, 2=death by adolescence and 3=adult life expectancy).

Cost analysis

Studies reporting the healthcare and social costs related to either ID or physical disability were identified in two additional literature searches. The literature searches were targeted, in that initial searches were conducted in PubMed and then modified for Google Scholar searches and included search terms from three different categories: genetic disease nomenclature, economic terminology and social impacts. Citations of any studies assessed as important by the authors were also reviewed in Google Scholar to broaden the search space. The objective was to integrate the available data to determine reliable estimates of the annual costs of caring for people with disability, and therefore, any study reporting healthcare and/or social costs related to ID and/or physical disability in a patient population diagnosed with a monogenic condition were included. Information from related conditions with similar levels of disability (such as autism spectrum disorder and cerebral palsy) was added to those where specific costings related to disability were not available or limited. Some assumptions were made when synthesising the extracted data from the identified studies. First, where data were available, costs specific to four age groups (children 0–17 years, young adults 18–29 years, adults 30–60 years and older adults >60 years) were identified. This was to ensure that health and social expenditures could be estimated over the entirety of an affected individuals lifespan (ie, majority of the common causes of ID are associated with a lifespan reaching adulthood). Further subdivisions in childhood costs based on age, and in adult costs based on employment status, were also synthesised due to the potential for variations in expenditures throughout childhood and adulthood, respectively.

Costs were further grouped based on the severity of the condition (mild, moderate and severe). Note that it was not always possible to ascertain the approach used by authors to classify patients as mild, moderate and severe, and therefore, classification into these groups across studies may not be consistent. For the purposes of our study, the groupings were largely based on the reporting of the terms mild, moderate and severe, rather than formal diagnostic criteria. Hence, there was a need to account for this uncertainty. Therefore, lower, middle and upper boundary estimates were determined for each subgroup when summing the costs to account for uncertainty. A pragmatic approach to estimating the lower, middle and upper bounds was taken, given the fact that more than three studies may have been available for a particular group and/or type of cost. In the most straightforward case (three studies available), the lower and upper boundary estimates were the minimum and maximum costs identified for that subgroup. In cases where four or more studies were identified, additional syntheses were required, which usually involved averaging identified estimates to obtain low, middle and upper estimates. A mean value was then calculated from the lower, middle and upper boundary estimates and presented with its associated range. When only one data source and SD was available, the mean was used as the middle boundary with plus and minus the SD to determine the upper and lower (fixed at 0 in cases of negative numbers) boundaries, respectively. Where only one data source was available and there was no measure of variance, the same estimate was used across all three boundaries. To account for the variability in use of certain high-cost services (such as accommodation), costs were adjusted based on the proportion of individuals reported to receive those services. For example, the accommodation costs for adults reported by Knapp *et al*[23] were estimated across four subgroups: (1) adults living in a private household, (2) adults living in supported accommodation, (3) adults living in residential care and (4) adults living in a hospital. Reported proportions of adults with ID in Australia living under each of these four categories[24] were therefore applied to the respective costs before totalling the costs to obtain the upper boundary estimate of accommodation costs for adults as well as elderly adults with ID. All costs were annualised (multiplied by 52 or 12 when initially reported as weekly or monthly costs, respectively), inflated and converted to 2018 US dollars using an appropriate component of a country-specific Consumer Price Index[25] or Wage Price Index,[26–29] depending on the country perspective taken in the original costing study, and rounded off in the text to two significant figures. All healthcare costs, accommodation costs, education costs and daytime activities were inflated to 2018 prices using country-specific Organisation for Economic Co-Operation and Development (OECD) all items non-food, non-energy Consumer Price Indexes. Income support and loss of productivity costs were inflated to 2018 prices using the public and private all industries Australian Wage Price Index (December 2018) for costs originally reported in Australian dollars[26] or a ratio of average annual nominal earnings for the years of interest for costs originally reported in British pound sterling,[27] or a ratio of the average hourly nominal production workers compensation for the years of interest for costs originally reported in US dollars,[28] or a ratio of the gross average monthly wages for the costs originally reported in Euros.[29] Carer costs (composed of informal care, external care and out-of-pocket costs) were inflated to 2018 prices using the public and private all industries Australian Wage Price Index (December 2018) for costs originally reported in Australian dollars[26] or a ratio of average annual nominal earnings for the years of interest for costs originally reported in British pound sterling,[27] or a ratio of the average hourly nominal production workers compensation for the years of interest for costs originally reported in US dollars,[28] or a ratio of the gross average monthly wages for the costs originally reported in Euros,[29] or using country-specific OECD all items non-food, non-energy Consumer Price Indexes[25] (out-of-pocket costs). All data used in the costing analysis and methods used to calculate the low, middle and upper estimates are provided in online supplementary excel file 1.

Disability costs were separated into healthcare and social costs for intellectual and physical disability. Healthcare costs included hospital services, community services and treatment/aids/adaptations costs. Social costs included accommodation, education, daytime activities, income support (benefit payments, disability

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support services and employment support), carer costs (informal care, external care, out-of-pocket and travel costs) and loss of productivity (carer and individual).

RESULTS

Identifiable monogenic disorders associated with disability

The most frequent aetiologies for ID detectable through clinical genomic sequencing are presented in online supplementary table S1.

The costs of ID

Eighteen costing studies of ID were identified that reported either healthcare or social costs for at least one of the subgroups of interest.[23 24 30–45] A synthesis of these costs is detailed in table 1, and the respective references used in each calculation are provided in online supplementary table S2.

Total healthcare costs associated with ID increased with age and severity of the disability until individuals reached adulthood. Healthcare costs were relatively smaller for children between the ages of 0 and 3 years regardless of the severity of the disability (range $10 000–$19 000) and were largest for children with a severe disability between the ages of 12 and 17 years (range $17 000–$37 000).

It has been underappreciated that the total costs of ID are driven substantially by social costs and that these are considerably larger than the associated healthcare costs. Total social costs associated with ID also increased with age and the severity of the disability until individuals reached young adulthood (ages 18–29 years), with one exception. Paradoxically, total costs for children 0–3 years were larger for those with moderate ID ($69 000) compared with those with severe ID ($64 000). This is largely driven by lower income support and higher informal care costs for children with moderate ID and may be the result of those with severe ID being more able to access external formal care services, thus reducing demand for informal family-based care. As children reached the ages of 4–11 years, the social costs increase substantially ($62 000–$246 000) largely due to the cost of special education and carer costs, and increase with severity of disability. Social costs for young adults are the largest compared with the other age groups, primarily due to the accommodation costs, and increase with disability severity ($144 000–$294 000).

Total costs increased by severity of ID and age, although costs were a little lower for older adults than those in young adulthood ($37 000–$90 000 for children age 0–3, $152 000–329 000 for young adults and $108 000–$252 000 for elderly adults).

The costs of physical disability

Of the 18 studies reporting the costs of ID, only 6[36 39 40 42 43 45] specifically provided details of whether or not the patient population assessed also suffered from physical disability. When specified, however, physical disability usually only affected a small proportion of the sample in addition to ID, making it difficult to ascertain what costs where attributable to only ID or only physically disability. Therefore, nine costing studies for the care of people with physical disability were identified that reported either healthcare or social costs for at least one of the age ranges, levels of severity and/or employment status.[46–54] Note that only two studies[49 50] indicated that a small proportion of their patient samples may also have some form of mild ID. A synthesis of the costs reported in these studies is detailed in table 2 and the respective references used in each calculation are also provided in online supplementary table S3.

Total healthcare costs related to physical disability were greatest for children with severe physical disability, ranging from $647 000 to $961 000 (hospital-based care) and from $31 000 to $69 000 (home-based care). Healthcare costs for the young adult and adult groups were considerably lower compared with the two child groups, ranging from $1400 to $5600 and from $8400 to $11 000, respectively.

Total social costs associated with physical disability were greatest in childhood as a result of relatively large benefit payments, travel costs, external care costs and carer loss of productivity. Unemployed young adults had very similar but slightly larger total social costs (range $34 000–$101 000) compared with unemployed adults (range $34 000–$97 000) due to the assumption that young adults incur some education costs in addition to daytime activity costs. Differences in total social costs between employed and unemployed young adults/adults were largely driven by the inclusion of carer loss of productivity only for employed individuals compared with the inclusion of both carer and individual loss of productivity for unemployed individuals.

The total costs of physical disability are the largest for children with a severe disability between the ages 0 and 17 years, ranging from $80 000 to $1.1 million. These very high total costs are the result of the extreme severity of disability in the child population (ventilator-dependent children) from the main study used in our analysis. These total costs may therefore only be incurred by a small proportion of children with disabilities. However, even if a small number of children incur these costs, the magnitude of the costs in treating and supporting these children will have substantial impacts on total expenditure for all children with a disability.

DISCUSSION

The overall economic cost of caring for people with ID is extremely high, for families, health systems and society. These costs average $172 000 per person per year and have been significantly underestimated. Similar to a 'submerged iceberg', the healthcare costs associated with ID are largely apparent to both healthcare providers and decision makers, but much greater hidden social costs remain unappreciated. Compared with existing studies that have estimated the costs associated with ID,[31 33 41] our estimates are comprehensive and therefore much larger. Our estimates include all relevant costs incurred both within the healthcare system and broader society, whereas other studies have limited their assessments to only certain types of social costs[33] or largely focused on healthcare costs and only a few types of social costs, with limited consideration of the full spectrum of costs affecting broader society.[31 41]

Currently, genomic testing in people with Mendelian disorders relies largely on whole-exome sequencing (WES) as a first-pass investigative methodology. WES trios including unaffected parents and an affected child are now routinely sequenced to increase test efficiency and utility as a significant proportion of people with ID have a de novo disease aetiology.[55] The sequencing costs associated with WES have now fallen and are reported to be at least US$500 per person.[20] The costs of whole-genome sequencing (WGS) are higher but have fallen markedly in recent years and are reported to be at least US$1700 per person for DNA sequencing.[20] Incorporating the cost of variant interpretation increases costs by ~US$450[56] plus the costs of computing infrastructure and data storage (~US$100 per genome).[57] Data analysis and interpretation costs are, however, decreasing for both WES and WGS as genotype–phenotype correlation databases[58] are populated and converted into automated queries.

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Table 1 Costs of intellectual disability per annum by age and severity of disability (2018, US$)

	Healthcare costs* (mean (lower and upper boundaries))				Social costs (mean (lower and upper boundaries))							Total costs (mean (lower and upper boundaries))
Age (years)/severity group	Hospital services costs	Community services costs	Treatment/aids/ adaptations costs	Total healthcare costs	Accommodation costs†	Education costs‡	Daytime activities costs§	Income support¶	Carer costs**	Loss of Productivity¶	Total social costs	Healthcare and social costs)
Children 0–3/mild	$13 431 (9222–17 639)	$962 (962)	$40 (26–55)	$14 432 (10 210–18 655)	$984 (374–1536)	$2521 (0–3782)	$6163 (0–13 029)	$12 154 (11 848–12 390)	$14 370 (14 370)	$10 321 (0–22 995)	$46 514 (26 592–68 102)	$60 946 (36 802–86 757)
Children 0–3/moderate	$13 431 (9222–17 639)	$962 (962)	$40 (26–55)	$14 432 (10 210–18 655)	$984 (374–1536)	$2521 (0–3782)	$6163 (0–13 029)	$11 626 (10 661–12 390)	$23 316 (23 316)	$10 321 (0–22 995)	$54 931 (34 350–77 048)	$69 364 (44 560–95 703)
Children 0–3/severe/profound	$13 431 (9222–17 639)	$962 (962)	$187 (93–280)	$14 579 (10 277–18 881)	$984 (374–1536)	$2521 (0–3782)	$6163 (0–13 029)	$12 615 (12 390–12 885)	$16 762 (16 762)	$10 321 (0–22 995)	$49 366 (29 526–70 989)	$63 945 (39 803–89 869)
Children 4–11/mild	$9297 (3175–17 639)	$5893 (431–11 355)	$929 (55–1802)	$16 119 (3662–30 796)	$3092 (1418–3949)	$41 594 (17 273–71 996)	$12 405 (11 781–13 029)	$12 476 (11 848–12 988)	$46 764 (15 787–77 741)	$12 662 (3506–22 995)	$129 007 (61 613–202 698)	$145 126 (65 275–233 493)
Children 4–11/moderate	$9297 (3175–17 639)	$5893 (431–11 355)	$929 (55–1802)	$16 119 (3662–30 796)	$3092 (1418–3949)	$41 594 (17 273–71 996)	$12 405 (11 781–13 029)	$11 948 (10 661–12 988)	$61 654 (24 732–98 575)	$12 662 (3506–22 995)	$143 369 (69 371–223 532)	$159 488 (73 033–254 327)
Children 4–11/severe/ profound	$9297 (3175–17 639)	$5893 (431–11 355)	$1075 (123–2028)	$16 266 (3730–31 021)	$3092 (1418–3949)	$41 594 (17 273–71 996)	$12 405 (11 781–13 029)	$12 772 (12 390–12 988)	$69 747 (18 178–121 315)	$12 662 (3506–22 995)	$152 286 (64 547–246 272)	$168 551 (68 276–277 293)
Children 12–17/mild	$7296 (3771–12 322)	$544 (431–657)	$926 (50–1802)	$8767 (4253–14 782)	$3494 (1736–4836)	$40 759 (31 994–47 020)	$6890 (706–13 029)	$12 395 (11 848–12 843)	$46 135 (14 528–77 741)	$12 653 (3443–23 032)	$122 326 (64 255–178 501)	$131 093 (68 508–193 283)
Children 12–17/moderate	$7296 (3771–12 322)	$544 (431–657)	$926 (50–1802)	$8767 (4253–14 782)	$3494 (1736–4836)	$40 759 (31 994–47 020)	$6890 (706–13 029)	$11 868 (10 661–12 843)	$61 024 (23 474–98 575)	$12 653 (3443–23 032)	$136 688 (72 013–199 335)	$145 455 (76 266–214 117)
Children 12–17/severe/ profound	$7296 (3771–12 322)	$17 904 (12 821–22 988)	$1073 (118–2028)	$26 274 (16 710–37 338)	$3494(1736–4836)	$40 759 (31 994–47 020)	$6890 (706–13 029)	$12 691 (12 390–12 843)	$69 117 (16 920–121 315)	$12 653 (3443–23 032)	$145 605 (67 189–222 076)	$171 878 (83 899–259 413)
Young adult 18–29/mild	$17 401 (7541–31 076)	$1398 (955–2110)	$136 (121–150)	$18 935 (8617–33 337)	$73 161 (51 511–86 335)	$2689 (1321–3758)	$8567 (3774–13 360)	$13 900 (11 848–15 541)	$74 503 (59 554–86 215)	$29 412 (15 495–40 604)	$202 232 (143 503–245 812)	$221 167 (152 120–279 149)
Young adult 18–29/moderate	$17 401 (7541–31 076)	$1398 (955–2110)	$136 (121–150)	$18 935 (8617–33 337)	$73 161 (51 511–86 335)	$2689 (1321–3758)	$8567 (3774–13 360)	$13 372 (10 661–15 541)	$91 374 (74 444–98 575)	$29 412 (15 495–40 604)	$218 575 (157 205–260 702)	$237 511 (165 823–294 039)
Young adult 18–29/severe/ profound	$17 401 (7541–31 076)	$2966 (1930–4002)	$282 (189–376)	$20 650 (9661–35 454)	$80 854 (51 511–99 169)	$2689 (1321-3758)	$8567 (3774–13 360)	$14 361 (12 885–15 541)	$104 350 (82 537–121 315)	$29 412 (15 495–40 604)	$240 233 (167 523–293 747)	$260 883 (177 184–329 201)
Adult 30–59/mild	$17 401 (7541–31 076)	$1398 (955–2110)	$136 (121–150)	$18 935 (8617–33 337)	$60 331 (21 390–86 335)	$0 (0)	$13 598 (9891–15 857)	$13 900 (11 848–15 541)	$74 503 (59 554–86 215)	$29 412 (15 495–40 604)	$191 744 (118 177–244 552)	$210 679 (126 794–277 889)
Adult 30–59/moderate	$17 401 (7541–31 076)	$1398 (955–2110)	$136 (121–150)	$18 935 (8617–33 337)	$63 061 (21 390–86 335)	$0 (0)	$13 413 (9891–15 857)	$13 372 (10 661–15 541)	$91 374 (74 444–98 574)	$29 412 (15 495–40 604)	$210 633 (131 880–259 442)	$229 568 (140 497–292 779)
Adult 30–59/severe/profound	$17 401 (7541–31 076)	$2966 (1930–4002)	$282 (189–376)	$20 650 (9661–35 454)	$75 890 (55 740–91 882)	$0 (0)	$7538 (6398–9344)	$14 361 (12 885–15 541)	$104 350 (82 537–121 315)	$29 412 (15 495–40 604)	$231 550 (173 054–278 686)	$252 200 (182 715–314 140)
Elderly adult >60/mild	$2316 (1199–3434)	$2402 (1858–2946)	$100 (75–126)	$4818 (3131–6506)	$60 331 (21 390–86 335)	$0 (0)	$11 522 (9528–13 515)	$13 419 (11 848–14 675)	$75 537 (60 026–87 810)	$2262 (2211–2329)	$162 669 (105 121–204 547)	$167 487 (108 252–211 052)
Elderly adult >60/moderate	$2316 (1199–3434)	$2402 (1858–2946)	$100 (75–126)	$4818 (3131–6506)	$63 061 (21 390–86 335)	$0 (0)	$11 522 (9528–13 515)	$12 891 (10 661–14 675)	$92 408 (74 916–99 609)	$2262 (2211–2329)	$181 743 (118 824–219 437)	$186 561 (121 955–225 942)
Elderly adult >60/severe/ profound	$2316 (1199–3 434)	$2402 (1858–2946)	$247 (142–351)	$4965 (3199–6731)	$75 890 (55 740–91 882)	$0 (0)	$11 522 (9528–13 515)	$13 880 (12 885-14 675)	$105 384 (83 009–122 910)	$2262 (2211–2329)	$208 535 (163 491–245 193)	$213 500 (166 690–251 925)

*All healthcare costs (hospital, community and treatment) were inflated to 2018 prices using country-specific OECD all items non-food, non-energy Consumer Price Indexes.[25]
†Accommodation costs were inflated to 2018 prices using country-specific OECD all items non-food, non-energy Consumer Price Indexes.[25]
‡Education costs were inflated to 2018 prices using country-specific OECD all items non-food, non-energy Consumer Price Indexes.[25]
§Daytime activities costs were inflated to 2018 prices using country-specific OECD all items non-food, non-energy Consumer Price Indexes.[25]
¶Income support and loss of productivity costs were inflated to 2018 prices using the public and private all industries Australian Wage Price Index (December 2018) for costs originally reported in Australian dollars[26] or a ratio of average annual nominal earnings for the years of interest for costs originally reported in British pound sterling,[27] or a ratio of the average hourly nominal production workers compensation for the years of interest for costs originally reported in US dollars.[28]
**Carer costs (composed of informal care, external care and out-of-pocket costs) were inflated to 2018 prices using the public and private all industries Australian Wage Price Index (December 2018) for costs originally reported in Australian dollars[26] or a ratio of average annual nominal earnings for the years of interest for costs originally reported in British pound sterling,[27] or a ratio of the average hourly nominal production workers compensation for the years of interest for costs originally reported in US dollars[28] (informal and external carer costs), or using country-specific OECD all items non-food, non-energy Consumer Price Indexes[25] (out-of-pocket costs).
OECD, Organisation for Economic Co-Operation and Development.

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Table 2 Costs of physical disability per annum by age, severity of disability and employment status (2018, US$)

	Healthcare costs* (mean (lower and upper boundaries))				Social costs (mean (lower and upper boundaries))							Total costs (mean (lower and upper boundaries))
Age (years)/severity group	Hospital services costs	Community services costs	Treatment/aids/ adaptations costs	Total healthcare costs	Accommodation costs†	Education costs‡	Daytime activities costs§	Income support¶	Carer costs**	Loss of productivity¶	Total social costs	(Healthcare and social costs)
Children 0–17/severe at home	$16 118 (0–31 141)	$5984 (5984)	$28 296 (25 310–31 388)	$50 398 (31 294–68 513)	$0 (0)	$12 418 (1179–23 657)	$0 (0)	$12 220 (12 220)	$64 286 (10 601–117 971)	$24 988 (24 988)	$113 911 (48 987–178 836)	$164 309 (80 280–247 348)
Children 0–17/severe in hospital	$775 850 (627 516–924 184)	$10 549 (10 549)	$17 374 (8842–26 000)	$803 773 (646 907–960 733)	$0 (0)	$7795 (0–16 726)	$0 (0)	$12 220 (12 220)	$49 686 (7693–94 488)	$30 234 (30 234)	$99 935 (50 147–153 668)	$903 708 (697 054–1 114 401)
Young adults 18–29/employed	$164 (164)	$1914 (578–2846)	$1682 (639–2562)	$3760 (1381–5572)	$2955 (2648–3568)	$0 (0)	$889 (0–1992)	$365 (365)	$12 814 (0–20 511)	$14 494 (10 981–17 711)	$31 516 (13 994-44 147)	$35 276 (15 375–49 719)
Young adults 18–29/ unemployed	$164 (164)	$1914 (578–2846)	$1682 (639–2562)	$3760 (1381–5572)	$2955 (2648–3568)	$2919 (0–4379)	$1992 (1992)	$8236 (8236)	$12 814 (0–20 511)	$44 354 (20 988–62 557)	$73 269 (33 863–101 243)	$77 029 (35 244–106 815)
Adults 30–60/employed	$7752 (7752)	$219 (0–353)	$1682 (639–2562)	$9652 (8390–10 666)	$2955 (2648–3568)	$0 (0)	$889 (0–1992)	$365 (365)	$12 814 (0–20 511)	$14 494 (10 981–17 711)	$31 516 (13 994–44 147)	$41 168 (22 384–54 814)
Adults 30–60/unemployed	$7752 (7752)	$219 (0–353)	$1682 (639–2562)	$9652 (8390–10 666)	$2955 (2648–3568)	$0 (0)	$1992 (1992)	$8236 (8236)	$12 814 (0–20 511)	$44 354 (20 988–62 557)	$70 350 (33 863–96 864)	$80 002 (42 253–107 530)

*All healthcare costs (hospital, community and treatment) were inflated to 2018 prices using country-specific OECD all items non-food, non-energy Consumer Price Indexes.[25]
†Accommodation costs were inflated to 2018 prices using country-specific OECD all items non-food, non-energy Consumer Price Indexes.[25]
‡Education costs were inflated to 2018 prices using country-specific OECD all items non-food, non-energy Consumer Price Indexes.[25]
§Daytime activities costs were inflated to 2018 prices using country-specific OECD all items non-food, non-energy Consumer Price Indexes.[25]
¶Income support and loss of productivity costs were inflated to 2018 prices using the public and private all industries Australian Wage Price Index (December 2018) for costs originally reported in Australian dollars[26] or a ratio of average annual nominal earnings for the years of interest for costs originally reported in British pound sterling,[27] or a ratio of the average hourly nominal production workers compensation for the years of interest for costs originally reported in US dollars,[28] or a ratio of the gross average monthly wages for the costs originally reported in Euros.[29]
**Carer costs (composed of informal care, external care and out-of-pocket costs) were inflated to 2018 prices using the public and private all industries Australian Wage Price Index (December 2018) for costs originally reported in Australian dollars[26] or a ratio of average annual nominal earnings for the years of interest for costs originally reported in British pound sterling,[27] or a ratio of the average hourly nominal production workers compensation for the years of interest for costs originally reported in US dollars,[28] or a ratio of the gross average monthly wages for the costs originally reported in Euros[29] (informal and external carer costs), or using country-specific OECD all items non-food, non-energy Consumer Price Indexes[25] (out-of-pocket costs).
OECD, Organisation for Economic Co-Operation and Development.

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Costs associated with clinical follow-up appointments, investigations and referrals also increase overall costs associated with genomic sequencing. These additional costs have been estimated to be approximately US$1000 per patient.[59]

Genomic testing may identify additional aetiologies in ~50% of patients undiagnosed by chromosome microarray.[8] WGS achieves a higher diagnostic rate for genetic disorders than WES[60 61] because of better coverage of protein-coding sequences and higher sensitivity for other types of mutations.[10] This equates to a potential total diagnosis rate of ~75% if genomic testing combined with chromosome microarray is used as a first-line testing approach.[7 10]

Genomic testing can result in a reduction in the time to a clinical diagnosis to under a week, resulting in fewer expensive and invasive diagnostic tests, and faster progression to gene-specific genetic counselling.[62] Genomic testing may also result in patients being referred to a clinical geneticist and/or an appropriate specialist earlier in the diagnostic odyssey, avoiding inefficient use of healthcare resources. The costs of prior negative diagnostic testing in patients who eventually receive a diagnosis through either traditional genetic diagnostic evaluations or genomic testing have been estimated to be between US$19 000[1] and US$25 000.[6] By contrast, genomic testing can result in savings to the healthcare system that exceed the costs of generating the data and undertaking the analysis for the entire tested cohort.[61]

As novel causes of ID are identified, the number of treatable forms of ID is expected to increase as new therapies are developed.[63] Although newborn screening is important to ensure optimal lifetime health outcomes for treatable conditions, it is unlikely that, in the short term, many effective treatments linked to genomic testing for ID will be available.[64] There are, however, many existing management options and therapies for ID, the costs of which are captured in table 1. Thus, improved diagnosis through genomic testing is unlikely to have a large impact on social expenditures for affected individuals in the short term.

The refinement of recurrence risk through gene identification has important impacts on families and the choices available to them. When the risk is high, it facilitates access to reproductive testing, such as prenatal diagnosis and in vitro fertilisation with preimplantation genetic screening. When the risk is low with the diagnosis of a de novo ID aetiology, reproductive confidence is often restored, the consequences being an increased number of healthy children. Increased reproductive options based on the availability of a specific molecular diagnosis are beginning to affect health and social expenditure, while emerging targeted treatments may also have a significant impact in the future. In the first instance, a corrected appreciation of the overall costs for people living with significant disabilities should allow for more appropriate levels of societal funding to enable improved living standards and appropriate allocation of healthcare and daily living resources.

Genomic testing has expanded into clinical settings and has replaced traditional diagnostic methods primarily early in life for Mendelian disorders.[65] The benefits of WES and WGS show the highest current utility in monogenic disorders such as ID. As genomic diagnostics replace single-gene testing, not only will savings of US$19 000-$25 000[1 6] that would have been expended on diagnostic odysseys accrue, but also such testing will also provide cumulative benefits throughout life such as preconception carrier screening and pharmacogenomics testing. Genomic diagnostics is, however, unlikely to replace inexpensive screening methodologies such as tandem mass spectrometry in the foreseeable future, with such testing remaining important due to its accuracy, low cost and ability to provide functional data.

This is one of the first studies to review and synthesise the potential economic and social benefits of implementing genomic testing. It also provides one of the most comprehensive syntheses of the healthcare and social costs of intellectual and physical disability as they relate to genetic disorders. This study therefore provides a foundation for more robust economic evaluations of genomic testing in ID.

The majority of studies (62%) used in our costing analysis of intellectual and physical disability were conducted in the UK, resulting potentially in cost distortions when applied to different countries. To account for this, lower, middle and upper boundary estimates were derived, and a mean value with its associated range was calculated to account for this uncertainty. Due to the limited data available concerning the cost of disability related to genetic conditions, it was considered reasonable to assume that cost estimates from conditions resulting in a similar type and degree of disability were comparable. Only 7[23 32 33 46 47 49 51] of the 27 studies used in the cost analysis reported the costs of intellectual and physical disability as the amount excess of routine healthcare and social expenditures (ie, attributable to disability only) (references highlighted in bold in online supplementary tables S2 and S3). Adjusting for population-level health and social expenditures would, however, be unlikely to alter our total cost estimates significantly due to the magnitude of the total health and social costs reported in our study. Finally, despite our costing analysis, including a wide range of healthcare and social costs, some costs were not captured (ie, there were limited data on the costs of aids and modifications), and so the costs presented here still represent an underestimate.

There are advantages of providing access to genomic testing for families with a child with ID as de novo events will be the aetiology in about 50% of cases: a single genomic investigation can therefore restore reproductive confidence by providing recurrence information and reassurance. The interpretation of individual genomic data will be iterative and its value will increase rapidly as genomic variants are integrated with population clinical information in genotype–phenotype databases.[13] Such international databases need to be established and maintained to provide privacy-protected genomic and linked medical information for evidence-based care. The availability of genotype–phenotype databases will improve the clinical utility of genomics and assist with targeting healthcare resources. The use of increasingly well-populated genotype–phenotype databases will also dramatically reduce the costs of analysis by correlating variants with clinical features. The availability of lower cost genomic testing combined with a high diagnostic utility and the potential to restore reproductive confidence will result in genomic testing becoming the standard for diagnostic medicine.

This study has produced a comprehensive accumulated dataset of the costs associated with the care of people with ID throughout life, which exceed many millions of dollars per person. The cost of care is many fold higher than that considered in the older literature and highlights the chasm between the support that people with ID and their families require and the low levels of current funding. These updated health and social costs should become the new reference point for the provision of appropriate funding support for people living with disabilities.

Contributors Conceptualisation: BD, DS, JSM and TR; methodology: BD, DS, TG, MF and TR; formal analysis and investigation: BD, C-AE, TG and MF; writing (original

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draft preparation): BD; writing (review and editing): DS, C-AE, TG, JSM, MF and TR; supervision: DS, JSM and TR; overall content guarantor: BD.

Funding TR, DS, MF, TG and C-AE were supported through the National Health and Medical Research Council (NHMRC) Centre for Research Excellence in Neurocognitive Disorders (grant ID 1117394).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iD
Brett Doble http://orcid.org/0000-0002-4948-8831

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Supplemental Information

The supplemental information includes a comprehensive list of genes and loci (Table S1) associated with intellectual disability along with data items, including when available, OMIM reference, associated gene(s), DECIPHER alleles, impact on mortality, and inheritance pattern. Table S2 and Table S3 list the references used in each calculation for the costs of intellectual and physical disability presented in Table 1 and Table 2 respectively in the main manuscript and an excel file (Supplementary Excel file 1) that provides all the data used in the costing analyses and the methods used to calculate the low, middle and upper estimates for each cost category (note this is a separate file to this document). Figure S1 provides a PRISMA flow diagram that details how monogenic diseases associated with intellectual disability were ascertained. A table of contents is provided listing each supplemental resource individually.

Table of Contents

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Table S1. The most frequent intellectual disability etiologies

Disease	OMIM	Gene	DECIPHER Alleles	Body System	Inheritance	Longevity[a]
KBG syndrome	148050	*ANKRD11*	*99*	Intellectual Disability Syndromic	Autosomal dominant	3
16q24.3 microdeletion syndrome		*ANKRD11*	*99*	Chromosomal	Autosomal dominant	3
Monosomy 22q13	606232	*SHANK3*	*98*	Chromosomal	Autosomal dominant	3
X-linked non-syndromic intellectual disability	300055	*MECP2*	*83*	Intellectual Disability Non-Syndromic	X-linked recessive	3
Rett syndrome	312750	*MECP2*	*83*	Intellectual Disability Syndromic	X-linked dominant	3
Wiedemann-Steiner syndrome	605130	*KMT2A*	*72*	Intellectual Disability Syndromic	Autosomal dominant	3
Coffin-Siris syndrome	135900	*ARID1B*	*67*	Intellectual Disability Syndromic	Autosomal dominant	3
Nicolaides-Baraitser syndrome	601358	*ARID1B*	*67*	Intellectual Disability Syndromic	Autosomal dominant	3
6q25 microdeletion syndrome	612863	*ARID1B*	*67*	Chromosomal	Autosomal dominant	3
Mental retardation, X-linked 102	300958	*DDX3X*	*65*	Intellectual Disability Non-Syndromic	X-linked dominant	3
Mental retardation, autosomal dominant 7	614104	*DYRK1A*	*60*	Intellectual Disability Non-Syndromic	Autosomal dominant	3
Autosomal recessive non-syndromic intellectual disability	249500	*MED13L*	*57*	Intellectual Disability Non-Syndromic	Autosomal recessive	3
Kleefstra syndrome due to a point mutation	610253	*EHMT1*	*55*	Intellectual Disability Syndromic	Autosomal dominant	3
9q34 microdeletion syndrome	610253	*EHMT1*	*55*	Chromosomal	Autosomal dominant	3
Microphthalmia, Lenz type	309800	*NAA10*	*54*	Ophthalmological	X-linked recessive	3

Doble B, *et al. J Med Genet* 2020;0:1–8. doi: 10.1136/jmedgenet-2019-106445

Disease	OMIM	Gene	DECIPHER Alleles	Body System	Inheritance	Longevity[a]
Periventricular nodular heterotopia	300049	*FLNA*	*53*	Central Nervous System	X-linked dominant	3
Frontometaphyseal dysplasia	305620	*FLNA*	*53*	Skeletal Dysplasias	X-linked dominant	3
Osteodysplasty, Melnick-Needles type	309350	*FLNA*	*53*	Skeletal Dysplasias	X-linked dominant	3
Otopalatodigital syndrome type 1	311300	*FLNA*	*53*	Skeletal Dysplasias	X-linked dominant	3
X-linked non-syndromic intellectual disability	309530	*IQSEC2*	*51*	Intellectual Disability Non-Syndromic	X-linked recessive	3
Severe intellectual disability-progressive postnatal microcephaly- midline stereotypic hand movements syndrome	309530	*IQSEC2*	*51*	Intellectual Disability Syndromic	X-linked recessive	3
Alpha-thalassemia - X-linked intellectual disability syndrome	301040	*ATRX*	*50*	Intellectual Disability Syndromic	X-linked recessive	3
Mental retardation hypotonic face syndrome	309580	*ATRX*	*50*	Intellectual Disability Syndromic	X-linked recessive	3
Epileptic encephalopathy, early infantile, 11	613721	*SCN2A*	*50*	Epilepsy Syndromes	Autosomal dominant	2
West syndrome	613721	*SCN2A*	*50*	Epilepsy Syndromes	Autosomal dominant	2
Glass syndrome	612313	*SATB2*	*49*	Intellectual Disability Syndromic	Autosomal dominant	3
2q33.1 microdeletion syndrome	612313	*SATB2*	*49*	Chromosomal	Autosomal dominant	3
Mental retardation, autosomal dominant 23 (Intellectual disability-facial dysmorphism syndrome due to SETD5 haploinsufficiency	615761	*SETD5*	*48*	Intellectual Disability Syndromic	Autosomal dominant	3
Cornelia de Lange syndrome 2	300590	*SMC1A*	*48*	Intellectual Disability Syndromic	X-linked recessive	3

Disease	OMIM	Gene	DECIPHER Alleles	Body System	Inheritance	Longevity[a]
Rubinstein-Taybi syndrome due to CREBBP mutations	180849	*CREBBP*	*46*	Intellectual Disability Syndromic	Autosomal dominant	3
Rubinstein-Taybi syndrome due to 16p13.3 microdeletion	610543	*CREBBP*	*46*	Chromosomal	Autosomal dominant	3
Koolen-De Vries syndrome due to a point mutation	610443	*KANSL1*	*46*	Intellectual Disability Syndromic	Autosomal dominant	3
17q21.31 microdeletion syndrome	610443	*KANSL1*	*46*	Chromosomal	Autosomal dominant	3
X-linked intellectual disability, Najm type (MICPCH)	300749	*CASK*	*44*	Intellectual Disability Syndromic	X-linked dominant	3
Early infantile epileptic encephalopathy		*CASK*	*44*	Epilepsy Syndromes	X-linked recessive	3
Duchenne muscular dystrophy	310200	*DMD*	*44*	Neuromuscular	X-linked recessive	3
Helsmoortel-van der Aa syndrome	615873	*ADNP*	*42*	Intellectual Disability Syndromic	Autosomal dominant	3
Smith-Magenis syndrome	182290	*RAI1*	*42*	Intellectual Disability Syndromic	Autosomal dominant	3
17p11.2 microduplication syndrome (Potocki-Lupski syndrome)	610883	*RAI1*	*42*	Chromosomal	Autosomal dominant	3
Mental retardation, autosomal dominant 5	612621	*SYNGAP1*	*40*	Intellectual Disability Non-Syndromic	Autosomal dominant	3
Severe feeding difficulties - failure to thrive - microcephaly due to ASXL3 deficiency (Bainbridge-Ropers syndrome)	615485	*ASXL3*	*39*	Intellectual Disability Syndromic	Autosomal dominant	3
Autosomal dominant non-syndromic intellectual disability		*TCF4*	*39*	Intellectual Disability Non-Syndromic	Autosomal dominant	3

Disease	OMIM	Gene	DECIPHER Alleles	Body System	Inheritance	Longevity[a]
Pitt-Hopkins syndrome	610954	*TCF4*	*39*	Intellectual Disability Syndromic	Autosomal dominant	3
Rubinstein-Taybi syndrome 2 (due to EP300 haploinsufficiency)	613684	*EP300*	*38*	Intellectual Disability Syndromic	Autosomal dominant	3
Mental retardation, autosomal dominant 9	614255	*KIF1A*	*38*	Intellectual Disability Non-Syndromic	Autosomal dominant	3
Neurofibromatosis type 1 due to NF1mutation or intragenic deletion	162200	*NF1*	*38*	Intellectual Disability Syndromic	Autosomal dominant	3
17q11 microdeletion syndrome	613675	*NF1*	*38*	Chromosomal	Autosomal dominant	3
17q11.2 microduplication syndrome	613675	*NF1*	*38*	Chromosomal	Autosomal dominant	3
Beta-propeller protein-associated neurodegeneration	300894	*WDR45*	*38*	Intellectual Disability Syndromic	X-linked dominant	3
Okur-Chung neurodevelopmental syndrome	617062	*CSNK2A1*	*37*	Intellectual Disability Syndromic	Autosomal dominant	3
Mental retardation, autosomal dominant 6	613970	*GRIN2B*	*37*	Intellectual Disability Non-Syndromic	Autosomal dominant	3
X-linked intellectual disability, Turner type	309590	*HUWE1*	*36*	Intellectual Disability Syndromic	X-linked recessive	3
Spinocerebellar ataxia type 29	117360	*ITPR1*	*36*	Cerebellar/Ataxias	Autosomal dominant	3
Mental retardation, autosomal dominant 32	616268	*KAT6A*	*36*	Cardiac	Autosomal dominant	3
intellectual disability - sparse hair - brachydactyly (Nicolaides-Baraitser syndrome)	601358	*SMARCA2*	*36*	Intellectual Disability Syndromic	Autosomal dominant	3

Disease	OMIM	Gene	DECIPHER Alleles	Body System	Inheritance	Longevity[a]
Congenital heart defects, dysmorphic facial features, and intellectual developmental disorder	617360	*CDK13*	*35*	Cardiac	Autosomal dominant	3
Cornelia de Lange syndrome 5	300882	*HDAC8*	*35*	Intellectual Disability Syndromic	X-linked recessive	3
Early infantile epileptic encephalopathy, 7	613720	*KCNQ2*	*35*	Epilepsy Syndromes	Autosomal dominant	3
Syndromic X-linked intellectual disability due to JARID1C mutation	300534	*KDM5C*	*35*	Intellectual Disability Syndromic	X-linked recessive	3
Early infantile epileptic encephalopathy, 4	612164	*STXBP1*	*35*	Epilepsy Syndromes	Autosomal dominant	3
Dravet syndrome	612164	*STXBP1*	*35*	Epilepsy Syndromes	Autosomal dominant	3
Epileptic encephalopathy, early infantile, 54	617391	*HNRNPU*	*34*	Epilepsy Syndromes	Autosomal Dominant	3
Desanto-Shinawi syndrome	616708	*WAC*	*33*	Intellectual Disability Syndromic	Autosomal dominant	3
Atypical Rett syndrome	300672	*CDKL5*	*32*	Intellectual Disability Syndromic	X-linked dominant	3
Early infantile epileptic encephalopathy	300672	*CDKL5*	*32*	Epilepsy Syndromes	X-linked dominant	3
West syndrome	300672	*CDKL5*	*32*	Epilepsy Syndromes	X-linked dominant	3
5q14.3 microdeletion syndrome	613443	*MEF2C*	*32*	Chromosomal	Autosomal dominant	3
Sotos syndrome 1	117550	*NSD1*	*32*	Overgrowth	Autosomal dominant	3
5q35 microduplication syndrome	117550	*NSD1*	*32*	Chromosomal	Autosomal dominant	3
CHARGE syndrome	214800	*CHD7*	*31*	Malformations	Autosomal dominant	3

Disease	OMIM	Gene	DECIPHER Alleles	Body System	Inheritance	Longevity[a]
COFS syndrome	214150	*ERCC6*	*31*	Intellectual Disability Syndromic	Autosomal recessive	2
Cockayne syndrome type 1	133540	*ERCC6*	*31*	Neoplastic	Autosomal recessive	2
Verheij Syndrome	615583	*PUF60*	*31*	Malformations	Autosomal dominant	3
Autism spectrum disorder due to AUTS2 deficiency (Mental retardation, autosomal dominant 26)	615834	*AUTS2*	*30*	Intellectual Disability Syndromic	Autosomal dominant	3
Severe intellectual disability-progressive spastic diplegia syndrome	615075	*CTNNB1*	*30*	Intellectual Disability Syndromic	Autosomal dominant	3
Intellectual disability-severe speech delay-mild dysmorphism syndrome	613670	*FOXP1*	*30*	Intellectual Disability Syndromic	Autosomal dominant	3
LEOPARD syndrome 1	151100	*PTPN11*	*29*	Intellectual Disability Syndromic	Autosomal dominant	3
Noonan syndrome 1	163950	*PTPN11*	*29*	Intellectual Disability Syndromic	Autosomal dominant	3
X-linked non-syndromic intellectual disability	300046	*USP9X*	*29*	Intellectual Disability Non-Syndromic	X-linked recessive	3
Autosomal dominant childhood-onset proximal spinal muscular atrophy without contractures	158600	*DYNC1H1*	*28*	Neuromuscular	Autosomal dominant	3
Mandibulofacial dysostosis-microcephaly syndrome	610536	*EFTUD2*	*28*	Craniofacial	Autosomal dominant	3
Kabuki syndrome 2	300867	*KDM6A*	*28*	Intellectual Disability Syndromic	Autosomal dominant	3

Disease	OMIM	Gene	DECIPHER Alleles	Body System	Inheritance	Longevity[a]
X-linked intellectual disability - cerebellar hypoplasia	300486	*OPHN1*	*28*	Intellectual Disability Non-Syndromic	X-linked recessive	3
Christianson syndrome	300243	*SLC9A6*	*28*	Intellectual Disability Syndromic	X-linked recessive	3
Cohen syndrome	216550	*VPS13B*	*28*	Intellectual Disability Syndromic	Autosomal recessive	3
Marshall-Smith syndrome	602535	*NFIX*	*27*	Overgrowth	Autosomal dominant	3
Sotos syndrome 2	614753	*NFIX*	*27*	Overgrowth	Autosomal dominant	3
Mental retardation, autosomal dominant 35	616355	*PPP2R5D*	*27*	Intellectual Disability Syndromic	Autosomal dominant	3
Intellectual disability with postnatal overgrowth	618430	*TCF20*	*27*	Intellectual Disability Non-Syndromic	Autosomal dominant	3
Mental retardation, autosomal dominant 44	601893	*TRIO*	*27*	Intellectual Disability Syndromic	Autosomal dominant	3
Atypical Rett syndrome	613454	*FOXG1*	*26*	Intellectual Disability Syndromic	Autosomal dominant	3
14q11.2 microduplication syndrome	613457	*FOXG1*	*26*	Chromosomal	Autosomal dominant	3
14q12 microdeletion syndrome	613457	*FOXG1*	*26*	Chromosomal	Autosomal dominant	3
Hypotonia-speech impairment-severe cognitive delay syndrome	615419	*NALCN*	*26*	Intellectual Disability Syndromic	Autosomal dominant/ recessive	3
Intellectual disability - obesity - brain malformations - facial dysmorphism	613192	*TRAPPC9*	*26*	Intellectual Disability Syndromic	Autosomal recessive	3
X-linked non-syndromic intellectual disability (Opitz-Kaveggia syndrome)	305450	*MED12*	*25*	Intellectual Disability Non-Syndromic	X-linked recessive	3

Disease	OMIM	Gene	DECIPHER Alleles	Body System	Inheritance	Longevity[a]
X-linked intellectual disability with marfanoid habitus (Lujan-Fryns syndrome)	309520	*MED12*	*25*	Intellectual Disability Syndromic	X-linked recessive	3
Ohdo syndrome, X-linked	300895	*MED12*	*25*	Intellectual Disability Syndromic	X-linked recessive	3
Myoclonic-atonic epilepsy	616421	*SLC6A1*	*25*	Epilepsy Syndromes	Autosomal dominant	2
Intellectual disability-developmental delay-contractures syndrome	314580	*ZC4H2*	*25*	Intellectual Disability Syndromic	X-linked recessive	3
Tall stature-intellectual disability-facial dysmorphism syndrome (Tatton-Brown-Rahman syndrome)	615879	*DNMT3A*	*24*	Intellectual Disability Syndromic	Autosomal dominant	3
Blepharophimosis-intellectual disability syndrome, SBBYS type	603736	*KAT6B*	*24*	Intellectual Disability Syndromic	Autosomal dominant	3
Genitopatellar syndrome	606170	*KAT6B*	*24*	Skeletal Dysplasias	Autosomal dominant	3
Juvenile myoclonic epilepsy	121201	*KCNQ3*	*24*	Epilepsy Syndromes	Autosomal dominant	3
Benign familial neonatal seizures, 2	121201	*KCNQ3*	*24*	Epilepsy Syndromes	Autosomal dominant	3
Mental retardation, autosomal recessive 65	618109	*KDM5B*	*24*	Intellectual Disability Syndromic	Autosomal recessive	3
White-Sutton syndrome	616364	*POGZ*	*24*	Intellectual Disability Syndromic	Autosomal dominant	2
Dravet syndrome	607208	*SCN1A*	*24*	Epilepsy Syndromes	Autosomal dominant	3
Malignant migrating partial seizures of infancy	604403	*SCN1A*	*24*	Epilepsy Syndromes	Autosomal dominant	3
Mental retardation, autosomal dominant 49	617752	*TRIP12*	*24*	Intellectual Disability Syndromic	Autosomal dominant	3

Disease	OMIM	Gene	DECIPHER Alleles	Body System	Inheritance	Longevity[a]
Autosomal dominant non-syndromic intellectual disability	616579	*CHAMP1*	*23*	Intellectual Disability Syndromic	Autosomal dominant	3
Severe intellectual disability-poor language-strabismus-grimacing face-long fingers syndrome	615074	*GATAD2B*	*23*	Intellectual Disability Syndromic	Autosomal dominant	3
Mental retardation, autosomal dominant 31	616158	*PURA*	*23*	Epilepsy Syndromes	Autosomal dominant	3
Schinzel-Giedion syndrome	269150	*SETBP1*	*23*	Intellectual Disability Syndromic	Autosomal dominant	2
Mental retardation, autosomal dominant 41 (Pierpont syndrome)	612376	*TBL1XR1*	*23*	Intellectual Disability Syndromic	Autosomal dominant	3
Mental retardation, X-linked 93	300659	*BRWD3*	*22*	Intellectual Disability Non-Syndromic	X-linked recessive	3
Lennox-Gastaut syndrome (Epileptic encephalopathy, childhood-onset)	615369	*CHD2*	*22*	Epilepsy Syndromes	Autosomal dominant	3
Mental retardation, X-linked 98	300524	*NEXMIF*	*21*	Intellectual Disability Syndromic	X-linked recessive	3
Geleophysic dysplasia 2	614185	*FBN1*	*20*	Skeletal Dysplasias	Autosomal dominant	3
Glaucoma - ectopia - microspherophakia - stiff joints - short stature (Weill-Marchesani syndrome 2, dominant)	608328	*FBN1*	*20*	Ophthalmological	Autosomal dominant	3
Kabuki syndrome 1	147920	*KMT2D*	*20*	Intellectual Disability Syndromic	Autosomal dominant	3
Proteus-like syndrome	158350	*PTEN*	*20*	Intellectual Disability Syndromic	Autosomal dominant	3
Macrocephaly-autism syndrome	605309	*PTEN*	*20*	Intellectual Disability Syndromic	Autosomal dominant	3

Disease	OMIM	Gene	DECIPHER Alleles	Body System	Inheritance	Longevity[a]
Bannayan-Riley-Ruvalcaba syndrome	158350	*PTEN*	*20*	Overgrowth	Autosomal dominant	3
Witteveen-Kolk syndrome	613406	*SIN3A*	*20*	Intellectual Disability Syndromic	Autosomal dominant	3
Mental retardation X linked, syndromic 33	300966	*TAF1*	*20*	Intellectual Disability Syndromic	X-linked recessive	3
Baraitser-Winter syndrome 1	243310	*ACTB*	*19*	Craniofacial	Autosomal dominant	3
AHDC1-related intellectual disability-obstructive sleep apnea-mild dysmorphism syndrome (Xia-Gibbs syndrome)	615829	*AHDC1*	*19*	Intellectual Disability Syndromic	Autosomal dominant	3
Early infantile epileptic encephalopathy	614558	*SCN8A*	*19*	Epilepsy Syndromes	Autosomal dominant	3
Myhre syndrome	139210	*SMAD4*	*19*	Intellectual Disability Syndromic	Autosomal dominant	3
Hereditary persistence of fetal hemoglobin-sickle cell disease syndrome (Dias-Logan syndrome)	617101	*BCL11A*	*18*	Haematological	Autosomal recessive	3
Intellectual disability - craniofacial dysmorphism - cryptorchidism	615009	*PACS1*	*18*	Intellectual Disability Syndromic	Autosomal dominant	3
Rolandic epilepsy - speech dyspraxia	245570	*GRIN2A*	*17*	Epilepsy Syndromes	Autosomal dominant	3
Early-onset epileptic encephalopathy and intellectual disability due to GRIN2A mutation	245570	*GRIN2A*	*17*	Epilepsy Syndromes	Autosomal dominant	3
Mowat-Wilson syndrome due to a ZEB2 point mutation	235730	*ZEB2*	*17*	Intellectual Disability Syndromic	Autosomal dominant	3

Disease	OMIM	Gene	DECIPHER Alleles	Body System	Inheritance	Longevity[a]
Mowat-Wilson syndrome due to monosomy 2q22	235730	*ZEB2*	*17*	Chromosomal	Autosomal dominant	3
Joubert syndrome 17	614615	*CPLANE1*	*16*	Central Nervous System	Autosomal recessive	3
Joubert syndrome with orofaciodigital defect	277170	*CPLANE1*	*16*	Central Nervous System	Autosomal recessive	3
Neurodevelopmental disorder with dysmorphic facies and distal limb anomalies	617755	*BPTF*	*15*	Intellectual Disability Syndromic	Autosomal dominant	3

[a] Longevity coded as 1=less than two years of life; 2=death by adolescence; and 3=adult life expectancy.

Table S2. References for cost analysis in Table 1

	Healthcare Costs				**Social Costs**							**Total Costs**
Age/Severity Group	**Hospital Services Costs**	**Community Services Costs**	**Treatment/ Aids/ Adaptations Costs**	**Total Healthcare Costs**	**Accomm-odation Costs**	**Education Costs**	**Daytime Activities Costs**	**Income Support**	**Carer Costs**	**Loss of Productivity**	**Total Social Costs**	**(Healthcare and Social Costs)**
Children 0-3 mild	L[1] M[1] U[1]	L[2] M[2] U[2]	L[2,3] M[2,3] U[2,3]	Sum of previous 3 columns	L[2,4,5] M[2,4] U[2,4]	L[2] M[4] U[4]	L[4] M[4] U[4]	L[2,6] M[6] U[2,4,6]	L[2,6] M[2,6] U[2,6]	L[2] M[2,4] U[4]	Sum of previous **6** columns	Sum of total HC and SC
Children 0-3 moderate	L[1] M[1] U[1]	L[2] M[2] U[2]	L[2,3] M[2,3] U[2,3]	Sum of previous 3 columns	L[2,4,5] M[2,4] U[2,4]	L[2] M[4] U[4]	L[4] M[4] U[4]	L[6] M[2,4,6] U[2,6]	L[2,6] M[2,6] U[2,6]	L[2] M[2,4] U[4]	Sum of previous **6** columns	Sum of total HC and SC
Children 0-3 severe/profound	L[1] M[1] U[1]	L[2] M[2] U[2]	L[2,7] M[2,7] U[2,7]	Sum of previous 3 columns	L[2,4,5] M[2,4] U[2,4]	L[2] M[4] U[4]	L[4] M[4] U[4]	L[2,6] M[2,4,6] U[6]	L[2,6] M[2,6] U[2,6]	L[2] M[2,4] U[4]	Sum of previous **6** columns	Sum of total HC and SC
Children **4**-11 mild	L[2,8] M[1,8] U[1]	L[8] M[2,8] U[2]	L[2,3] M[2,3,8] U[3,8]	Sum of previous 3 columns	L[2,4,5] M[4,5] U[2,4]	L[2,4] M[2,4] U[4]	L[4] M[4] U[4]	L[6] M[2,4,6] U[4,6]	L[2,6] M[2,6] U[6]	L[2] M[2,4] U[4]	Sum of previous **6** columns	Sum of total HC and SC
Children **4**-11 moderate	L[2,8] M[1,8] U[1]	L[8] M[2,8] U[2]	L[2,3] M[2,3,8] U[3,8]	Sum of previous 3 columns	L[2,4,5] M[4,5] U[2,4]	L[2,4] M[2,4] U[4]	L[4] M[4] U[4]	L[6] M[2,4,6] U[4,6]	L[2,6] M[2,6] U[6]	L[2] M[2,4] U[4]	Sum of previous **6** columns	Sum of total HC and SC
Children **4**-11 severe/profound	L[2,8] M[1,8] U[1]	L[8] M[2,8] U[2]	L[2,7] M[2,7,8] U[7,8]	Sum of previous 3 columns	L[2,4,5] M[4,5] U[2,4]	L[2,4] M[2,4] U[4]	L[4] M[4] U[4]	L[2,6] M[2,4,6] U[4,6]	L[2,6] M[2,6] U[6]	L[2] M[2,4] U[4]	Sum of previous **6** columns	Sum of total HC and SC
Children 12-17 mild	L[2,8] M[1,8] U[1]	L[8] M[2,8] U[2]	L[2,3] M[2,3,8] U[3,8]	Sum of previous 3 columns	L[2,4,5] M[4,5] U[2,4]	L[4] M[2,4,9] U[2]	L[4] M[4,9] U[4]	L[6] M[2,4,6] U[4,6]	L[2,6] M[2,6] U[6]	L[2,9] M[2,4,9] U[4,9]	Sum of previous **6** columns	Sum of total HC and SC
Children 12-17 moderate	L[2,8] M[1,8] U[1]	L[8] M[2,8] U[2]	L[2,3] M[2,3,8] U[3,8]	Sum of previous 3 columns	L[2,4,5] M[4,5] U[2,4]	L[4] M[2,4,9] U[2]	L[4] M[4,9] U[4]	L[6] M[2,4,6] U[4,6]	L[2,6] M[2,6] U[6]	L[2,9] M[2,4,9] U[4,9]	Sum of previous **6** columns	Sum of total HC and SC
Children 12-17 severe/profound	L[2,8] M[1,8] U[1]	L[9] M[9] U[9]	L[2,7] M[2,7,8] U[7,8]	Sum of previous 3 columns	L[2,4,5] M[4,5] U[2,4]	L[4] M[2,4,9] U[2]	L[4] M[4,9] U[4]	L[2,6] M[2,4,6] U[4,6]	L[2,6] M[2,6] U[6]	L[2,9] M[2,4,9] U[4,9]	Sum of previous **6** columns	Sum of total HC and SC
Young adult 18-29 mild	L[2] M[1,2,4] U[4]	L[2] M[3,10] U[11]	L[2,3] M[2,3] U[2,3]	Sum of previous 3 columns	L[4] M[5,12] U[2,5]	L[6] M[2,4,6] U[2]	L[2,4] M[2,4,13] U[4,13]	L[6] M[2,4,6] U[2,4,6]	L[3,6] M[6] U[3,6]	L[4] M[2,4] U[4]	Sum of previous **6** columns	Sum of total HC and SC
Young adult 18-29 moderate	L[2] M[1,2,4] U[4]	L[2] M[3,10] U[11]	L[2,3] M[2,3] U[2,3]	Sum of previous 3 columns	L[4] M[5,12] U[2,5]	L[6] M[2,4,6] U[2]	L[2,4] M[2,4,13] U[4,13]	L[6] M[2,4,6] U[2,4,6]	L[3,6] M[3,6] U[6]	L[4] M[2,4] U[4]	Sum of previous **6** columns	Sum of total HC and SC

	Healthcare Costs				Social Costs							Total Costs
Age/Severity Group	**Hospital Services Costs**	**Community Services Costs**	**Treatment/ Aids/ Adaptations Costs**	**Total Healthcare Costs**	**Accomm-odation Costs**	**Education Costs**	**Daytime Activities Costs**	**Income Support**	**Carer Costs**	**Loss of Productivity**	**Total Social Costs**	**(Healthcare and Social Costs)**
Young adult 18-29 severe/profound	L[2] M[1,2,4] U[4]	L[7,14] M[7,14,15] U[7,15]	L[2,7] M[2,7] U[2,7]	Sum of previous 3 columns	L[4] M[2,5] U[5,12]	L[6] M[2,4,6] U[2]	L[2,4] M[2,4,13] U[4,13]	L[6] M[2,4,6] U[2,4,6]	L[3,6] M[3,6] U[6]	L[4] M[2,4] U[4]	Sum of previous **6** columns	Sum of total HC and SC
Adult 30-59 mild	L[2] M[1,2,4] U[4]	L[2] M[3,10] U[11]	L[2,3] M[2,3] U[2,3]	Sum of previous 3 columns	L[10,16] M[10,16,17] U[2,5]	L[a] M[a] U[a]	L[10] M[10,11,17] U[3]	L[6] M[2,4,6] U[2,4,6]	L[3,6] M[6] U[3,6]	L[4] M[2,4] U[4]	Sum of previous **6** columns	Sum of total HC and SC
Adult 30-59 moderate	L[2] M[1,2,4] U[4]	L[2] M[3,10] U[11]	L[2,3] M[2,3] U[2,3]	Sum of previous 3 columns	L[10,16] M[10,16,17] U[2,5]	L[a] M[a] U[a]	L[10] M[10,11,17] U[3]	L[6] M[2,4,6] U[2,4,6]	L[3,6] M[3,6] U[6]	L[4] M[2,4] U[4]	Sum of previous **6** columns	Sum of total HC and SC
Adult 30-59 severe/profound	L[2] M[1,2,4] U[4]	L[7,14] M[7,14,15] U[7,15]	L[2,7] M[2,7] U[2,7]	Sum of previous 3 columns	L[14] M[7,16,17] U[2,5]	L[a] M[a] U[a]	L[17] M[7,14] U[7]	L[6] M[2,4,6] U[2,4,6]	L[3,6] M[3,6] U[6]	L[4] M[2,4] U[4]	Sum of previous **6** columns	Sum of total HC and SC
Elderly adult >60 mild	L[18] M[18] U[18]	L[18] M[18] U[18]	L[3,18] M[3,18] U[3,18]	Sum of previous 3 columns	L[10,16] M[10,16,17] U[2,5]	L[a] M[a] U[a]	L[18] M[18] U[18]	L[6] M[2,4,6] U[2,4,6]	L[3,6,18] M[6,18] U[3,6,18]	L[4] M[2,4] U[4]	Sum of previous **6** columns	Sum of total HC and SC
Elderly adult >60 moderate	L[18] M[18] U[18]	L[18] M[18] U[18]	L[3,18] M[3,18] U[3,18]	Sum of previous 3 columns	L[10,16] M[10,16,17] U[2,5]	L[a] M[a] U[a]	L[18] M[18] U[18]	L[6] M[2,4,6] U[2,4,6]	L[3,6,18] M[3,6,18] U[6,18]	L[4] M[2,4] U[4]	Sum of previous **6** columns	Sum of total HC and SC
Elderly adult >60 severe/profound	L[18] M[18] U[18]	L[18] M[18] U[18]	L[7,18] M[7,18] U[7,18]	Sum of previous 3 columns	L[14] M[7,16,17] U[2,5]	L[a] M[a] U[a]	L[18] M[18] U[18]	L[6] M[2,4,6] U[2,4,6]	L[3,6,18] M[3,6,18] U[6,18]	L[4] M[2,4] U[4]	Sum of previous **6** columns	Sum of total HC and SC

Health costs (HC); Lower boundary (L); Middle boundary (M); Not applicable (NA); Social costs (SC); Upper boundary (U)

References 2, 4, and 6 have been bolded to highlight where costs estimates have been specifically reported to be in excess (i.e. related to only the costs associated with disability).

Note reference 5 is the source used to adjust costs based on the proportion of individuals reported to receive those services and is not a source of cost data.

[a]Assume $0 cost as any education for (elderly) adults would be provided through daytime activities

Table S3. References for cost analysis in Table 2

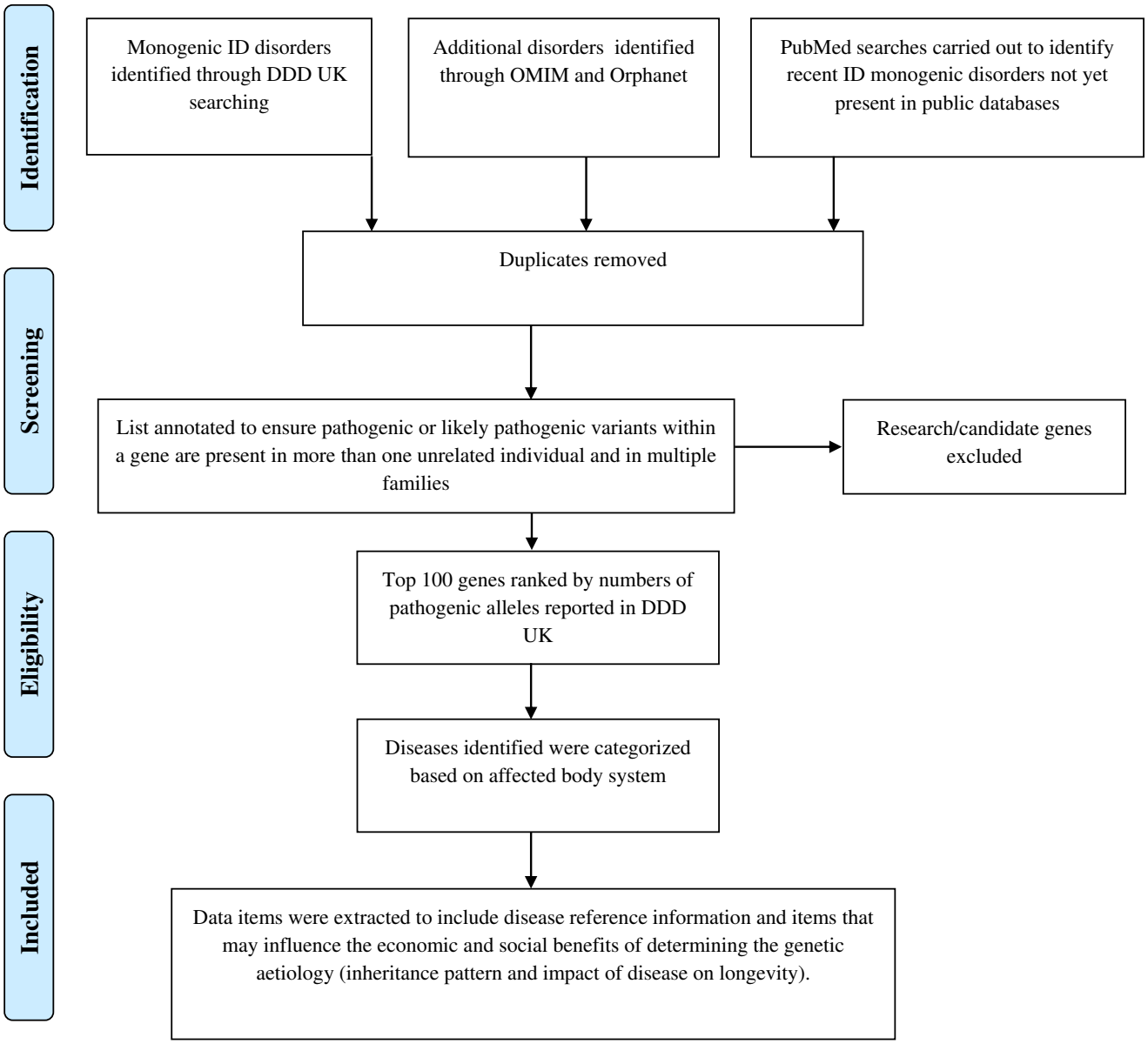
	Healthcare Costs				Social Costs							Total Costs
Age/Severity Group	**Hospital Services Costs**	**Community Services Costs**	**Treatment/ Aids/ Adaptations Costs**	**Total Healthcare Costs**	**Accomm-odation Costs**	**Education Costs**	**Daytime Activities Costs**	**Income Support**	**Carer Costs**	**Loss of Productivity**	**Total Social Costs**	**(Healthcare and Social Costs)**
Children 0-17 severe at home	L[19] M[20] U[19]	L[19] M[19] U[19]	L[19] M[19,20] U[19]	Sum of previous 3 columns	L[a] M[a] U[a]	L[19] M[19] U[19]	L[a] M[a] U[a]	L[21] M[21] U[21]	L[19,21] M[19,21] U[19,21]	L[21] M[21] U[21]	Sum of previous 6 columns	Sum of total HC and SC
Children 0-17 severe in hospital	L[19] M[19] U[19]	L[19] M[19] U[19]	L[19] M[19] U[19]	Sum of previous 3 columns	L[a] M[a] U[a]	L[19] M[19] U[19]	L[a] M[a] U[a]	L[21] M[21] U[21]	L[19,21] M[19,21] U[19,21]	L[21] M[21] U[21]	Sum of previous 6 columns	Sum of total HC and SC
Young adults 18-29 employed	L[22] M[22] U[22]	L[22] M[23] U[23]	L[24,25] M[24-26] U[24,25]	Sum of previous 3 columns	L[22] M[22] U[22,25]	L[a] M[a] U[a]	L[a] M[22] U[22]	L[22,27] M[22,27] U[22,27]	L[a] M[24] U[24,25]	L[27] M[27] U[27]	Sum of previous 6 columns	Sum of total HC and SC
Young adults 18-29 unemployed	L[22] M[22] U[22]	L[22] M[23] U[23]	L[24,25] M[24-26] U[24,25]	Sum of previous 3 columns	L[22] M[22] U[22,25]	L[a] M[22] U[22]	L[22] M[22] U[22]	L[27] M[27] U[27]	L[a] M[24] U[24,25]	L[27] M[21,27] U[21,27]	Sum of previous 6 columns	Sum of total HC and SC
Adults 30-60 employed	L[26] M[26] U[26]	L[a] M[25] U[24]	L[24,25] M[24-26] U[24,25]	Sum of previous 3 columns	L[22] M[22] U[22,25]	L[a] M[a] U[a]	L[a] M[22] U[22]	L[22,27] M[22,27] U[22,27]	L[a] M[24] U[24,25]	L[27] M[27] U[27]	Sum of previous 6 columns	Sum of total HC and SC
Adults 30-60 unemployed	L[26] M[26] U[26]	L[a] M[25] U[24]	L[24,25] M[24-26] U[24,25]	Sum of previous 3 columns	L[22] M[22] U[22,25]	L[a] M[a] U[a]	L[22] M[22] U[22]	L[27] M[27] U[27]	L[a] M[24] U[24,25]	L[27] M[21,27] U[21,27]	Sum of previous 6 columns	Sum of total HC and SC

Health costs (HC); Lower boundary (L); Middle boundary (M); Social costs (SC); Upper boundary (U)

References 19, 20, 22, and 24 have been bolded to highlight where costs estimates have been specifically reported to be in excess (i.e. related to only the costs associated with disability)

[a]Assume $0 costs

Figure S1. PRISMA flow diagram illustrating how a list of monogenic diseases associated with intellectual disability (ID) was ascertained



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