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ORIGINAL PAPER

Cost-Effectiveness Analysis Comparing Pre-diagnosis Autism Spectrum Disorder (ASD)-Targeted Intervention with Ontario's Autism Intervention Program

Melanie Penner[2,4,8,9] · Meera Rayar[3,4,8,9] · Naazish Bashir[4,11] · S. Wendy Roberts[5,12] · Rebecca L. Hancock-Howard[1] · Peter C. Coyte[1]

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Abstract Novel management strategies for autism spectrum disorder (ASD) propose providing interventions before diagnosis. We performed a cost-effectiveness analysis comparing the costs and dependency-free life years (DFLYs) generated by pre-diagnosis intensive Early Start Denver Model (ESDM-I); pre-diagnosis parent-delivered ESDM (ESDM-PD); and the Ontario Status Quo (SQ). The analyses took government and societal perspectives to age 65. We assigned probabilities of Independent, Semi-dependent or Dependent living based on projected IQ. Costs per person (in Canadian dollars) were ascribed to each living setting. From a government perspective, the ESDM-PD produced an additional 0.17 DFLYs for $8600 less than SQ. From a societal perspective, the ESDM-I produced an additional 0.53 DFLYs for $45,000 less than SQ. Pre-diagnosis interventions targeting ASD symptoms warrant further investigation.

Keywords Autism spectrum disorder · Cost-effectiveness · Behavior therapy · Independent living · Economics

Introduction

Autism spectrum disorder (ASD) is associated with significant costs for treatment, special education and accommodations in adulthood (Barrett et al. 2012; Cimera and Cowan 2009; Knapp et al. 2009). The rising incidence of ASD coupled with its significant resource use through the lifespan poses high costs to governments (The Standing Senate Committee on Social Affairs, Science and Technology 2007). ASD has high societal costs due to caregiver

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✉ Melanie Penner
mpenner@hollandbloorview.ca

Peter C. Coyte
peter.coyte@utoronto.ca

[1] Institute of Health Policy, Management and Evaluation, University of Toronto, 155 College St., Suite 425, Toronto, ON M5T 3M6, Canada

[2] Present Address: Autism Research Centre, Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital, 150 Kilgour Rd., Toronto, ON M4G 1R8, Canada

[3] Post-Graduate Medical Education - Pediatric Hematology/Oncology, University of Toronto, 500 University Ave., Toronto, ON M5G 1V7, Canada

[4] Child Health Evaluative Sciences, The Hospital for Sick Children, 686 Bay St., Toronto, ON M5G 0A4, Canada

[5] Integrated Services for Autism and Neurodevelopmental Disorders (ISAND), 5734 Yonge St., Suite 605, Toronto, ON M2M 4E7, Canada

[8] Clinician Investigator Program, University of Toronto, 2366 Medical Sciences Building 1 Kings College Circle, Toronto, ON M5S 1A8, Canada

[9] Masters of Science Program in Health Services Research, Institute of Health Policy, Management and Evaluation, 155 College St., Toronto, ON M5T 3M6, Canada

[11] Doctoral Program in Health Services Research, Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ONM5T 3M6, Canada

[12] Professor Emerita, Department of Paediatrics, University of Toronto, Toronto, ON, Canada

burden and lost productivity for both caregivers and individuals with ASD (Buescher et al. 2014; Dudley and Emery 2014). These costs are higher for individuals with more severe ASD and with co-occurring intellectual disability (Buescher et al. 2014; Jarbrink and Knapp 2001).

Early Intensive Behavioural Intervention (EIBI) has been extensively studied and shown to be effective for treatment of ASD (Eldevik et al. 2009; Virues-Ortega 2010). EIBI generally consists of at least 20 h of therapy per week for an average duration of at least 6 months, and often upwards of 2 years (Virues-Ortega 2010). Gains from ASD interventions, such as EIBI, have traditionally been measured using adaptive skills, language, and cognitive measures (IQ) (Eldevik et al. 2009; Perry et al. 2011; Virues-Ortega 2010); however, because of its relatively recent adoption and young targeted age group, the impact of EIBI on the future independence of its participants is still unknown.

In Ontario, publicly funded EIBI is available to children with a diagnosis of ASD "at the more severe end of the spectrum," (Ontario Ministry of Child and Youth Services 2006). Motiwala et al. (2006) performed a cost-effectiveness analysis using published literature and showed that expanding EIBI to all Ontario children with ASD would increase dependency-free life years (DFLYs) and produce cost-savings. The projections for DFLYs in the Motiwala et al. model were based on functional classification at the completion of EIBI (such as the participation in mainstream education reported by Lovaas (1987)). Consequently, the Motiwala et al. model may therefore reflect an optimistic view of the long-term effects of EIBI.

The high demand for EIBI and its limited capacity has created significant wait times, as high as 4 years in some Ontario regions (Gordon 2012). This is both distressing for families and negatively impacts outcomes (Flanagan et al. 2012; Freeman and Perry 2010; Granpreesheh et al. 2009; Perry et al. 2011). Evidence from the Ontario EIBI program shows significant differences in the response to EIBI based on age at enrolment, with children starting treatment under the age of four responding better than older children (Perry et al. 2011).

The emphasis on earliest possible intervention has led to the development of interventions for very young children with ASD. One such intervention is the Early Start Denver Model (ESDM), which combines behavioural and developmental approaches into treatment aimed at children as young as 15 months (Rogers and Dawson 2009). Dawson et al. (2010) demonstrated significant cognitive gains in young children with ASD who received the ESDM delivered by a trained therapist for 20 h per week over 2 years compared with controls who received community interventions. A subsequent publication reporting a parent-delivered ESDM model with 1 h per week of therapist instruction produced cognitive benefits compared with baseline, but was not significantly more efficacious when compared with a community control group (Rogers et al. 2012). Of note, the control group in this study was able to seek out their own community-based interventions, and in the end received significantly more hours of intervention compared with the treatment group. These interventions included applied behavioural analysis, speech/language therapy, and ASD-targeted interventions such as Treatment and Education of Autistic and related Communication Handicapped Children (TEACCH); and the Developmental, Individual Difference, Relationship-based approach (DIR).

Unfortunately, the wait times in Ontario prevent most toddlers and preschool children from accessing evidence-based interventions in a timely manner (Auditor General of Ontario 2013). An urban regional municipality in Ontario has proposed providing ASD-targeted therapy (such as the ESDM) to children referred to generic developmental early intervention (EI) programs who display early flags of ASD, but who have not yet received a diagnosis. The aim of this service delivery model is to improve effectiveness of ASD interventions by maximizing the developmental potential of young children during a critically important period of brain development (Dawson 2008). As yet, there has been no evaluation of the potential cost-effectiveness of this service delivery model.

The objective of this study was to perform a cost-effectiveness analysis (CEA) evaluating the costs and dependency-free life years (DFLYs) generated by comparing two pre-diagnosis interventions, intensive ESDM (ESDM-I) and pre-diagnosis parent-delivered ESDM (ESDM-PD), with the Ontario Status Quo (SQ), which consists of limited access to EIBI after diagnosis. Our analysis used published literature to synthesize an incremental cost-effectiveness ratio for each intervention and is the first to link published intervention outcomes with projected adult outcomes. Gains in IQ were used as a surrogate marker to predict DFLYs. Costs and outcomes were analysed from both government and societal perspectives.

Methods

Target Population

The target population for this analysis was toddlers aged fifteen to 36 months with undifferentiated developmental concerns. In Ontario, children under six with developmental concerns are eligible to receive publicly funded developmental EI (which addresses general developmental needs and is not ASD-specific). We assumed that a child from this target population has a 30 % probability of

having ASD based on the study by Turygin et al. (2014). Children without ASD were not carried forward in the model and were not ascribed any costs or benefits.

Perspective and Time Horizon

The analysis took two perspectives. The provincial government payer perspective is highly relevant given that financing and delivery of ASD services in Canada is under the jurisdiction of the provincial government. The societal perspective includes all costs to governments and families, and is also germane because of the high ASD-related caregiving costs assumed by families (Dudley and Emery 2014). The time horizon includes costs and benefits until age 65, the traditional age of retirement. Age 65 was used as the upper age limit in the costing study by Dudley and Emery (2014), because after this age, caregiving costs increase for all individuals and would be difficult to attribute solely to the effects of ASD. Age 65 was also used as the upper limit in the study by Motiwala et al. (2006).

Comparators

Status Quo

In Ontario, the Status Quo ASD intervention (SQ, illustrated in Fig. 1) is the Autism Intervention Program, which provides EIBI to approximately 37 % of children with ASD at the "more severe end of the spectrum (Motiwala et al. 2006; Ontario Ministry of Child and Youth Services 2006)." Unfortunately, this program has long wait times, with only 33 % of recipients in one study accessing EIBI before age 4 (Perry et al. 2011). In this study, children who accessed EIBI before age four had significantly improved outcomes compared to those with later access.

Experimental Comparators

The two randomized controlled trials of the ESDM with differing intensities informed the experimental comparators, which provide ASD-targeted interventions to children who screen positive for signs of ASD before they receive a diagnosis. Children in the more intensive ESDM program (ESDM-I in this analysis, Fig. 2) published by Dawson et al. (2010) receive the intervention delivered by a trained therapist for 20 h per week over a 2-year period. Children in the parent-delivered ESDM model (ESDM-PD in this analysis, Fig. 3) published by Rogers et al. (2012) receive 1 h per week of trained therapist intervention over twelve weeks, with the remainder of intervention to be delivered by parents in the home environment.

Screening in ESDM Comparators

Patients in both ESDM comparators maintain the 30 % probability of having ASD (Turygin et al. 2014) and undergo screening with the *Modified Checklist for Autism in Toddlers – Revised with Follow Up Interview* (M-CHAT-R/F). The MCHAT-R/F is a screening test for ASD that has been validated in children aged 16–30 months (Robins et al. 2014). The sensitivity and specificity of the M-CHAT-R/F are 0.85 and 0.99, respectively. These were used as the True Positive and True Negative probabilities; the respective False Negative rate was 0.15 and the False Positive rate was 0.01. True positive cases received the ESDM pre-diagnosis intervention. True negative cases only incurred the cost of screening and were not carried forward in the model because their costs and outcomes would not differ between the three comparators. Patients who screened falsely negative on MCHAT-R/F would be diagnosed with ASD at a future date. To reflect the potential delay in diagnosis, these patients were not given an option of entering EIBI before age four in the model. Patients who screened falsely positive on M-CHAT-R/F received the ESDM but no further treatment. No benefits were ascribed to false positive cases.

Effectiveness

Our aim is to predict changes in future independence based on the type of intervention and the age at which it was delivered. We used IQ as the surrogate marker linking gains from interventions to predictions of future independence. IQ is a standardized, norm-referenced measure of human intelligence that is frequently reported as an outcome measure of ASD interventions (Eldevik et al. 2009; Perry et al. 2011; Virues-Ortega 2010). While IQ does not encompass the full complexity of ASD, it has been shown to account for some of the heterogeneity seen in this condition (Munson et al. 2008) and has been incorporated into models of clinical outcomes (Coplan and Jawad 2005). Finally, IQ was the only available measure to use as a predictor of future independence based on published cohort data (Howlin and Moss 2012).

Prediction of IQ Based on Treatment Profile

The calculated expected IQs for each treatment profile are presented in Table 1 and described below.

Status Quo (Fig. 1) The expected mean baseline IQ of children qualifying for EIBI in Ontario was assumed to be 45.5 based on a 2011 study of this program (Perry et al. 2011). The same study reported that only 97 of 296 children eligible for EIBI in their sample entered the program before age four (33 %). The IQ outcomes were

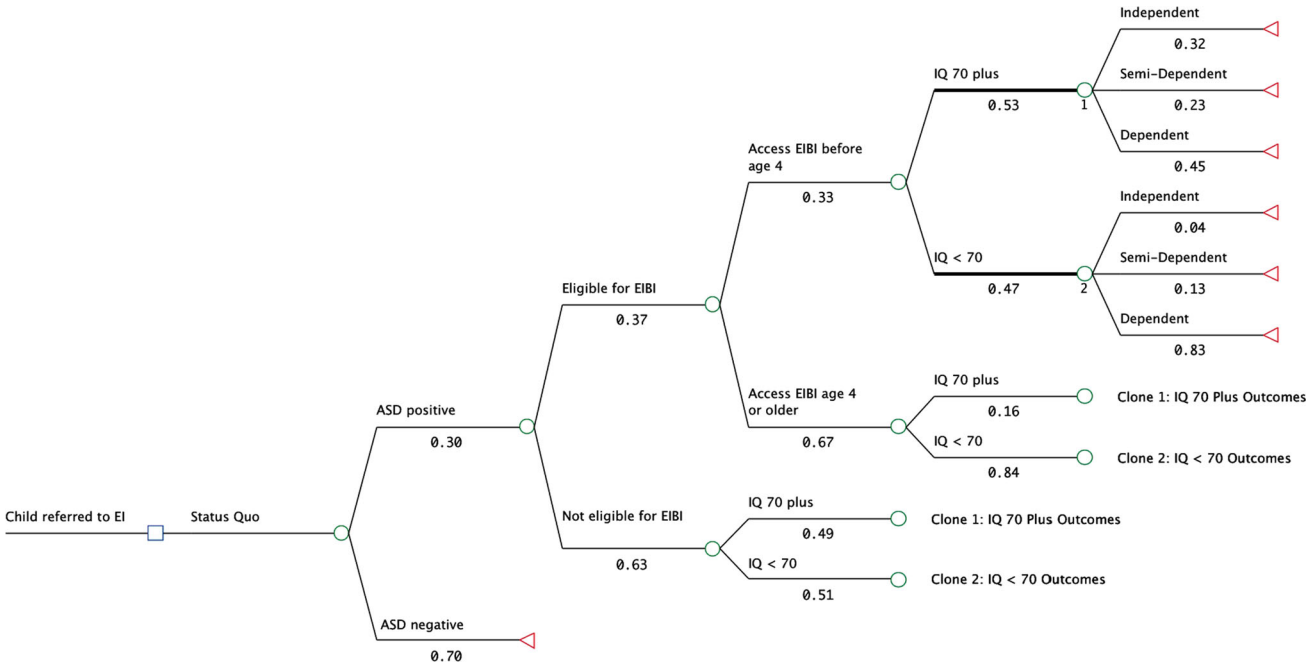

Fig. 1 Status Quo pathway. This figure shows the Status Quo pathway (the current system of care for children in Ontario). Decision nodes are presented with *squares*, chance nodes with *circles*, and terminal nodes with *triangles*. Probabilities of following each pathway are presented below the branches. Clone 1 represents the independence outcomes for children with an IQ of 70 or greater and is identical to the branches emanating from ASD Positive → Eligible for EIBI → Access EIBI before age 4 → IQ 70 plus. Clone 2 represents the independence outcomes for children with an IQ of less than 70 and is identical to the branches emanating from ASD Positive → Eligible for EIBI → Access EIBI before age 4 → IQ < 70. Children without ASD were not carried forward in the model and were ascribed no costs or effects and in this model were assumed to have similar costs and outcomes to their typically developing peers

significantly different between children who began before and after age four, with respective IQ gains of 25.9 and 5.5 points (Perry et al. 2011). Our model assumed that the expected mean IQ of children who are not eligible for EIBI (based on eligibility criteria of having moderate to severe ASD) was similar to a general sample of children with ASD, reported to be 69.4 (Charman et al. 2011). While higher than the baseline IQ for those entering EIBI, this is still a conservatively low estimate of the IQ of those who would not qualify for EIBI, as it includes individuals more severely affected by ASD.

ESDM-I (Fig. 2) In this pathway, the child is referred to generic developmental EI and undergoes screening with the MCHAT-R/F. Positive screens receive the ESDM-I, and true positive cases gained 17.6 IQ points, the value reported in the study by Dawson et al. (2010). Due to the length of this treatment, these children were not able to access EIBI before age four. The 17.6 IQ points gained from the ESDM-I intervention were added to the expected IQ gains for children who attended and did not attend EIBI (see Table 1).

ESDM-PD (Fig. 3) The child is referred to generic developmental EI and undergoes screening with the MCHAT-R/F. Positive screens receive the ESDM-PD, and true positive cases gain 4.94 IQ points (Rogers et al. 2012). This group has the possibility of entering EIBI before the age of four. Expected IQs were calculated as described above (Table 1).

Prediction of Outcome Based on Stratified IQ

An IQ of 70 was chosen as a level for stratification because it is the level below which an individual with ASD qualifies for a label of intellectual disability, which was used as a predictor of dependency outcomes in multiple studies (Howlin and Moss 2012). In our model, we determined the critical baseline IQ for each treatment profile, which was the lowest pre-intervention IQ that would reach a final post-intervention IQ of 70 or higher based on the expected gains from the treatment profile (Table 1). In this model, treatment profiles with higher expected IQ gains had a lower critical baseline IQ. The critical baseline IQ was converted to a Z-score using the mean and standard deviation of the baseline IQ distribution. The right- and left-tailed probabilities for this Z-score were used to determine the probability of a post-intervention IQ above or below 70 for each treatment profile.

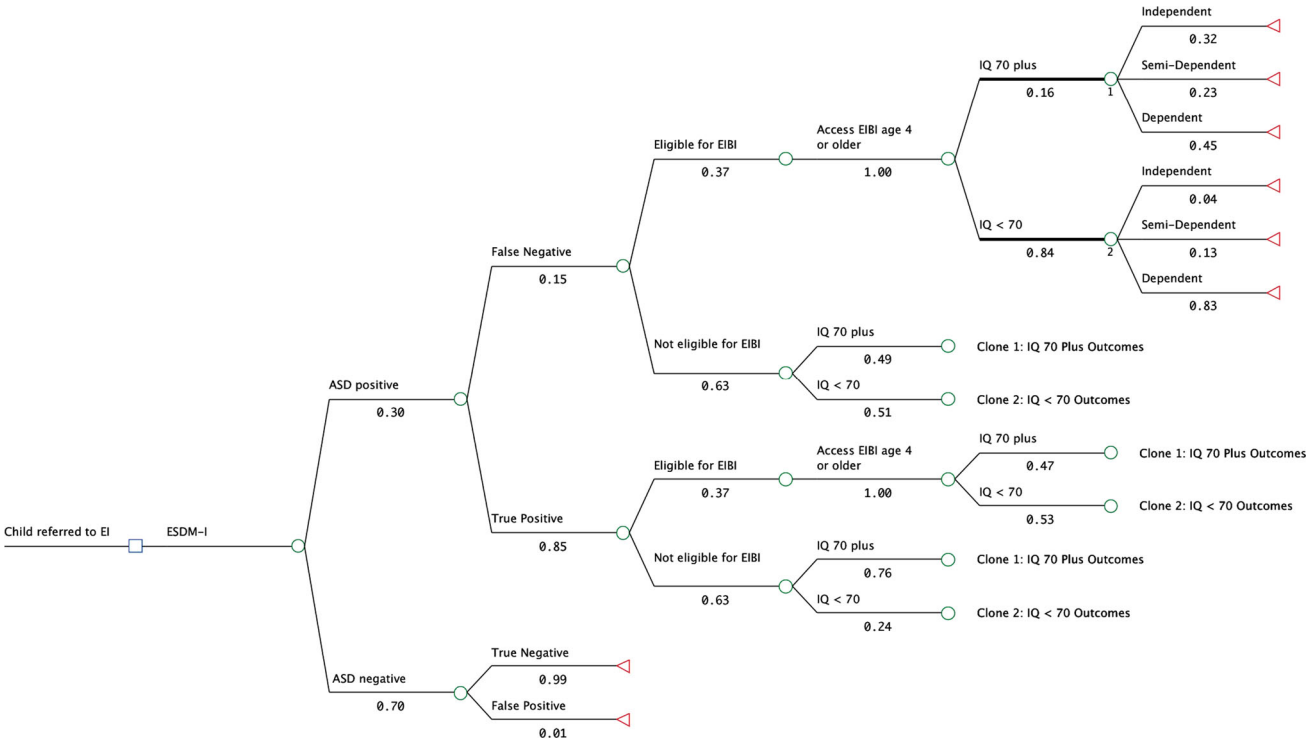

Fig. 2 Pre-Diagnosis Intensive ESDM pathway (ESDM-I). A figure of the decision analytic model for the ESDM-I pathway is presented. Clone 1 represents the independence outcomes for children with an IQ of 70 or greater and is identical to the branches emanating from ASD Positive → False Negative → Eligible for EIBI → Access EIBI age 4 or older → IQ 70 plus. Clone 2 represents the independence outcomes for children with an IQ of less than 70 and is identical to the branches emanating from ASD Positive → False Negative → Eligible for EIBI → Access EIBI age 4 or older → IQ < 70. True negative cases were not carried forward in the model and were not ascribed costs or effects. False positive cases were ascribed the costs of ESDM-I but no benefits. False negative cases were prevented from entering EIBI prior to age four as a penalty for delayed diagnosis

Each IQ stratum above and below 70 was assigned a probability of achieving an Independent, Semi-dependent, and Dependent outcome (Table 2). These outcome categories were respectively paired with the Good, Fair, and Poor outcomes reported in an adult cohort by Howlin et al. (2004). This study was used as the base case because it reported outcomes for individuals with a performance IQ above and below 70. Ranges were informed by additional adult cohort studies that described Good, Fair, and Poor outcomes by IQ (Howlin and Moss 2012).

Modelling Dependency Outcomes

The chosen effect measure was dependency-free life years (DFLYs). We defined a dependency-free life year as a year of life with a similar level of independence as a typically developing individual. This was the measure used in the previous cost-effectiveness analysis performed by Motiwala et al. (2006) which assumed that an Independent outcome from age five would result in 60 DFLYs gained, a Semi-dependent outcome would gain 30 DFLYs and a child with a Dependent outcome would not gain any DFLYs. Our model also assigned 60 DFLYs to an Independent outcome, 30 DFLYs to a Semi-dependent outcome, and zero DFLYs to a Dependent outcome in order to enhance comparisons.

Ideally, quality-adjusted life years (QALYs) would have been used as the outcome in this analysis in accordance with cost-utility analysis methods. This would allow for a comparison of cost-effectiveness across disorders, as well as facilitating a comparison against accepted thresholds for willingness-to-pay per QALY. (Drummond et al. 2005). Unfortunately, no health utility values have been reported for ASD interventions, and we were unable to derive utility estimates based on the current health utility literature for ASD (Payakachat et al. 2012; Tilford et al. 2012).

Resource Use and Costs

Resources relevant to ASD were identified using published costing papers by Motiwala et al. (2006), Dudley and Emery (2014), and Lavelle et al. (2014), as well as the recent report from the Auditor General for Ontario (2013). Resources related to the ESDM were taken from the budget

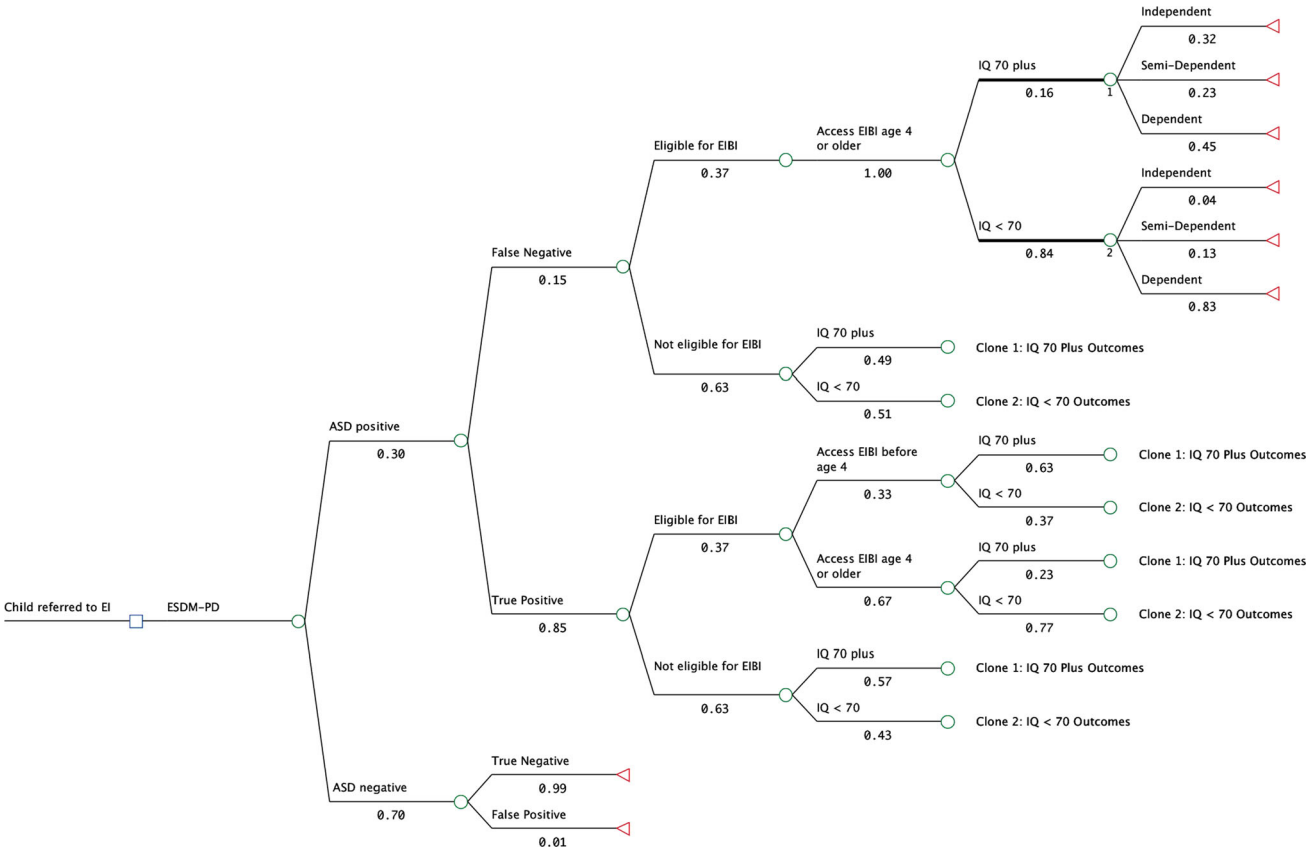

Fig. 3 Pre-Diagnosis Parent-Delivered ESDM pathway (ESDM-PD). A figure of the decision analytic model for the ESDM-PD pathway is presented. Clone 1 represents the independence outcomes for children with an IQ of 70 or greater and is identical to the branches emanating from ASD Positive → False Negative → Eligible for EIBI → Access EIBI age 4 or older → IQ 70 plus. Clone 2 represents the independence outcomes for children with an IQ of less than 70 and is identical to the branches emanating from ASD Positive → False Negative → Eligible for EIBI → Access EIBI age 4 or older → IQ < 70. True negative cases were not carried forward in the model and were not ascribed costs or effects. False positive cases were ascribed the costs of ESDM-I but no benefits. False negative cases were prevented from entering EIBI prior to age four as a penalty for delayed diagnosis

for a pilot project designed to deliver ESDM to children with red flags for ASD referred to generic developmental EI prior to diagnosis.

All costs were recorded in 2013 Canadian dollars ($1.00 Canadian = $0.97 US in 2013; Bank of Canada 2014a). Costs from documents that were published prior to 2013 were updated using the Consumer Price Index (Bank of Canada 2014b). Costing estimates were made for individuals from time of 2 years of age (the approximate time of entry to the model) to age 65.

Intervention Costs

A detailed table of costs associated with interventions is presented in Online Resource 1. We assumed that an early childhood therapist (ECT) would perform screening with the MCHAT-R/F during a 1-h intake session for the ESDM pathways. ECT training costs per child were determined by dividing the ESDM training cost for one ECT by the number of clients estimated to receive the ESDM from an individual ECT over 2 years based on the intensity and duration of the two ESDM programs (two clients for the ESDM-I and 160 clients for the ESDM-PD). The cost of the Ontario Autism Intervention Program was determined from the Ontario Government's Auditor General's report (Auditor General of Ontario 2013).

Provincial Costs

A detailed breakdown of provincial costs is included in Table 3. We assumed that due to the concerns raised about ASD in the screening process, a developmental assessment by a pediatrician would be subsequently required for all children who screen positive on the M-CHAT-R/F, as well as for false negative cases. Costs of these assessments were based on Ontario Health Insurance Plan Schedule of Benefits (Ontario Ministry of Health and Long-Term Care 2013).

Additional costs associated with provincial programs for ASD were applied to Semi-dependent and Dependent

Table 1 Calculation of IQ outcome probabilities based on treatment profile

Treatment profile	Expected baseline mean IQ	Expected IQ gain	Critical baseline IQ to reach IQ 70 (Z-score)	Probability above 70	Probability below 70
ESDM-I only	69.40 (SD 24.10)	17.60	52.4 (−0.71)	0.76	0.24
ESDM-I plus EIBI > 4	45.50 (SD 19.24)	17.60 + 5.50	46.9 (0.07)	0.47	0.53
ESDM-PD only	69.40 (SD 24.10)	4.94	65.06 (−0.18)	0.57	0.43
ESDM-PD plus EIBI > 4	45.50 (SD 19.24)	4.94 + 5.50	59.56 (0.73)	0.23	0.77
ESDM-PD plus EIBI < 4	45.50 (SD 19.24)	4.94 + 25.92	39.14 (−0.33)	0.63	0.37
EIBI > 4 only	45.50 (SD 19.24)	5.50	64.5 (0.99)	0.16	0.84
EIBI < 4 only	45.50 (SD 19.24)	25.92	44.08 (−0.074)	0.53	0.47
No treatment	69.40 (SD 24.10)	0	70 (0.025)	0.49	0.51

All treatment profiles are listed in the left-hand column

Where a child received both EIBI and ESDM, the IQ gains were assumed to be cumulative (the child keeps the gains from the ESDM and received additional gains from EIBI). The critical baseline IQ was the lowest baseline IQ value expected to reach a final IQ of 70 or higher based on the expected gains from each treatment profile; this was calculated as the difference between 70 and the expected IQ gain. This value was converted to a Z-score using the original baseline mean IQ distribution. The right- and left-tailed probabilities for the Z-score represented the probability of having an IQ above or below 70 (respectively)

Table 2 Outcome probabilities by IQ group

Our model	Howlin et al. (2004)	Probability if IQ ≥ 70 (range)	Probability if IQ < 70 (range)	Description
Independent	Very good, good	0.32 (0.1–0.48)	0.04 (0–0.08)	Can display high levels of independence. Generally in work but requires some degree of support in daily living
Semi-dependent	Fair	0.23 (0.23–0.45)	0.13 (0–0.23)	Some degree of independence, and although requires support and supervision does not need specialist residential provision
Dependent	Poor, very poor	0.45 (0.29–0.45)	0.83 (0.69–1)	Requiring special residential provisions, high level of support

Probabilities for achieving independent, Semi-dependent and Dependent outcomes were matched with very good/good, fair, and poor/very poor outcomes in the study by Howlin et al. 2004). Outcomes in the Howlin study were classified based on performance IQ. Ranges were informed by additional studies reporting adult outcome by IQ (Cederlund et al. 2008; Engstrom et al. 2003; Farley et al. 2009; Gillberg and Steffenburg 1987; Howlin et al. 2000, 2004; Larsen and Mouridsen 1997; Rumsey et al. 1985; Szatmari et al. 1989)

individuals and included annual respite funding and a one-time allotment for transition services (Auditor General of Ontario 2013). Semi-dependent and Dependent individuals qualify for the Special Services at Home program which provides $3360 annually to children and youth with disabilities to purchase services and programs (Auditor General of Ontario 2011). Semi-dependent and Dependent individuals were assumed to receive special education services from age four to the completion of high school at age 18. This analysis utilized 2004 individual student-level funding amounts for Semi-dependent (Intensive Support Amount 2) and Dependent (Intensive Support Amount 3) individuals (Zegarac et al. 2008).

For Semi-dependent and Dependent individuals over the age of 18, adult day programs and vocational training are provided through the Passport Program funded by the Ontario Ministry of Community and Social Services (Auditor General of Ontario 2011). As adults, Dependent individuals were assumed to receive funding from the Ontario Disability Support Program (ODSP) for residential placements as well as a personal need allowance (Ontario Disability Support Program 2013). Semi-dependent individuals would be eligible for wage compensation through ODSP (Ontario Disability Support Program 2013).

The Ontario government funds health care costs for physician and hospital service use. The costs of physician outpatient appointments and hospital admissions were determined from the Ontario Physician Schedule of Benefits (Ontario Ministry of Health and Long-Term Care 2013) and the Canadian Institute for Health Information (Canadian Institute for Health Information 2008, 2014), respectively. Costs used in the model represent additional costs related to ASD on top of the base amount for members of the general population (Lavelle et al. 2014).

Societal Perspective

The societal perspective includes all costs to government and caregivers, as well as costs to society due to lost production. A detailed breakdown of societal costs is included in Table 3. Government transfer of funds to individuals and families (including Special Services at Home and ODSP)

Table 3 Model parameters

Parameter	Value	Range	Standard error, distribution	References
Underlying ASD in early intervention population	0.30	0.28–0.31	0.01; Beta	Turygin et al. (2014)
M-CHAT-R/F sensitivity	0.85	0.79–0.92	0.03; Beta	Robins et al. (2014)
M-CHAT-R/F specificity	0.99	0.99–0.99	0	Robins et al. (2014)
Eligible for EIBI	0.37	0.25–0.5	0.1 (Assumed); beta	Motiwala et al. (2006)
If eligible, access EIBI before age 4	0.33	0.28–0.38	0.03	Perry et al. (2011)
IQ $\geq$ 70 if ESDM-I and EIBI age 4+	0.47	0.16–0.78	0.16; Normal	Dawson et al. (2010), Perry et al. (2011)
IQ $\geq$ 70 if ESDM-I and no EIBI	0.76	0.45–1.0	0.16; Normal	Charman et al. (2011), Dawson et al. (2010)
IQ $\geq$ 70 if ESDM-PD and EIBI before age 4	0.63	0.32–0.94	0.16; Normal	Rogers et al. (2012), Perry et al. (2011)
IQ $\geq$ 70 if ESDM-PD and EIBI age 4+	0.23	0–0.54	0.16; Normal	Rogers et al. (2012), Perry et al. (2011)
IQ $\geq$ 70 if ESDM-PD and no EIBI	0.57	0.26–0.88	0.16; Normal	Charman et al. (2011), Rogers et al. (2012)
IQ $\geq$ 70 if no ESDM, EIBI before age 4	0.53	0.22–0.84	0.16; Normal	Perry et al. (2011)
IQ $\geq$ 70 if no ESDM, EIBI age 4+	0.16	0–0.47	0.16; Normal	Perry et al. (2011)
IQ $\geq$ 70 if no ESDM, no EIBI	0.49	0.18–0.80	0.16; Normal	Charman et al. (2011)
Independent outcome if IQ $\geq$ 70	0.16	0.11–0.23	0.2; Beta	Howlin et al. (2004)
Semi-dependent outcome if IQ $\geq$ 70	0.38	0.34–0.41	0.2; Beta	Howlin et al. 2004)
Dependent outcome if IQ $\geq$ 70	0.46	0.37–0.55	0.2; Beta	Howlin et al. (2004)
Independent outcome if IQ $<$ 70	0.01	0–0.13	0.2; Beta	Howlin et al. (2004)
Semi-dependent outcome if IQ $<$ 70	0.08	0.01–0.37	0.2; Beta	Howlin et al. (2004)
Dependent outcome if IQ $<$ 70	0.91	0.50–0.99	0.2; Beta	Howlin et al. (2004)
Independent individual	60 DFLYs			Motiwala et al. (2006)
Semi-dependent individual	30 DFLYs			Motiwala et al. (2006)
Dependent individual	0 DFLYs			Motiwala et al.(2006)
M-CHAT-R/F screening	$45			Derived from pilot project budget
EIBI cost	$56,000/year for 2 years			Auditor General of Ontario (2013)
ESDM-I cost	$100,994			Derived from pilot project budget
ESDM-PD cost	$692			Derived from pilot project budget
ASD diagnostic assessment	$396			Ontario Ministry of Health and Long-Term Care (2013)
Special education (ages 5–18): Semi-dependent individuals	$14,057/year for 14 years			Zegarac et al. (2008)
Special education (ages 5–18): Dependent individuals	$31,629/year for 14 years			Zegarac et al. (2008)

Table 3 continued

Parameter	Value	Range	Standard error, distribution	References
Special Services at Home funding[a] (Semi-dependent and Dependent individuals, age 5–18)	$3360/year for 14 years			Auditor General of Ontario (2013)
Respite care (Dependent individuals, ages 5–18)	$963/year for 14 years			Auditor General of Ontario (2013)
Transition to adult care services (Semi-dependent and Dependent individuals, age 18)	$1500			Auditor General of Ontario (2013)
Passport program (Semi-dependent and Dependent individuals, age 18–65)	$6275/year for 47 years			Ontario Disability Support Program (2013)
Income support[a] (Semi-dependent and Dependent individuals, age 18–65)	$13,032/year for 47 years			Ontario Disability Support Program (2013)
Health care: Independent individual, age 5–65	$316/year for 60 years	$257–$385		Canadian Institute for Health Information (2008), Lavelle et al. (2014)
Health care: Semi-dependent individual, age 5–65	$631/year for 60 years	$513–$770		Canadian Institute for Health Information (2008), Lavelle et al. (2014)
Health care: Dependent individual, age 5–65	$947/year for 60 years	$770–$1155		Canadian Institute for Health Information (2008), Lavelle et al. (2014)
Caregiver costs[b]: Independent individual, age 14–17	$16,734/year for 4 years	$13,387–$20,081		Dudley et al. (2014), Statistics Canada (2014)
Caregiver costs[b]: Semi-dependent individual, age 14–17	$34,810/year for 4 years	$27,848–$41,772		Dudley et al. (2014), Statistics Canada (2014)
Caregiver costs[b]: Dependent individual, age 14–17	$91,041/year for 4 years	$72,833–$109,249		Dudley et al. (2014), Statistics Canada (2014)
Caregiver costs[b]: Independent individual, age 18–65	$20,490/year for 47 years	$16,392–$24,589		Dudley et al. (2014), Statistics Canada (2014)
Caregiver costs[b]: Semi-dependent individual, age 18–65	$54,746/year for 4 years	$43,797–$65,696		Dudley et al. (2014), Statistics Canada (2014)
Caregiver costs[b]: Dependent individual, age 18–65	$137,945/year for 47 years	$110,356–$165,534		Dudley et al. (2014), Statistics Canada (2014)
Productivity loss[b]: Semi-dependent individuals, age 18–65	$24,850/year for 47 years	$19,880–$29,820		Statistics Canada (2014)
Productivity loss[b]: Dependent individuals, age 18–65	$49,700/year for 47 years	$39,760–$59,640		Statistics Canada (2014)

All parameters included in the model are presented, along with ranges used in one-way sensitivity analyses, and standard errors and distributions used in the probabilistic sensitivity analyses. Where no range is included, there is no associated uncertainty with this variable. Note that only model parameters relating to intervention effectiveness were tested in the probabilistic sensitivity analysis

[a] Costs only applied to Provincial perspective

[b] Costs only applied to Societal perspective

was considered a transfer payment and was not included in the societal perspective (Drummond et al. 2005). Caregiver costs were derived from Dudley et al. (2014). Caregiver hours were determined based on daily caregiver activities required for each functional outcome. The average salary of a social assistant ($19.77/h) from Statistics Canada was applied to the total caregiver hours to obtain caregiver costs (Statistics Canada 2014). A detailed breakdown of caregiver costs is presented in Online Resource 1.

The model considered the individual's lost productivity as a cost associated with each functional status. All Dependent individuals were assumed not to engage in paid employment, while Semi-dependent individuals were assumed to work 20 h a week in paid employment, and Independent individuals 40 h of employment per week. The national average hourly wage ($24.85/h) was employed to determine the cost of productivity loss.

Analysis

All model parameters with associated ranges and standard error values are summarized in Table 3. TreeAge Pro software (v. 2013) was used to create and analyze the decision model. A discount rate of 3 % was applied to costs and effects (Drummond et al. 2005). Expected costs and DFLYs for each comparator were determined. Incremental cost effectiveness ratios (ICERs) were calculated if the base case analysis showed the experimental comparator (ESDM-I or ESDM-PD) had both increased costs and increased DFLYs compared to the SQ. Additional one-way sensitivity analyses were performed based on absolute ranges derived from 95 % confidence intervals for each input. The impact of this uncertainty in the model was assessed with Tornado diagrams. Additionally, a probabilistic sensitivity analysis was performed to assess joint parameter uncertainty in the effectiveness parameters by assigning distributions based on the variables' means and standard deviations. Parameter uncertainty was modelled with normal distributions for IQ and beta distributions for the remaining parameters. Ten thousand Monte Carlo simulations were performed and the results are presented with incremental cost effectiveness scatterplots comparing each program, 95 % confidence intervals for the ICER estimates, and cost-effectiveness acceptability curves.

Results

Provincial Perspective

The cost effectiveness frontier for the provincial base case can be found in Fig. 4. The Status Quo (SQ) program cost (in present value terms) an average of approximately $186,000 per person to age 65 and generated an average of 1.98 DFLYs per person. The ESDM-Parent Delivered model (ESDM-PD) had an average cost of approximately $178,000 per person to age 65 and generated 2.15 DFLYs per person. The ESDM-Intensive model (ESDM-I) cost an average of approximately $199,000 per person for 2.51 DFLYs. The cost of ESDM-PD was the lowest, resulting in savings of nearly $9,000 per person (present value) over the lifetime when compared with the Status Quo. It dominated the SQ, producing more DFLYs for a lower cost.

ICERs were calculated for the ESDM-I. Compared to the SQ, the ESDM-I cost an additional $12,237 per person to age 65 and generated an additional 0.53 DFLYs, resulting in an ICER of approximately $23,000/DFLY. Compared with the ESDM-PD, the ESDM-I cost an additional $20,871 and generated an additional 0.36 DFLYs, with an ICER of approximately $58,000/DFLY.

Provincial Sensitivity Analysis

Multiple one-way sensitivity analyses are summarized in the Tornado diagram in Fig. 5, which measures the impact of uncertainty on the ICER comparing ESDM-I with ESDM-PD. The ICER was most sensitive to uncertainty associated with predicting IQ based on treatment profile and the probability of Independent, Semi-dependent and Dependent outcomes based on IQs above or below 70. Uncertainty attached to health cost, the only provincial cost with variability, had a minimal effect.

A scatterplot of the incremental cost and effectiveness estimates from the probabilistic sensitivity analysis comparing ESDM-I with ESDM-PD is presented in Fig. 6. The 95 % confidence intervals for all ICERs generated by the PSA are wide, indicating considerable uncertainty in the effectiveness parameters: -$615,000 to $779,000 per additional DFLY for ESDM-I versus SQ; -$1073,000 to $1157,000 per additional DFLY for ESDM-PD versus SQ; and -$694,000 to $985,000 per additional DFLY for ESDM-I versus ESDM-PD.

The provincial cost-effectiveness acceptability curve is presented in Fig. 7. The cost-effectiveness acceptability curve shows the most cost-effective options at different willingness-to-pay thresholds. The result of this analysis shows that at a willingness-to-pay below $58,000 per DFLY, the ESDM-PD was the preferred option; however, above this threshold, the ESDM-I becomes the optimal choice.

Societal Perspective

The cost effectiveness frontier for the societal base case can be found in Online Resource 4. Effects (DFLYs) for the programs are the same as those in the provincial

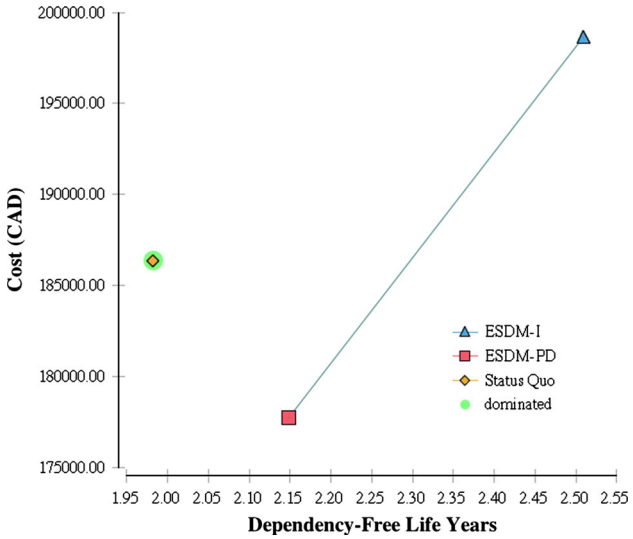

Fig. 4 Provincial cost-effectiveness frontier—base-case. The connecting line indicates the incremental differences in both costs and effectiveness between undominated comparators

Program	Cost	Increased Cost	Effect (DFLYs)	Increased Effect	ICER
Status Quo	$186,373		1.98		
ESDM-PD	$177,740	N/A	2.15	0.17	N/A – dominates SQ
ESDM-I	$198,611	$20,871*	2.51	0.36*	$57,975*

* Compared with ESDM-PD

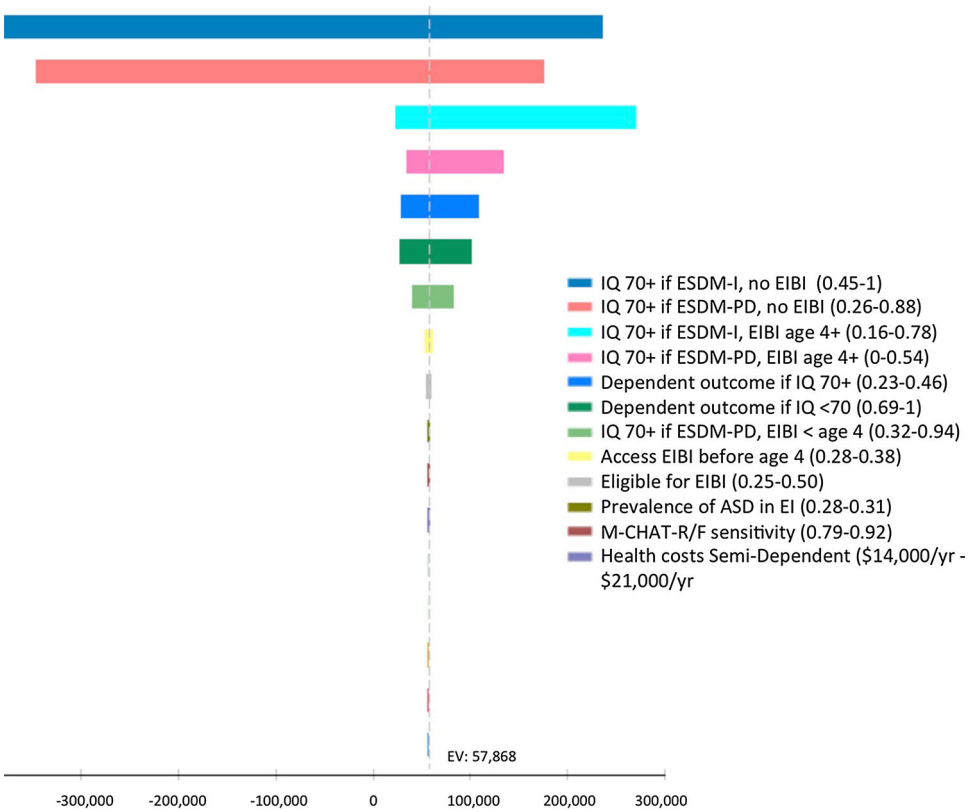

Fig. 5 Tornado analysis (ICER)—provincial perspective. This Tornado diagram shows the impact of uncertainty (based on ranges of possible values for each variable) on the ICER estimates for the ESDM-I versus ESDM-PD comparison. ICER values are presented on the horizontal axis. Each parameter is represented by a *bar stacked on the vertical axis*. The *width of the bar* shows the impact of the range of uncertainty attached to that value on the ICER. Expected value (EV) is the ICER from the base case

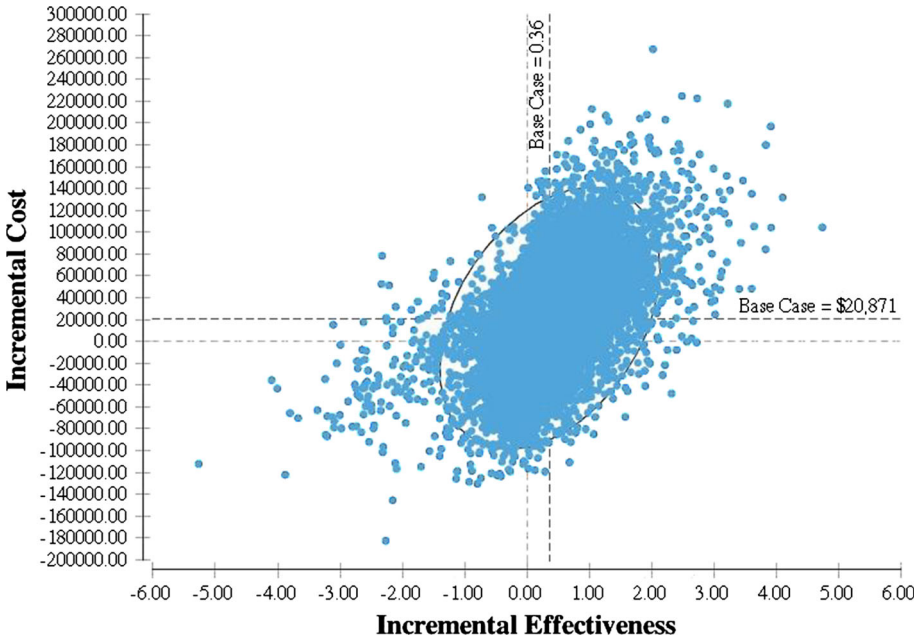

Fig. 6 Incremental cost-effectiveness scatterplot for ESDM-I versus ESDM-PD—provincial perspective. Incremental costs are plotted on the *vertical axis* and incremental effectiveness (DFLYs) on the *horizontal axis*. *Ellipses* represent the 95 % confidence interval of plotted values

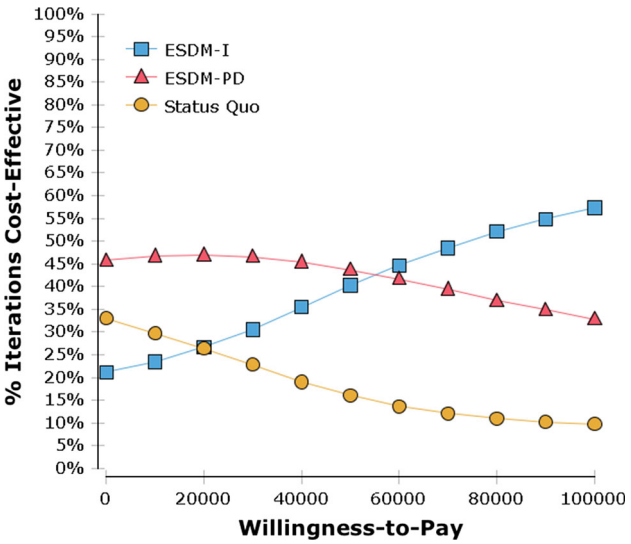

Fig. 7 Cost-effectiveness acceptability curve—provincial perspective. This figure shows the results of the rankings of cost-effectiveness based on 10,000 Monte Carlo simulations according to provincial willingness to pay (WTP)

perspective. From the societal perspective (including caregiver time and productivity loss), the ESDM-I dominates all other strategies and saves approximately $44,000 per person to age 65 compared with SQ.

Societal Sensitivity Analysis

Multiple one-way sensitivity analyses (Online Resource 5) followed a similar pattern to the provincial analysis, though with added impact of uncertainty in caregiver costs and productivity losses, particularly for dependent individuals. The societal probabilistic sensitivity analysis (Online Resource 6) again showed wide 95 % confidence intervals; -$3309,000 to $4246,000 for the ESDM-I versus ESDM-PD. The provincial cost-effectiveness acceptability curve (Online Resource 7) shows the ESDM-I to be the preferred option 40 % of the time with a willingness-to-pay of zero, up to 52 % of the time with a willingness-to-pay of $100,000 per additional DFLY.

Discussion

This is the first cost-effectiveness analysis (CEA) evaluating interventions delivered prior to a diagnosis targeted at the features of ASD, as well as the first to link published intervention benefits with projected adult outcomes. Our CEA shows that pre-diagnosis intervention with a parent-delivered ESDM (ESDM-PD) dominated the Ontario Status Quo (SQ) from a provincial perspective, with an intensive ESDM (ESDM-I) becoming the preferred strategy at a willingness-to-pay of approximately $58,000 per additional dependency-free life year (DFLY). From a societal perspective, the ESDM-I was the most effective and cost the least of all comparators.

The significant cost associated with ASD was an important model driver, as even a small increase in independence deflected a large proportion of the future costs. The addition of caregiver costs and productivity losses in the societal model was sufficient to make the ESDM-I the lowest cost option, despite only a small increase in effectiveness. Our estimates of societal costs were conservative

and did not include caregiver productivity loss, which is a likely scenario given the caregiving burden in ASD (Cidav et al. 2012).

An additional consideration is whether costs would increase in a scenario of increased referrals for pre-diagnosis programs, which would increase the number of children screened and also the number of false positive cases who received the intervention (without benefit, in our model). The magnitude of potential increased referrals is difficult to judge, as clinicians and caregivers are already encouraged to have a low threshold to refer for generic developmental EI services. Still, this scenario highlights the importance of using screening tools with both high sensitivity and specificity for ASD.

The overall levels independence from SQ, ESDM-PD, and ESDM-I were small, as were the differences in effect between the models. These small incremental gains, when paired with considerable parameter uncertainty in the model, produced extremely wide confidence intervals for the estimated ICERs. IQ was the only available surrogate between benefits of early intervention and prediction of adult independence; however, the projections of independence for individuals with average-range IQ are low (Howlin et al. 2004). Though ASD interventions produce gains in other areas, increased IQ is consistently the most robust gain from EIBI (Virues-Ortega 2010). Our model suggests that IQ gains alone are not likely to produce large gains in independence. Better predictors of adult independence are needed, and these factors should inform how ASD intervention programs are designed and evaluated.

Though our analysis strived to model the incorporation of pre-diagnosis intervention into existing infrastructure, there are additional implementation considerations for decision-makers. Implementation could face human resource barriers in training early childhood therapists to administer the ESDM (or similar program) with acceptable fidelity. Regional differences may lead to difficulties accessing trained therapists in some locations. In the early adoption of a pre-diagnosis model, pilot programs may be useful to evaluate these and other barriers, and to develop strategies unique to the needs of each jurisdiction.

Limitations

There are several limitations to our model. Most of these have to do with the limited availability of outcome data in the scientific literature. There are no randomized controlled trials of pre-diagnosis interventions targeting ASD. The ESDM studies are based on children who have a diagnosis of ASD; we assumed that benefits in children prior to diagnosis would be similar. Younger age was associated with greater improvement in the Rogers (2012) study, indicating that this was a reasonable assumption. This analysis took a conservative approach by not assuming any secondary prevention of ASD, which is a possibility given the shift to milder diagnostic subtypes seen in the Dawson (2010) study. The possibility of secondary prevention has been raised in a recent paper by Rogers et al. (2014), who showed lower rates of diagnosed ASD in a sample of seven symptomatic infants who received a parent-delivered model of the ESDM, compared to a group of symptomatic infants whose parents declined the intervention. Replication of these findings is necessary and secondary prevention may produce further cost savings.

We assumed that gains in IQ from successive application of ESDM followed by EIBI would be cumulative, though there is no evidence of this. In our model, the assumptions of cumulative effect are relevant for 37 % of children with ASD who receive EIBI in Ontario. The assumption of cumulative intervention effects results in upwardly biased estimates of effectiveness, though variability around all IQ estimates was tested in the sensitivity analyses.

We made a conservative assumption that there would be no difference in the rates of EIBI eligibility for children who received the ESDM. A decrease in the number of children with moderate to severe ASD would decrease the number eligible for EIBI, producing further savings.

We were limited in our choice of outcomes and chose DFLYs, which were used in a previous ASD cost-effectiveness analysis (Motiwala et al. 2006). Because DFLYs are not a widely reported outcome measure, there is no available standard or threshold for society's willingness-to-pay. Our results need to be placed in a broader decision-making context to evaluate the value of treatment programs for ASD. In the future, adding generic health utility tools to intervention studies (such as the Health Utilities Index-3, which has been validated in ASD; Tilford et al. 2012) will allow for cost-utility analysis, which is the preferred method to measure cost-effectiveness across health states and programs (Canadian Agency for Drugs and Technology in Health 2006).

Our model is specific to the context of early intervention for ASD; however, the linking of IQ gains and future independence may have future applications for other populations with neurodevelopmental disorders. Due to the considerable uncertainty in our model, which focused exclusively on ASD, we suggest caution in extrapolating the results to other populations.

Conclusions

Pre-diagnosis ASD-targeted intervention may be associated with cost savings from both provincial and societal perspectives compared to current Ontario service models; however, predicted gains in independence based on

increased IQ remain low with all programs. Caregiver costs were a significant driver in cost-effectiveness estimates; consequently, from a societal perspective the pre-diagnosis intensive ESDM generated both cost-savings and enhanced outcomes relative to both the status quo and pre-diagnosis parent-delivered ESDM. Randomized controlled trials of pre-diagnosis interventions targeting features of ASD are warranted and should include generic health utility measurement to allow for cost-utility analysis.

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