

Cost-Effectiveness of Autism Diagnostic Based on Genetic Testing

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Abstract

Background: Autism Spectrum Disorder (ASD) is a highly heritable polygenetic disorder with several degrees of handicap. Novel genetic diagnostics for Autism Spectrum Disorder promise an earlier diagnosis than psychometric diagnostics, but their cost-effectiveness is unproven.

Objective: To model the clinical pathway from diagnosis to early intervention (EI) and outcome in scenarios with genetic diagnostics compared to just psychometric diagnosis that follows a current guideline (Status Quo).

Methods: Early diagnosis based on genetic testing leads to more intensive and effective early intervention. Future scenarios assume genetic screening (Screening), genetic testing on request (GenADD), or genetic testing in cases with a family history of ASD (Predisposition). Simulations on Markov models using software TreeAge v. 2018 and parameters found in the literature. The time horizon reached from birth to the 15th year of life with cycle length 1 year. The models were stratified by autism severity, i.e. IQ initially below 70 or above. Effectiveness was both, dependency free life years (DFLY) gained by correct diagnosis and successful treatment, and the number of diagnosed patients that became independent after treatment. We choose the insurance view. Just direct costs for diagnostics and treatment were considered. Probabilistic sensitivity analyses (PSA) explore assumptions of different parameters, like the sensitivity of the genetic test, using the precisions stated in the literature or possible future developments.

Results: Status Quo is the most cost-effective scenario with the current parameter values. The other scenarios follow in the order of Predisposition, GenADD, and Screening. All scenarios with genetic tests have a higher number of detection than Status Quo. Intensified early intervention may be cost effective with horizon 67 years. The currently high false positive rate of genetic testing might be detrimental to that.

Discussion: Low precision of published parameter estimates led to wide confidence intervals for our estimates of cost-effectiveness. Our model shows that Screening and GenADD should not be an option for inaccurate genetic tests. Once they are more accurate, the potential of early intervention may unfold.

Conclusion: Further evaluations with better data need to underpin the current results.

Introduction

Autism Spectrum Disorder (ASD) is a development disability characterized by lifelong difficulties in social interaction, communication, restricted and repetitive interests and behaviors and sensory sensitivities. ASD is a generic term for a number of mental disorders [1]. The prevalence of ASD is increasing [2], and the United States of America Centers for Disease Control estimated the prevalence of ASD to be 16.8 in 1000 children for the year 2014 [3]. Between 30% and 60 % have an intellectual disability (ID) (IQ < 70) [4–7]. There are slightly different diagnostic strategies for ASD. The first tier in the US strategy encompasses the genetic diagnostic for monogenic fragile–X syndrome [8]. The NICE guideline is similar to the AWMF guideline and focuses on ID of the patient [9]. It also recommends the genetic diagnostic for fragile-X syndrome to establish etiology. The German AWMF guideline (028 – 018) for ASD diagnosis recommends the parent questionnaire Autism Diagnostic Interview - Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS) applied to the child [10]. The highest diagnostic accuracy is obtained when both diagnostic tests are used in combination [11]. The genetic investigation of the toddler is not recommended as routine diagnostic method and should be used in special cases.

An important approach is very early intervention (EI) [12–15]. Piccininni et al. [16] stated the cost-effectiveness of reduced waiting time on EI. The earlier the diagnosis is made, the higher are the chances of obtaining relief of symptoms, but “the early detection of this disorder remains a big challenge” [17]. Currently, between 36 and 70 months are required between first concerns expressed by parents and the professional diagnosis of ASD [18, 19]. Noterdaeme et al. pointed out that the first diagnosis by autism-diagnosis specialists is made at a mean age of 76 months [20]. The time for probably most effective EI is lost because of a lack of diagnosis. This time is considered a missed opportunity [21]. Effectivity of EI, namely that 42% of

autistic children, younger than 46 months, who got 40 hours of EI per week, reached the normal school and a self-determined life without limitations [22] was partly replicated in Germany [23]. Other studies replicated the limited success of 10 hours per week [24] with the percentage of toddlers with ASD, functioning within age expectations after EI at 12 % after 13 hours per week for 90 weeks (71 “active”). Penner et al. [7] evaluated different EI programs from Canada and USA. The “Early Intensive Behavioral Intervention” (EIBI) program generally consists of 20 hours of therapy per week for a maximum of two years. A recent survey of intervention usage [25] stated the percentage for ASD children getting EI in Germany as 92.3 % for a mean 4.2 hours per week. This is in contrast to Norway, where 97.1% of ASD children were getting EI 19.5 hours per week on average with a variance that suggests that some patients receive the intensity needed for a good effect.

Genetic testing might be an alternative to psychometric testing for early diagnosis, and it can be employed immediately after birth. In fact, genetics play a major role in ASD. Twin studies show a high heritability > 90 % in siblings with predisposition [26, 27]. Whole genome sequencing (WGS) is the emerging diagnostic tool with the potential to use a wide variety of genetic information [28]. Many genetic loci for ASD have been identified through linkage or association analysis [29–33]. There are a large number of different genes influencing the different autistic disorder syndromes. The SFARI database (SFARI.org) counts over 1000 suspicious genes [34, 35]. ASD is the product of the interplay between genetic variants, and their diagnosis should be a combination of multiple genetic markers [36]. The following genetic syndromes are known etiologies of ASD: Angelmann-, CHARGE-, Fragile-X-, tuberous sclerosis, de Lange-, Prader-Willi-, Lujan-Fryns-, Crowden-, Cohen-, Bannayan-Riley-Ruvalcaba-, Rett-, Smith-Lemli-Opitz-, Smith-Magenis-, DeGeorge-, Timothy-, Williams-Beuren-, Phelan-McDermid-, Sotos-Syndrome [8, 36, 37]. About 3% of ASD cases can be linked to monogenic syndromes, such as fragile-X syndrome or tuberous sclerosis [38]. The fragile-X syndrome causes a very small (< 1 %) portion of ASD [38]. The outcome-oriented approach would be to summarize all genetic mutations or disorders in a single genetic test that detects patients needing similar EI with a good sensitivity. Such a test is currently unavailable. Currently available commercial genetic testing covers only parts of the genetic spectrum. None of these tests covers the entire spectrum. The FDA has not cleared any of the genetic tests for ASD for commercial use. Tammimies and Miller provide a comparative value that can be used as the sensitivity of a genetic test. This value is 15.8% (95% CI 9.1% -24.7%) [39, 40]. Specialized laboratories offer genetic tests for rare forms of autism. The tests rely on next generation sequencing (NGS) and whole genome sequencing (WGS), which identifies large DNA deletions or duplications. Overall, about 100 laboratory-developed genetic panels are in use [29, 41]. WGS has the potential to become a standard diagnostic tool in clinical practice [28].

Lifetime societal cost of ASD, including care and lost productivity, were estimated at 2.4 million US\$ per case with ID, and 1.4 million US\$ without ID [4]. Health care expenditures increased sharply over the past years [42]. Leigh et al. predict a gain of costs higher than those for stroke and hypertension up to 2025 based on the increase in prevalence [43]. It is therefore critical to the patient, his/her family, and to society to reduce the impact of ASD. Penner et al. further analyzed the impact of EI programs on Disability Free Life Years (DFLY). The examined programs were the EIBI and the “Early Start Denver Model” (ESDM). They showed an increase of DFLY at a reduction of costs compared to the current EI program in Ontario, Canada [7]. Reduced waiting times and their cost-effectiveness were evaluated to savings of CN\$53.000 per individual based on DFLY [16]. There is not only a medical, but an economic impact of the time of beginning and duration of EI. A current study from Ireland shows the structure of costs for EI and other expenditures. The average resources used for a family amounted to over 28.000 € (\$24.900) per year including indirect costs [44].

The primary aim of this study was, therefore, to evaluate the cost-effectiveness of genetic diagnostics compared to the current psychometric diagnosis. We further studied the impact of EIBI on the cost-effectiveness on the models and scenarios.

Methods

We developed a decision analytic Markov model for our simulations. The parameters (Table 1) used in our model were the results of a literature research.

The state transition diagram (Fig. 1) shows the different states and possible transitions of patients between states of the Markov model. The diagram shows the flow through the model scenario, from left to right. For a better understanding, we included birth into the diagram in dashed line. The structure at the top of the diagram shows the flow in a simple way, beginning with the diagnosis, transition to EI and to states assumed stable. Our model divides into the strata “ASD + ID undiagnosed”, “ASD undiagnosed” and “No ASD”. These are fixed genetic traits. Any improvement in ID or other symptoms is accounted for by transition to the states “Independent”, “Semidependent”, “Dependent” and “True Negative” at the outcome. Circular arrows indicate the realistic assumption that people may stay in a state for more than one cycle and give rise to a distribution of times in a state. The model was used to evaluate four different scenarios. We also evaluated the scenarios by variation of EI. First we used the current EI and afterwards we simulated the model with intensive EIBI. Further information about the scenarios follows in the paragraph: “Models and comparators”. Based on early diagnosis and intervention, patients can reach a normal school and grow up to a life with greatly reduced need for care.

The software used for the evaluation was TreeAge 2017.

Population

The number of children in this simulation was the number of births in Germany in the year 2015. For the “Predisposition” scenario, we assumed the “recurrence risk ratio”, which describes the proportion of ASD patients, who have a family history of ASD.

Moreover, we factored in the proportion of ASD patients with higher and lower IQ, because the literature states different expenses and outcomes in care and EI given IQ under or over 70. We chose a sensitivity of the genetic test on ASD: 0.17, between those published [39, 40, 45]. Further parameters are listed in Table 1a and 1b.

Table 1.1: Model parameters for the Markov model

er	Value	Range	TD color	Reference
ce ASD	0.0168	0.016 - 0.017		CDC: MMWR, vol. 63. p. 28. (2018) [3]
ce of ID among ASD	0.316	0.3 - 0.332		CDC: MMWR, vol. 63. p. 28. (2018) [3]
nsitivity	0.92	0.843 - 0.968		Bolte et al. : (2005) Z Kinder Jugendpsychiatr Psychother 33(1), 5-14. [64]
ecificity	0.99	0.946 - 1		Bolte et al. : (2005) Z Kinder Jugendpsychiatr Psychother 33(1), 5-14. [64]
nsitivity	0.904	0.849 - 0.947		Bolte et al. : (2004) Z Kinder Jugendpsychiatr Psychother 33(1), 5-14. [66]
ecificity	0.48	0.299 - 0.666		Bolte et al. : (2005) Z Kinder Jugendpsychiatr Psychother 33(1), 5-14. [64]
est sensitivity	0.17	0.136 - 0.205		Carayol et al. : (2010) Molecular Autism 1(1), 4. [67]
est specificity	0.93	0.879 - 0.967		Carayol et al. : (2010) Molecular Autism 1(1), 4. [67]
Germany 2015	737,575	700,000 -800,000		GBI [68]
agree to Genetic Test	0.786	0.764 - 0.807		Int J Mol Sci, 18(5), DOI: 10.3390/ijms18051078 [69]
Recurrence Risk of non ASD	0.07	0.001 - 0.073		Ozonoff et al.: (2011) Pediatrics 2011;128:e488-e495 [26]
	1			Motiwala et al. Healthcare policy = Politiques de sante, 1(2), 135-151[70]
f	0.5			Motiwala et al. Healthcare policy = Politiques de sante, 1(2), 135-151
on leaving intensive early ion per year no ID	0.45			Penner et al. : (2015) DOI:10.1007/s10803-015-2447;Charman et al. and Piccinninni et al. DOI:10.1001/jamapediatrics.2016.2695[6,16]
on leaving intensive early ion per year (for the first 5 years n) ID	0.17	0.01 - 0.2		Penner et al. : (2010) DOI:10.1007/s10803-015-2447 Landa et al. DOI: 0.1080/09540261.2018.1432574[54]
sitive in the FP branch remaining itive	0.3			Stadnick et al. (2015) DOI:10.1016/j.rasd.2015.08.007 [71]
noID)	0.32			Howlin et al. Journal of Child Psychology and Psychiatry 45:2 (2004), pp 212-229[56]
ep. noID)	0.23			Howlin et al. Journal of Child Psychology and Psychiatry 45:2 (2004), pp 212-229[56]
oID)	0.45			Howlin et al. Journal of Child Psychology and Psychiatry 45:2 (2004), pp 212-229[56,72]
ID)	0.04			Howlin et al. Journal of Child Psychology and Psychiatry 45:2 (2004), pp 212-229[56]
ep. ID)	0.13			Howlin et al. Journal of Child Psychology and Psychiatry 45:2 (2004), pp 212-229[56]
o)	0.83			Howlin et al. Journal of Child Psychology and Psychiatry 45:2 (2004), pp 212-229[56]
entconcerned				Table S3
timationnoASD				Table S3
parentconcerned				Table S3
parentnotconcerned				Table S3

Table 1.2: Cost parameters for the Markov model

er	Value	Range	TD color	Reference
etic test	€ 368.28	<i>€ 300 - 1,000</i>		Specialist interview, based on EBM
etic test Maximum	€ 890	<i>€ 300 - 1,000</i>		Plöthner et al. DOI:10.1007/s10198-016-0815-0 [28]
R	€ 343.83	<i>€ 500 - 600</i>		Specialist interview, based on EBM, verified with Galliver et al. 2017 [73]
DS	€ 400.70 €	<i>€400 - 500</i>		Specialist interview, based on EBM, verified with Galliver et al. 2017 [73]
cost, include early tion ID	€ 736.98			Roddy et al. DOI: 10.1177/1362361318801586 [44] Perry et al. DOI: 10.1016/j.rasd.2010.07.003 Salomone et al. DOI: 10.1177/1362361315577218
cost, include early tion ID j	€ 2,534.35			Roddy et al. DOI: 10.1177/1362361318801586 [44] Perry et al. DOI: 10.1016/j.rasd.2010.07.003 Salomone et al. DOI: 10.1177/1362361315577218
cost, include early tion no ID	€ 396.88			Roddy et al. DOI: 10.1177/1362361318801586 [44] Perry et al. DOI: 10.1016/j.rasd.2010.07.003 Salomone et al. DOI: 10.1177/1362361315577218
cost, include early tion no ID 5	€ 359.24			Roddy et al. DOI: 10.1177/1362361318801586 [44] Perry et al. DOI: 10.1016/j.rasd.2010.07.003 Salomone et al. DOI: 10.1177/1362361315577218
EIBI Canada for 2 years	€ 38,295.04=Can\$ 56,000 per year			Penner et al : DOI:10.1007/s10803-015-2447

The values of the ranges based on literature (blue) confidence intervals. Expert interview ranges (red) and own speculative ranges (purple) in the column "Range". Further own speculative ranges of expert interview are printed in *italic font*, based on own estimation. The column "TD color"

Perspective, time horizon

We choose the evaluation view: "payer perspective" [46] or, more specifically, the "insurance" perspective and calculated the direct medical costs of diagnosis and treatment for EI. Educational-, care and assistance-, respite care- or living-costs are not included. Further comorbidity is not included. The German structure of costs for EI is very complex [47, 48]. We had to use data from Ireland [44] and Canada [7] for the EIBI instead, that seem similar.

The Markov model calculates 16 cycles from birth to the end of the 15th year of life. The duration of the cycles was one year.

Models, comparators

The first scenario "Status quo" shows the current psychometric diagnosis with the parent questionnaire ADI-R and children diagnostic ADOS recommended by the German guideline published by AWMF [49]. The decision tree within the Markov model is illustrated in Fig. 2. The second scenario "Screening" assumes that postpartum genetic screening for ASD is recommended for all newborn. The third scenario "Predisposition" assumes that the genetic test is offered only to newborns with a genetic predisposition to ASD in the family history. The last scenario "Genetic test on request" offers the additional genetic testing of a newborn at the parent's request.

Figure 2 shows the scenario "Status quo". The other scenarios are available as supplementary Figures S1, S2 and S3. We divided the cohort of ASD patients into the more or less severe ends of the spectrum "IQ < 70" (ID) and "IQ > 70" with proportion 31.6% ID based on CDC data of Christensen et al. 2018 [3]

The simulated models were time dependent, as were probabilities of patients taking their children to ADI-R and ADOS. Probability of leaving EI given ID was 0.48145 for the first 5 years and 0.77912 for the subsequent years based on Perry et al. [50]. The probability of leaving EI given no ID was 0.51855 for the first 5 years and 0.22087 for the subsequent years. The

model calculated with probabilities collected in tables. Every row of the tables shows one cycle/year and the value for the probability and the calculated cost for the cycle. The values for the costs and probabilities of EI with ID, before and after the age of 4 (cycle 5) are listed in the Tables S2 and S3 in the Appendix. The EIBI costs are converted from \$CD into € at the current exchange rate. We included the EIBI costs for two years at the third and fourth year of life for the Children with ID following Penner et al.

The transition probability values for the dependent, independent and semi dependent branches in the EIBI model are calculated based on the Meta-Analysis from Reichow et al. [51, 52]. We used the increase in IQ (IQ difference) from Reichow et al. and calculated the reduced probability to stay dependent(see Appendix).

Cost and effectiveness

All parameters used in the models are based on a literature review and on expert opinion and are collected in the Table 1a and 1b [44, 25]. We calculated the medical costs based on Roddy et al. [44] and the weekly duration of care from Salomone et al. [25]. Detailed descriptions of the calculation of the costs are listed in the Appendix. The simulation results are listed in Table 2.

The costs of EI and medical services change over the years and will be dependent on the IQ level of the child. Penner and Roddy et al. [50, 7] reported an IQ growth based on the beginning and intensity of the EI. We stratified the cost in the first 5 cycles and the remaining cycles. We further divided the children into the groups of IQ < 70 and IQ > 70. The following costs were calculated: The yearly costs for children up to 5 years of age without ID amount to 396.88 € and for children over 5 years without ID will be 359.24 €. The costs for children of less than 5 years with ID amount to of 736.98 € and for children over 5 years with ID will be 2.534.35 €. This information is based on recent Irish data [44] and confirmed with UK data [4]. All cost from Ireland were converted to € by the exchange rate of 2014 and discounted to the current values. The converted EIBI costs from Canada amount to 38.295.04 €. A discount rate of 5 % [53] was applied to costs. Detailed information is listed in the Appendix.

The measures of effectiveness were the number of ASD patients reaching semi- or independence and the number of dependency-free patient years (DFLY) for the semi dependent and independent patients up to 67 years of age, the statutory retirement age in Germany, after which everyone may be admitted to old-age homes.

The numbers of false positive test results were calculated for each scenario (Figures S5.1 and S5.2), as the subsequent EI could overburden the health care system.

We assume for simplicity that the probability of semi- or independence after EI does not change with age.

Sensitivity analysis

We combined multiple one-way sensitivity analyses in the tornado diagram (TD), where each parameter for the one-way analysis is represented by its range. The parameter ranges were extracted from the references given in Table 1. When a reference was not available or it was not possible to extract a range, we used the *italic font* in the row to indicate our own estimation of feasible values.

A probabilistic sensitivity analysis (PSA) was based on the parameter distributions given in the Table S1 in the Appendix. We used beta distributions for probabilities. One thousand Monte Carlo simulations were performed, and the results are presented with cost effectiveness scatterplots and CEAC comparing the scenarios. The cost-effectiveness acceptability curve (CEAC) for the models with EI or with EIBI were computed.

Results

Given a birth cohort of 737.575 and the prevalence 0.0168, 12.391 children should be affected by ASD.

The EI and EIBI models show similar results for the scenarios in descending order. The highest number of independent or semi dependent children are reached the “Screening” scenario followed by the scenarios “Genetic test on request”, “Predisposition” and finally “Status quo” (Fig. 3.1). The costs also follow this order. The scenario “Screening” is the most expensive scenario, followed by the scenarios “Genetic test on request”, “Predisposition” and finally “Status quo”.

EIBI would produce 50% more independent persons at three times the cost. These results are also valid for the effectivity measure DFLY (Fig. 3.2). The scenarios “Status quo” and “Predisposition” are very close in their cost-effectivity in EI treatment and EIBI. The scenario with the highest NMB is “Screening” with a cost of 132.720.485 €, an effectiveness of 4.814 successfully treated children at a CE of 27.565 €/Pat and NMB 1.070.976.144 € at the EI model. The cost with EIBI under “Screening” were 202.536.297 €, an effectiveness of 7.145 successfully treated ASD patients at a CE of 28.346 €/Pat and NMB 1.583.713.379 €.

The cost-effectivities of “Predisposition” and “Status quo” are close to each other for DFLY, too.

The effectivity for the scenario “Status quo” reaches 3.885 children and for the “Predisposition” 4.019 children in the EI model and for the EIBI models a number of 6.195 children at “Status quo” and 6.331 successfully treated children at “Predisposition”. The CE-ratio shows a slightly higher level in “Predisposition” with 8.899 €/Pat, compared with the CE-ratio of 8.838 €/Pat at the scenario “Status quo”. The evaluation of DFLY also shows similar incremental results. The scenario “Status quo” reaches 30.532 DFLY and the “Predisposition” 31.182 DFLY in the EI model and for the EIBI models 47.668 DFLY in “Status quo” and 48.337 independent children in “Predisposition”.

The DFLY CE-ratio values are even closer. “Status quo” reaches a CE-ratio of 1.125 €/Pat in “Predisposition” 1.146 €/Pat for the EI model and for the EIBI models 2.186 €/Pat in “Status quo” and 2.187 €/Pat in “Predisposition”.

The results are shown in the Tables 2.1 and 2.2.

Table 2.1: Cost and effectiveness: Number of independent patients and of dependency free life years (DFLY) after just EI. ICER = incremental cost-effectiveness ratio, NMB = net monetary benefit, CE = cost-effectiveness

Scenario	Total cost (€)	Incremental cost (€)	Effectiveness	Incremental Effectiveness	ICER	NMB	CE-ratio
<u>At least semi-independent patients</u>							
Status Quo	34.346.482	0	3.885	0	0	937.123.565	8.838
Predisposition	35.765.752	1.419.269	4.019	133	10.656	9.690.005.37	8.899
Genetic test on request	84.174.296	48.408.544	4.581	562	86.146	1.061.075.542	18.374
Screening	132.720.485	48.546.189	4.814	233	207.651	1.070.976.144	27.565
<u>DFLY</u>							
Status Quo	34.346.310	0	30.532	0	0	7.598.705.0877	1.125
Predisposition	35.765.575	1.419.264	31.182	650	2.183	7.759.802.854	1.146
Genetic test on request	84.174.104	48.408.529	34.249	3.066	15.786	8.477.999.288	2.458
Screening	132.720.485	48.546.189	35.524	1.276	38.053	8.748.391.505	3.736

Table 2.2: Cost and effectiveness: Number of independent patients and of dependency free life years (DFLY) after EIBI or EI. ICER = incremental cost-effectiveness ratio, NMB = net monetary benefit, CE = cost-effectiveness

Scenario	Total cost (€)	Incremental cost (€)	Effectiveness	Incremental Effectiveness	ICER	NMB	CE-ratio
<u>At least semi-independent patients</u>							
Status Quo	104.210.174	0	6.195	0	0	1.444.515.959	16.821
Predisposition	105.729.174	1.519.000	6.331	136	11.140	1.477.082.976	17.000
Genetic test on request	154.201.129	48.471.955	6.906	574	84.348	1.572.277.521	22.328
Screening	202.536.297	48.335.167	7.145	239	202.168	1.583.713.379	28.346
<u>DFLY</u>							
Status Quo	104.210.174	0	47.668	0	0	11.812.865.693	2.186
Predisposition	105.729.174	1.519.000	48.337	669	2.270	11.978.671.893	2.187
Genetic test on request	154.201.129	48.471.955	51.481	3.144	15.418	12.716.183.320	2.995
Screening	202.536.297	48.335.167	52.789	1.308	36.953	12.994.848.758	3.837

The evaluation of the false positive patients (FPP) showed the following results. The summary of the EI model shows 655 FPP in the scenario "Status quo", 837 FPP in "Predisposition", 7.016 FPP in "Genetic test on request" and 13.375 FPP in the "Screening" scenario. The EIBI model shows the same number of FPP, but on a higher number of independent children. The Figures S5.1 and S5.2 show the diagrams of FPP of the scenarios in the Appendix.

The EI model CEAC shows that scenario "Predisposition" has a higher probability to be more cost-effective than "Status quo" at a WTP exceeding 31.000 €. The scenario "Genetic test on request" takes over at WTP 81.400 €. The "Screening" scenario would require a WTP of 207.600 €.

The TD (Fig. 5) combines multiple one-way sensitivity analyses and displays the influence of several parameters on all scenarios. The NMB was most sensitive to uncertainty in both, EI and EIBI models, to changes in the parameter birth-rate followed by the cost and the sensitivity of the ADIR test. The genetic test sensitivity and cost are following on the subsequent ranks. TD diagrams of the EI and EIBI models show a higher Expected Value (EV) of NMB of 240 M € for the EIBI model and 185 M € for EI.

The Figures S6.1 and S6.2 show the number of (semi-)independent persons after EI at the evaluated cycles. The scenario "Screening" and "Genetic test on request" reach a higher rate of (semi-)independent persons in the first 4 years. This effect is stronger for the EIBI Model. The scenarios "Status quo" and "Predisposition" are on a lower level in the first 4 years. The EIBI model shows a steeper slope in the years four to eight.

The probability diagram at Figure S4.1 shows the probabilities of the ASD children reaching the states "independent", "independentID" and "Semi dependent" after EI.

We can see a slightly higher probability in the scenario "Genetic test on Request", compared to the scenario "Predisposition". The "Predisposition" scenario shows beginning treatments in year four, compared to the scenario "Genetic test on Request", where the EI begins in year two. The scenarios "Status quo" and "Screening" show similar results.

Figure S4.2 shows the TP and FP probabilities at the exemplary scenarios "Status quo" and "Screening test on request". The red line shows the probability of the FPP. The diagram shows a high probability for FP at the scenario "Screening". We can see similar results in scenarios "Predisposition" and Genetic test on Request". The results can be confirmed by Figure S5.2, where we see a much higher number of the FP patients in the scenario "Screening", compared to the scenario "Status quo".

Generally we see a slightly higher number of TP patients at the EIBI model. However these differences are small. Figure S5.1 and S5.2 show the number of TP and FP patients for the models EI and EIBI.

Discussion

This Markov-model is different from the decision tree models used before [7, 16]. Besides taking a dynamic view with time dependent parameters, it considers genetic testing. We compared two models that differed by the presence or absence of a costly, effective EI during the first five years.

We constrained the evaluation to the first 16 years, because variable costs and effectiveness are limited the first years of life [54]. In the first six years of life, parents for the first time notice behavior patterns and, between the fourth and sixth year of life, when children enter preschool and school [23, 20, 21], definitive diagnoses are reached that guide EI.

Our models show a higher rate of patients reaching independence in the genetic testing scenarios and a higher independence rate after EIBI, compared to the current EI. The closest scenario to the Status Quo is the Predisposition scenario. Untargeted genetic testing and screening are much more expensive and not efficient. This seems to be interesting because our data is only from literature research and should be repeated with real data. The extension of EI to EIBI should be kept in mind for families with genetic predisposition.

EIBI seems like a huge investment, that may pay off. It would be facilitated by early detection, e.g. genetic testing. Genetic tests produce so many FP, as of now, that the investment in EIBI would not be cost-effective, if combined with such tests. Once accuracy of the genetic diagnostics will increase, the numbers of FPP will decrease, and the combination can be expected to be cost-effective.

The high FP rate in the scenarios "Screening" and "Genetic test on request" are a result that could be expected because of the low sensitivity of the genetic test. These scenarios are not cost effective and would overwhelm the health system by treating a high number of healthy toddlers. Costs would be driven less by costs for genetic testing, but rather by treating numerous children with false positive tests. The Figure S5 shows the numbers of the false positives by cycle and scenario.

The differences between EI and EIBI are not just the number of treatment hours per week and duration of EI programs and therefore the much higher costs of EIBI but the higher effectivity, too. That gain is limited to early youth. The time for genetic testing is important. The best time for targeted genetic testing is the prenatal or postnatal time. The earlier the diagnosis is made, the higher are the chances of obtaining relief of symptoms. This should be done before children reach age three years [55] for the children to reach a normal school and an independent life. Our model is constrained on the first years of life up to the juvenile age. Further models should investigate the adult effects of these children.

We stratified by intellectual disability, operationalized as $IQ < 70$. This is a common threshold in the current literature. It based on the research of Howlin et al. [56]. Reichow et al. shows several other aspects of the improved skill after EIBI, e.g. communication, behavior or social competence.

This study does not include parental stress and informal care, because there is little data. The evaluation of DFLY doesn't encompass all the costs and restrictions of ASD. Further research into these aspects would be particularly interesting.

ASD is a polygenic distortion and a simplification of a very complex distortion system. ASD is a bundle of genetic distortions. Only a small proportion, 3%, is monogenic, where the current healthcare economic methodology is fitting. Currently, the gene-environment interaction not entirely clear. The next question is the interaction between the genetic markers. Several markers

were found only recently. At the moment it is not clear, how many more markers there are. The interaction between markers is unclear. Not all markers are in a summary effect. There are several other inheritance factors like polygenic, oligo genic effects or CNVs and other gene gene interactions[57]. The current polygenic research of ASD explores polygenic risk scores (PRS) based on GWA's on large numbers of individuals. The GWA results base on a defined number of exclusive regions and their markers [58]. The question of interaction impacts between these markers is not answered. The main problems of multiple distortions under the term "ASD" are also existent. Li et al, [59] show the usage of PRS combined with selected training sets for ASD individuals. This seems to be an interesting approach for PRS and real usage. Further research must answer these questions, however.

The "payer" view of evaluation was chosen meaning "insurance" in Germany. Only the cost for diagnosis and treatment were regarded. The social view that regards loss of productivity and informal care may reach other conclusions. This issue is mirrored in the choice of effectiveness measure. Dependency free life years (Penner et al.) seem more feasible than quality adjusted life years (QALY). Willingness to pay would depend on the specific cost of being dependent or semi-dependent for many years.

The number of economic studies is low (Buescher et al., Leigh et al., Penner et al, Lavelle et al. and Amendah et al. [60, 4, 7, 16, 43, 61]; One [43] pointed out, that there were over 200 economic studies within the last 15 years in the field of diabetes, which shows the disparity of research in the economic field. The quality of economic evaluations of genetic testing could be better [62].

Limitations

We used data from Germany [63, 64, 38], Ireland [44], Canada [7] and UK [4] in our models. Cost assumptions may be greatly distorted as a result. As a result of the literature review, we were forced to make some simplifications.

Autism spectrum disorder (ASD) is an acronym for a bundle of neurologic and cognitive behavioral anomalies. It includes several forms of ASD, with mild and strong characteristics or forms.

The stratification of the parameter IQ was also a simplification, but necessary at the available data.

The comorbidity was not fully regarded, though it is an essential cost driver and has a strong influence on EI.

Current genetic tests cover only part of the ASD spectrum or disorders involving ASD. The methodology covering the whole genetic spectrum is not proven. It could be a promising strategy to focus on monogenic distortions, though only 3% of the ASD patients are affected [38]. We did not develop economic methodology for that mixed strategy.

Forecasting of prices is possible in a limited period of time, whereas forecasting for a time period up to 50 years includes several uncertainties. Making a reliable forecast in trend of prices, one could assume an increasing sensitivity of genetic tests at a falling price. The cost of EI will rise in time, because more patients are diagnosed and earlier.

Negative effects on parents, relatives, caregivers and siblings are not included in this model. We do not have robust data on the successfully treated ASD patients at this time, and the model does not cover recurrences. Based on the available data, it is not possible to calculate further economic impacts for the future or on gross domestic product (GDP).

Conclusion

The guideline from UK (NICE/cg128) [9] and the guideline from Germany (AWMF) [49] recommend psychometric diagnostics. The tools are diverse. Both guidelines don't recommend untargeted, but the targeted use of genetic diagnostics. Using genetic diagnostics ensures the detection of rare distortions like the fragile-x syndrome. Our results support this recommendation. Untargeted genetic testing for ASD is currently not a cost-effective alternative to the current psychometric diagnosis of ASD. Untargeted genetic testing scenarios would burden, if not overburden, the current healthcare system. This might change with

better diagnostic accuracy. Further reliable data on the financial and medical burden of ASD on patients and caregivers is necessary for the analysis from other viewpoints.

Declarations

Ethics approval: This article does not contain any studies with human participants or animals performed by any of the authors. Not applicable

Consent for publication: Not applicable

Availability of data and materials: Data used, based on intensive literature review. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Authors contributions: The first idea to this research problem and economical background come from WRR. WRR carried out the literature review, developed and designed the methodology for the model and realized the calculations in the TreeAge Software.

RV generated several solutions for statistical problems, results and background, especially for the sensitivity analysis.

The interpretation of data (results and discussion) was made by both authors.

The design of the manuscript was made by both authors. Both authors read and approved the final manuscript.

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Figures

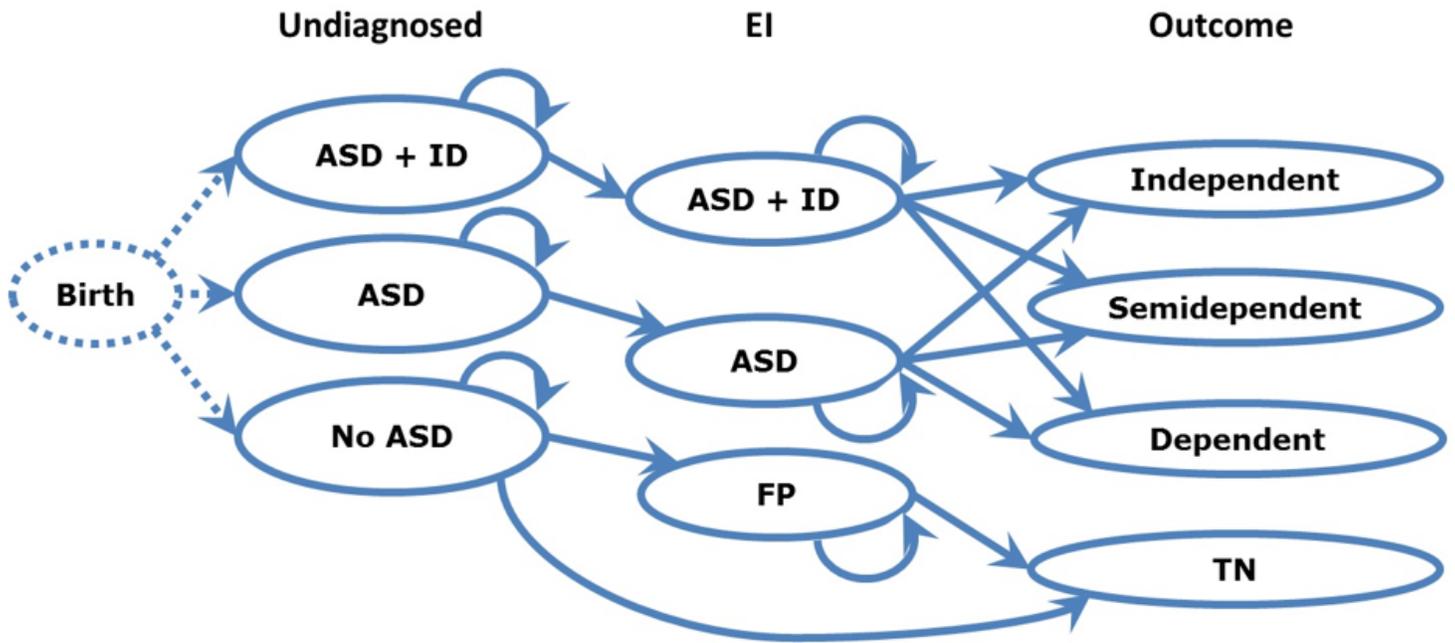


Figure 1

States and transitions in the Markov model Status Quo The bubble diagram shows the states and the transitions of the scenario "Status Quo". We categorized the states for clarity into the categories "Diagnostic", "EI" and "Outcome". EI = Early Intervention, ASD = Autism Spectrum Disorder, ID = Intellectual Disability, FP = False Positive, TN = True Negative.

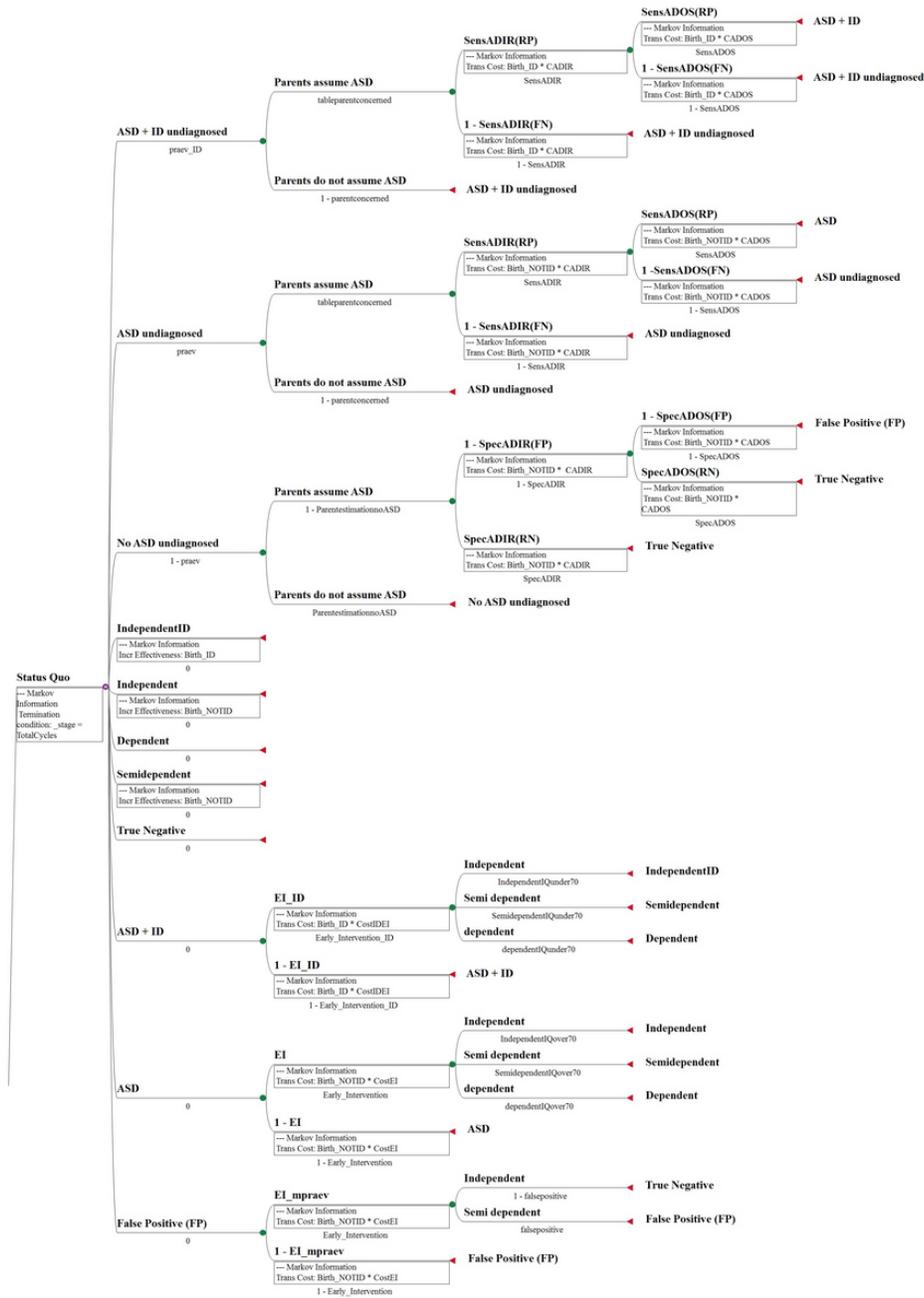


Figure 2

Decision tree for scenario Status Quo: Psychiatric diagnosis of ASD following the German guideline Markov nodes are presented in purple circles with "M". Change nodes are presented in green circles and terminal nodes are presented in red triangles. The scenario begins at the upper left states "ASD + ID undiagnosed" with ID and "ASD undiagnosed" without ID to the left. When the toddlers pass the diagnostic state to the right and will be diagnosed positive, then they reach the EI state at "ASD + ID" and "ASD" and get the EI treatment. After this EI, they will reach the final states "IndependentID", "Independent", "Semidependent", "Dependent" or "True Negative". The branches: "SensADIR", "SensADOS" describe the sensitivity of the diagnostic tests. The branches: "parents assume ASD" includes probabilities of parents getting their child tested. The branches: "SpecADIR", "SpecADOS" describe the specificity of the diagnostic tests. The branches: "EI_ID" and "EI" include the probabilities for entering and staying in early intervention with ID, without ID and for the branch False Positive, where people without ASD are getting EI.

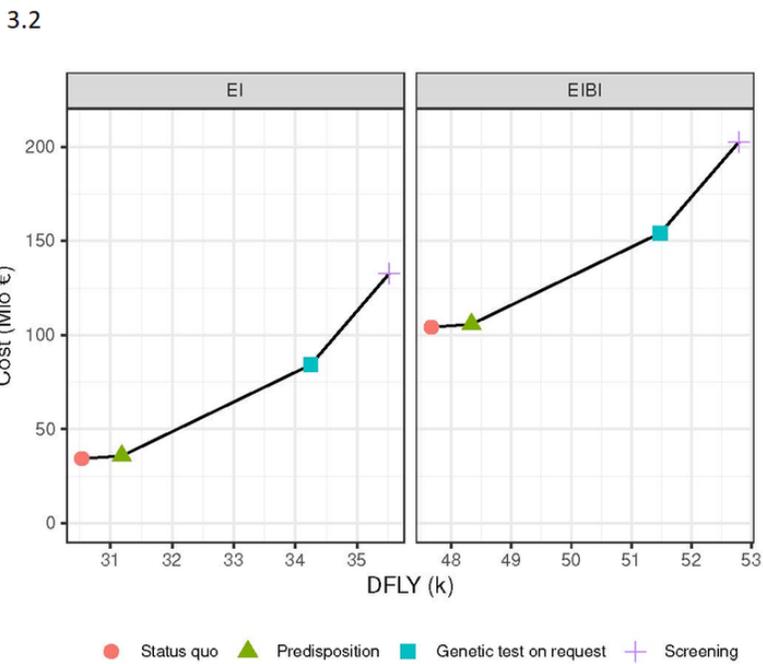
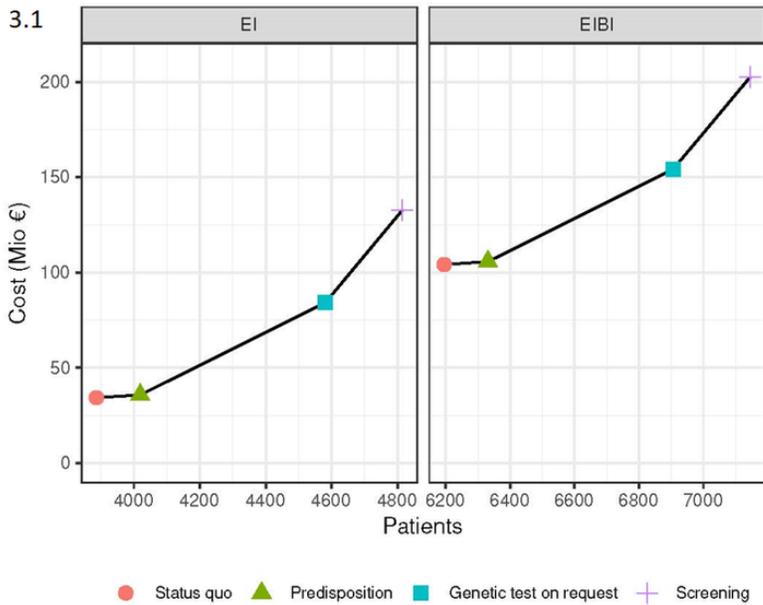


Figure 3

1 Cost-effectiveness analysis for the number of (semi-)independent patients. 2 Cost-effectiveness analysis for the number of dependency free life years (DFLY). Fig shows the cost-effectiveness analysis. Effectivity is number of semi- or independent patients in the first row and number of DFLY gained in the second row, while costs are for 16 cycles. The connecting line shows that no scenario is dominated by others.

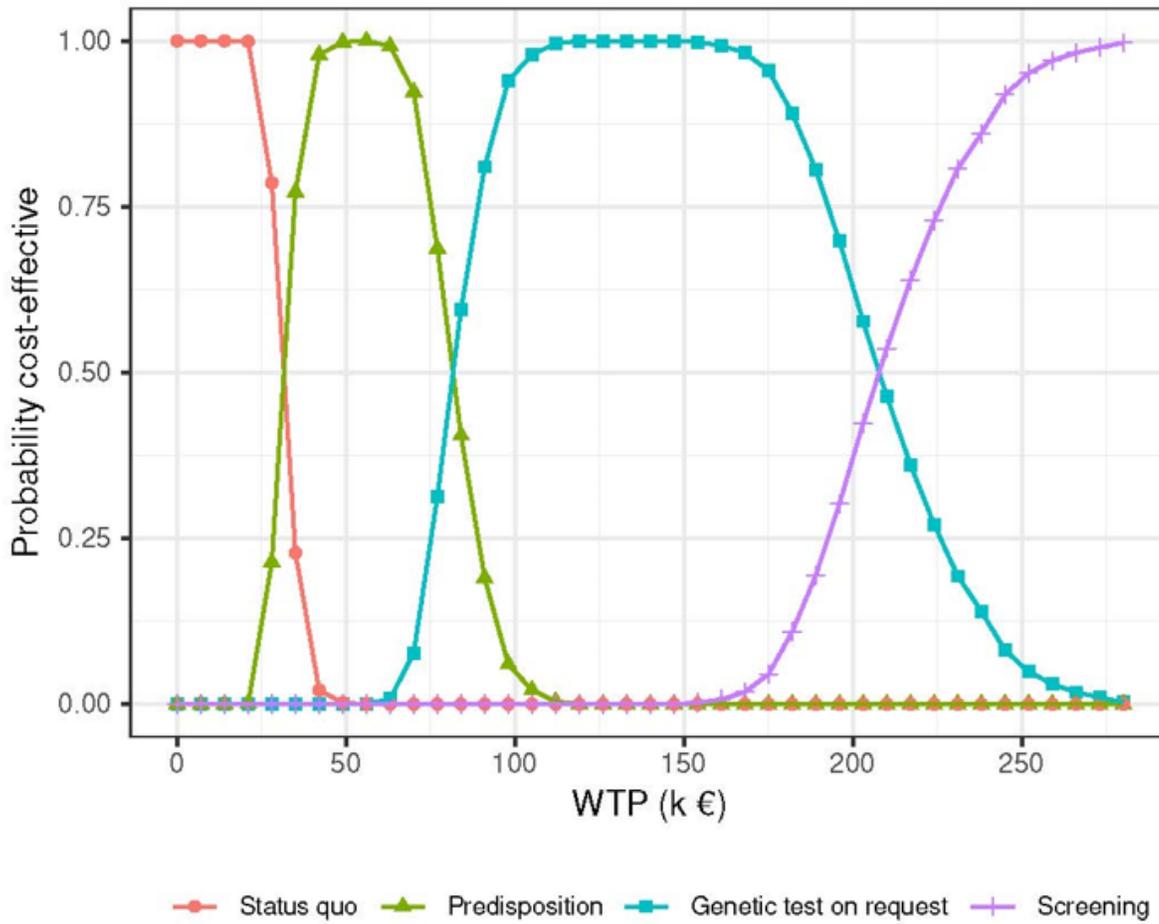


Figure 4

Cost-effectiveness acceptability curve for the model with just early intervention. The cost-effectiveness acceptability curve based on 1000 iterations places the intersection point between the scenarios "Status quo" and "Predisposition" at €31.000 per year of patient reaching (semi-)independence.

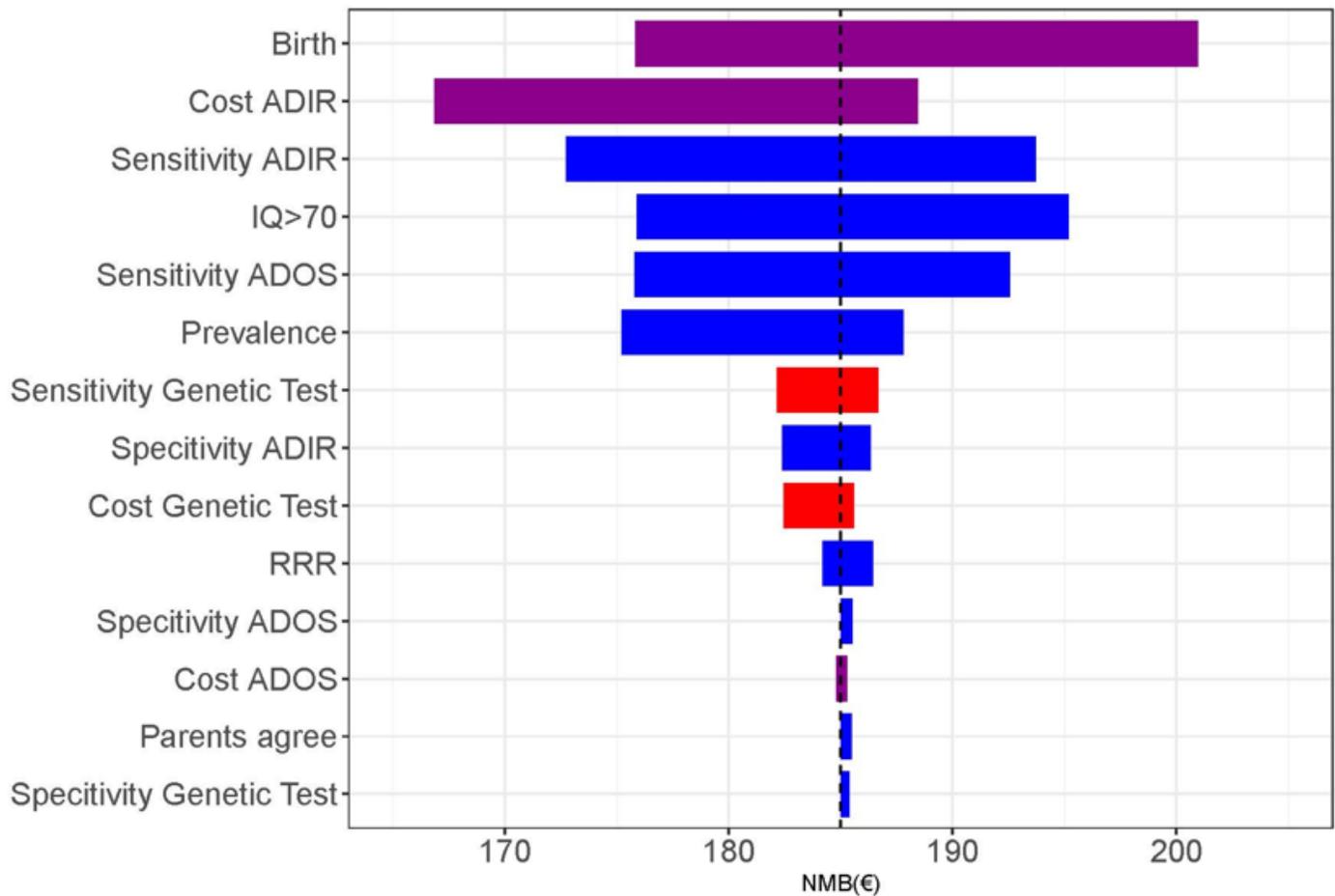


Figure 5

Tornado diagram for just early intervention: Change in net monetary benefit over all scenarios and 16 cycles. The univariate sensitivity analyses are based on confidence intervals (blue), ranges of references (purple) and speculative ranges (red) of the variables in Tables 1a and 1b. The width of the bars shows the impact of the range of uncertainty attached to the NMB. The base case NMB is 185 M €. The model including EIBI shows similar influences and ranks.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Appendixto.docx](#)
- [ConsolidatedHealthEconomicEvaluationReportingStandardsChecklist.docx](#)