A Cost Utility Analysis of Iron Deficiency Screening for Infants at 18 months

Sarah Carsley[1,a] PhD, Rui Fu[2,a] MSc, Cornelia M. Borkhoff[2,3,4] PhD, Nadine Reid PhD[2], Eva Baginska[2] MBA, Catherine S. Birken[2-4,6] MD MSc, Jonathon L. Maguire[2,4-6] MD MSc, Rebecca Hancock-Howard[2] PhD, Patricia C. Parkin[2,3,4b] MD, and Peter C. Coyte[2,b] PhD

Affiliations:
[1]Health Promotion, Chronic Disease and Injury Prevention, Public Health Ontario, Toronto, Ontario
[2]Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario
[3]Child Health Evaluative Sciences, Peter Gilgan Centre for Research and Learning, the Hospital for Sick Children, Toronto, Ontario
[4]Division of Pediatric Medicine and the Pediatric Outcomes Research Team (PORT), Department of Pediatrics, University of Toronto Faculty of Medicine, The Hospital for Sick Children, Toronto, Ontario
[5]Department of Pediatrics, St. Michael's Hospital and Li Ka Shing Knowledge Institute, Toronto, Ontario
[6]Department of Nutritional Sciences, University of Toronto, Toronto, Canada

[a]These authors contributed equally as co-first authors.
[b]These authors contributed equally as co-senior authors.

Corresponding Author:
Sarah Carsley
Public Health Ontario
480 University Avenue, Suite 300
Toronto, ON, M5G 1V2
Tel: 647-260-7710
Email: sarah.carsley@oahpp.ca

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ABSTRACT

Background: Iron deficiency (ID) is the world's most prevalent micronutrient disorder, with a peak prevalence in children six months to three years of age, a sensitive period for neurodevelopment. Previous studies show that chronic, severe ID may result in poor cognitive and functional outcomes. The study objective was to examine the cost-utility of a proposed ID screening program for 18-month old infants.

Methods: A decision tree model was used to estimate the costs (in 2019 Canadian dollars, where $1.00CAD=$0.75USD) and quality-adjusted life years (QALYs) associated with three ID screening strategies: no screening; universal screening; and targeted screening for a high-risk population. A societal perspective was used and lifetime QALY gains were assessed. Outcomes and costs were derived from the literature and prospectively collected data. One-way and probabilistic sensitivity analyses were performed to assess parameter uncertainty.

Results: Compared with no screening, the incremental costs to society of universal and targeted screening programs were $2286.06/QALY and $1676.94/QALY, respectively. Using a willingness-to-pay threshold of $50,000/QALY, both programs were cost-effective. Compared with a targeted screening program, a universal screening program would cost an additional $2965.96 to gain one QALY, rendering it a cost-effective option. The study findings were robust to extensive sensitivity analyses.

Interpretation: A proposed universal screening program for ID was cost-effective over the lifespan compared with both no screening (current standard of care) and a targeted screening program for high-risk infants. Policy makers and physicians may consider expanding the recommended 18-month Enhanced Well-Baby Visit to include screening for ID.

INTRODUCTION

Iron deficiency (ID) is the world's most prevalent micronutrient disorder, with a peak prevalence in children six months to three years of age.[1] Early childhood is a sensitive period for neurodevelopment, and overlaps with a period of rapid growth and transitions in feeding, which may result in inadequate daily iron intake.[2] In developed countries, the prevalence of ID in young children is approximately10-15%; ID may progress to anemia (iron deficiency anemia, IDA) with a prevalence of approximately 2%.[3,4]

ID in infancy is associated with neurocognitive deficits, which may persist into adulthood. For example, Lozoff and colleagues followed a cohort of Costa Rican infants (mean age 17 months) through to 25 years of age.[5-9] Compared with those who were iron sufficient in infancy (either before and/or after iron therapy), those with chronic, severe ID in infancy demonstrated poor long-term neurocognitive outcomes (such as lower cognitive scores) and functional outcomes (such as grade repetition, referral for special services, and poor school completion). Animal models support these findings; recent studies in piglets demonstrate that early life ID results in reduced brain volumes and microstructural changes, as well as cognitive deficits.[10-12]

The current standard of care for children identified with iron deficiency anemia (IDA) is treatment with oral iron for three to six months, which is effective in increasing the hemoglobin concentration.[13] Two randomized trials (one in infants with IDA, another in infants with non-anemic ID) suggest that treatment with oral iron also improves developmental outcomes.[14,15] Given the potential for non-anemic ID to progress to IDA, early detection and intervention, particularly through diet advice and/or oral iron treatment, may be beneficial.[16]

There is no current Canadian recommendation for screening for ID. The American Academy of Pediatrics (AAP) recommends universal screening for anemia through measurement of hemoglobin at 12 months of age.[2] However, screening for anemia has limitations, as the rapidly developing brain may be exposed to chronic ID by the time anemia is detected.[17] We recently assessed a screening strategy for ID using serum ferritin in 1,735 Canadian children, aged one to three years, attending primary care.[18] Our results supported serum ferritin, rather than hemoglobin, as a more promosing screening test for ID and an optimal time for screening at 15 to 18 months. The Canadian Paediatric Society (CPS) recommends an 18-month Enhanced Well-Baby Visit (EWBV) which has been implemented in the Province of Ontario with physician incentives and would be an ideal opportunity to screen for ID.[19,20] However, it is recognized that the cost of screening for ID using serum ferritin has not yet been assessed.[21]

The purpose of this analysis was to model the long-term cost-utility of a proposed screening program for ID using serum ferritin in 18 month old infants during a scheduled health supervision visit in the general population and in a targeted high-risk population in Ontario, Canada.

METHODS

Target Population

The target population for this cost-utility analysis was infants 18 months of age attending a scheduled 18-month EWBV.

Model Structure

A decision tree model (Figure 1) was used to estimate the costs and quality-adjusted life years (QALYs) to obtain incremental cost-effectiveness ratios (ICERs) associated with three ID screening strategies, including 1) no screening; 2) a universal screening program; and 3) a

targeted screening program for a high-risk population (see below). With the understanding that ID during the sensitive period for neurodevelopment may lead to long-term poor functional outcomes, a lifetime time horizon was chosen in our analysis.[22,23]

The model included health states at four terminal nodes, including: 1) "Healthy, untreated": if ID was not present and treatment unneccesary, 2) "Healthy, after treatment": if ID was detected and treated successfully, 3) "Poor functional outcomes, after treatment": if ID was detected and treatment was unsuccessful, and 4) "Poor functional outcomes, untreated": if ID was not detected and not treated. The analysis was conducted from a societal perspective, wherein all costs irrespective of payer were included. An annual discounting rate of 1.5% was used to adjust costs and outcomes to current values, based on the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines.[23] Analyses were performed using TreeAge Pro Software 18.2.1(Williamstown, MA). We followed guidelines for economic evaluations of newborn screening.[24]

Data Sources

We populated the model with data from the literature and prospectively collected data from our ongoing study called 'Optimizing Early Child Development in the Primary Care Practice Setting' (OptEC Study), which is described in a study protocol.[16] This study is embedded in our pediatric primary care research network called *TARGet Kids!* (www.targetkids.ca).[3] The recruitment process for the OptEC study simulates our proposed ID screening program because blood is obtained from young children attending a scheduled health supervision visit in primary care. Laboratory measures include complete blood count (CBC, including hemoglobin), serum ferritin, and C-reactive protein (CRP).

Base Case Model Inputs

Prevalence of ID

The prevalence of ID in the general and high-risk infant populations was derived from data from the OptEC study (Table 1). High-risk infants were defined as those with two or more risk factors for ID, about 35.5% of the total population.[25-33] In the base-case analysis, ID was defined as a serum ferritin <12 μg/L, as recommended by the World Health Organization and the American Academy of Pediatrics.[2,34] In the sensitivity analysis, ID was defined as a serum ferritin <18 μg/L, a cut-off derived from our recent analysis of data from the OptEC study (Supplementary Table 1).[16]

Sensitivity and specificity of the screening test

Under both screening strategies, we proposed screening for ID using serum ferritin, a commonly available test. Guyatt et al. analyzed data from 55 studies in adults that examined laboratory tests of iron status and histologic examination of bone marrow.[35] The authors concluded that serum ferritin is the most accurate test for the diagnosis of ID. As there is no similar study in children, we used estimates from the study by Guyatt et al.

Probability of poor functional outcomes

Poor functional outcomes were considered either a direct consequence of ID or due to causes other than ID. We also considered whether or not the infants with ID received treatment with oral iron. The estimates used for our base case came from two published randomized controlled trials and a long-term observational study (see Table 1).

Many studies demonstrate that before treatment, ID in infancy is associated with poor neurodevelopmental and functional outcomes.[5,14,15] To estimate the probability of poor functional outcomes in children with ID in infancy without treatment, we referred to data from the long-term studies by Lozoff and colleagues.[6,9] At 10 years of age, Lozoff et al. reported that

children with chronic, severe ID in infancy, compared with children with good iron status in infancy, had higher rates of grade repetition (26% vs 12%) and referral for special services (21% vs 7%).[6] We used the average of these rates as estimates of the probability of poor functional outcomes in children with untreated ID (23.5%) and due to causes other than ID (9.5%). These estimates were more conservative than reported by Lozoff et al. in the same cohort at 25 years of age, when rates of incompletion of secondary school were compared (58% vs 20%).[9]

To estimate the probability of poor functional outcomes in children with ID in infancy with treatment, we referred to data from the randomized trials of infants with IDA and non-anemic ID, which found that mental development scores reversed in those receiving four months of oral iron, compared with placebo.[14,15] Therefore, we used the same rate as for children with good iron status in the cohort followed by Lozoff and colleagues (9.5%).[6]

Utility Scores

A QALY encompasses both quality and duration of life, and is calculated by mulplying the utility score by life expectancy. Calculations of lifetime QALYs under the four terminal nodes are detailed in Table 1 and 2. We assumed that cognitive deficits beginning in infancy leading to poor functional outcomes in adulthood does not lead to early mortality; therefore, we assumed all children to have an 80.5-year life expectancy at 18-months of age.[36]

A utility score of 1.0 was assigned to healthy children not requiring treatment. A utility score of 0.84 was assigned to children with poor functional outcomes. This was derived from the average of two sources. First, a median utility of 0.87 was reported in a study of parents to young children, three to 36 months of age, in which parents were presented with a scenario describing a child's illness, and resulting poor functional outcomes such as problems with learning, behavioural, attentional, or social skills, and slightly lower intelligence.[37] Second, a mean utility

of 0.82 was found in a study of adults for mild cognitive impairment using the Clinical Dementia Rating scale vignettes in combination with time trade-off questions.[38]

Treatment of ID with oral iron supplementation may be associated with minor gastrointestinal adverse events such as abdominal pain, vomiting, diarrhea, or constipation.[13] Therefore, a utility score of 0.815 was assigned to a 4-month treatment period.[39] A median utility of 1.0 has previously been identified for venipuncture, when parents were presented a scenario in which poor functional outcomes were possible; therefore, this was not included in the model.[37]

Costs

Both direct and indirect costs were considered in our analysis (Table 1). The direct medical cost of the screening test was obtained from the Ontario Health Insurance Plan (OHIP) Laboratory Test Schedule of Benefits (effective April 2017)[40] and was adjusted to present value (January 2019) using the Canadian Consumer Price Index.[41] Although screening for ID may be based on serum ferritin alone, in order to derive a conservative cost estimate for the screening test, we included the additional cost for both hemoglobin and CRP (CRP is recommended by the AAP to exclude the possibility of acute inflammation). In the base-case analysis, we assumed an urban location for the calculation of the specimen collection fee under both screening strategies. Alternative patient locations that were associated with different fees were assessed in sensitivity analyses. The unit price of the targeted screening program was $6.52 more expensive (Table 1) than the universal strategy to account for increased clinician time (20 minutes instead of 10 minutes) to identify infants at risk. Direct treatment cost of a four month period of a commonly prescribed oral iron supplement (ferrous sulfate) was estimated from Ontario Drug Benefit Formulary/Comparative Drug Index ($170.00 including a pharmacy dispensing fee).[42]

We included the indirect (or time) cost paid by parents to attend a laboratory for phlebotomy (Table 1). Estimation of salary loss was based on Statistics Canada labour statistics on the average weekly wage in January 2019 and 0.5-days off work.[43] Parents were assumed to drive to the laboratory and park for two hours. Arrival by public transportation and taking up to a full day off work were considered in sensitivity analyses.

We did not include the cost of the 18-month visit, as this visit is currently recommended for all infants and is covered by the Ontario Health Insurance Plan. To be conservative, we did not include direct or indirect lifetime costs of poor functional outcomes.

Sensitivity analysis

Extensive one-way sensitivity analyses were conducted to assess the uncertainty of the ICERs by varying the single-parameter values according to the ranges presented in Supplemental Table 1. Probabilistic sensitivity analyses using 100,000 Monte Carlo simulations was performed to assess the simultaneous uncertainty around multiple variables using distributions specified in Supplemental Table 2.

RESULTS

Base case

We considered a group of average-risk and at-risk 18-month-old infants where: the prevalence of ID among average-risk infants was 12.1%; the prevalence of ID among at-risk infants was 25.0%; the proportion of at-risk infants in the population was 35.5%. The cost of each screening strategy per child was $144.81 for universal, screen negative; $314.81 for universal, screen positive; $151.33 for targeted, screen negative; $321.33 for targeted, screen positive; and $0.00 for no screening. Results of the base-case analysis for the two screening strategies compared with no screening, as well as the base-case comparison between the

universal and the targeted screening program are presented in Table 3. Compared with no screening, a universal and a targeted screening program cost society an additional $162.98 and $63.06, respectively, in exchange for 0.07 and 0.04 QALY gains in a lifetime (Figure 2). The ICER for the universal and the targeted screening programs relative to no screening was $2,286.06/QALY and $1,676.94/QALY, respectively. Using two common willingness-to-pay thresholds of $50,000 and $100,000 per QALY,[44] both screening strategies were cost-effective over no screening. Compared with the targeted program, the universal program was $99.96 more expensive while producing 0.03 additional QALYs in a lifetime, giving an ICER of $2,965.96/QALY. Therefore, the universal screening program is considered cost-effective compared with the targeted program.

Sensitivity analyses

One-way sensitivity analyses

Tornado diagrams that demonstrate the results of the one-way sensitivity analyses can be seen in Figure 3. The base-case conclusions were robust to all single-parameter variations. When the probability of ID-associated poor functional outcomes was as low as 8.4%, the ICER of a universal and targeted screening programs reached $11,679.36/QALY and $8,888.30/QALY, respectively compared with no screening (Figure 3), still far below the threshold of $50,000/QALY. When comparing the universal program to the targeted program, the ICER peaked at $14,565.99/QALY. The most impactful parameter was the probability of ID-associated poor functional outcomes (Figure 3).

Probabilistic sensitivity analyses

Probabilistic sensitivity analyses comparing the cost-utility of universal screening to no screening, targeted screening to no screening, and universal screening to targeted screening are

presented in Figure 3. The analysis showed that 98.8% and 99.0% of the time, the ICER for universal screening or targeted screening as compared with no screening would be below the threshold of $50,000. When comparing a universal screening strategy to targeted screening, the former was cost-effective 98.5% of the time.

INTERPRETATION

Our findings suggest that a universal screening program for ID can be a cost-effective strategy compared with the current practice of no screening. In the base case, the universal screening program was also cost-effective compared with a targeted screening program of high-risk infants. These results were robust to extensive one-way and probability sensitivity analyses. Using two common willingness-to-pay thresholds of $50,000 and $100,000 per QALY, both screening strategies were cost-effective over no screening.[44]

In our analysis, we assumed that no further costs were incurred as a result of poor functional outcomes. This assumption is conservative, as there may be direct and/or indirect costs associated with public or private developmental or educational assessments and interventions for individuals with developmental difficulties, which may be incurred at any time during their pre-school, school-age and adult years. In our model, once the present value of the lifetime cost associated with poor functional outcomes exceeded $12,000, both screening programs would be cost-saving compared with no screening.

We identified one published economic analysis of anemia prevention conducted by Shaker et al. in infants 9 to 12 month of age, set in the US where anemia screening (with hemoglobin) is currently recommended.[45] The authors concluded that screening using an alternative test called reticulocyte hemoglobin content was an affordable strategy as compared with hemoglobin alone. Their analysis differed from our analysis in several ways. First, Shaker et al. did not include a 'no screening' strategy. Second, whereas Shaker et al. used reticulocyte

hemoglobin content as their screening test, we used serum ferritin, which is a test that is more widely available and well-known to physicians.[2] Third, we proposed screening at 18 months of age while Shaker et al. proposed screening at nine to 12 months. We selected the 18-month visit as our previous analysis found that serum ferritin is lowest between 15 and 24 months, and that hemoglobin does not change significantly between 12 and 24 months.[18] Finally, Shaker et al. included the cost of one year of supplemental health care use for children with untreated ID, whereas we did not.

The goal of screening for ID is early detection and treatment before progression to chronic, severe ID or IDA. A Cochrane systematic review identified eight trials of iron treatment in young children with IDA; however, only one study used a duration of treatment (four months) consistent with current standard of care.[46] This randomized trial found that developmental scores were reduced in the infants with IDA before treatment, and reversed after iron treatment (compared with placebo), with follow-up scores similar to healthy children with iron sufficiency.[15] Another randomized trial in infants with non-anemic ID similarly found that developmental scores were reduced before treatment, and improved after iron treatment.[14] The observational studies by Lozoff and colleagues, who followed a cohort of Costa Rican children to 25 years of age, found that those with chronic, severe ID in infancy demonstrated poor long-term cognitive and functional outcomes, as compared with those who were iron sufficient in infancy (either before and/or after iron therapy).[5-9] Together, this body of literature suggests that early detection of ID followed by a good response to oral iron treatment may lead to more favourable outcomes; and late detection of ID may be accompanied by slow response to oral iron treatment and poor long-term outcomes.

Both universal and targeted screening for ID were cost-effective in our analysis. However, for the targeted screening program, the results suggest that the costs saved by restricting the program to high-risk infants is offset by the loss of QALYs for unscreened average-risk children. This is likely driven by the small incremental cost difference between the universal and the targeted program (about $100). Because a universal program will always produce more QALYs, it is important to consider the cost of the QALYs gained. In our analysis, the incremental cost was about $100 ($99.92). In other words, an additional $100 spent would be exchanged for a $1,500 worth of effectiveness (0.03 extra QALYs*$50,000/QALY = $1,500), which is highly cost-effective.

Strong recommendations have been made for investment in early childhood, considering the evidence supporting the developmental origins of health and disease. Nobel Prize winning University of Chicago Economics Professor James Heckman developed the 'Heckman equation', which describes a high return on investment for preventive initiatives early in the life course.[47-49] In keeping with this theory, screening and treatment for ID in early childhood has the potential to improve outcomes throughout the life course, with a modest economic investment.

The Canadian Paediatric Society, in a position statement supported by the College of Family Physicians of Canada, recommends an 18-month Enhanced Well-Baby Visit (EWBV), with the overall goal of "strengthening the early childhood development system across Canada through a series of activities."[20] The Province of Ontario has implemented this visit and provided physician fee incentives.[19] This would be an ideal visit at which to add screening for ID, and is aligned with the goal of improving child developmental outcomes. In the context of a primary care practice setting, treatment of ID with diet advice and prescription of oral iron is feasible and utilizes the expertise of physicians and other members of the health care team.

There are several recognized limitations of cost-effectivness analyses.[50,51] The main limitation of our analysis relates to the assumptions for the model and source of the data. Specifically, there were no sources to estimate the sensitivity and specificity of serum ferritin in children (therefore, data from adults was used) and ID-specific utility scores (therefore, data from similar scenarios was used). Sources to estimate the probability of poor functional outcomes were methodologically strong and included randomized controlled trials and a long-term observational study; however, these studies were conducted in developing countries. Further, we did not include future costs that might be incurred as a result of poor functional outcomes due to inadequate data sources, leading to a conservative estimate of costs. However, the inclusion of these costs would increase the cost-effectiveness of the two screening programs compared with no screening. Despite these limitations, our findings were robust following extensive sensitivity analyses and were largely driven by the low cost of the screening test and treatment; the short duration of the treatment; the low reduction of life quality associated with the potential side effect of receiving the treatment; and the probability of an important functional outcome over a long time horizon.

The guidelines for economic evaluations of newborn screening recommend discussing ethical and distributional issues.[24] We believe there are fewer ethical issues associated with screening for ID at 18 months of age as compared with screening for rare metabolic diseases in newborns. Considering the distribution of costs and benefits, given the possible association between social determinants and ID,[7] screening has the potential to reduce health disparities.

There are several opportunities for future research. These include understanding the values and preferences of parents and practitioners for screening for ID; development of a risk stratification tool that could be used as a component of targeted screening (similar to tools used

for assessing risk of diabetes in adults);[52] and validation of a point-of-care tool for serum ferritin to improve convenience and reduce cost.[21,53]

In summary, a proposed universal screening program for ID was cost-effective over the lifespan compared with both no screening (current standard of care) and a targeted screening program for high-risk infants. Policy makers and physicians may consider expanding the recommended 18-month EWBV to include screening for ID.

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Table 1: Parameter inputs for the base case scenario

Parameter	Base Case	Data Source/Reasoning
Prevalence of iron deficiency		
General population	12.1%	OpTEC study data
At-risk population	25.0%	OpTEC study data
Proportion of at-risk children in the general population	35.5%	OpTEC study data (2 or more risk factors)
Probability of poor functional outcomes		
Untreated		
Due to ID	23.5%	Lozoff et al., 2000
Not due to ID	9.5%	Idiradinata and Pollitt, 1993
After iron supplementation treatment		
Due to ID	9.5%	Idiradinata and Pollitt, 1993
Not due to ID	9.5%	Idiradinata and Pollitt, 1993
Screening test efficiency		
Sensitivity	58.6%	Guyatt et al., 1992
Specificity	98.9%	Guyatt et al., 1992
Utility Parameter Inputs		
Utility of having iron supplementation treatment (utilityTreat)	0.815	Accounting for potential sides effects (constipation) of receiving iron supplementation NICE 2010
Utility of living with poor functional outcomes (utilityPoorFunOut)	0.84	Assuming children will experience utility loss due to cognitive impairment Bennet et al., 2000; Ekman et al., 2007
Costs (CAD)		
Universal screening		
Adjusted lab costs total (uninflated)	**$28.48 ($27.80)**	Inflated to present value (January 2019) using the monthly Canadian Consumer Price Index[1]
Laboratory services	$10.67	OHIP Schedule of Benefits (CBC, Ferritin, and CRP[2])
Administration	$6.37	Ontario Nurse Association (assuming a 10-minutes nursing time)[3]
Patient documentation and specimen collection fee	$10.76	OHIP Schedule of Benefits (urban location)
Patient-borne cost total	**$116.33**	
Salary loss	$103.21	The average weekly wages for Canadians (permanent employees) are $1,032.12 in January 2019.[4] In the base-case, one parent is assumed to take 0.5-days off work.
Travel expense	$13.12	One parent is driving a conventional

		vehicle for 15 km (round-trip) to the screening location. Using $0.96/L for regular gasoline[4] and a fuel consumption level of 7.8 L/100 km[5], the total cost for gas is $1.12 per round trip. In the base case, a 2-hour parking time is assumed (parking rate: $6/hour[6]) which gives $12 cost for parking.
Total cost, universal screening	**$144.81**	Lab costs + patient-borne costs
Targeted screening		
Adjusted lab costs total (uninflated)	**$35.00 ($34.16)**	Inflated to present value (January 2019) using the monthly Canadian Consumer Price Index[1]
Laboratory services	$10.67	OHIP Schedule of Benefits (CBC, Ferritin, and CRP[2])
Administration	$12.73	Ontario Nurse Association (assuming a 20-minutes nursing time)
Patient documentation and specimen collection fee	$10.76	OHIP Schedule of Benefits (urban location)
Patient-borne cost	**$116.33**	As above
Total cost, targeted screening	**$151.33**	Lab costs + patient-borne costs
Treatment cost (CAD)		
Ferrous Sulfate – 4 month treatment	$170.00	$168.63 including dispensing fee[8]

[1]Canadian Consumer Price Index: 130.4 (April 2017); 133.6 (January 2019). Source: Statistics Canada: https://www150.statcan.gc.ca/t1/tbl1/en/cv.action?pid=1810000413

[2]OHIP Schedule of Benefits for Laboratory Services (April 1, 2017): CBC, $3.98; ferritin, $2.97; CRP, $3.72.

[3]Using an hourly rate of $38.19 (for 5-years full-time registered nurse; effective April 1, 2017). Source: Ontario Nurse Association: https://www.ona.org/wp-content/uploads/ona_2016hospitalawardhighlights_20160912.pdf?x72008

[4]Statistics Canada labour statistics: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1410032002&pickMembers%5B0%5D=3.3

[5]Ontario gasoline price on Feb 11, 2019: https://www.ontario.ca/page/motor-fuel-prices

[6]Fuel consumption ratings by Natural Resources Canada: http://oee.nrcan.gc.ca/fcr-rcf/public/index-e.cfm (using the measures of the Honda Civic Coupe, Canada's best-selling car for 21st consecutive years)

[7]Parking rate at the Hospital for Sick Children, Toronto, Ontario: https://www.preciseparklink.com/sick-kids-hospital-parking

[8]Ontario Drug Benefit Formulary/Comparative Drug Index. Available from: https://www.formulary.health.gov.on.ca/formulary/

Table 2: Calculating effectiveness

Terminal Node Health State	Formula	Reasoning
Healthy, Untreated	QALYs (healthy, untreat) = RemainLifeExp*1 = 80.5	Assuming screening occurs at 18 months, and health state is experienced for all years following test (using life expectancy of 82 years[1])
Healthy, After Treatment	QALYs (healthy, treat) = (RemainLifeExp - 0.33) +(0.33)*utilityTreat	Assumes there is some decrease in utility for four months during iron supplementation
Poor functional outcomes, Untreated	QALYs (poor functional outcomes, untreat) = RemainLifeExp* utilityPoorFunOut	Assumes that ID is not detected and treated, and resulting health state is experienced for all years following test
Poor functional outcomes, After Treatment	QALYs (poor functional outcomes, treat) = (RemainLifeExp – 0.33)* utilityPoorFunOut +(0.33)*utilityTreat	Assumes that ID is not treated despite supplementation, and this health state experiences both decreased utilities from poor functional outcomes, and short-term decrease in utility due to supplementation.

[1]Source: Statistics Canada life tables: https://www150.statcan.gc.ca/n1/pub/84-537-x/2018002/xls/2014-2016_Tbl-eng.xlsx

Table 3: Cost-utility analysis results under base case assumptions

Strategy	Cost	Effect (QALYs)	Incremental Cost	Incrremental Effect (QALYs)	ICER
Two Screening Programs vs. No Screening					
No Screening	0	23.82	-	-	-
Targeted Screening	63.06	23.86	63.06	0.04	1676.94
Universal Screening	162.98	23.89	162.98	0.07	2286.06
Universal Screening vs. Targeted Screening					
Targeted Screening	63.06	23.86	-	-	-
Universal Screening	162.98	23.89	99.92	0.03	2965.96

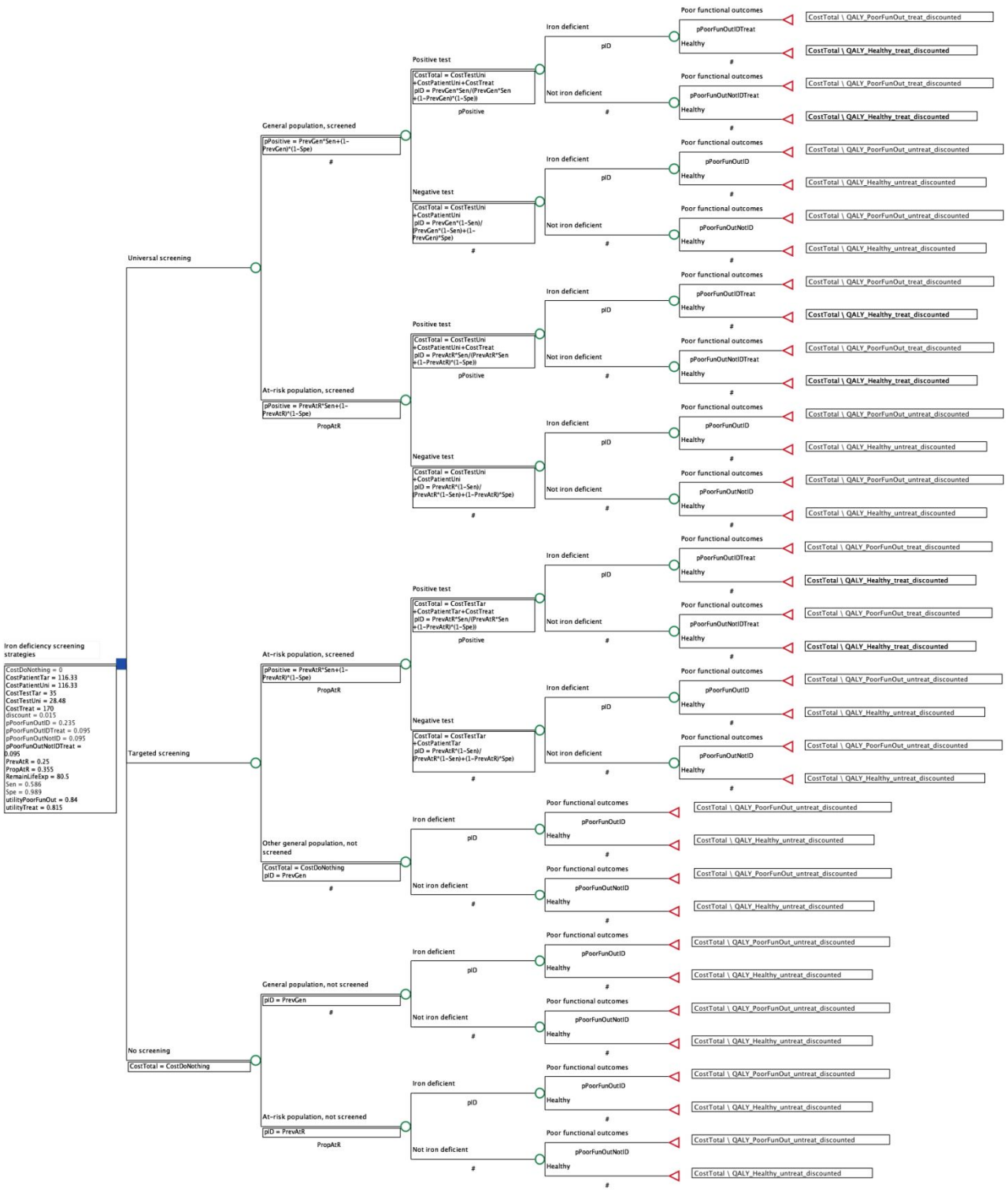

Figure 1: Decision Tree

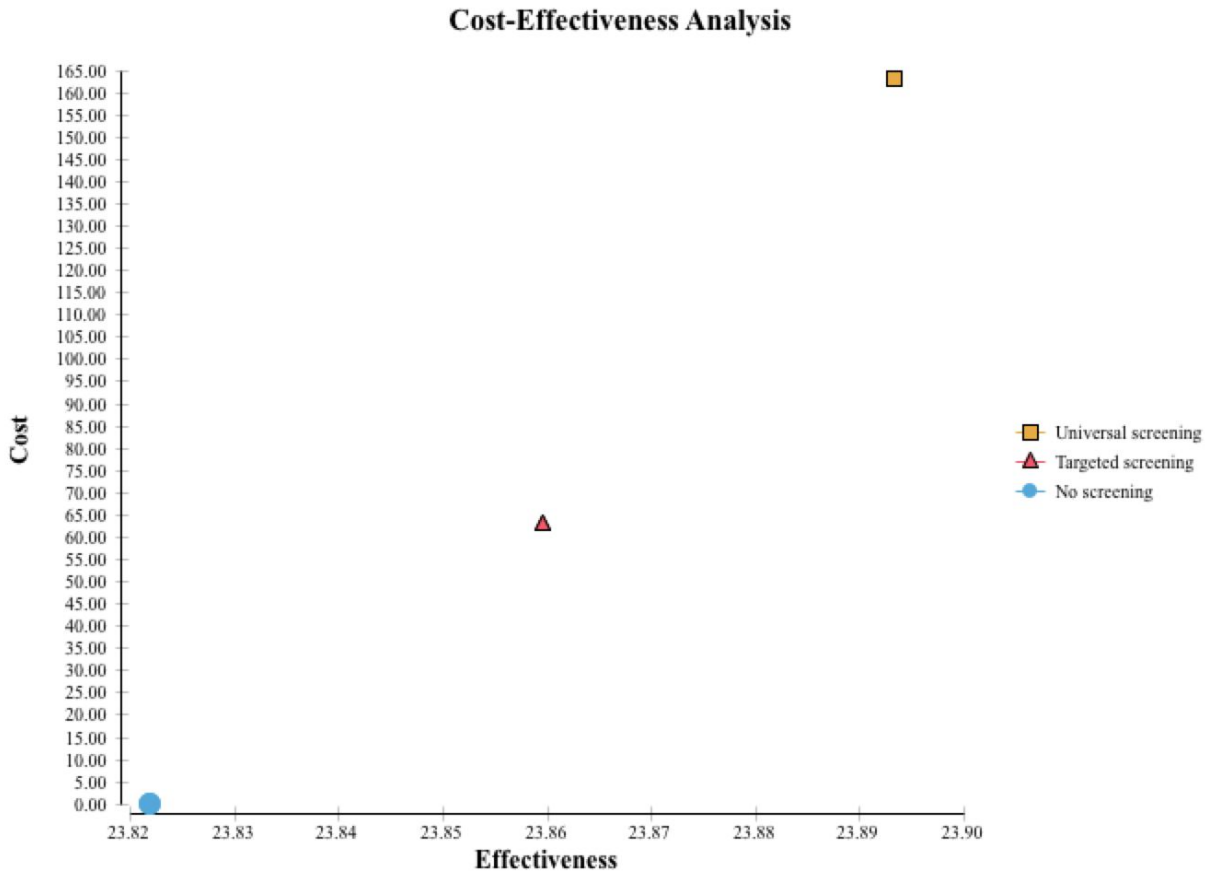

Figure 2: Cost-Effectiveness Plane for Three Screening Strategies

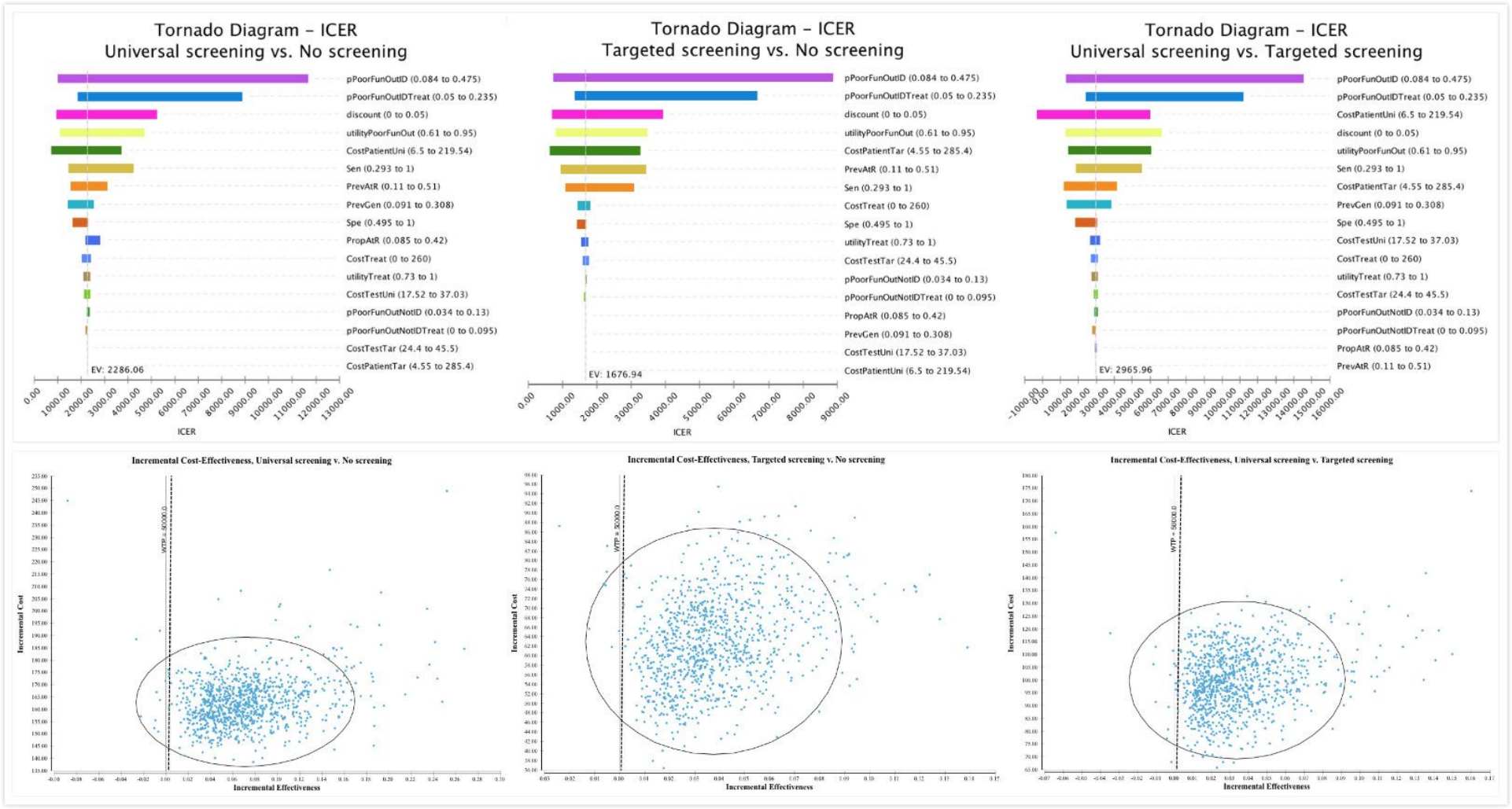

Figure 3: Top: One-way sensitivity analyses comparing universal screening vs. no screening, targeted vs. no screening, and universal vs. targeted screening. Botton: Probabilistic sensitivity analyses results (from left to right) comparing universal screening vs. no screening, targeted vs. no screening, and universal vs. targeted screening

Supplemental Table 1: Sensitivity analyses model inputs

	Base case	Low estimate	High estimate
Disease prevalence			
Iron deficiency, general	0.121	0.091	0.308
Data Source	<12mg/L, from Target Kids! Unpublished data	Maguire et al., 2013	<18mg/L, from Target Kids! Unpublished data
Iron deficiency, at-risk	0.250	0.11	0.51
Data Source	<12mg/L, from Target Kids! Unpublished data	<12mg/L, from Target Kids! Unpublished data	<18mg/L, from Target Kids! Unpublished data
Probability of poor functional outcomes			
Due to ID, untreated	0.235	0.084	0.475
Data Source	Lozoff et al., 2000	<18mg/L, from Target Kids! Unpublished data	Carroll & Downs, 2006*
Not ID, untreated	0.095	0.034	0.13
Data Source	Idiradinata and Pollitt, 1993	Simpson et al, 2003†	Rosenberg et al., 2008‡
After iron supplement treatment, not ID	0.095	0	0.095
Data Source	Idiradinata and Pollitt, 1993	Expert opinion	Idiradinata and Pollitt, 1993
After iron supplement treatment, ID	0.095	0.05	0.235
Data Source	Idiradinata and Pollitt, 1993	Idiradinata and Pollitt, 1993	Lozoff et al., 2000
Proportion of at-risk children in the targeted screening program			
Proportion of at-risk children	0.355	0.085	0.42
Data Source	OpTEC trial; 2 or more risk factors	OpTEC Trial; 3 or more risk factors	OpTEC Trial; 1 risk factor
Test accuracy			
Sensitivity	0.586	0.293	1
Data Source	Guyatt et al., 1992	Base case * 0.5	-
Specificity	0.989	0.495	1
Data Source	Guyatt et al., 1992	Base case * 0.5	-
Cost ($)			
Total test cost, universal screening program	28.48	17.52	37.03
Data Source	include CRP, Ferritin, and CBC; urban location	w/o CBC or CRP; pick-up only	base case * 1.3, to include the base case targeted cost

Total test cost, targeted screening program	35.00	24.04	45.50
Data Source	include CRP, Ferritin, and CBC; urban	w/o CBC or CRP; pick-up only	base case * 1.3
Total treatment cost	170.00	0	260.00
Data Source	Prescription price (including dispensing fee): $168.63	Ontario Drug Benefit program	Over-the-counter price (including tax): $259.79
Patient-borne cost, universal screening program	116.33	6.5	219.54
Data Source	Driving, 1/2 day off	Using the TTC (roundtrip), no day off	Driving, full-day off
Patient-borne cost, targeted screening program	116.33	4.55	285.40
Data Source	same with base case universal screen	Low estimate for universal screen * 0.7	High estimate for universal screen * 1.3
Utility measures			
Utility of living with poor functional outcomes	0.84	0.61	0.95
Data Source	Ekman et al., 2007	Ekman et al., 2007	Ekman et al., 2007
Utility of having iron supplementation (4-mo)	0.815	0.73	1
Data Source	Considering utility loss by constipation, NICE 2010	base case * 0.9	No change in life quality during the 4-month time
Discounting rate			
Discounting rate	0.015	0	0.05
Data Source	CADTH	undiscounted	expert opinion

*Carroll AE, Downs SM. Comprehensive cost-utility analysis of newborn screening strategies. Pediatrics. 2006;117(5 Pt 2):S287-95.
†Simpson GA, Colpe L, Greenspan S. Measuring functional developmental delay in infants and young children: prevalence rates from the NHIS-D. Paediatric and perinatal epidemiology. 2003;17(1):68-80.
‡Rosenberg SA, Zhang D, Robinson CC. Prevalence of developmental delays and participation in early intervention services for young children. Pediatrics. 2008;121(6):e1503-9.

Supplemental Table 2: Parameter Distributions for Probability Sensitivity Analyses

Parameter	Variable Name	Point Estimate	Probability Distribution
Costs			
Cost of test, universal screen	CostTestUni	28.48	Gamma
Cost of test, targeted screen	CostTestTar	35.00	
Patient-borne, universal screen	CostPatientUni	116.33	
Patient-borne, targeted screen	CostPatientTar	116.33	
Cost of treatment	CostTreat	170.00	
Prevalence of ID			
General population	PrevGen	0.121	Beta
At-risk population	PrevAtR	0.25	
Proportion of children included in the targeted screen	PropAtR	0.355	Beta
Probability of developing poor functional outcomes			
Due to ID, untreated	pPoorFunOut	0.235	Beta
Not due to ID, untreated	pPoorFunOutNotID	0.095	
Due to ID, treated	pPoorFunOutIDTreat	0.095	
Not due to ID, treated	pPoorFunOutNotIDTreat	0.095	
Test efficacy			
Sensitivity	Sen	0.586	Beta
Specificity	Spe	0.989	
Utility			
Living with poor functional outcomes	utilityPoorFunOut	0.84	Beta
Having iron supplementation treatment	utilityTreat	0.815	