**Figure S1. Incremental cost-effectiveness ratio for newborn screening for Pompe disease by cost of alglucosidase alfa (ERT), $/QALY**

Abbreviations: ERT, enzyme replacement therapy; QALY, quality adjusted life year; AWP, average wholesale price.

**Figure S2. Health state probabilitiesa**

**a. Infantile-onset Pompe disease with cardiomyopathy, b. Infantile-onset Pompe disease without**

**clinically identified and treated cardiomyopathy, clinically identified and treated**

Mild symptoms

No symptoms

No

Severe symptoms

Dead from other causes

Mild symptoms

Dead from other causes

**c. Infantile-onset Pompe disease with cardiomyopathy, d. Infantile-onset Pompe disease without**

**newborn screened and treated cardiomyopathy, newborn screened and treated**

Severe symptoms

Dead from Pompe

disease

Mild symptoms

aTrajectories determined using the transition probabilities outlined in Table S1.

**Table S1. Annual transition probabilities and treatment effectiveness**

a. Clinically diagnosed, untreated

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **No symptoms** | **Mild** | **Severe** | **Pompe disease**  **death** |
| **Infantile-onset with cardiomyopathy** |  |  |  |  |
| No symptoms | - | - | - | - |
| Mild |  | 0.2240 | 0.1450 | 0.6310 |
| Severe |  |  | 0.0070 | 0.9930 |
| **Infantile-onset without cardiomyopathy** |  |  |  |  |
| No symptoms | - | - | - | - |
| Mild |  | 0.9399 | 0.0237 | 0.0364 |
| Severe |  |  | 0.9330 | 0.0670 |

b. Clinically diagnosed, treated

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **No symptoms** | **Mild** | **Severe** | **Pompe disease**  **death** |
| **Infantile-onset with cardiomyopathy, age <5a** |  |  |  |  |
| No symptoms | - | - | - | - |
| Mild |  | 0.9667 | 0.0334 | 0.0000 |
| Severe |  |  | 0.7716 | 0.2284 |
| **Infantile-onset with cardiomyopathy, age ≥5b** |  |  |  |  |
| No symptoms | - | - | - | - |
| Mild |  | 0.9323 | 0.0677 | 0.0000 |
| Severe |  |  | 0.9460 | 0.0540 |
| **Infantile-onset without cardiomyopathy, all agesc** |  |  |  |  |
| No symptoms | - | - | - | - |
| Mild |  | 0.9962 | 0.0038 | 0.0000 |
| Severe |  |  | 0.9893 | 0.0107 |

a Treatment effectiveness relative to untreated: 0.770

b Treatment effectiveness relative to untreated: 0.930

c Treatment effectiveness relative to untreated: 0.840

c. Screened, treated

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **No symptoms** | **Mild** | **Severe** | **Pompe disease**  **death** |
| **Infantile-onset with cardiomyopathya** |  |  |  |  |
| No symptoms | 0.9993 | 0.0007 | 0.0000 | 0.0000 |
| Mild |  | 0.9993 | 0.0007 | 0.0000 |
| Severe |  |  | 0.9950 | 0.0050 |
| **Infantile-onset without cardiomyopathya** |  |  |  |  |
| No symptoms | 0.9999 | 0.0001 | 0.0000 | 0.0000 |
| Mild |  | 0.9999 | 0.0001 | 0.0000 |
| Severe |  |  | 0.9997 | 0.0003 |
| **Late-onset (all scenarios)b** |  |  |  |  |
| No symptoms | 0.9801 | 0.0130 | 0.0060 | 0.0009 |
| Mild |  | 0.9690 | 0.0300 | 0.0010 |
| Severe |  |  | 0.9990 | 0.0010 |

a Treatment effectiveness relative to untreated: 0.995

b Treatment effectiveness relative to untreated: 0.000 (no one is treated)

Note: The expert panel provided estimates of the number of individuals in each health state at different ages, given different screening and treatment scenarios. The health trajectories assumed for the first 3 years of life were based on published and unpublished research.1,2 We then calculated transition probabilities that resulted in simulated disease trajectories that correspond to the assumptions of the expert panel (see Figure S2 for the simulated disease trajectories). Among the clinically identified, we had to create separate transition probabilities for those <5 and those ≥5 to capture the rapid disease progression during the first few years of life.

1. Kishnani PS, Hwu WL, Mandel H, Nicolino M, Yong F, Corzo D. A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. *J Pediatr.* 2006;148(5):671-676.

2. Chen LR, Chen CA, Chiu SN, et al. Reversal of cardiac dysfunction after enzyme replacement in patients with infantile-onset Pompe disease. *J Pediatr.* 2009;155(2):271-275 e272.

**Table S2. Epidemiology and probabilities of screening and diagnostic outcomes for Pompe disease, by identification and treatment scenario**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Input** | **Base** | **Low** | **High** | **Source** |
| **Epidemiology** |  |  |  |  |
| Incidence of Pompe disease (annual, per 100,000) | 2.5 | 1 | 2.5 | 1 |
| Screening test characteristics |  |  |  |  |
| Sensitivity | 0.9322 | 0.9315 | 0.9329 | 2, expert opinion |
| Specificity | 0.9999 | - | - |  |
| **Screening and diagnostic outcomes** |  |  |  |  |
| **Newborn screening** |  |  |  |  |
| Probability of initial positive test | 0.000065533 | 0.000033507 | 0.000733532 | 3, assumption |
| Probability of positive test on confirmatory testing | 0.5117 | 1 | 0.045747884 |  |
| Probability of false negative test on initial test | 0.00000244 | 0.000002464029 | 0.00000241 |  |
| **Among confirmed positives** |  |  |  |  |
| Probability of infantile-onset Pompe disease | 0.298 | 0.226 | 0.384 | 1, 3, 4 |
| Conditional probability of infantile-onset with cardiomyopathy | 0.85 | 0.702 | 0.943 | Expert opinion |
| Conditional probability of infantile-onset without cardiomyopathy | 0.15 | 0.057 | 0.298 |  |
| Probability of late-onset Pompe disease | 0.417 | 0.335 | 0.502 | 1, 3, 4 |
| Probability of probable late-onset Pompe disease (healthy) | 0.285 | 0.115 | 0.439 |  |
| **Among false negatives** |  |  |  |  |
| Probability of infantile-onset Pompe disease | 0.000 | 0.000 | 0.036 | Assumptiona |
| Probability of late-onset Pompe disease | 0.417 | 0.335 | 0.502 |  |
| Probability of probable late-onset Pompe disease (healthy) | 0.583 | 0.462 | 0.665 |  |
| **Clinically identified and treated** |  |  |  |  |
| Probability of Pompe disease | 0.000025 | 0.000001 | 0.000025 | 1 |
| Conditional probability of infantile-onset Pompe disease | 0.4 | 0.303 | 0.503 | 1, 3, 4, expert opinion |
| Conditional probability of infantile-onset without cardiomyopathy/treated | 0.05 | 0.006 | 0.169 | 5,expert opinion |
| Conditional probability of infantile-onset without cardiomyopathy untreated | 0.10 | 0.000 | 0.292 |  |
| Conditional probability of infantile-onset with cardiomyopathy | 0.85 | 0.702 | 0.943 |  |
| Conditional probability of late-onset Pompe disease | 0.6 | 0.497 | 0.697 | 1, 3, 4, expert opinion |

**Table S2 cont. Epidemiology and probabilities of screening and diagnostic outcomes for Pompe disease, by identification and treatment scenario**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Input** | **Base** | **Low** | **High** | **Source** |
| **Clinically identified and untreated** |  |  |  |  |
| Probability of Pompe disease | 0.000025 | 0.000001 | 0.000025 | 1 |
| Conditional probability of infantile-onset Pompe disease | 0.4 | 0.303 | 0.503 | 1, 3, 4, expert opinion |
| Conditional probability of infantile-onset with cardiomyopathy | 0.85 | 0.702 | 0.943 | 5,expert opinion |
| Conditional probability of infantile-onset without cardiomyopathy | 0.15 | 0.057 | 0.298 |  |
| Conditional probability of late-onset Pompe disease | 0.6 | 0.497 | 0.697 | 1,3, 4,expert opinion |

aAssumed to be the same as clinically identified and untreated.

[1] Scott CR, Elliott S, Buroker N, Thomas LI, Keutzer J, Glass M, et al. Identification of infants at risk for developing Fabry, Pompe, or mucopolysaccharidosis-I from newborn blood spots by tandem mass spectrometry. J Pediatr. 2013;163:498-503.

[2] Kemper AR, Comeau AM, Green NS, Goldenberg A, Ojodu J, Prosser LA, et al. Evidence report: newborn screening for pompe disease [cited 2018 November] Available from: <https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/rusp/previous-nominations/pompe-external-evidence-review-report-2013.pdf>

[3] Chiang S-C, Hwu W-L, Lee N-C, Hsu L-W, Chien Y-H. Algorithm for Pompe disease newborn screening: Results from the Taiwan screening program. Mol Gen Met. 2012;106:281-6.

[4] Mechtler TP, Stary S, Metz TF, De Jesus VR, Greber-Platzer S, Pollak A, et al. Neonatal screening for lysosomal storage disorders: feasibility and incidence from a nationwide study in Austria. Lancet. 2012;379:335-41.

[5] Kishnani PS, Hwu WL, Mandel H, Nicolino M, Yong F, Corzo D. A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. J Pediatr. 2006;148:671-6.

**Table S3. Cost inputs**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Cost Inputs (annual, 2016 $)a** | **Base** | **Low** | **High** | **Source** |
| Screening test for Pompe disease per child | $6.40 | $6.40 | $17.5 | Personal  communicationb |
| Genetic and other confirmatory tests for those who screen positive | $2,382 | $1,802 | $3,300 | 1, personal communicationc |
| Enzyme replacement treatmentd |  |  |  |  |
| Age 1 | $75,475 | $71,828 | $117,624 | 2 |
| Age 5 | $135,856 | $129,290 | $211,723 |
| Age 10 | $256,616 | $244,214 | $399,922 |
| Age 15 | $407,567 | $387,869 | $635,170 |
| Age 25 | $483,043 | $459,697 | $752,794 |
| Age 50 | $513,233 | $488,428 to | $799,843 |
| Enzyme replacement therapy deliverye | $14,300 | $10,882 | $96,000 | 3 |
| **Non-Pompe disease related medical costs** |  |  |  |  |
|  | Varies by age | $1,162 | $6,014 | 4 |
| **Probable Pompe disease, asymptomatic** |  |  |  |  |
| Watchful waitingf | $437 | - |  | 1, 5 |
| Appointment timeg  **Diagnostic evaluation and tests in the absence of a screening diagnosish**  Appointment timeg | $51  $20,504  $1,594 | -  - |  | 6  1, 5  6 |
| **Pompe disease, mild symptoms** |  |  |  |  |
| Medical costs (all) | Varies by age | $7,303 | $14,257 | 1, 7 , expert opinion i |
| Informal caregiving | $18,928 | $12,915 | $18,928 | 8, 9j |
| Appointment time | $2,160 | $1,490 | $2,160 | k |
| Transition to mild health statel | $19,260 | -- |  | 10 m |
| **Pompe disease, severe symptoms** |  |  |  |  |
| Medical costs (all) | Varies by age | $84,367 | $90,476 | 11, 1, expert opinion i |
| Formal caregiving | $87,360 | $57,512 | $87,360 | n |
| Informal caregiving | $151,424 | $103,318 | $151,424 | 9o |
| Appointment time | $0 | -- |  | p |
| Transition to severe health state q | $59,808 | $38,892 | $66,681 | 7 |

a. Cost inputs, per person

a All costs were adjusted to 2016 dollars using the Gross Domestic Product price deflator

b Correspondence with New Jersey, New York, Michigan, and Missouri newborn screening programs

c Estimates from Greenwood Genetics Center, Emory University, Prevention Genetics, Baylor, Gene Dx, Cincinnati Children's Hospital, Seattle Children's Hospital, Duke University, LabCorp, Mayo Clinic, and Michigan Medicine Genetics Laboratories.

d A one time cost of $7,594 for immune tolerance induction was also applied in the first year of life to 25% of those with infantile-onset Pompe disease and cardiomyopathy. For more details see Table S3d. Redbook wholesale acquisition cost with a 23% discount was used for the base case. Lower bound estimate represents government-negotiated price; upper bound estimate reflects average wholesale price. CDC weight projections12 were used for dosage estimates (we assumed those with Pompe disease are 95% of the national average weight), assuming 26 doses/year of 20 mg/kg; see Table S3c, for details.

e Estimated price for home and hospital infusion (CMS Physician Fee Schedule price was not available for home infusion); assumes ERT infusion lasts 6 hours; first year 50%-75% assumed to occur at home and after that 100% at home; range based on CMS Physician Fee Schedule and expert opinion; see Table S3d, for details.

f Additional health care utilization for patients diagnosed with Pompe disease but without symptoms, annual estimate: 1 additional outpatient visit; lab work including creatine kinase-MB, comprehensive panel, and urine hex4 test

g Visits were assumed to take 2 hours6, multiplied this by the US average hourly earnings9 of $25.71

h Additional costs of prolonged evaluation and diagnostic testing for cases identified clinically in the absence of NBS included additional outpatient and emergency room visits and lab tests.

iTypes of services derived from Kishnani et al 2006 7; number of services determined in consultation with a genetic counselor; costs assigned according to the CMS Physician Fee Schedule1; see Table S3f for micro-costing details

j 14 hours of informal care per week multiplied by average hourly earnings9 of $25.71

k 42 extra medical appointments, each requiring 2 hours of time6; multiplied by the US average hourly earnings9; estimates for transportation costs were not available and have not been included

l Includesenvironmental modifications/renovations; extra medical equipment including wheelchair and other assistive devices. Also includes gastrostomy for transition to severe health state.

m Derived from DeVivo et al (2011)10 which reported time costs for a patient with a spinal cord injury resulting in incomplete motor function

n 8 hours per day 7 days per week, at a wage of $30 per hour; this wage reflects a combination of nurse and home health provider wages13; distribution determined by expert opinion.

o 16 hours per day 7 days a week multiplied by the US average hourly earnings9

p Assuming these individuals are not engaged in productive activities and therefore would not incur opportunity costs for appointments

q Wheel chair equipment and environmental changes: derived from data on patients with a spinal cord injury resulting in complete or partial paralysis 10 Cost also includes gastronomy costs.

b. Cost of genetic and other confirmatory tests

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Cost input** | **Base** | **Low** | **High** | **Source** |
| **Genetic tests** |  |  |  |  |
| GAA enzyme test a | $86 | $11 | $263 | Primary data analysisb |
| GAA sequencing testc | $1,193 | $1,115 | $1,351 |  |
| GAA deletion/duplication testd | $556 | $263 | $1,027 |  |
| Percent receiving GAA deletion/duplication test | 10% | 5% | 15% | Assumption |
| **Procedures** |  |  |  |  |
| Chest X-ray | $46 | $23 | $69 | 1 |
| Electrocardiogram | $17 | $17 | $17 |
| Echocardiogram | $450 | $240 | $659 |
| Electromyography | $246 | $246 | $246 |
| **Lab tests** |  |  |  |  |
| Creatine kinase-MB | $12 | $9 | $20 | 5 |
| Comprehensive Panel | $19 | $14 | $32 |
| Urine Hex4 | $69 | $43 | $148 |  |

a GAA (acid-α-glucosidase) enzyme test is performed twice, CPT 82657

b MarketScan analysis of 2016 data

c CPT 81406

d Charges reported by Greenwood Genetics Center, Emory University, Prevention Genetics, Baylor, Gene Dx, and Cincinnati Children's Hospital. Assumed 52.7% cost/charge ratio.

c. Cost of alglucosidase alfaa

| **Age (years)** | **Average weight (kg)b** | **Number of Units Every 2 weeksc** | **Annual Costd** | **Lower Estimatee** | **Upper Estimatef** |
| --- | --- | --- | --- | --- | --- |
| <1 | 7.1 | 3 | $45,285 | $43,097 | $70,574 |
| 1 | 10.5 | 5 | $75,475 | $71,828 | $117,624 |
| 2 | 13.0 | 6 | $90,570 | $86,193 | $141,149 |
| 3 | 15.2 | 7 | $105,666 | $100,559 | $164,674 |
| 4 | 17.2 | 8 | $120,761 | $114,924 | $188,198 |
| 5 | 20.1 | 9 | $135,856 | $129,290 | $211,723 |
| 6 | 22.8 | 10 | $150,951 | $143,655 | $235,248 |
| 7 | 25.4 | 11 | $166,046 | $158,021 | $258,773 |
| 8 | 30.0 | 13 | $196,236 | $186,752 | $305,822 |
| 9 | 34.2 | 15 | $226,426 | $215,483 | $352,872 |
| 10 | 38.5 | 17 | $256,616 | $244,214 | $399,922 |
| 11 | 44.7 | 19 | $286,807 | $272,945 | $446,971 |
| 12 | 49.3 | 21 | $316,997 | $301,676 | $494,021 |
| 13 | 55.1 | 24 | $362,282 | $344,772 | $564,595 |
| 14 | 59.6 | 26 | $392,472 | $373,504 | $611,645 |
| 15 | 63.4 | 27 | $407,567 | $387,869 | $635,170 |
| 16 | 65.3 | 28 | $422,662 | $402,235 | $658,694 |
| 17 | 67.0 | 29 | $437,757 | $416,600 | $682,219 |
| 18 | 69.7 | 30 | $452,852 | $430,966 | $705,744 |
| 19 | 70.1 | 30 | $452,852 | $430,966 | $705,744 |
| 20-29 | 74.5 | 32 | $483,043 | $459,697 | $752,794 |
| 30-49 | 79.4 | 34 | $513,233 | $488,428 | $799,843 |
| 50-59 | 80.0 | 34 | $513,233 | $488,428 | $799,843 |
| 60-69 | 79.8 | 34 | $513,233 | $488,428 | $799,843 |
| 70-79 | 76.6 | 33 | $498,138 | $474,062 | $776,318 |
| 80+ | 68.5 | 29 | $437,757 | $416,600 | $682,219 |

a We used the case definition developed by the Evidence Review Workgroup for the ACHDNC to determine eligibility for ERT: *Affected subjects have GAA enzyme activity <5% confirmed in leukocytes, fibroblasts, or muscle and have at least one pathologic mutation (i.e., not mutations associated with pseudodeficiency) on each allele. We chose to accept enzyme activity < 5% although the true enzyme activity level for those with the infantile-onset Pompe disease is typically much lower (i.e., <1%). However, some assays may not be able to detect enzyme activity that low, and therefore are only able to report <5%. In addition to low GAA enzyme activity, affected infants must have hypertrophic cardiomyopathy or muscle weakness before 1 year of age. Those with hypertrophic cardiomyopathy or significant cardiomegaly were classified as having classic infantile-onset Pompe disease. Otherwise, subjects were classified as having nonclassic infantile-onset Pompe disease. Identification of mutations known to be associated with Pompe disease can be supportive of the diagnosis. 14*

*Because GAA enzyme activity is not consistently reported, individuals were also considered to have infantile-onset Pompe disease if the GAA was reported to be low during the newborn period with associated cardiomyopathy or weakness and had mutations associated with infantile-onset Pompe disease.*

bRepresents 95% of the CDC Anthropometric Reference Data for Children and Adults: United States, 2007-201015. cEach unit is 50 mg; total number of units is calculated as average weight x 20 mg/kg rounded up to the nearest unit.

dWholesale acquisition cost 2 with a 23% discount was used for a cost of $580.54 per 50 mg unit.

e$552.52 per 50 mg unit; government-negotiated price for VA, DoD, Bureau of Indian Affairs, and Coast Guard.

f$904.80 per 50 mg unit-average wholesale price 2.

d. Costs of immune tolerance induction and enzyme replacement treatment

| **Variable** | **Base** | **Low** | **Upper** | **Source** |
| --- | --- | --- | --- | --- |
| **Immune tolerance induction** |  |  |  |  |
| Methotrexate, 50mg (2ml and 25 mg/ml) | $4 | $2 | $5 | 2 |
| Rituximab, 100mg (10 ml and 10 mg/ml) | $774 | $655 | $964 |  |
| Gammagard S/D, 5000mg (IGA<1ug/ml) | $844 | $283 | $1,012 |  |
| Number of doses of methotrexate for one session of ITI | 9 | - | - |  |
| Doses of rituximab required for 1 session of ITI | 4 | - | - |  |
| Doses of IVIG required for 1 session of ITI | 2 | - | - |  |
| Rituximab dose(mg/m^2) if BSA<0.5 | 12.5 | - | - |  |
| Rituximab dose (mg/m^2) if BSA>0.5 | 375 | - | - |  |
| IVIG dose (mg/kg) | 450 | - | - |  |
| Provider visit to receive a methotrexate injection | $133 | - | - |  |
| Rituximab infusion, hospital (1-2 h) | $263 | $89 | $338 | 16 |
| IVIG infusion, hospital (1-2 h) | $263 | $89 | $338 | 2 |
| Probability of requiring 2nd session of ITI at 5 months | 0 | 0 | 0.5 | Assumption |
| Proportion of infantile-onset Pompe disease receiving ITI (% CRIM negative) | 0.25 | 0.2 | 0.5 | 17 |
| Proportion of weight for Pompe disease patients compared to the national average weight by age | 0.95 | 0.9 | 1 | Assumption |
| Average BSAa | varies by age | 0.288 | 2.014 | 15 |
| **Enzyme replacement therapy** |  |  |  |  |
| Infusion into a vein, up to 1 hourb | $143 | $0 | $21,564 | 18, Primary data analysis |
| Infusion into a vein, each additional hourc | $86 | $0 | $1,670 |  |
| Estimated length of ERT infusion at hospital | 6 hours | - | - | Assumption |
| **Total costs for hospital infusions** | $550 | $166 | $15,000d |  |
| Home infusion, per visit, up to 2 hourse, or each additional hourf | $110 | $48 | $250 | 18, Primary data analysis |
| Estimated length of ERT infusion at home | 6 hours | - | - | Assumption |
| **Total costs for home infusions** | $558 | $135g | $4,000d |  |
| Percent of infusions at home (1st year infantile) | 50% |  |  | Assumption |
| Percent of infusions at home (after 1st year) | 100% |  |  |  |

Abbreviations: IGA, immune globulin antibodies; ITI, immune tolerance induction; IVIG, intravenous immunoglobulin; BSA, body surface area; CRIM, cross-reactive immunological material; ERT, enzyme replacement therapy.

a BSA conversion formula: 0.024265\*(height^0.3964) \*(weight^0.5378)

b CPT 96365

c CPT 96366

d Estimate from expert opinion

e CPT 99601

f CPT 99602

g Estimate assumes an 82% ratio of home infusion to hospital infusion costs2

e. Annual medical expenditures, non-Pompe disease related4

|  |  |
| --- | --- |
| **Age** | **Medical Expenditures** |
| <26 | $1,162 |
| 26-34 | $2,887 |
| 35-44 | $4,076 |
| 45-54 | $4,931 |
| 55-64 | $5,513 |
| 65-74 | $6,014 |
| 75+ | $5,967 |

f. Medical costs, Pompe disease

| **Medical Services** | **Cost** | **Services per Year** | **Lower Est.** | **Upper Est.** | **Total Annual Costs** | **Lower Bound** | **Upper Bound** | **Source** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Mild Pompe disease** |  |  |  |  |  |  |  |  |
| **Outpatient Visits** |  |  |  |  |  |  |  |  |
| Standard outpatient visita | $129 | 2 | 1 | 6 | $258 | $129 | $773 | 7, 1, Expert opinion |
| Physical therapy (adults only)b | $35 | 12 | 6 | 24 | $423 | $211 | $845 |
| Occupational therapy (adults only)b | $35 | 12 | 6 | 24 | $423 | $211 | $845 |
| Speech therapyc | $84 | 12 | 6 | 24 | $1,002 | $501 | $2,005 |
| Nutritional therapyd | $34 | 2 | 1 | 6 | $68 | $34 | $204 |
| Orthoticse | $38 | 1 | 0 | 2 | $38 | $0 | $77 |
| **Emergency visits** |  |  |  |  |  |  |  | 1, Expert opinion |
| Emergency outpatient visita | $129 | 1 | 1 | 2 | $129 | $129 | $258 |
| **Additional procedures** |  |  |  |  |  |  |  | 7,1, Expert opinion |
| Cardio/pulmonary consultation before exercisef | $782 | 0.33 | 0.25 | 0.5 | $258 | $196 | $391 |
| 12-lead electrocardiogram with interpretation and reportg | $17 | 1 | 1 | 1 | $17 | $17 | $17 |
| Pulse oximetry, heart rate, perceived exertional efforth | $3 | 4 | 2 | 6 | $13 | $6 | $19 |
| Limited overnight monitoring with pulse oximetryi | $25 | 1 | 1 | 1 | $25 | $25 | $25 |
| Full polysomnographyj | $610 | 0 | 0 | 0.25 | $0 | $0 | $152 |
| Capnographyk | $8 | 1 | 0 | 2 | $8 | $0 | $15 |
| Pulmonary function testsl | $37 | 1 | 0.5 | 4 | $37 | $18 | $147 |
| Inhaled bronchodilators with airway clearance techniques, assisted coughing maneuversm | $92 | 1 | 0.5 | 2 | $92 | $46 | $185 |
| Oral stimulation & non-nutritive suckingn | $80 | 0.25 | 0 | 0.5 | $20 | $0 | $40 |
| Videofluoroscopic swallowing testo | $88 | 0.25 | 0 | 0.5 | $22 | $0 | $44 |
| Fall Risk assessmentp | $33 | 1 | 0.5 | 2 | $33 | $17 | $67 |
| Tympanometryq | $13 | 0.5 | 0 | 1 | $6 | $0 | $13 |
| Auditory evoked potentials, comprehensiver | $137 | 0.5 | 0 | 1 | $68 | $0 | $137 |
| Air and bone audiometrys | $37 | 0.5 | 0 | 1 | $19 | $0 | $37 |
| **Laboratory tests** |  |  |  |  |  |  |  |  |
| Creatine kinase-MBt | $12 | 1 | 1 | 1 | $12 | $12 | $12 | 5, Expert opinion |
| Comprehensive Panelu | $19 | 1 | 1 | 1 | $19 | $19 | $19 | Expert opinion |
| Urine Hex4 | $148 | 1 | 1 | 1 | $148 | $148 | $148 | Expert opinion, personal communication v |

f cont. Medical costs, Pompe disease

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Medical Services** | **Cost** | | **Services per Year** | **Lower Est.** | **Upper Est.** | **Total Annual Costs** | | **Costs - Lower Est.** | **Costs - Upper Est.** | **Source** |
| **Medications** |  | |  |  |  |  | |  |  |  |
| Metoclopramide, childw | - | | - | - | - | $2,116 | | - | - | 2, Expert opinion |
| Metoclopramide, adultx | - | | - | - | - | $4,231 | | - | - |
| Ranitidine, childy | - | | - | - | - | $5,578 | | - | - |
| Ranitidine, adultz | - | | - | - | - | $5,976 | | - | - |
| Reflux medication, average, child | - | | - | - | - | $3,847 | | - | - |  |
| Reflux medication, average, adult | - | | - | - | - | $5,104 | | - | - |  |
| **Severe Pompe disease** |  | |  |  |  |  | |  |  |  |
| **Outpatient visits** |  | |  |  |  |  |  | |  |  |
| Standard outpatient visita | $130 | | 8 | 6 | 10 | $1,039 | | $779 | $1,299 | 7, 1, Expert opinion |
| Physical therapyb | $35 | | 52 | 48 | 52 | $1,831 | | $1,690 | $1,831 |
| Occupational therapyb | $35 | | 52 | 48 | 52 | $1,831 | | $1,690 | $1,831 |
| Speech therapyc | $84 | | 52 | 48 | 52 | $4,344 | | $4,010 | $4,344 |
| Nutritional therapyd | $34 | | 8 | 6 | 10 | $272 | | $204 | $340 |
| Oral function therapyaa | $87 | | 1 | 0 | 2 | $87 | | $0 | $174 |
| **Emergency visits** | |  |  |  |  |  |  | |  |  |
| Emergency outpatient visita | $130 | | 2 | 1 | 2 | $260 | | $130 | $260 | 1, Expert opinion |
| Emergency room visit | $1,000 | | 0 | 0 | 2 | $0 | | $0 | $2,000 | Expert opinion, Primary data analysisbb |
| Hospitalizationcc | $46,264 | | 0.5 | 0 | 1 | $23,132 | | $0 | $46,264 | 19, Expert opinion |
| **Additional procedures** |  | |  |  |  |  | |  |  |  |
| Cardio/pulmonary consultation before exercisef | $782 | | 0.5 | 0.5 | 0.5 | $391 | | $391 | $391 | 11, 1, Expert opinion |
| Pulse oximetry, heart rate, perceived exertional efforth | $3 | | 8 | 8 | 8 | $26 | | $26 | $26 |
| 12-lead electrocardiogram with interpretation and reportg | $17 | | 4 | 4 | 4 | $69 | | $69 | $69 |
| Full polysomnographyj | $610 | | 0.25 | 0.25 | 0.25 | $152 | | $152 | $152 |
| Tympanometryq | $13 | | 0.5 | 0.5 | 0.5 | $6 | | $6 | $6 |
| Auditory evoked potentials, comprehensiver | $137 | | 0.5 | 0.5 | 0.5 | $68 | | $68 | $68 |
| Air and bone audiometrys | $37 | | 0.5 | 0.5 | 0.5 | $19 | | $19 | $19 |
| **Lab tests** |  | |  |  |  |  | |  |  |  |
| Creatine kinase-MBt | $12 | | 1 | 1 | 1 | $12 | | $12 | $12 | 5, Expert opinion |
| Comprehensive Panelu | $19 | | 1 | 1 | 1 | $19 | | $19 | $19 |  |
| Urine Hex4 | $148 | | 1 | 1 | 1 | $148 | | $148 | $148 | Expert opinion, personal communication |

f cont. Medical costs, Pompe disease

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Medical Services** | **Cost** | **Services per Year** | **Lower Est.** | **Upper Est.** | **Total Annual Costs** | **Lower Est.** | **Upper Est.** | **Source** |
| **Equipment** |  |  |  |  |  |  |  |  |
| Ventilator equipmentdd | - | - | - | - | $10,008 | $10,008 | $10,008 | 13 |
| Wheelchair equipment, 1st yearee | - | - | - | - | $5,426 | $4,182 | $8,525 | 10 |
| Tube feeding | - | - | - | - | $30,217 | $18,694 | $51,546 | 20 |
| **Medications** |  |  |  |  |  |  |  |  |
| **Reflux medications** |  |  |  |  |  |  |  |  |
| Metoclopramide, childw | - | - | - | - | $2,116 | - | - | 2, Expert opinion |
| Metoclopramide, adultx | - | - | - | - | $4,231 | - | - |
| Ranitidine, childy | - | - | - | - | $5,578 | - | - |
| Ranitidine, adultz | - | - | - | - | $5,976 | - | - |
| Reflux medication, average, child | - | - | - | - | $3,847 | - | - |  |
| Reflux medication, average, adult | - | - | - | - | $5,104 | - | - |  |
| **Medications for cardiomyopathy** |  |  |  |  |  |  |  |  |
| **Diuretics** |  |  |  |  |  |  |  |  |
| Furosemideff | - | - | - | - | $893 | - | - | 2, Expert opinion |
| Chlorothiazidegg | - | - | - | - | $341 | - | - |
| Spironolactonehh | - | - | - | - | $198 | - | - |
| Diuretics, average | - | - | - | - | $478 | - | - |  |
| **ACE-inhibitors** |  |  |  |  |  |  |  |  |
| Enalapril maleateii | - | - | - | - | $45 | - | - |  |
| Captopriljj | - | - | - | - | $192 | - | - |
| Lisinoprilkk | - | - | - | - | $3 | - | - |
| ACE-inhibitor average | - | - | - | - | $80 | - | - |  |
| **Other cardiac drugs** |  |  |  |  |  |  |  |  |
| Carvedilolll | - | - | - | - | $451 | - | - |  |
| Digoxinmm | - | - | - | - | $530 | - | - |

a CPT99215

b CPT 97530

c CPT92507

d CPT 97802

e CPT97760

f CPT 78451

g CPT 93000

h CPT 94760

i CPT 94762

j CPT 95808

k CPT 94770

l CPT94010

m CPT 31725

n CPT 92610

o CPT 92611

p CPT 97750

q CPT 92567

r CPT 92585

s CPT 92553

t CPT 82550

u CPT 80053

v Duke University Department of Pediatrics

w 20 mg/day at $0.29/mg (wholesale acquisition cost)

x 40 mg/day at $0.29/mg (wholesale acquisition cost)

y 280 mg/day at $0.05/mg (wholesale acquisition cost)

z 300 mg/day at $0.05/mg (wholesale acquisition cost)

aa CPT 92526

bb Adult emergency department visit, moderate severity. Primary data analysis of 2016 MarketScan data conducted in December 2016.

cc DRG 207 - Respiratory system diagnosis w ventilator support 96+ hours

dd Derived from ventilator costs for person with Duchenne muscular dystrophy, adjusted to 2016 US dollars

ee Wheelchair equipment costs assumed to be similar to patients with tetraplegia (C5-C8) AIS A B or C, inflated to 2016 US dollars. Annual medical equipment costs were assumed to be $0 but with an upper estimate $1,579. This upper estimate is derived from DeVivo et. al. (2011)10 for patients with a spinal cord injury resulting in incomplete motor function.

ff 38 mg/day at $0.06/mg (wholesale acquisition cost); dosage for a child who weighs 18.86 kg2

gg 375 mg/day at $0.001/mg (wholesale acquisition cost); dosage for a child who weighs 18.86 kg2

hh 45 mg/day at $0.01/mg (wholesale acquisition cost); dosage for a child who weighs 18.86 kg2

ii 2 mg/day at $0.08/mg (wholesale acquisition cost); dosage for a child who weighs 18.86 kg2

jj 12 mg/day at $0.04/mg (wholesale acquisition cost); dosage for a child who weighs 18.86 kg2

kk 1 mg/day at $0.01/mg (wholesale acquisition cost); dosage for a child who weighs 18.86 kg2

ll 6 mg/day at $0.20/mg (wholesale acquisition cost); dosage for a child who weighs 18.86 kg2

mm 0.2 mg/day at $7.70/mg (wholesale acquisition cost)

g. Quality of life adjustments

|  |  |  |  |
| --- | --- | --- | --- |
| **Health State** | **Value** | **Range** | **Source** |
| Mild symptoms with Pompe disease, <18y | 0.799 | 0.750- 0.844 | 21 |
| Mild symptoms with Pompe disease, ≥18 y | 0.853 | 0.811- 0.892 |  |
| Severe symptoms with Pompe disease, 0-1 y | 0.399 | 0.341- 0.457 |  |
| Severe symptoms with Pompe disease, 2-17 y | 0.466 | 0.407 - 0.525 |  |
| Severe symptoms with Pompe disease, ≥18 y | 0.536 | 0.480- 0.594 |  |
| QALY loss due to transient positive screen | -0.0005 | -- | 22 |
| Spillover QALY loss among caregivers of child with mild symptoms | -0.072 | -0.042, -0.103 | 21 |
| Spillover QALY loss among caregivers of child with severe symptoms, no cardiomyopathy | -0.131 | -0.090, -0.173 |  |
| Spillover QALY loss among caregivers of child with severe symptoms, cardiomyopathy | -0.18 | -0.129, -0.230 |  |

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**Table S4. One-way sensitivity analyses per 4,000,000 person birth cohort**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Input** | | **Strategy** | **Costa** | **QALYa** | **Incremental**  **Cost** | **Incremental**  **QALY** | **ICERb** |
| **Screening test cost** | | | | | | | |
| Low | $1.00 | Clinically diagnosed, untreated | $72,917 | 30.45150 | - | - | - |
|  |  | Clinically diagnosed, treated | $72,995 | 30.45163 | $78 | 0.000127 | $611,564 |
|  |  | Screened, treated | $73,039 | 30.45174 | $44 | 0.000117 | $378,676 |
| High | $17.50 | Clinically diagnosed, untreated | $72,917 | 30.45150 | - | - | - |
|  | | Clinically diagnosed, treated | $72,995 | 30.451626 | $78 | 0.000127 | $611,564 |
|  | | Screened, treated | $73,050 | 30.45174 | $55 | 0.000117 | $474,119 |
| **Confirmatory genetic test cost** | | | | | | | |
| Low | $1,140.00 | Clinically diagnosed, untreated | $72,917 | 30.45150 | - | - | - |
|  | | Clinically diagnosed, treated | $72,995 | 30.45163 | $78 | 0.000127 | $611,564 |
|  | | Screened, treated | $73,039 | 30.45174 | $44 | 0.000117 | $378,783 |
| High | $1,768.00 | Clinically diagnosed, untreated | $72,917 | 30.45150 | - |  | - |
|  | | Clinically diagnosed, treated | $72,995 | 30.45163 | $78 | 0.000127 | $611,564 |
|  | | Screened, treated | $73,039 | 30.45174 | $44 | 0.000117 | $379,136 |
| **Other confirmatory test cost** | | | | | | | |
| Low | $662.04 | Clinically diagnosed, untreated | $72,917 | 30.45150 | - | - | - |
|  | | Clinically diagnosed, treated | $72,995 | 30.45163 | $78 | 0.000127 | $611,564 |
|  | | Screened, treated | $73,039 | 30.45174 | $44 | 0.000117 | $378,676 |
| High | $1,531.72 | Clinically diagnosed, untreated | $72,917 | 30.45150 | - | - | - |
|  | | Clinically diagnosed, treated | $72,995 | 30.45163 | $78 | 0.000127 | $611,564 |
|  | | Screened, treated | $73,039 | 30.45174 | $44 | 0.000117 | $379,165 |
| **ERT costs** | | | | | | | |
| Low | | Clinically diagnosed, untreated | $72,917 | 30.4515 | - | - | - |
|  | | Clinically diagnosed, treated | $72,982 | 30.45163 | $65 | 0.000127 | $510,906 |
|  | | Screened, treated | $73,017 | 30.45174 | $35 | 0.000117 | $302,696 |
| High | | Clinically diagnosed, untreated | $72,917 | 30.4515 | - | - |  |
|  | | Clinically diagnosed, treated | $72,998 | 30.45163 | $81 | 0.000127 | $639,864 |
|  | | Screened, treated | $73,045 | 30.45174 | $47 | 0.000117 | $402,003 |

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Input** | | **Strategy** | | **Costa** | | **QALYa** | **Incr. Cost** | **Incr. QALY** | **ICERb** |
| **ERT delivery cost** | | | | | | | | | |
| Low | $10,882 | | Clinically diagnosed, untreated | | $72,917 | 30.45150 | - | - | - |
|  | | | Clinically diagnosed, treated | | $72,994 | 30.45163 | $77 | 0.000127 | $606,435 |
|  | | | Screened, treated | | $73,038 | 30.45174 | $44 | 0.000117 | $375,568 |
| High | $96,000 | | Clinically diagnosed, untreated | | $72,917 | 30.4515 | - |  | - |
|  | | | Clinically diagnosed, treated | | $73,010 | 30.45163 | $93 | 0.000127 | $734,174 |
|  | | | Screened, treated | | $73,064 | 30.45174 | $53 | 0.000117 | $458,358 |
| **Informal care hourly wage** | | | | | | | | | |
| Low | $17.74 | | Clinically diagnosed, untreated | | $72,917 | 30.45150 | - | - | - |
|  | | | Clinically diagnosed, treated | | $72,992 | 30.45163 | $76 | 0.000127 | $595,307 |
|  | | | Screened, treated | | $73,037 | 30.45174 | $45 | 0.000117 | $388,109 |
| High | $25.71 | | Clinically diagnosed, untreated | | $72,917 | 30.45150 | - |  | - |
|  | | | Clinically diagnosed, treated | | $72,995 | 30.451626 | $78 | 0.000127 | $611,564 |
|  | | | Screened, treated | | $73,039 | 30.45174 | $44 | 0.000117 | $378,892 |
| **Health utility weights** | | | | | | | | | |
| Low |  | | Clinically diagnosed, untreated | | $72,917 | 30.45150 | - | - | - |
|  | | | Clinically diagnosed, treated | | $72,995 | 30.45162 | $78 | 0.000119 | $651,563 |
|  | | | Screened, treated | | $73,039 | 30.45173 | $44 | 0.000116 | $379,888 |
| High |  | | Clinically diagnosed, untreated | | $72,917 | 30.45150 | - |  | - |
|  | | | Clinically diagnosed, treated | | $72,995 | 30.45164 | $78 | 0.000134 | $578,137 |
|  | | | Screened, treated | | $73,039 | 30.45175 | $44 | 0.000117 | $378,395 |
| **Treatment effectiveness** | | | | | | | | | |
| Low |  | | Clinically diagnosed, untreated | | $72,915 | 30.45150 | - | - | - |
|  | | | Clinically diagnosed, treated | | $72,976 | 30.45160 | $59 | 0.000099 | $599,269 |
|  | | | Screened, treated | | $73,024 | 30.45171 | $48 | 0.000115 | $420,434 |
| High |  | | Clinically diagnosed, untreated | | $72,915 | 30.45150 | - | - | - |
|  | | | Clinically diagnosed, treated | | $73,006 | 30.45164 | $89 | 0.000143 | $625,651 |
|  | | | Screened, treated | | $73,038 | 30.45174 | $32 | 0.000102 | $311,180 |

**Table S4 cont. One-way sensitivity analyses per 4,000,000 person birth cohort**

Abbreviations: Incr., incremental; QALYs, quality adjusted life years; ICER, incremental cost effectiveness ratio; ERT, enzyme replacement therapy.

a These are average per person costs and QALYs for the entire 4,000,000-person birth cohort.

b Incremental comparisons are clinically diagnosed, treated vs. clinically diagnosed, untreated and screened, treated vs. clinically diagnosed, treated.

**Table S5. Sensitivity analysis, cost of alglucosidase alfa, societal perspective per 4,000,000 person birth cohort**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Alglucosidase alfa,**  **% discount of AWP** | **Strategy** | **Costsa** | **QALYsa** | **Incremental Costs** | **Incremental QALYs** | **ICERb** |
| **0%** | Clinically diagnosed, untreated | $72,917 | 30.45150 |  |  |  |
|  | Clinically diagnosed, treated | $73,013 | 30.45163 | $96 | 0.00012696 | $757,191 |
|  | Screened, treated | $73,070 | 30.45174 | $57 | 0.00011656 | $490,641 |
| **10%** | Clinically diagnosed, untreated | $72,917 | 30.45150 |  |  |  |
|  | Clinically diagnosed, treated | $73,005 | 30.45163 | $88 | 0.00012696 | $693,875 |
|  | Screened, treated | $73,056 | 30.45174 | $52 | 0.00011656 | $442,055 |
| **20%** | Clinically diagnosed, untreated | $72,917 | 30.45150 |  |  |  |
|  | Clinically diagnosed, treated | $72,997 | 30.45163 | $80 | 0.00012696 | $630,559 |
|  | Screened, treated | $73,043 | 30.45174 | $46 | 0.00011656 | $393,468 |
| **30%** | Clinically diagnosed, untreated | $72,917 | 30.45150 |  |  |  |
|  | Clinically diagnosed, treated | $72,989 | 30.45163 | $72 | 0.00012696 | $567,243 |
|  | Screened, treated | $73,029 | 30.45174 | $40 | 0.00011656 | $344,882 |
| **40%** | Clinically diagnosed, untreated | $72,917 | 30.45150 |  |  |  |
|  | Clinically diagnosed, treated | $72,981 | 30.45163 | $64 | 0.00012696 | $503,927 |
|  | Screened, treated | $73,015 | 30.45174 | $35 | 0.00011656 | $296,295 |
| **50%** | Clinically diagnosed, untreated | $72,917 | 30.45150 |  |  |  |
|  | Clinically diagnosed, treated | $72,973 | 30.45163 | $56 | 0.00012696 | $440,610 |
|  | Screened, treated | $73,002 | 30.45174 | $29 | 0.00011656 | $247,709 |
| **60%** | Clinically diagnosed, untreated | $72,917 | 30.45150 |  |  |  |
|  | Clinically diagnosed, treated | $72,965 | 30.45163 | $48 | 0.00012696 | $377,294 |
|  | Screened, treated | $72,988 | 30.45174 | $23 | 0.00011656 | $199,122 |
| **70%** | Clinically diagnosed, untreated | $72,917 | 30.45150 |  |  |  |
|  | Clinically diagnosed, treated | $72,957 | 30.45163 | $40 | 0.00012696 | $313,978 |
|  | Screened, treated | $72,974 | 30.45174 | $18 | 0.00011656 | $150,535 |
| **80%** | Clinically diagnosed, untreated | $72,917 | 30.45150 |  |  |  |
|  | Clinically diagnosed, treated | $72,949 | 30.45163 | $32 | 0.00012696 | $250,662 |
|  | Screened, treated | $72,961 | 30.45174 | $12 | 0.00011656 | $101,949 |
| **90%** | Clinically diagnosed, untreated | $72,917 | 30.45150 |  |  |  |
|  | Clinically diagnosed, treated | $72,941 | 30.45163 | $24 | 0.00012696 | $187,345 |
|  | Screened, treated | $72,947 | 30.45174 | $6 | 0.00011656 | $53,362 |

Abbreviations: QALYs, quality adjusted life years; ICER, incremental cost effectiveness ratio.

a These are average per person costs and QALYs for the entire 4,000,000-person birth cohort.

bIncremental comparisons are CI & treated vs. CI & untreated, and NBS treated vs. CI & treated.

**Table S6. Summary results, including family spillover, discounted per 4,000,000 person birth cohort**

a. Health sector perspective, spillover included for all ages

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Strategy | Costsa | QALYsa | Incremental Costs | Incremental QALYs | $/QALYb |
| Clinically diagnosed, untreated | $72,916 | 30.45150 | - | - | - |
| Clinically diagnosed, treated | $72,986 | 30.45161 | $71 | 0.00011217 | $630,228 |
| Screened, treated | $73,034 | 30.45173 | $48 | 0.00011858 | $400,654 |

b. Societal perspective, spillover included for all ages

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Strategy | Costsa | QALYsa | Incremental Costs | Incremental QALYs | $/QALYb |
| Clinically diagnosed, untreated | $72,917 | 30.45150 |  |  |  |
| Clinically diagnosed, treated | $72,995 | 30.45161 | $78 | 0.00011217 | $692,229 |
| Screened, treated | $73,039 | 30.45173 | $44 | 0.00011858 | $372,441 |

c. Health sector perspective, spillover included for children only

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Strategy | Costsa | QALYsa | Incremental Costs | Incremental QALYs | $/QALYb |
| Clinically diagnosed, untreated | $72,916 | 30.45150 |  |  |  |
| Clinically diagnosed, treated | $72,986 | 30.45162 | $71 | 0.000119412 | $591,987 |
| Screened, treated | $73,034 | 30.45174 | $48 | 0.000119451 | $397,743 |

d. Societal perspective, spillover included for children only

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Strategy | Costsa | QALYsa | Incremental Costs | Incremental QALYs | $/QALYb |
| Clinically diagnosed, untreated | $72,917 | 30.4515 |  |  |  |
| Clinically diagnosed, treated | $72,995 | 30.45162 | $78 | 0.000119412 | $650,226 |
| Screened, treated | $73,039 | 30.45174 | $44 | 0.000119451 | $369,735 |

Abbreviations: QALYs, quality adjusted life years

a These are average per person costs and QALYs for the entire 4,000,000-person birth cohort.

b Incremental comparisons are clinically diagnosed, treated vs. clinically diagnosed, untreated and screened, treated vs. clinically diagnosed, treated.

**Table S7. Sensitivity analysis of dosage and frequency of alglucosidase alfa, annual newborn cohort of 4,000,000**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcomesa** | **40 mg/kg of Alglucosidase Alfa Every Other Week** | | **40 mg/kg of Alglucosidase Alfa Every Week** | |
| **Clinically Diagnosed & Treated** | **Newborn Screening & Treated** | **Clinically Diagnosed & Treated** | **Newborn Screening & Treated** |
| Total costs (healthcare sectorb) | $292,188,516,881 | $292,551,358,911 | $292,690,328,693 | $293,406,888,704 |
| Total costs (societal) | $292,221,381,600 | $292,570,841,214 | $292,723,193,411 | $293,426,371,006 |
| Incremental costs (healthcare sectorb) | -- | $362,842,030 | -- | $716,560,011 |
| Incremental costs (societal) | -- | $349,459,614 | -- | $703,177,595 |
| Total QALYs | 121,806,506 | 121,806,973 | 121,806,506 | 121,806,973 |
| Incremental QALYs | -- | 466 | -- | 466 |
| ICER (healthcare sector) | -- | $778,096 | -- | $1,536,627 |
| ICER (societal) | -- | $749,399 | -- | $1,507,929 |

Abbreviation: ICER=incremental cost-effectiveness ratio.

a Costs and QALYs are discounted at 3% to 2016 USD.

b The healthcare sector perspective includes all but non-medical and informal caregiving costs.

**Table S8. Discounted summary results, base case per 4,000,000 person birth cohort**

a. Health sector perspective

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Strategy | Costa | QALYsa | Incremental Costs | Incremental QALYs | $/QALYb |
| Clinically diagnosed, untreated | $72,916 | 30.4515 |  |  |  |
| Clinically diagnosed, treated | $72,986 | 30.45163 | $71 | 0.000127 | $556,788 |
| Screened, treated | $73,034 | 30.45174 | $48 | 0.000117 | $407,594 |

b. Societal perspective

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Strategy | Costsa | QALYsa | Incremental Costs | Incremental QALYs | $/QALYb |  |
| Clinically diagnosed, untreated | $72,917 | 30.4515 |  |  |  | |
| Clinically diagnosed, treated | $72,995 | 30.45163 | $78 | 0.000127 | $611,564 | |
| Screened, treated | $73,039 | 30.45174 | $44 | 0.000117 | $378,892 | |

Abbreviations: QALYs, quality adjusted life years

a These are average per person costs and QALYs for the entire 4,000,000-person birth cohort.

b Incremental comparisons are clinically diagnosed, treated vs. clinically diagnosed, untreated and screened, treated vs. clinically diagnosed, treated.

**Table S9. Undiscounted summary results, base case per 4,000,000 person birth cohort**

a. Health sector perspective

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Strategy | Costsa | QALYsa | Incremental Costs | Incremental QALYs | $/QALYb |
| Clinically diagnosed, untreated | $288,244 | 79.12927 |  |  |  |
| Clinically diagnosed, treated | $288,436 | 79.12959 | $193 | 0.000313 | $615,063 |
| Screened, treated | $288,597 | 79.12994 | $161 | 0.000355 | $453,284 |

b. Societal perspective

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Strategy | Costsa | QALYsa | Incremental Costs | Incremental QALYs | $/QALYb |
| Clinically diagnosed, untreated | $288,246 | 79.12927 |  |  |  |
| Clinically diagnosed, treated | $288,455 | 79.12959 | $209 | 0.000313 | $666,966 |
| Screened, treated | $288,611 | 79.12994 | $156 | 0.000355 | $439,310 |

Abbreviations: QALYs: quality adjusted life years

a These are the undiscounted average per person costs and QALYs for the entire 4,000,000-person birth cohort.

b Incremental comparisons are clinically diagnosed, treated vs. clinically diagnosed, untreated and screened, treated vs. clinically diagnosed, treated.

**Table S10. Undiscounted disaggregated costs and QALYs, annual newborn cohort of 4,000,000**

|  |  |  |  |
| --- | --- | --- | --- |
| **Category** | **Clinically diagnosed, untreated** | **Clinically diagnosed, treated** | **Screened,**  **treated** |
| Screening/confirmation | $0 | $0 | $26,224,278 |
| ERT, including delivery/ITI | $0 | $712,398,660 | $1,358,405,139 |
| Medical costs, Pompe disease related | $4,511,991 | $35,776,216 | $22,495,736 |
| Medical costs, non-Pompe disease related | $1,152,966,549,504 | $1,152,971,957,554 | $1,152,977,881,772 |
| Informal care | $7,467,819 | $69,604,014 | $48,064,677 |
| Formal care | $3,283,071 | $24,882,884 | $4,390,966 |
| Non-medical costs (environmental modification, appointment time costs) | $1,830,181 | $4,728,447 | $6,402,999 |
| Undiscounted QALYs | 316,517,089 | 316,518,342 | 316,519,764 |

Abbreviations: ERT, enzyme replacement therapy; ITI, immune tolerance induction; QALYs, quality adjusted life years.

**Table S11. Impact Inventory**

|  |  |  |
| --- | --- | --- |
| **Type of impact** | **Healthcare sector perspective** | **Societal perspective** |
| **Formal healthcare sector** |  |  |
| ***Health outcomes*** |  |  |
| Longevity effects  ERT treatment extends life; newborn screening allows for an earlier start to treatment and better health outcomes | 🗹 | 🗹 |
| Health related quality of life effects  ERT treatment reduces disease progression, improving quality of life | 🗹 | 🗹 |
| Other health effects  Spillover impact on caregivers’ health related quality of life were included in a sensitivity analysis | 🗹 | 🗹 |
| ***Medical costs*** |  |  |
| Medical costs paid by third-party payers  Included costs of provider visits, procedures, labs etc. | 🗹 | 🗹 |
| Medical costs paid for out-of-pocket  Out-of-pocket costs were not included | 🞏 | 🞏 |
| Future related medical costs  Patients who survive longer incur costs related to ERT and other Pompe disease-related medical services | 🗹 | 🗹 |
| Future unrelated medical costs  Patients who survive longer incur medical expenditures not specific to Pompe disease | 🗹 | 🗹 |
| **Informal healthcare sector** |  |  |
| Patient time costs  Included for each Pompe disease-related provider visit among those with no/mild symptoms. Not included for those with severe symptoms as patient would not be able to engage in productive activities (market or non-market). | 🞏 | 🗹 |
| Unpaid caregiver costs  Included, differential for mild and severe disease states | 🞏 | 🗹 |
| Transportation costs  Not included | 🞏 | 🞏 |
| **Non-healthcare sectors** |  |  |
| Productivity losses  Not included | 🞏 | 🞏 |
| Consumption  Not included | 🞏 | 🞏 |
| Cost of social services  Pompe disease has not been associated with cognitive impairment; education costs and other social services not included | 🞏 | 🞏 |
| Cost of crimes related to intervention  Not applicable to condition | 🞏 | 🞏 |

Abbreviations: ERT, enzyme replacement therapy.