Quantifying the Economic Burden of Neonatal-Onset Ornithine Transcarbamylase Deficiency in the United States

PT 14

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OBJECTIVE

This study aimed to estimate the economic burden of neonatal-onset OTCD in the pediatric years from the U.S. healthcare system and societal perspective.

INTRODUCTION

Urea cycle disorders (UCDs) are a group of rare genetic metabolic conditions where the body cannot properly remove ammonia, resulting in hyperammonemia with risk of seizures, coma, death, and developmental delays.

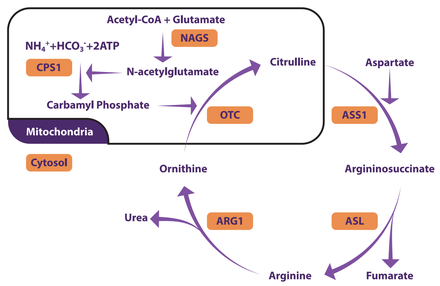
Ornithine transcarbamylase deficiency (OTCD), the most common UCD and an X-linked disorder, is especially severe in neonatal-onset cases due to near-total enzyme loss.

Despite adherence to standard of care therapies and medical interventions, neonatal OTCD has high mortality and survivors often suffer irreversible neurological injury from recurrent hyperammonemia.

Current OTCD treatments are primarily supportive and often involve costly care settings like pediatric neonatal intensive care units.

At present, liver transplantation is the only curative option, which still carries morbidity, mortality risks, and inability to reverse neurological injury.

Figure 1: The Urea Cycle



METHODS

Hybrid modeling approach combining a decision tree with a Markov-style long-term framework, where an initial decision tree captures early OTCD clinical events (HAC, coma, death, liver transplant), followed by annual state-based transitions to project outcomes and costs over 1-, 5-, and 10-year horizons.

Patient cohorts stratified by age of onset and sex, reflecting OTCD heterogeneity (neonatal, pediatric late-onset, adult late-onset; male/female), with health states defined by survival, transplant status, and neurocognitive outcomes.

Transition probabilities informed by published literature and registry data, prioritizing U.S. sources where available; OTCD-specific evidence was supplemented with broader UCD data and proxy conditions when direct evidence was limited.

Clinical expert input used to address evidence gaps, including HAC frequency, transplant utilization (particularly in neonates), coma risk, and long-term assumptions where real-world data are sparse.

Costs assigned to all modeled health states and transitions, incorporating direct medical costs (HAC hospitalizations, liver transplantation, drugs, long-term care), indirect caregiver costs, and end-of-life costs, inflated to 2025 USD.

Figure 2: Decision Tree Model

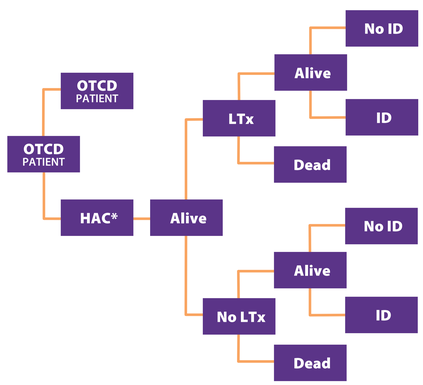


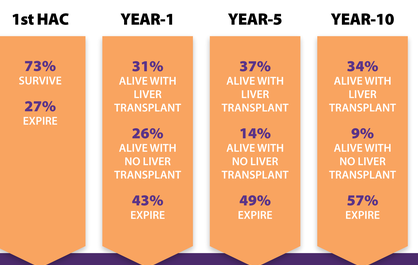
Figure 2 illustrates our OTCD patient decision tree model.

The model estimates the risk of hyperammonemic crisis and tracks survival, coma, and liver transplantation outcomes.

Cognitive outcomes are categorized for all survivors, distinguishing between mild and moderate/severe intellectual disability.

Patients are ultimately grouped as alive and transplanted, alive and not transplanted, or deceased, with follow-up up to 10 years.

For neonatal male OTCD patients the transition through various health states occurs rapidly (Figure 3) with the model projecting 57% of patients would be dead, 34% would be alive following liver transplantation, and 9% would be alive without transplantation at end of year 10.



DEFINING THE COSTS

The model cost inputs were gathered from a focused literature review and public cost sources, prioritizing US-specific and relevant evidence. When OTCD-specific data was lacking, information from broader UCD or similar diseases was used.

Table 1: Cost of HAC

Hospitalization	Without Coma	With Coma
Neonatal and Pediatric	$113,538	$164,378
Adult Late (>12yrs.)	$53,677	$83,498

HAC frequency is a primary driver of acute mortality and cost; coma probability influences ICU use, therefore higher cost, and long-term neurocognitive sequelae.

Table2: Scavenger Treatment Cost

Annual Costs of Treatment with Scavenger Therapy	
Neonatal	$303,296
Pediatric Late (1mth-12yrs)	$285,404
Adult Onset	$506,538

Scavenger therapy for OTCD is a supportive, lifelong treatment that requires ongoing adjustments and monitoring to maintain metabolic balance, resulting in substantial medical costs.

The inability of scavenger therapy to address the underlying metabolic defect often leads to additional economic burdens due to recurrent hyperammonemia and hospitalization utilization.

Table 3: Transplant Cost

Liver Transplant Cost	
Neonatal and Pediatric Late	$544,414
Adult Onset	$269,536

Liver transplantation (LTx) is the highest-cost interventions in the OTCD model. Because transplantation is often life-saving for patients with severe neonatal-onset disease, LTx costs occur early in the patient journey, while contributing a large share of lifetime expenditures. Graft failure remains a risk.

Figure 3: Sankey Diagram (Neonatal Male)

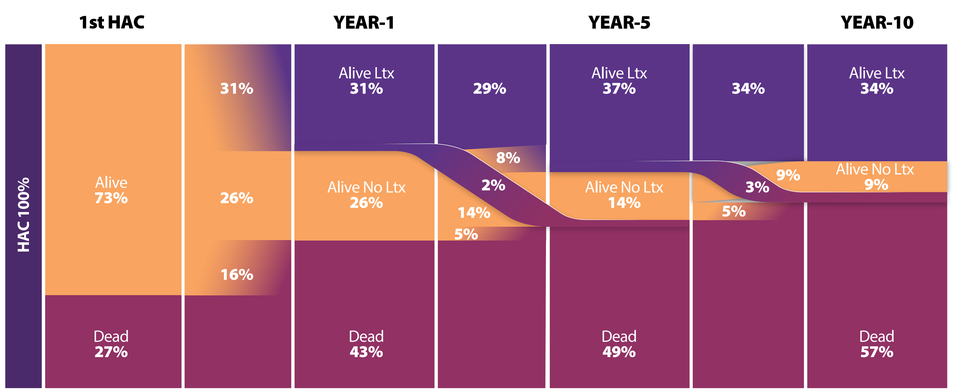


Figure 4: Other Costs

Cognitive Disability Costs

Cognitive disability imposes substantial economic burden. Annual intellectual disability (ID)-related costs were derived from published literature and vary by age of onset, reflecting medical, behavioral, and support services required to manage long-term neurocognitive impairment.

Onset Group	Annual Cognitive Disability Costs
Neonatal	$107,893
Pediatric	$102,109
Adult Onset	$48,710

Caregiver Costs

OTCD patients frequently require ongoing caregiver support. All infants and children were assumed to need full-time care, while 10% of adults were assumed to require caregiving assistance. Indirect cost estimates were drawn from a study focused on metabolic rare diseases and include productivity losses for patients and caregivers, work loss, home modifications, secondary treatments, travel and accommodation.

Onset Group	Annual Indirect Costs
Neonatal	$83,907
Pediatric	$83,907
Adult Onset	$83,907

(***10% Require Caregiving***)

End-of-Life Costs

End-of-life costs are the medical, caregiving, and support expenses incurred during the last months before death. These costs are often substantially higher than regular care because patients require more intensive medical management and increased caregiver support.

Onset Group	End-of-Life Costs
Neonatal	$42,840
Pediatric	$42,840
Adult Onset	$51,341

Cognitive disability leads to significant annual expenses for medical, behavioral, and support services, varying by age of onset.

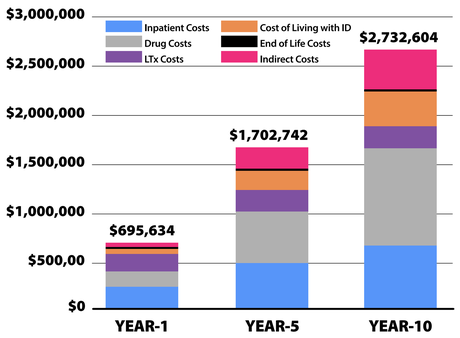
OTCD patients often require ongoing caregiving; all children need full-time care, and 10% of adults require assistance, with indirect costs including productivity losses and related expenses.

End-of-life care results in markedly higher medical and support costs due to increased management and caregiver needs.

RESULTS

Total costs increase substantially over the first 10 years of life, with early costs driven by hospitalization and ICU care, and longer-term costs increasingly driven by liver transplant, chronic drug costs, indirect costs, and supportive care needs.

Figure 5: Cost by Category



Mean per-patient total costs for neonatal males OTCD patients were estimated to reach $2.7 million during the first 10 years of life, of which $2.3 million were attributable to direct medical costs. Costs were initially driven by inpatient HAC management and liver transplantation, with longer-term costs increasingly attributable to chronic nitrogen scavenger therapy, intellectual disability–related care, and caregiving.

Table 4: Total Costs for a Neonatal Male 1, 5 and 10 Years

Direct Costs	YEAR-1	YEAR-5	YEAR-10
Inpatient Costs	$232,008	$482,345	$668,846
Drug Costs	$161,275	$542,617	$1,024,687
LTx Costs	$185,015	$229,087	$230,813
Cost of Living with ID	$51,039	$201,965	$365,707
End of Life Costs	$18,340	$21,111	$24,445
SUBTOTAL	**$647,677**	**$1,477,125**	**$2,314,498**
Indirect Costs	$47,986	$225,617	$418,106
TOTAL	**$695,662**	**$1,702,742**	**$2,732,604**

DISCUSSION

The model uses published OTCD data and clinical expert input to ensure evidence-based, clinically relevant parameters for assessing both short- and long-term outcomes.

OTCD imposes significant medical and societal costs, particularly for neonatal-onset patients due to frequent hyperammonemic crises, liver transplantation needs, and ongoing care requirements such as scavenger therapy and intellectual disability risk.

Key limitations include the model's restricted 10-year horizon, inability to capture quality-of-life impacts and broader long-term effects on families, lack of retransplant experience, undervaluation of mortality reduction, and limited real-world data on rare disease outcomes.

CONCLUSION

Neonatal-onset OTCD imposes a profound economic burden if illness alongside excess morbidity and early mortality during the pediatric years.