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Financing and Reimbursement of Cures in the US

RESEARCH BRIEF

By MIT NEWDIGS FoCUS Project

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Pediatric inpatient costs of select orphan conditions with potential gene therapy launches. Gene therapy cures for hereditary genetic conditions are likely to reach the United States market in the coming decades. Several disease areas with potential cures are orphan conditions, which affect fewer than 200,000 patients in the US.[1] To understand the current cost burden associated with managing orphan conditions, we analyzed 55,188 pediatric inpatient stays across disease areas including select hemoglobinopathies, bleeding disorders, lysosomal storage diseases, cystic fibrosis, and other enzymatic deficiencies. We find national pediatric inpatient cost estimates of nearly $1 billion in 2016, attributable to our eleven orphan diseases of interest—despite accounting for less than one percent of pediatric inpatient stays that year.

POTENTIAL CURES TARGET A HETEROGENEOUS GROUP OF DISEASES

There are several gene therapy trials seeking United States (US) Food and Drug Administration (FDA) approval for hereditary conditions, from which we have selected representative diseases to illustrate the impact that the approval of these drugs will have on the US healthcare system (Box 1). Our population of interest includes a diverse group of diseases, from rapidly fatal without early intervention (i.e. gene therapy, hematopoietic cell transplantation, or enzyme replacement therapy), such as adenosine deaminase deficiency with severe combined immunodeficiency (ADA-SCID), to sickle cell disease (SCD) in which the current standard of care has increased life expectancy enough to become a chronic condition.

For the purposes of this brief we have classified them into hemoglobinopathies (SCD and beta thalassemia [BT]), bleeding disorders (hemophilia A [HAA] and B [HAB]), lysosomal storage diseases (Pompe [PD], Von Gierke [VG], Gaucher [GD], and mucopolysaccharidosis Type III [MPS-III]), cystic fibrosis (CF) and other enzymatic deficiency (ADA-SCID, ornithine transcarbamylase deficiency [OTCD]). In the US these diseases are classified as orphan diseases with fewer than 200,000 people affected by each condition.[1] See Appendix Table 1 for detailed information on our disease areas

KEY TAKEAWAYS

Aggregate inpatient hospitalization costs for pediatric stays among eleven genetic orphan diseases were roughly $1 billion USD in 2016.

Medicaid and private insurance including HMO plans were the primary expected payers for over 91% of these costs (57% and 34%, respectively) in 2016.

Cell and gene therapies may result in significantly decreased disease-related hospitalizations among children in our target population.

of interest including estimates for incidence and age of onset.

During our selection process, we took into consideration our ability to identify the patient population using International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes. Some diseases' ICD-10-CM codes were too ambiguous, due to them being grouped under a broader descriptive code (e.g. Canavan's disease coded under Z83.49—family history of other endocrine, nutritional and metabolic diseases) and thus were not selected.

Additionally, it was imperative to include conditions in which there was potential approval of curative gene therapy treatments in the US and we therefore excluded those without current gene therapy trials on clinicatrials.gov (e.g. Netherton Syndrome). Overall, the selected conditions have diverse mechanisms of disease, age of onset, rate of progression, level of disability, management, and complications—factors which contribute to cost-burden at different stages of life and to different payers.

HEALTHCARE COSTS ASSOCIATED WITH PEDATRIC INPATIENT STAYS

Inpatient stays are costly healthcare events that can be disproportionately expensive for individuals with rare genetic diseases, given their complex needs. They provide a part of the picture when determining overall healthcare resource utilization within a condition, but do not fully characterize all direct economic burdens associated with treatment. Individuals with rare genetic diseases may be more likely to be hospitalized, or hospitalized for longer, for interventions that may otherwise be carried out in an outpatient setting. In the future, such conditions may be treated by one-time curative therapies so that these costs may be avoided, along with costs associated to the intensive comprehensive care upon diagnosis and the subsequent outpatient visits and management.

There is limited information regarding the overall direct and indirect healthcare cost burdens from managing orphan conditions in the first decades of life. We aim to describe part of the direct economic burden associated with these conditions, by looking solely at pediatric inpatient hospitalizations.

See Appendix Table 1 for more detailed information on notable costs.

EMPIRICAL APPROACH: METHODS

We used the Kids' Inpatient Database (KID) for the year 2016, Healthcare Cost and Utilization Project (HCUP), from the Agency for Healthcare Research and Quality (AHRQ), to analyze stays for select orphan diseases with potentially durable treatments or cures in the US FDA pipeline.[2] The HCUP KID database is sampled from 4,200 U.S. community hospitals in the US and contains information on patients admitted under the age of 21. It is the largest publicly-available all-payer pediatric inpatient care database in the US. HCUP provides discharge weights per stay which allows for construction of nationally representative estimates.

Box 1. Our orphan diseases of interest, selected by ability to identify with ICD-10-CM, *in brief*

- **Sickle cell disease** and **beta thalassemia**, caused by an abnormality in the beta gene and beta protein ratio, respectively. This leads to early destruction of red blood cells, vessel obstruction, among other symptoms.
- **Hemophilia A and B**, caused by a deficiency of a clotting factor. As a result, these patients experience life-threatening bleeding.
- **Pompe, Von Gierke, Gaucher,** and **mucopolyssacharidosis-III (MPS-III)**, caused by an enzyme deficiency that leads to the accumulation of glycogen (Pompe and Von Gierke), glucocerebroside (Gaucher) and glucosaminoglycans (MPS-III) that results in cellular dysfunction and clinical abnormalities.
- **Adenosine deaminase deficiency**, in most cases due to an enzyme deficiency that results in the inhibition of DNA synthesis and inadequate/absent immune response to infections.
- **Ornithine transcarbomylase deficiency**, caused by an enzymatic deficiency that results in the accumulation of ammonia.
- **Cystic fibrosis**, caused by a mutation that leads to an abnormal cellular transmembrane protein. Clinically, this leads to thicker mucous in the lungs, pancreatic insufficiency, and frequent infections.

To classify inpatient stays as disease-related, we utilized ICD-10-CM diagnosis codes. When a patient is admitted, they may be assigned up to 30 diagnosis codes for their stay. We looked over all 30 of these possible diagnosis slots per stay in the KID database. Stays with any of our orphan diseases of interest in any of these slots were included in our study. We then classified stays into mutually exclusive categories by orphan disease based on diagnosis present.

In cases where a stay had multiple orphan disease diagnoses (<1% of cases), we used the primary orphan diagnosis. Cases with missing total charges (<3% of cases) were excluded from our analysis. We converted charges to estimated costs using HCUP hospital-level cost-to-charge (CCR) ratios. Costs reflect the actual expenses incurred by hospitals in providing care, not necessarily the amount paid by payers. We performed all statistical procedures using Stata/SE software version 15.1 (StataCorp, College Station, TX). Our study solely utilized a limited data set (HCUP KID) and thus institutional review board (IRB) review was not required.

RESULTS

We found significant pediatric inpatient hospitalization costs associated with our orphan diseases of interest in 2016. Across 55,188 representative stays, we estimated total financial cost to US payers of $998.8M.

By disease area

Average pediatric hospitalization costs varied widely across disease areas, as shown in Figure 1. Costs were highest for ADA-SCID $91,636, (95% confidence interval [CI] = $26,072 to 157,199) and lowest for SCD $9,141, (95% CI = $8,538 to 9,744). Average cost per hospitalization across all of our disease areas was $18,098, (95% CI = $16,394 to 19,801). This contrasted with the average hospitalization cost for other pediatric stays: $7,700, (95% CI = $7,161 to 8,240) ($p<0.05$, for all comparisons). Despite being only 24.0% of pediatric hospitalizations, stays for CF accounted for $414.8M (41.5%) of the total cost burden among these orphan diseases. This discrepancy is likely attributable to hospitalizations for pulmonary disease and costly lung transplants. Approximately 16.4% of lung transplants globally are performed in patients with CF.[3]

By payer

Medicaid and private plans including HMO were the primary expected payer for over 92% of pediatric orphan hospitalizations. Among these, average hospitalization cost for Medicaid covered stays was $16,034, (95% CI= $14,351 to 17,718) relative to the private payer stay average of $22,021, (95% CI = $19,745 to 24,298) ($p<0.0001$). In aggregate, Medicaid and private payers were primary payers for stays costing $909.0 million (91.0%) in 2016.

Length of stay (LOS)

In addition to costs, we studied LOS in days, across disease areas and by payer. Mean pediatric LOS ranged from 4.12 days, (95% CI= 3.99 to 4.25) for SCD to 20.89 days, (95% CI= 7.73 to 34.06) for ADA-SCID. Mean LOS was 3.99 days, (95% CI= 3.90 to 4.08) for other stays ($p<0.05$ for all comparisons except SCD, $p=0.0943$). As expected, LOS was positively correlated with total inpatient cost within pediatric orphan disease stays ($r = 0.61$, $p<0.0001$).

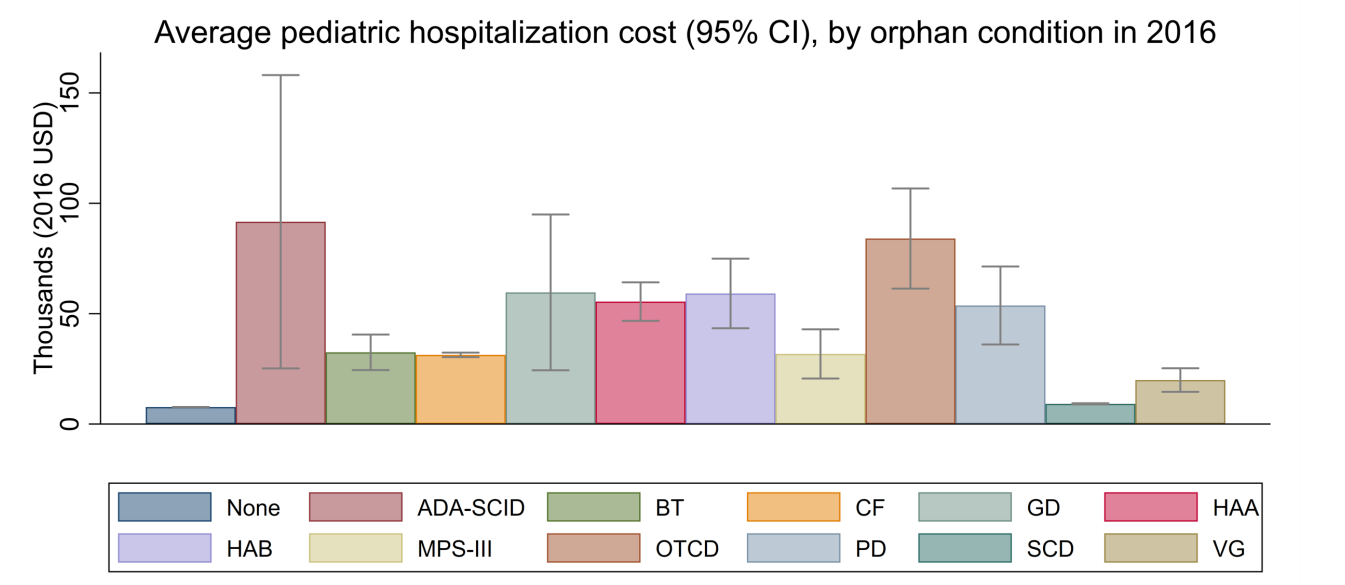
See Appendix Table 2 for detailed breakdown of total and average pediatric hospitalization costs by disease area and payer.

CONCLUSIONS

Our analysis provides an estimate of pediatric inpatient costs that may be avoidable if durable therapies are developed and provided to patients within the first two decades of life. We estimate that nearly $1 billion in healthcare costs are attributable to pediatric hospitalizations for ADA-SCID, BT, CF, GD, HAA, HAB, MPS-III, OTCD, PD, SCD, or VG. By disease area, SCD accounted for most stays (67.0%) and $338.2M (33.9%) of total hospitalization costs. For our disease areas of interest, hospitalization stays do not necessarily correlate to hospitalization costs and other factors often come into play (i.e., CF).

Breakdowns by primary expected payer showed significant burden to both Medicaid and private plans including HMO.

Despite being the primary expected payer in 64.1% of pediatric hospitalizations, Medicaid only bore $566.9M (56.8%) of the total cost burden in 2016. This was in contrast to private payers which accounted for 28.1% of stays but faced costs of $342.1M (34.3%). Other payers overall,



Source: Primary analysis of pediatric HCUP KID database (2016). Figures are weighted to provide national estimates.

Figure 1. Mean pediatric inpatient stay costs (95% CI), by disease area (2016)

including Medicare, were primary expected payers for <10% of cases and <10% of total costs ($89.8M).

We acknowledge limitations within our approach. Our unit of analysis is hospital stay and hence it is not possible to measure resource utilization by patient. Our primary outcome of interest is healthcare costs which are a measure of actual expenses incurred including wages, supplies, and utilities. However, costs are estimated from charges and are not necessarily the amount each payer is ultimately responsible for. In addition, there are many cost areas not accounted for in our analysis, namely outpatient and pharmacy costs, which may be a large part of the direct economic burden of treating a disease. Average pediatric hospitalization costs from estimates generated using community hospitals in the US are unlikely to represent true average costs within academic or other treatment centers.

Like in other analyses which utilize ICD-10-CM diagnosis codes, disease identification in administrative data is imperfect. Since not all disease areas have codes to stratify by severity or complications, we do not provide separate hospitalization costs by these populations. This approach means our average pediatric hospitalization costs estimates likely overestimate (underestimate) costs for less (more) severe cases. As well, validation studies are necessary to confirm diagnostic accuracy across disease areas.

Lastly, the pathogenesis, age of onset, and natural histories of the selected conditions are very distinct. For instance, individuals with ADA-SCID require early intervention and isolation, and the main treatment option is HSCT, which is managed in an inpatient basis.[4] This contrasts with individuals with SCD, in which fetal hemoglobin usually decreases at two to four months of age and symptoms of disease have a later onset.

Moreover, SCD children in the US often survive into adulthood.[5] This is believed to be due to an early comprehensive care plan management (e.g. newborn screening, prophylactic penicillin, vaccinations, periodic evaluations, etc.), as well as improvements in quality of care and timely interventions, all of which may contribute to the decreased morbidity and mortality in early childhood.[5-9] For this reason, the inpatient cost at this age may not truly reflect the lifetime costs of any of these conditions.

Curative therapies provided to pediatric populations have the potential to avoid significant resource utilization across disease areas. Depending on treatment uptake and age of administration, avoidable inpatient healthcare costs in these disease areas may be as high as $1 billion USD. Additional research is necessary to characterize complete direct cost burdens (outpatient, pharmacy, professional, etc.) and indirect cost burdens to patients and caregivers.

ABOUT FOCUS

The MIT NEWDIGS consortium FoCUS Project (Financing and Reimbursement of Cures in the US) seeks to collaboratively address the need for new, innovative financing and reimbursement models for durable and curable therapies that ensure patient access and sustainability for all stakeholders. Our mission is to deliver an understanding of financial challenges created by these therapies leading to system-wide, implementable precision financing models. This multi-stakeholder effort gathers developers, providers, regulators, patient advocacy groups, payers from all segments of the US healthcare system, and academics working in healthcare policy, financing, and reimbursement in this endeavor.

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Appendix Table 1. Epidemiology and notable costs for orphan diseases of interest

Condition*	Incidence	Age of onset†	Notable costs
ADA-SCID	1/200,000 births[10]	Infancy, neonatal	• Infections • Bone Marrow Transplant (BMT)/Hematopoietic Stem Cell Transplant (HSCT) • Enzyme replacement therapy (ERT) • Other: Anti-infectives (antifungals, antibiotics, antivirals), IVIG
BT	1/100,000 births[11]	Infancy, childhood	• BMT • Blood transfusions • Complications: Venous thrombosis, HIV, Hep. C • Other: Chelation Therapy, osteoporosis prevention, vitamin D
CF	1/3,200 Caucasians, 1/10,000 Hispanics, 1/10,500 Native Americans, 1/15,000 African Americans, and 1/30,000 Asian American births[12, 13]	All ages	• Organ Transplant: Liver and Lung/Heart and Lung • Upper respiratory and Pulmonary complications • ERT • Other: CFTR modulators, Pulmozyme
GD	1/63,000 births[14, 15]	All ages	• Surgical: joint replacement, splenectomy • HSCT • Blood transfusions • ERT and substrate reduction • Other: analgesics, calcium, vitamin D
HAA	1/5,000 male births†	Infancy, neonatal	• Severe bleeding episodes • Surgical: total joint replacement • Factor administration (acute and/or prophylactic) • Other: desmopressin, inhibitor therapy and screening
HAB	1/30,000 male births†	Infancy, neonatal	• See HAA
MPS-III	1.26/100,000 births[16]	Childhood	• Supportive care • Other: hernia repair, orthopedic procedures
OTCD†	1/8,200 births[17]	Neonatal, all ages	• Hyperammonemic crisis and/or coma • Organ Transplant: Liver transplant • Hemodialysis • Other: gastrostomy, ammonia scavenger therapy, supplements, monitoring
PD	1/21,979 births[18]	Antenatal, neonatal, childhood, adolescent, adult	• Ventilatory assistance • Surgical: contractures, tracheostomy • Infections • ERT • Complications: cardiac disease • Other: monitoring, physical therapy, nutrition, respiratory training (e.g. CPAP)
SCD	1/85,000 births[19]	All ages	• Vaso-occlusive crises • Blood transfusions • Surgical: splenectomy, HSCT • Infections • Complications: Acute Chest Syndrome, Stroke, splenic sequestration • Other: Hydroxyurea, antibiotics, analgesics, chelation therapy
VG	1/100,000 births[20]	Infancy, neonatal	• Organ Transplant: Liver, kidney • Surgical: percutaneous ethanol injections and radiofrequency for hepatic adenomas • Infections • Other: nutritional therapy, monitoring

ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; ADA-SCID, adenosine deaminase deficiency with severe combined immunodeficiency; BT, beta thalassemia; CF, cystic fibrosis; GD, Gaucher disease; HAA, hemophilia A; HAB, hemophilia B; MPS-III, mucopolysaccharidosis III; OTCD, ornithine transcarbamylase deficiency; PD, Pompe disease; SCD, sickle cell disease; VG, Von Gierke disease.

*ICD-10-CM diagnoses: ADA-SCID, D81.3; BT, D56.1; CF, E84X; GD, E75.22; HAA, D66; HAB, D67; MPS-III, E76.22; OTCD, E72.4; PD, E74.02; SCD, D57.X sans D57.3X; VG, E74.01. † Estimates obtained from *Orphanet*

Appendix Table 2. Costs and pediatric inpatient hospitalization resource utilization by orphan disease and payer, 2016

Category	National Stays* No. (%)	Total Cost (95% CI)	Mean Cost (95% CI)	Mean LOS (95% CI)
Orphan condition				
ADA-SCID	34 (0.1%)	$3.2M (0.5, 5.8)	$91636 (26072, 157199)	20.9 (7.7, 34.1)
BT	614 (1.1%)	$19.9M (9, 30.8)	$32487 (21075, 43898)	7.5 (5.8, 9.3)
CF	13239 (24%)	$414.8M (333.5, 496)	$31329 (28466, 34193)	10.2 (9.8, 10.5)
GD	147 (0.3%)	$8.8M (2.9, 14.7)	$59638 (26046, 93230)	11.1 (8.1, 14.1)
HAA	2181 (4%)	$120.9M (87.4, 154.5)	$55462 (43087, 67836)	4.9 (4.5, 5.4)
HAB	442 (0.8%)	$26.1M (13.9, 38.4)	$59144 (38191, 80098)	6.7 (5, 8.3)
MPS-III	117 (0.2%)	$3.7M (1.6, 5.9)	$31771 (16602, 46941)	6.7 (4.9, 8.5)
OTCD	414 (0.8%)	$34.8M (20.4, 49.2)	$84036 (56669, 111403)	9.5 (7.4, 11.5)
PD	249 (0.5%)	$13.4M (7, 19.7)	$53697 (33936, 73459)	12.2 (8.6, 15.8)
SCD	37000 (67%)	$338.2M (281.8, 394.6)	$9141 (8538, 9744)	4.1 (4, 4.3)
VG	752 (1.4%)	$15M (9.5, 20.5)	$19928 (13208, 26647)	7.3 (5.6, 9)
Payer type†				
Medicare	485 (0.9%)	$5.6M (3.9, 7.3)	$11506 (9572, 13439)	5.6 (5, 6.3)
Medicaid	35358 (64.1%)	$566.9M (464.8, 669.1)	$16034 (14351, 17718)	5.6 (5.3, 5.8)
Private	15533 (28.1%)	$342.1M (274.8, 409.3)	$22021 (19745, 24298)	6.3 (6, 6.6)
Self-pay	1143 (2.1%)	$19.8M (11.1, 28.5)	$17311 (12135, 22487)	5.2 (4.5, 5.9)
Other/Unknown	2668 (4.8%)	$64.4M (37.7, 91.1)	$24134 (17666, 30602)	6.5 (5.9, 7)
Total	55188	$998.8M (828.8, 1168.7)	$18098 (16394, 19801)	5.8 (5.6, 6)

CI, confidence interval; LOS, length of stay (days); M, million; ADA-SCID, adenosine deaminase deficiency; BT, beta thalassemia; CF, cystic fibrosis; GD, Gaucher disease; HAA, hemophilia A; HAB, hemophilia B; MPS-III, mucopolysaccharidosis III; OTCD, ornithine transcarbamylase deficiency; PD, Pompe disease; SCD, sickle cell disease; VG, Von Gierke disease.

*Nationally representative estimates obtained using hospital-level discharge weights on data from 4,200 community hospitals.

†Primary expected payer.

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