HHS Public Access

Author manuscript

J Pediatr. Author manuscript; available in PMC 2021 August 01.

Published in final edited form as:

J Pediatr. 2020 August ; 223: 136–140. doi:10.1016/j.jpeds.2020.05.005.

Treatment Discontinuation by 3 Years After Levothyroxine Initiation among Children Diagnosed with Congenital Hypothyroidism

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Abstract

Background: Newborn screening identifies infants with congenital hypothyroidism (CH) for whom levothyroxine (L-T_4) prevents cognitive impairment but also can identify infants with transient hypothyroidism. For some, transient hypothyroidism can be ruled out by thyroid gland imaging; otherwise, it is confirmed when thyroid stimulating hormone (TSH) concentrations remain normal after a supervised trial off L-T_4, typically after age 3 years.

Objectives: To measure the rates of thyroid gland imaging and L-T_4 discontinuation and to assess whether discontinuation was monitored with TSH testing.

Methods: This is a retrospective analysis of claims data from the IBM® MarketScan® Databases for children born during 2010–2016 and continuously enrolled in a non-capitated employer-sponsored private health insurance plan or in Medicaid for ≥36 months from the date of the first filled L-T_4 prescription.

Results: —263 privately-insured and 241 Medicaid-enrolled children met the inclusion criteria. More privately-insured than Medicaid-enrolled children had imaging between the first filled prescription and 180 days after the last filled prescription (24.3% vs. 12.9%; P=0.001). By 36 months, 35.7% discontinued L-T_4, with no difference by insurance status (P=0.48). Among those

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Contributors' Statement

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of Interest: None of the authors have a commercial association that might pose or create a conflict of interest with the information presented in this manuscript.

Prior Presentation

Portions of this work were presented at the 2019 APHL Newborn Screening and Genetic Testing Symposium, Chicago, IL (April 9, 2019).

who discontinued, 29.1% of privately-insured children and 47.7% of Medicaid-enrolled children had no claims for TSH testing within the next 180 days (P=0.01).

Conclusions: Nearly one-third of children with suspected CH discontinued L-T_4 by 3 years and fewer Medicaid-enrolled than privately-insured children received timely follow-up TSH testing. Future studies are indicated to understand the quality of care and developmental outcomes for children with CH and barriers to guideline adherence in evaluating for transient CH.

Introduction

Congenital hypothyroidism (CH) is a preventable cause of intellectual disability that is detected by newborn screening programs in the United States (US) and around the world. Prior to the introduction of CH newborn screening, about 1 in 7,000 children in high-income countries experienced clinical CH, about 30% of whom (1 in 20,000) developed intellectual disability as a result of late-diagnosed or undiagnosed CH; untreated children with subclinical CH experienced lesser degrees of cognitive impairment.[1] Newborn screening identifies about 1 in 2,000 infants with CH in the US, who as a result of timely treatment are not at increased risk of intellectual disability.[1] Although most infants with CH do not initially show clinical signs or symptoms, prevention of long-term intellectual disability requires prompt treatment with thyroid hormone replacement (i.e., levothyroxine [L-T_4]).[2] According to recommendations from the American Academy of Pediatrics, the American Thyroid Association, and the Lawson Wilkins Pediatric Endocrine Society, infants with CH should be treated as soon as possible with L-T_4, ideally within two weeks after birth, with frequent monitoring to adjust dosing and to evaluate growth and development.[3,4] To minimize delays to treatment, guidelines recommend that infants begin care before it is known whether the CH is permanent, which requires long-term treatment, or transient, in which case L-T_4 can be discontinued. Most cases (65–85%) of CH are ultimately classified as permanent. Most often this determination is based on laboratory testing, but in certain circumstances, it can be based on thyroid gland imaging.[5,6] Causes of permanent CH include thyroid dysgenesis, defects in thyroid hormone synthesis, thyroid hormone receptor mutations, and disorders causing hypopituitarism.[7]

When a newborn screening result is outside the normal range, further testing is needed. CH is usually confirmed through laboratory testing that shows the thyroid stimulating hormone (TSH) concentration is elevated and the free thyroxine (FT_4) concentration is low. Infants with elevated TSH but normal FT_4 concentrations on confirmatory testing are also typically considered to have CH and begun on L-T_4, although these infants are more likely to have transient CH. Differentiating between permanent and transient CH can be challenging because of the physiologic postnatal TSH surge, prematurity and other perinatal complications affecting TSH concentration through delayed maturation of the hypothalamic-pituitary axis, and difficulties evaluating other less common causes of transient CH, including increased TSH response to thyroid-releasing hormone, presence of antithyroid antibodies, thyroid morphology abnormalities, and thyroperoxidase or thyrotropin receptor gene sequence variations.[8–11]

Determination of permanent versus transient CH is generally not possible at the time of diagnosis in the newborn.[3] Thyroid imaging (e.g., thyroid ultrasonography, uptake scans with iodine 123 or sodium technetium 99m pertechnetate) can be definitive; if the thyroid gland is ectopic or absent, CH is permanent.[3] However, imaging cannot always predict whether CH will be permanent or transient. Longitudinal TSH testing provides an indirect approach to determining whether CH is permanent. Generally, with normal growth of the child, the L-T_4 requirement will increase, leading to a rise in TSH concentration if the dose is not adjusted, which is suggestive of permanent CH.[3] Alternatively, if after age 3 years, there is still a question of whether CH might be transient (e.g., L-T_4 requirement has not increased with growth as expected), a clinically supervised trial of phasing out or decreasing the dose of L-T_4 during a 4–6 week period that is monitored with TSH testing is recommended.[3,4]

We previously found that between 2001 and 2006, approximately 38% of children with CH no longer had prescriptions for L-T_4 filled by 3 years after initiating treatment based on administrative claims data for privately-insured and Medicaid-enrolled children.[12] This rate of discontinuation raised questions about the degree to which some children did not receive appropriate care, families were not adherent with L-T_4 treatment, or transient CH was more common than suspected.[12] Subsequently, the Michigan Department of Health surveyed endocrinologists regarding the 3-year follow-up of 152 newborns with CH detected between 2003 and 2007 and reported that nearly half (45%) of the children were lost to follow-up.[13] Of the 84 cases with follow-up, 4 had not been evaluated to determine whether they had transient or permanent CH and 8 were in the process of a trial of L-T_4. Among the remaining 72 children, 34 had suspected permanent CH based on either the need for greater doses of L-T_4 or thyroid imaging findings. Among the other 38 children, 23 (61%) had a medically supervised trial of L-T_4 dose reduction or discontinuation, 20 of whom were classified as having permanent CH, and in 15 (39%) the family stopped L-T_4 without a medically supervised trial. The researchers reported that all 15 were clinically deemed as transient cases, with documented laboratory reports for 3 and physician reports of normal TSH concentrations for the other 12. The overall rate of loss to follow-up and the proportion whose family stopped therapy continues to raise concern about long-term follow-up and the potential for suboptimal intellectual outcomes.

The objective of our study is to evaluate the rate of discontinuation of thyroid hormone treatment in a relatively recent cohort of US children treated for CH. In our previous study of discontinuation,[12] we could only describe when children were no longer filling prescriptions for L-T_4 but could not evaluate the proportion of children who had thyroid gland imaging or who had follow-up TSH testing. These are now available to us in the more current claims databases, allowing for a significantly better understanding of thyroid hormone discontinuation. Although the importance of long-term follow-up after newborn screening[14] has been expounded upon since our previous study, we are not aware of any specific efforts targeted specifically to CH. By describing patterns of discontinuation with testing information, these results could inform policy makers and clinicians about opportunities to improve long-term follow-up for CH and reduce the risk of preventable intellectual disability.

Methods

We conducted a retrospective analysis of health insurance claims for children with CH to determine the duration of thyroid hormone replacement with L-T_4 based on prescription refills. For those individuals who no longer had L-T_4 prescriptions after the first three years of L-T_4 treatment, we evaluated whether there were claims for relevant imaging tests or laboratory tests for TSH concentration.

Data Sources

We analyzed claims data from the IBM® MarketScan® Commercial Database from January 1, 2010 through April 30, 2019 and the MarketScan Multi-State Medicaid Database from January 1, 2009 through December 31, 2018. Both databases include inpatient and outpatient encounters with diagnosis and procedure codes and outpatient pharmacy claims. Both include an encrypted enrollee identification number that can be used for longitudinal analysis. The Commercial claims database is a nationwide convenience sample of employer-sponsored private health insurance plans. The Medicaid claims database includes claims data from 8–11 unidentified states, varying by year. We accessed both databases via IBM MarketScan Treatment Pathways 4.0, an online analytic platform using a dynamic version of the data that is stored on IBM Watson Health™ servers and includes plans that report outpatient pharmacy claims.

In order to have complete claims data for each privately-insured subject, we accessed two overlapping Treatment Pathways Commercial samples, one for claims from January 1, 2010 through July 31, 2017 and one with claims from January 1, 2012 through April 30, 2019. We used data from the first sample on births from 2010–2014 and from the second sample on births from 2012–2016, to allow for 3 years of follow-up. Many, but not all, enrollees were included in both samples. The Medicaid database included all years in one file.

Subjects

We classified infants treated for CH based on a first filled outpatient prescription for L-T_4 within 90 days of the first claim associated with a live birth claim and a second filled prescription between 7 and 185 days after the first one. We retained children who were enrolled in the same health plan for at least 36 months in non-capitated plans from the date of the first L-T_4 claim. Records for individuals with presumed CH were exported and merged in a spreadsheet file, then deduplicated on the basis of enrollee identification number.

To protect subject confidentiality, birth year, but not exact birth date, is available in MarketScan research databases. No information is available regarding race/ethnicity in the Commercial data. No information on the clinicians who established diagnoses, provided prescriptions, or ordered laboratory tests is available in either Commercial or Medicaid data.

Thyroid Imaging, L-T_4 Discontinuation, and Follow-up TSH Testing

Thyroid imaging testing was based on claims at any date with procedure codes 78000–78014 for either thyroid imaging or thyroid uptake nuclear medicine imaging, along with

76536 for ultrasound imaging of the soft tissues of the neck, including the thyroid gland. We calculated the date of L-T_4 discontinuation as the last day of a filled prescription within the study period plus the days supplied by that prescription. Follow-up TSH testing was based on claims for TSH testing (procedure codes 84443, 80438, and 80439) within 180 days after the date of the last filled prescription.

Data Analysis

Chi-squared tests of association were used to evaluate categorical data and the Kruskal-Wallis test was used to evaluate differences in medians for the time to TSH testing. Kaplan-Meier analysis was used to evaluate the rate of continuation of L-T_4 since initiation. All analyses were conducted with Stata statistical Software (College Station, TX). We considered differences with $P<0.05$ to be statistically significant.

Results

Study Population

In the private insurance database, we identified 667 infants out of 1,187,981 live births during 2010–2014 (birth prevalence of 1:1,781) who met the case definition for presumed CH (i.e., ≥2 filled prescriptions for L-T_4). Similarly, we identified 649 infants with presumed CH out of 1,034,439 live births during 2012–2016 (birth prevalence of 1:1,594). After deduplication, 263 children were enrolled for at least 36 months in non-capitated private health insurance plans. In the Medicaid database, we identified 587 infants out of 728,417 live births (birth prevalence of 1:1,241) who met the case definition for presumed CH, of whom 241 children were enrolled for at least 36 months in non-capitated Medicaid health insurance plans.

Thyroid Gland Imaging

Privately-insured children treated with L-T_4 were about twice as likely to have received imaging at any time as those in the Medicaid database, 24.3% vs. 12.9% (P=0.001).

Discontinuation Rates

The figure presents the Kaplan-Meier curve for continuation of L-T_4 treatment. By 3 years after treatment initiation, 32.7% of privately-insured children and 35.7% of Medicaid-enrolled children had discontinued thyroid hormone treatment (P=0.48). Of those who discontinued L-T_4, more than half of the privately-insured and Medicaid-enrolled children did so between 2 and 3 years after treatment initiation (65.1% vs. 58.1%; P=0.21).

Discontinuation and Follow-up TSH Testing

Among those who discontinued L-T_4 prior to 3 years, 29.1% of those with private insurance and 47.7% enrolled in Medicaid did not have a TSH test in the 180 days following the date of the last filled prescription (P=0.01). For those who did have a TSH test in the next 180 days, the median number of days and interquartile range (IQR) did not differ (P=0.51) for those with private insurance (63; IQR: 38–89) and those enrolled in Medicaid (59; 41–89). The likelihood of having follow-up TSH testing within 180 days did not vary by the age of

discontinuation (privately-insured: P=0.68, Medicaid-enrolled: P=0.74). For privately-insured children, having a TSH test within 180 days was associated with an increased likelihood of receiving thyroid gland imaging (29.5% vs. 8%; P=0.03) but not for Medicaid-enrolled children (8.9% vs. 7.3%; P=0.79).

Discussion

Clinical guidelines for the management of CH after newborn screening underscore the importance of close medical management, including TSH assessment soon after discontinuation of L-T_4. Similar to our previous study of claims data from 2001–2006,[12] we found that about one-third of children with CH discontinued thyroid hormone treatment by 3 years. This rate is higher than the generally expected rate of transient CH,[6] although consistent with some clinical observations.[5] Of children in the present study who stopped treatment, nearly one-third of privately-insured children and one-half of Medicaid-enrolled children did not have TSH testing within the subsequent 180 days. For all children with CH, the rate of thyroid gland imaging was fairly low, which is consistent with the US clinical guidelines that do not call for routine imaging.[3] The proportion with thyroid imaging claims was about twice as high for privately-insured children compared to those enrolled in Medicaid.

For this analysis, we relied on a large administrative claims database since there is no US registry of patients with CH. While claims data have inherent limitations, a retrospective study within individual clinics is not feasible because children with CH can be taken care of by a variety of clinician types (e.g., pediatric endocrinologists, adult endocrinologists, pediatricians, family physicians).[15] Survey studies of outcomes following newborn screening have been limited by low response rates.[13] In particular, families of patients who no longer receive active CH management might be less likely to respond or to provide valid information.

One interesting observation while conducting this analysis is that the rate of thyroid imaging appeared to vary by census divisions from 2012–2016, with the highest rate in the Mountain states and the lowest rate in the Pacific states (40% vs. 8%). We chose not to include this finding in the formal analysis because of incomplete data across all subjects and the overall small sample size. This finding may reflect regional variation in the approach to CH management and further emphasizes the need to understand care delivery at the local level.

One possible future opportunity to better understand care delivery for children with CH is to analyze linked administrative health, education, and newborn screening records for multiple years of births. For example, one report described two separate analyses based on linking newborn screening records on 362,390 births in metropolitan Atlanta, Georgia during 1981–1991 with surveillance data on developmental disabilities and linking data on 520,625 children born 1981–1995 to special education records.[16] Another study linked newborn screening records for 354,137 children born in New South Wales, Australia during 1994–2002 to education records and records for 149,569 children born during 2002–2008 to developmental assessments.[17] However, neither study was able to assess the impact of treatment patterns on outcomes. The metropolitan Atlanta study reported that one of the two

children with confirmed CH who accessed speech and language therapy services was non-adherent to treatment, but the investigators were unable to access clinical data for the majority of children with CH.[16]

We cannot directly determine the degree to which each case of discontinuation of treatment prior to 3 years was appropriate or whether there was any harm associated with stopping L-T_4. Newborn screening is highly sensitive and, therefore, by design should identify some infants with transient CH for whom stopping treatment is appropriate. In fourteen states, infants are routinely screened a second time at around two weeks of age.[18–20] Most (75–80%) of the infants identified only on the second screen have transient CH, suggesting this subpopulation may be more likely to discontinue L-T_4 and have subsequent reassuring TSH concentrations.[6,18] We are unable to determine in this analysis whether an infant was identified with a first or second newborn screening test.

Newborn screening also identifies many infants with subclinical CH.[1] Whether stopping treatment for children with subclinical CH might be appropriate is unclear,[21] particularly since one study from Australia reported that children with TSH concentrations that fell slightly below the newborn screening cutoff had higher risk of poorer educational and developmental outcomes than those with TSH concentrations above the screening cutoff, who were presumably treated.[17]

There are several limitations to this study. Most importantly, there are limitations to the use of claims data; we do not have laboratory or imaging results or clinical notes, so we cannot comment on whether laboratory or imaging results were appropriately acted upon or whether those who discontinued treatment were more likely to have transient or subclinical CH. It is important to recognize that even when TSH testing occurred after L-T_4 discontinuation, we cannot determine whether this was in the context of a medically supervised trial of treatment discontinuation. This study cannot predict the degree to which inappropriate discontinuation occurs or the number of children who might be adversely affected. We have limited demographic information and no specific information about the healthcare providers. Health plan enrollment attrition also limited the total number of children who could be followed for 3 years. However, we set a low standard for evidence of follow-up testing to identify the minimum potential magnitude of problems related to unmonitored discontinuation, and nearly all children continued to be enrolled in their insurance plans for 180 days following discontinuation of L-T_4.

Despite these limitations, these results signal that a substantial number of children, with more enrolled in Medicaid than privately insured, may not receive recommended care, potentially putting them at risk for intellectual impairment. This study underscores the need for new approaches to monitor long-term outcomes following newborn screening, such as integrated electronic health record systems with such monitoring capabilities.[22] Newborn screening for CH can achieve its goal of optimizing child health and development if clinicians and families work together to assure that those children who need it continue to receive medical management for the condition.

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Acknowledgments

Funding: None

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Abbreviations:

CH	congenital hypothyroidism
TSH	thyroid stimulating hormone
T4	thyroxine
FT_4	free thyroxine
L-T_4	levothyroxine
US	United States

References

1. Grosse SD, Van Vliet G. Prevention of intellectual disability through screening for congenital hypothyroidism: how much and at what level? Arch Dis Child 2011;96:374–379. [PubMed: 21242230]
2. Oerbeck B, Sundet K, Kase BF, Heyerdahl S. Congenital hypothyroidism: influence of disease severity and L-thyroxine treatment on intellectual, motor, and school-associated outcomes in young adults. Pediatrics 2003;112:923–930. [PubMed: 14523187]
3. American Academy of Pediatrics, American Thyroid Association, Lawson Wilkins Pediatric Endocrine Society. Update of newborn screening and therapy for congenital hypothyroidism. Pediatrics 2006;117:2290–2303. [PubMed: 16740880]
4. Leger J, Oliveri A, Donaldson M, Torresani T, Krude H, van Vliet G, et al. European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. J Clin Endocrinol Metab 2014;99:363–384. [PubMed: 24446653]
5. Eugster EA, LeMay D, Zerin JM, Pescovitz OH. Definitive diagnosis in children with congenital hypothyroidism. J Pediatr 2004;144:643–647. [PubMed: 15127002]
6. Ford GA, Denniston S, Sesser D, Skeels MR, LaFranchi SH. Transient versus permanent congenital hypothyroidism after the age of 3 years in infants detected on the first versus second newborn screening test in Oregon, USA. Horm Res Paediatr 2016;86:169–177. [PubMed: 27595483]
7. Rastogi MV, LaFranchi SH. Congenital hypothyroidism. Orphanet J Rare Dis 2010;5:17. [PubMed: 20537182]
8. Brown RS, Bellisario RL, Botero D, Fournier L, Abrams CA, Cowger ML, et al. Incidence of transient congenital hypothyroidism due to maternal thyrotropin receptor-blocking antibodies in over one million babies. J Clin Endocrinol Metab 1996;81:1147–1151. [PubMed: 8772590]
9. Calaciura F, Motta RM, Miscio G, Fichera G, Leonardi D, Carla A, et al. Subclinical hypothyroidism in early childhood: a frequent outcome of transient neonatal hyperthyrotropinemia. J Clin Endocrinol Metab 2002;87:3209–3214. [PubMed: 12107226]
10. Srinivasan R, Harigopal S, Turner S, Cheetham T. Permanent and transient congenital hypothyroidism in preterm infants. Acta Paediatr 2012;101:e179–182. [PubMed: 22107264]

11. Woo HC, Lizarda A, Tucker R, Mitchell ML, Vohr B, Oh W, et al. Congenital hypothyroidism with a delayed thyroid-stimulating hormone elevation in very premature infants: incidence and growth and developmental outcomes. J Pediat. 2011;158:538–542. [PubMed: 21232766]
12. Kemper AR, Ouyang L, Grosse SD. Discontinuation of thyroid hormone treatment among children in the United States with congenital hypothyroidism: findings from health insurance claims data. BMC Pediatr 2010;10:9. [PubMed: 20156344]
13. Korzeniewski SJ, Grigorescu V, Kleyn M, Young WI, Birbeck G, Todem D, et al. Transient hypothyroidism at 3-year follow-up among cases of congenital hypothyroidism detected by newborn screening. J Pediatr 2013;162:177–182. [PubMed: 22878110]
14. Kemper AR, Boyle CA, Aceves J, Dougherty D, Figge J, Fisch JL, et al. Long-term follow-up after diagnosis resulting from newborn screening: Statement of the US Secretary of Health and Human Services' Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. Genet Med 2008; 10:259–261. [PubMed: 18414208]
15. Rosenthal NA, Bezar E, Mann S, Bachrach LK, Banerjee S, Geffner ME, et al. Primary care provider management of congenital hypothyroidism identified through newborn screening. Ann Thyroid Res 2017;3:95–101. [PubMed: 28868522]
16. Van Naarden Braun K, Yeargin-Allsopp M, Schendel D, Fernhoff P. Long-term developmental outcomes of children identified through a newborn screening program with a metabolic or endocrine disorder: a population-based approach. J Pediatr 2003;143:236–242. [PubMed: 12970640]
17. Lain SJ, Bentley JP, Wiley V, Roberts CL, Jack M, Wilcken B, et al. Association between borderline neonatal thyroid-stimulating hormone concentrations and educational and developmental outcomes: a population-based record-linkage study. Lancet Diabetes Endocrinol 2016;4:756–765. [PubMed: 27453174]
18. Pitts L, McCormick W, Mick GJ. Congenital Hypothyroidism: 8-year experience using 2 newborn screens in Alabama. Horm Res Paediatr 2019;91:319–328. [PubMed: 31390650]
19. Jones DE, Hart K, Shapira SK, Murray M, Atkinson-Dunn R, Rohrwasser A. Identification of primary congenital hypothyroidism based on two newborn screens - Utah, 2010–2016. MMWR Morb Mortal Wkly Rep 2018;67:782–785. [PubMed: 30024866]
20. Shapira SK, Hinton CF, Held PK, Jones E, Harry Hannon W, Ojodu J. Single newborn screen or routine second screening for primary congenital hypothyroidism. Mol Genet Metab 2015;116:125–132. [PubMed: 26293295]
21. Lain S, Trumpff C, Grosse SD, Olivieri A, Van Vliet G. Are lower TSH cutoffs in neonatal screening for congenital hypothyroidism warranted? Eur J Endocrinol 2017;177:D1–D12. [PubMed: 28694389]
22. Kemper AR, Boyle CA, Brosco JP, Grosse SD. Ensuring the life-span benefits of newborn screening. Pediatrics 2019; 144:e20190904. [PubMed: 31694980]

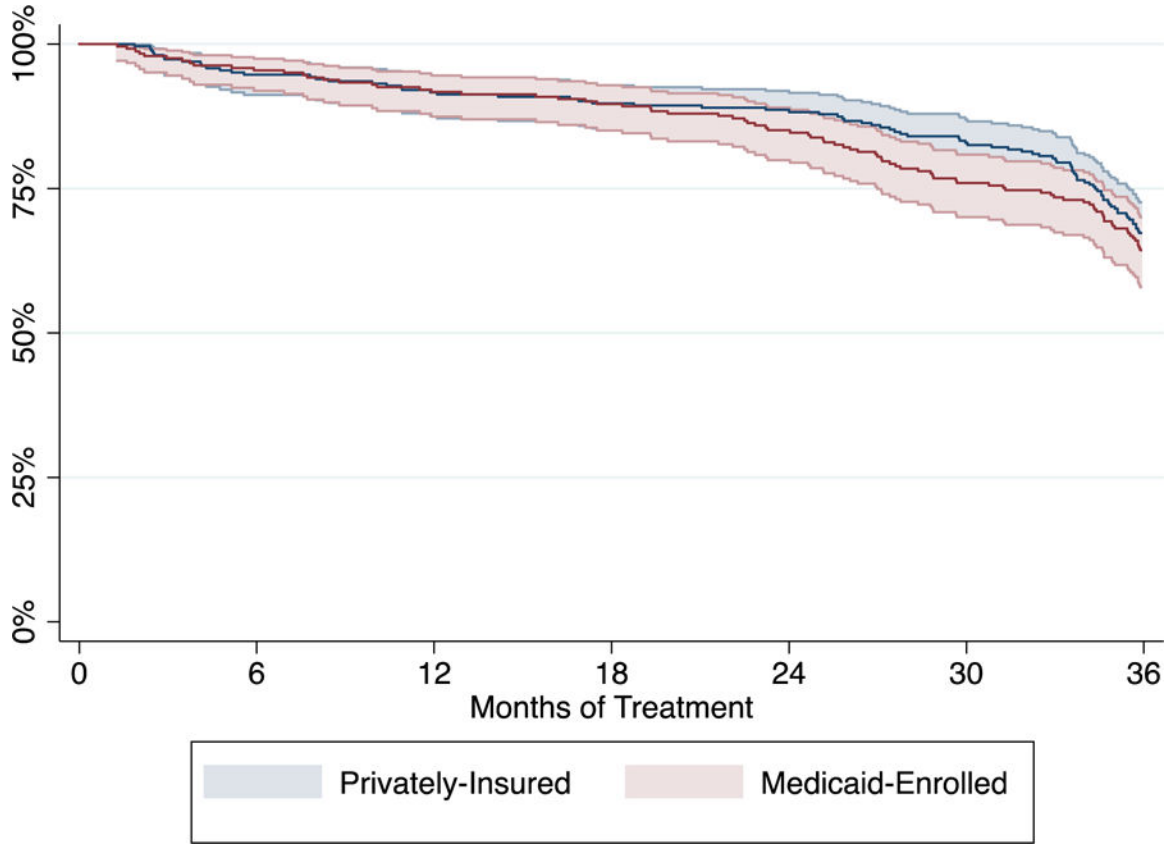

Figure.

Proportion of subjects receiving thyroid hormone treatment over time stratified by insurance status. The shaded area is the 95% confidence interval.