ORIGINAL ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Out-of-Pocket Medical Costs and Third-Party Healthcare Costs for Children With Down Syndrome

Andrew Kageleiry,[1] David Samuelson,[1] Mei Sheng Duh,[1] Patrick Lefebvre,[2] John Campbell,[3] and Brian G. Skotko[4,5]*

[1]Analysis Group, Inc., Boston, Massachusetts

[2]Groupe d'analyse, Ltée, Montréal, Quebec, Canada

[3]Department of Economics, Harvard University, Cambridge, Massachusetts

[4]Division of Medical Genetics, Department of Pediatrics, Massachusetts General Hospital, Boston, Massachusetts

[5]Harvard Medical School, Boston, Massachusetts

Manuscript Received: 24 June 2016; Manuscript Accepted: 27 October 2016

Prior analyses have estimated the lifetime total societal costs of a person with Down syndrome (DS); however, no studies capture the expected medical costs that patients with DS can expect to incur during childhood. The study utilized the OptumHealth Reporting and Insights administrative claims database from 1999 to 2013. Children with a diagnosis of DS were identified, and their time was divided into clinically relevant age categories. Patients with DS in each age category were matched to controls without chromosomal conditions. Out-of-pocket medical costs and third-party expenditures were compared between the patient-age cohorts with DS and matched controls. Patients with DS had significantly higher mean annual out-of-pocket costs than their matched controls within each age and cost category. Total annual incremental out-of-pocket costs associated with DS were highest among individuals from birth to age 1 ($1,907, $P < 0.001$). The main drivers of the incremental out-of-pocket costs associated with DS were inpatient costs in the 1st year of life ($925, $P < 0.001$) and outpatient costs in later years (ranging $183–$623, all $P < 0.001$). Overall, patients with DS incurred incremental out-of-pocket medical costs of $18,248 between birth and age 18 years; third-party payers incurred incremental costs of $230,043 during the same period. Across all age categories, mean total out-of-pocket annual costs were greater for individuals with DS than those of matched controls. On average, parents of children with DS pay an additional $84 per month for out-of-pocket medical expenses when costs are amortized over 18 years. © 2016 Wiley Periodicals, Inc.

Key words: Down syndrome; children; out-of-pocket costs; third-party payers

How to Cite this Article:
Kageleiry A, Samuelson D, Duh MS, Lefebvre P, Campbell J, Skotko BG. 2016. Out-of-pocket medical costs and third-party healthcare costs for children with Down syndrome.
Am J Med Genet Part A 9999A:1–11.

INTRODUCTION

With prenatal testing for Down syndrome (DS) rapidly evolving, an increasing number of expectant couples must make decisions about their pregnancy options, often with limited time and information [Skotko, 2005]. Among the many questions asked: How expensive is it to raise a child with DS? Can our family afford to pay for the medical expenses? What can we reasonably expect to be covered by our medical insurance provider? While the decision to continue or terminate a pregnancy often involves complex considerations, accurate and up-to-date information on health care expenditures is an important element for some families.

Since October 2011, noninvasive prenatal screening (NIPS), utilizing plasma cell-free DNA, has enabled expectant couples to learn as early as 9 weeks into gestation whether their fetus might have DS [Bianchi et al., 2012; Nicolaides et al., 2012; Norton et al., 2012; Zimmermann et al., 2012]. As research continues, marketing widens, and insurance coverage expands, more expectant women will have access to NIPS, inevitably leading to a greater number of couples receiving a prenatal diagnosis of DS.

Andrew Kageleiry and David Samuelson are co-first authors.
Abbreviations: CPI, Consumer Price Index; DS, Down syndrome; HMO, Health maintenance organization; NIPS, Noninvasive prenatal screening; POS, Point of service; PPO, Preferred provider organization.

*Correspondence to:
Brian Skotko, M.D., M.P.P., Massachusetts General Hospital, 185 Cambridge Street, Room 2222, Boston, MA 02114.
E-mail: bskotko@mgh.harvard.edu

Article first published online in Wiley Online Library (wileyonlinelibrary.com): 00 Month 2016
DOI 10.1002/ajmg.a.38050

Researchers have made arguments that prenatal testing for DS is cost effective, and their calculations generally include an incremental lifetime cost of raising a child with DS (i.e., the excess lifetime cost compared to a typically developing child) [Ball et al., 2007; Cuckle et al., 2013; Song et al., 2013]. Ball et al. [2007] concluded that the incremental "societal cost of raising and caring for an individual with DS is $762,748," adjusted to 2006 USD. Song et al. [2013] more recently stated that the incremental "cost of Down syndrome" was $677,000 in 2012 USD, with a range that could be as high as $800,000 over a lifetime. Cuckle et al. [2013] price the lifetime incremental costs around $900,000 in 2013 USD. All of these papers, however, draw their data from the same primary source where incremental *direct* costs (e.g., extra expenses from inpatient hospital stays, outpatient medical visits, long-term care, developmental services, and special education) and *indirect* costs (e.g., lost productivity due to morbidity and early mortality) were estimated for "the entire lifespan" for persons with DS born in California in 1988 [Waitzman et al., 1994]. This study is now dated and demographically non-applicable to many parts of the United States. Perhaps most importantly, these studies estimated *societal* costs (relevant for cost-effectiveness and cost-benefit studies) and not *individual* costs, which are likely of greater interest to expectant parents.

Few studies have estimated such costs. According to the 2009–2010 National Survey of Children with Special Healthcare Needs, approximately 23.6% of families who have a child with DS reported that they pay $1,000 or more in out-of-pocket medical expenses each year [Child and Adolescent Health Measurement Initiative, 2009/2010]. About 32% of these families reported that DS "caused financial problems for the family" [Child and Adolescent Health Measurement Initiative, 2010/2009]. Based on the paucity of such information in the existing literature, the primary purpose of this study is to use a large database to estimate the incremental out-of-pocket medical costs for patients with DS, between birth to 18 years of age, in the United States. We also calculate the total health care expenditures for private third-party payers in order to provide updated data for policymakers and other key stakeholders.

MATERIALS AND METHODS

Data

This retrospective matched-cohort study was conducted utilizing data from the OptumHealth Reporting and Insights database. The data are based on administrative claims for privately insured individuals covered by 82 self-insured Fortune 500 companies with operations in a broad array of industries and job classifications across the United States. The OptumHealth database contains medical claims (dates of service, diagnoses received, procedures performed, places of service, and payment amounts), outpatient pharmacy claims (fill dates, national drug codes, and payment amounts), and eligibility information (patient demographics and enrollment history) for over 18 million individuals, including primary subscribers as well as their covered beneficiaries (i.e., spouses and dependents). The database covers the period from Q1 1999 to Q1 2013 and has been cited frequently in numerous peer-reviewed studies of medical costs [Loftus et al., 2014; Rice et al., 2014a,b; Tandon et al., 2014].

Patient Selection

Patients with at least one medical claim associated with a diagnosis of DS (ICD-9-CM code: 758.0x) were eligible for inclusion in the study cohort. Patients were also required to be enrolled in their family insurance plan as a child (i.e., <18 years of age) and to have an identifiable mother and/or father on the insurance plan (formally designated as the "plan subscriber" or "spouse of the subscriber"). Patients were further required to have discernible demographic, enrollment, and parental characteristics which were used in a later matching algorithm.

Individuals without any diagnoses for chromosomal conditions (ICD-9-CM code: 758.xx) in their observable medical claims were eligible for inclusion as potential controls. These patients were also required to be enrolled as children, have an identifiable mother and/or father, and have the same aforementioned characteristics to be used in the matching algorithm.

The current study was conducted to estimate the incremental yearly medical and pharmacy out-of-pocket costs incurred by patients with DS relative to controls without DS across a number of different developmental time periods. Accordingly, the period of observation during which patients were enrolled in their insurance plan was split into clinically relevant age categories. Following the American Academy of Pediatrics healthcare guidelines for patients with DS, the following time periods were studied: <1 year old, 1 to <3 years old, 3 to <5 years old, 5 to <13 years old, and 13 to <18 years old [Bull, 2011]. After selection, patients in both the study and potential control cohorts were assigned to one or more age categories depending on the period during which they were enrolled in their insurance plan. For individuals with more than one continuous enrollment period, only the first was selected, regardless of length; patients who were continuously enrolled across multiple age groups were assigned to each of the respective groups (Fig. 1).

Matching Algorithm

To control for observable confounding factors, a greedy matching algorithm was used to match, in a one-to-four ratio, individuals within each observed age category in the study cohort ("patient-age observations") to patients within the same age group in the potential control [Miettinen, 1969; Bergstralh and Kosanke, 1995, 2004]. Greedy matching randomly locates study-control pairs that meet a pre-specified set of criteria; this method is distinct from optimal matching algorithms in that it maximizes sample size while also reducing selection bias [Parsons, 2001]. Patient-age observations were matched exactly on gender, length of continuous eligibility within an age group (±180 days), the calendar year (exact), and their age (±1 year) at the beginning of continuous eligibility within an age group and the average age of their parent(s) at the time of their birth (±1 year). Such parental characteristics were included in the matching algorithm to control for differences in factors that may affect a parent's choice for his or her child's medical care. Additionally, an unconditional logistic regression propensity score was estimated for each patient-age observation, modeling the likelihood of a patient-age observation being in the DS cohort. Controlling for the patient's demographic region, parental health insurance plan type and parental work industry,

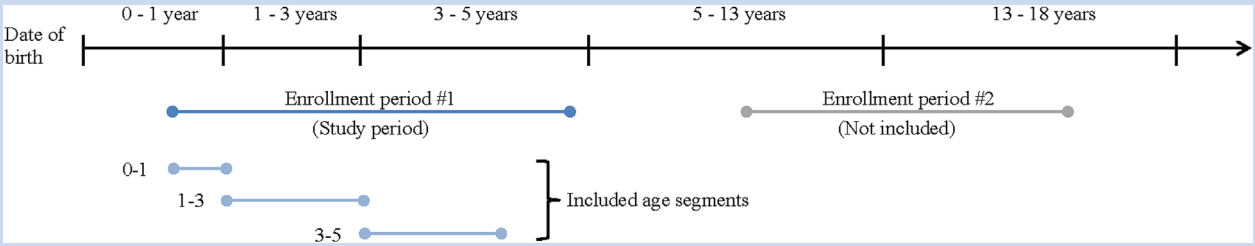

FIG. 1. In this example, a person with Down syndrome was enrolled in an insurance plan during two separate continuous periods. Only the first enrollment period was used for our calculations; data were included in the 0 to <1, 1 to <3, and 3 to <5 age segments. [Color figure can be viewed at wileyonlinelibrary.com].

patient-age observations in the DS, and potential control group were required to match to within a quarter of a standard deviation of the estimated propensity score.

Outcomes

Following the matching process, average yearly health care utilization costs were calculated for each patient within each age group. Using all medical and pharmacy claims during the relevant age ranges, costs included all out-of-pocket co-pay and co-insurance payments to measure the direct, real-world costs incurred by patients and their parents. All costs were adjusted to 2013 USD using the medical care component of the Consumer Price Index (CPI); costs were annualized over the entire relevant age period by summing all incurred costs (by category) and dividing by the length of the individual's continuous eligibility within the age group [United States Bureau of Labor Statistics, 2014]. A similar approach was used to assess the mean annual costs to private third-party payers (insurers), by measuring all of such incurred payments for the same medical care received by the selected patients. For this analysis, the real-world costs reimbursed by insurers were summarized; these values will differ from the initial amounts charged by healthcare providers.

Statistical Analyses

Prior to matching, descriptive characteristics were compared between study and potential control individuals. Comparisons employed Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables. Following the matching process, individuals with DS and their matched controls were compared within each observed age category on a subset of the same descriptive characteristics. These comparisons utilized Wilcoxon signed-rank tests for continuous variables and McNemar tests for categorical variables.

Average yearly health care utilization costs (both to patients and third-party payers) were compared between the respective patient-age cohorts with DS and matched control individuals. Cost categories included inpatient, outpatient, emergency room, home health agency, and other medical costs (e.g., laboratory/pathology costs). Pharmacy costs were also summarized separately. All cost dimensions were compared using Wilcoxon signed-rank tests.

All analyses were performed using SAS Version 9.3 (SAS Institute, Cary, NC), and statistical significance was evaluated at the 0.05 level (two-sided).

RESULTS

Patient Selection and Characteristics

A total of 5,167 individuals with DS and 5,673,804 individuals without chromosomal conditions were initially selected after all inclusion/exclusion criteria were applied (Table I). A majority of patients in each initial group had both an identifiable mother and father. Patients in the study cohort and potential control groups differed on a number of dimensions (Table II). A greater number of identified patients with DS were male (54.1% vs. 51.1%, $P < 0.001$); these individuals also had significantly longer continuous follow-up time in their selected observation period (4.05 vs. 2.83 years, $P < 0.001$). Patients in the study cohort also had parents with a significantly greater average age at the time of their birth compared to the initial control group (33.53 vs. 30.12 years, $P < 0.001$). Patients in the two initial groups also differed on a number of other demographic factors, such as region, insurance plan type, and other parental characteristics.

Following the matching process, patients were compared within patient-age groups on a similar set of demographic characteristics. These patient-age cohorts were found to be statistically similar on most dimensions, where most remaining statistical differences were not clinically meaningful (see Supplementary Materials).

Out-of-Pocket Costs for Patients With DS

Across all age categories, mean total out-of-pocket annual costs were found to be greater among individuals with DS compared to their matched controls. In terms of incremental costs, annual out-of-pocket payments incurred by the cohort with DS relative to controls without DS were found to be $1,907 higher per year for children <1 year old; $1,673 higher per year for children 1 to <3 years old; $1,263 higher per year for children 3 to <5 years old; $973 higher per year for children 5 to <13 years old; and $537 higher per year for patients 13 to <18 years old (all $P < 0.001$, Fig. 2). Patients with DS were also found to have significantly higher mean annual out-of-pocket costs than their matched controls within individual

TABLE I. Selection of Individuals With DS and Individuals Without Chromosomal Anomalies

Selection criteria		Count	
Selection of individuals with DS (pre-match study group)			
Step 0.	All beneficiaries	18,028,545	
Step 1.	Identify individuals with at least one diagnosis for DS[a,b]	7,918	
Step 2.	Identify children with co-enrolled parent		
	a) Individual is enrolled as a child[c]	5,230	
	b) Individual has an identifiable mother and/or father[d,e]	5,167	
		Mother: 4,879	Father: 4,621
Selection of individuals without DS (pre-match potential control group)			
Step 0.	All beneficiaries	18,028,545	
Step 1.	Identify individuals without any diagnoses for chromosomal anomalies[a,f]	18,008,380	
Step 2.	Identify children with co-enrolled parent		
	a) Individual is enrolled as a child[c]	5,739,023	
	b) Individual has an identifiable mother and/or father[d,e]	5,673,804	
		Mother: 5,230,957	Father: 4,998,205

DS, Down syndrome.
[a]Diagnoses assessed in medical claims from Q1 1999 to Q1 2013.
[b]DS was defined as ICD-9-CM: 758.0x.
[c]Individual was classified as a child of a beneficiary on their insurance enrollment.
[d]The oldest woman/man classified as a subscriber or spouse on a family insurance enrollment is assumed to be the mother/father (respectively).
[e]Individuals are also required to have identifiable information used in matching, including gender, date of birth, region, insurance plan type, and parent work industry.
[f]Chromosomal anomalies were defined as ICD-9-CM: 758.xx.

cost categories for all age groups. The greatest incremental costs were found to be inpatient costs in the 1st year of life ($1,183 vs. $259, incremental: $925, $P < 0.001$) and outpatient costs in later years (incremental costs ranging $183–$623, all $P < 0.001$) (Table III). Incremental out-of-pocket pharmacy expenditures and emergency room costs were smaller and similar across all age groups for patients with DS.

The total incremental cost incurred to patients with DS between birth and age 18 can be calculated assuming that incremental costs within each age category are constant for each year within that time period. This approach suggests that individuals with DS are observed to incur incremental out-of-pocket medical costs of $18,248 between birth and age 18 years when compared to similar individuals without chromosomal conditions. When the costs are amortized over 18 years, parents who have children with DS pay, on average, an additional $84 per month for medical expenses.

Total Healthcare Expenditures to Third-Party Payers

Across all age categories, mean total healthcare expenditures were found to be significantly greater among individuals with DS compared to their matched controls. The annual incremental costs associated with DS incurred to third-party payers were found to be $80,864 per year for children <1 year old; $18,950 per year for children 1 to <3 years old; $11,228 per year for children, 3 to <5 years old; $7,586 per year for children, 5 to <13 years old; and $5,627 per year for patients, 13 to <18 years old (all $P < 0.001$, see Table IV). The total incremental cost incurred to third-party payers for patients with DS between birth and age 18 can be calculated assuming that incremental costs within each age category are constant for each year within that time period. This approach suggests that individuals with DS are observed to incur incremental total healthcare expenditures of $230,043 between birth and age 18 years when compared to similar individuals without chromosomal conditions. When the costs are amortized over 18 years, third-party companies pay, on average, an additional $1,065 per month for medical expenses for persons with DS.

DISCUSSION

Caregivers who have children with DS paid, on average, an additional $18,248 in out-of-pocket medical expenses when compared to parents of children without DS between the ages of birth to 18 years. When amortized over this time period, this amounts to an extra $84 per month. These medical expenses included inpatient costs, outpatient costs, emergency room visits, home health agency costs, and outpatient pharmacy costs. The most costly services were inpatient costs in the 1st year of life when the need for surgery is greatest. During this time, approximately 40–50% of infants with DS are identified as having a cardiac condition, many of whom will need surgical repair [Bull, 2011]. Gastrointestinal complications such as a tracheoesophageal fistula, duodenal obstruction, Hirschsprung disease, and an imperforate anus may also necessitate surgery [Freeman et al., 2009]. Likewise, cataracts can also occur during this timeframe, requiring surgical correction by an ophthalmologist [Creavin and Brown, 2009]. Still others develop infantile spasms, requiring hospitalization for medication control of their seizures

TABLE II. Baseline Characteristics Among Individuals With DS and Potential Controls, Before Matching

	Study group (N = 5,167)	Control group (N = 5,673,804)	*P*-value[a]
Descriptive characteristics			
Male, n (%)	2,795 (54.1%)	2,899,244 (51.1%)	<0.001*
Age at earliest enrollment[b] (years), mean ± SD	9.61 ± 10.85	9.87 ± 7.79	<0.001*
Region, n (%)			
Northeast	863 (16.7%)	1,049,800 (18.5%)	<0.001*
Midwest	1,347 (26.1%)	1,283,872 (22.6%)	<0.001*
South	1,731 (33.5%)	2,002,110 (35.3%)	0.007*
West	844 (16.3%)	1,105,953 (19.5%)	<0.001*
Unknown	382 (7.4%)	232,069 (4.1%)	<0.001*
Insurance plan type, n (%)			
Health maintenance organization (HMO)	559 (10.8%)	952,641 (16.8%)	<0.001*
Indemnity	578 (11.2%)	347,075 (6.1%)	<0.001*
Point of service (POS)	993 (19.2%)	1,143,764 (20.2%)	0.09*
Preferred provider organization (PPO)	2,760 (53.4%)	2,830,818 (49.9%)	<0.001*
Other	277 (5.4%)	399,506 (7.0%)	<0.001*
Family characteristics			
Identifiable mother	4,879 (94.4%)	5,230,957 (92.2%)	<0.001*
Identifiable father	4,621 (89.4%)	4,998,205 (88.1%)	0.003*
Average age of parents at individual's birth[c] (years), mean ± SD	33.53 ± 6.47	30.12 ± 6.74	<0.001*
Age of mother at individual's birth	32.78 ± 6.59	29.29 ± 6.64	<0.001*
Age of father at individual's birth	34.42 ± 6.85	31.45 ± 7.15	<0.001*
Parent work industry, n (%)			
Financial services	686 (13.3%)	752,855 (13.3%)	0.99*
Healthcare	350 (6.8%)	434,635 (7.7%)	0.02*
Manufacturing/energy	823 (15.9%)	853,008 (15.0%)	0.07*
Retail/consumer goods	399 (7.7%)	600,057 (10.6%)	<0.001*
Shipping/transportation	913 (17.7%)	995,923 (17.6%)	0.83*
Technology	1,311 (25.4%)	1,543,845 (27.2%)	0.003*
Other	685 (13.3%)	493,481 (8.7%)	<0.001*
Years of continuous follow-up			
Years, mean ± SD	4.05 ± 3.31	2.83 ± 2.93	<0.001*
Year category, n (%)			
≥1 year	4,078 (78.9%)	3,557,799 (62.7%)	<0.001*
≥2 years	3,401 (65.8%)	2,632,686 (46.4%)	<0.001*
≥5 years	1,491 (28.9%)	964,866 (17.0%)	<0.001*
≥10 years	387 (7.5%)	238,195 (4.2%)	<0.001*

DS, Down syndrome; SD, standard deviation.
* *P*-value <0.05.
[a] *P* values were calculated using Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables.
[b] Among patients with more than one continuous enrollment period, the earliest period was selected for the study.
[c] Age is an average of both parents' age at child's birth when both parents are identifiable; if only one parent is identified, that age is included. Age of mother/father at child birth is only reported among patients for whom that parent is identified.

[Arya et al., 2011]. Inpatient costs decrease as children age, consistent with the fact that children with DS develop fewer medical conditions requiring hospitalizations, as they get older.

Incremental out-of-pocket costs for outpatient visits, emergency room visits, home health agency utilization, and pharmacy costs were not substantial and were not meaningfully different between patients with DS of varying ages. Nonetheless, these costs were still greater for the study group than controls without DS, likely reflecting the additional co-pays that are associated with multidisciplinary outpatient appointments for patients with DS. Many children with DS are included as secondary subscribers under their parents' employer-subsidized healthcare plans. To this extent, those families who have higher deductibles might end up having more out-of-pocket expenses simply because children with DS typically have more outpatient appointments than neurotypically developing peers have. Children and adolescents with non-mosaic DS are also automatically eligible for Medicaid as either a primary or secondary healthcare insurance; however, co-pays can vary based on parental income and differing state regulations. For example, a single-parent, low-income household might have all of the out-of-pocket healthcare expenditures for a child with DS covered by Medicaid; whereas, a middle-income household might have a monthly co-pay for the same Medicaid coverage.

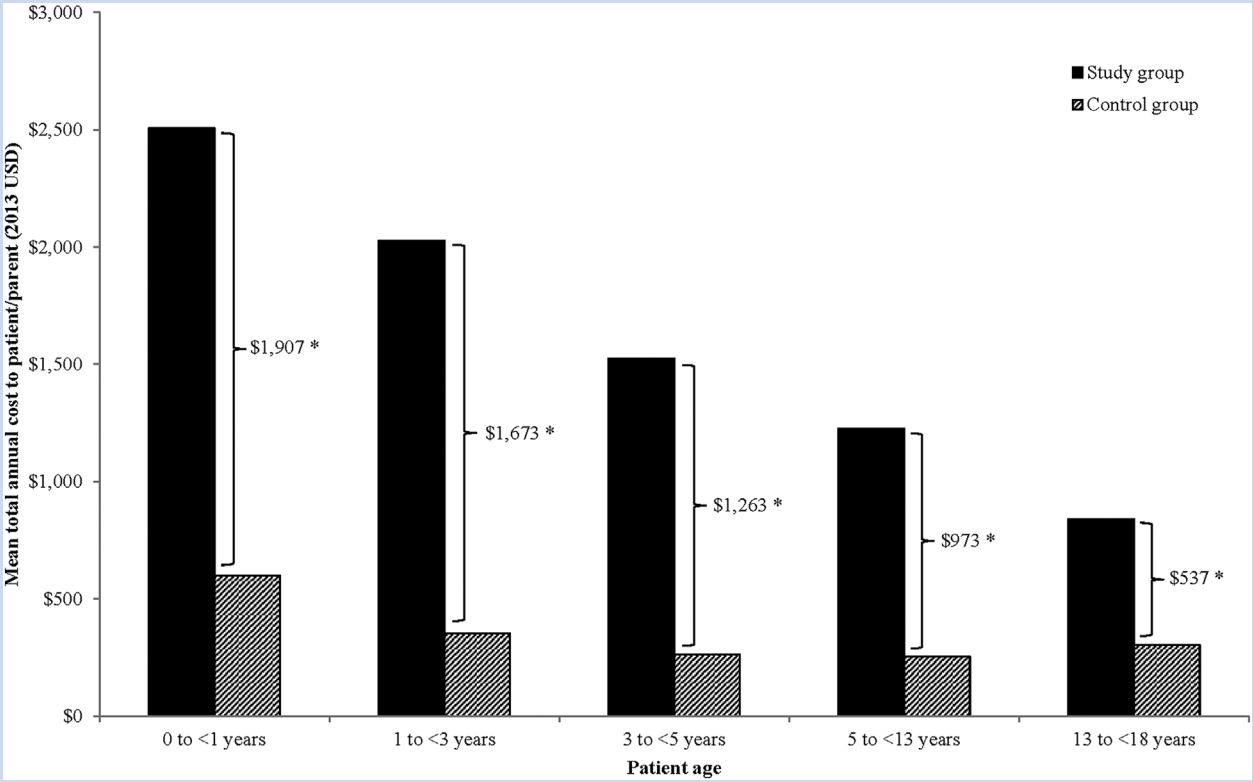

FIG. 2. Incremental out-of-pocket medical costs decreased as patients with Down syndrome became older. **P*-value <0.05; *P* values calculated using Wilcoxon signed-rank tests.

Third-party insurers can expect to pay, on average, an additional $230,043 in medical expenses for patients with DS, ages birth to 18 years, when compared to the costs for children without DS. In their sub-analyses, Waitzman et al. [1994] estimated that the lifetime incremental inpatient and outpatient costs for patients with DS were approximately $104,741, when adjusted to 2013 USD. The lower lifetime costs Waitzman et al. [1994] compared to the adolescent costs assessed in this study is likely due, in part, to the increasing costs of healthcare since Waitzman et al.'s analysis in 1988. Because the frequency of medical care associated with DS decreases after the 1st year of life, it is possible that the rate of identification of children with DS also decreases with age in our sample. Accordingly, our estimates of cost (both out-of-pocket and that incurred by third-party payers) are potentially overestimates to the extent that individuals selected into the study cohort may have sought more frequent care, increasing their likelihood of submitting claims associated with a diagnosis of DS. This effect may not have been observed by Waitzman et al. [1994], as their analysis was based on a population-based sample.

Recent cost-effectiveness analyses for NIPS have used incremental "lifetime" costs for DS, ranging from about $680,000 to $900,000 (when adjusted to 2013 USD) [Ball et al., 2007; Cuckle et al., 2013; Song et al., 2013]. However, these data were derived from a source that included direct costs associated with special education services, long-term care, and developmental services, and the indirect costs associated with lost wages due to the morbidity and early mortality associated with DS [Waitzman et al., 1994]. As medical insurers typically do not cover these expenses, the use of $680,000–$900,000 is a significant overestimate for the purposes of cost-effectiveness analyses for NIPS.

Our study is not without limitation. As with all studies utilizing insurance claims data, missing information may have resulted in selection bias, confounding, or measurement error. Likewise, the accuracy of the matching was limited to the granularity of the data provided to the algorithm; for example, patients were matched exactly on parental health insurance plan type by major categories, so it is possible that some residual confounding could occur within such categories. While our data come from a robust and comprehensive database, OptumHealth Reporting and Insights is not population-based, and therefore, the results might not be applicable to all families who have children with DS. However, OptumHealth Reporting and Insights captures approximately 3% of the total estimated U.S. population with DS under the age of 19 (Table V) and is similar to the overall U.S. population with regards to population share by age group, gender, and U.S. Census division (Table VI). Families who are covered, in full, by Medicaid or Medicare are not captured in this database. Additionally, those families in which neither parent is covered by one of the companies in this database would not be represented. However, a range of work industries—including shipping/transportation and financial services—are among the included

TABLE III. Mean Annual Cost to Patient/Parent Among Individuals With DS and Matched Controls, by Age Category[a]

	Study group	Control group	Cost difference	*P*-value[b]
Age 0 to <1				
	N = 1,371	N = 5,484	–	–
Total annual cost, mean ± SD	$2,506 ± $3,721	$599 ± $1,579	$1,907	<0.001*
Total medical cost	$2,357 ± $3,647	$551 ± $1,549	$1,806	<0.001*
Inpatient	$1,183 ± $2,888	$259 ± $1,346	$925	<0.001*
Outpatient	$705 ± $946	$232 ± $439	$473	<0.001*
Emergency room	$106 ± $710	$44 ± $211	$63	<0.001*
Home health agency	$335 ± $1,133	$14 ± $175	$322	<0.001*
Other	$27 ± $173	$4 ± $33	$23	<0.001*
Total pharmacy cost	$149 ± $384	$47 ± $131	$102	<0.001*
Age 1 to <3				
	N = 1,457	N = 5,828	–	–
Total annual cost, mean ± SD	$2,026 ± $3,354	$353 ± $801	$1,673	<0.001*
Total medical cost	$1,826 ± $3,123	$305 ± $768	$1,521	<0.001*
Inpatient	$480 ± $1,334	$64 ± $503	$416	<0.001*
Outpatient	$796 ± $1,228	$173 ± $342	$623	<0.001*
Emergency room	$76 ± $271	$52 ± $242	$23	<0.001*
Home health agency	$442 ± $1,894	$11 ± $103	$431	<0.001*
Other	$33 ± $203	$5 ± $111	$27	<0.001*
Total pharmacy cost	$201 ± $934	$48 ± $107	$153	<0.001*
Age 3 to <5				
	N = 1,407	N = 5,628	–	–
Total annual cost, mean ± SD	$1,525 ± $2,467	$262 ± $611	$1,263	<0.001*
Total medical cost	$1,356 ± $2,326	$214 ± $552	$1,142	<0.001*
Inpatient	$412 ± $1,135	$33 ± $193	$379	<0.001*
Outpatient	$663 ± $1,064	$137 ± $351	$526	<0.001*
Emergency room	$56 ± $218	$36 ± $206	$21	<0.001*
Home health agency	$203 ± $1,408	$3 ± $63	$201	<0.001*
Other	$22 ± $116	$6 ± $159	$16	<0.001*
Total pharmacy cost	$168 ± $404	$48 ± $155	$120	<0.001*
Age 5 to <13				
	N = 2,126	N = 8,504	–	–
Total annual cost, mean ± SD	$1,227 ± $2,286	$254 ± $582	$973	<0.001*
Total medical cost	$1,043 ± $2,169	$196 ± $462	$847	<0.001*
Inpatient	$275 ± $849	$34 ± $214	$240	<0.001*
Outpatient	$559 ± $1,035	$127 ± $290	$432	<0.001*
Emergency room	$41 ± $167	$27 ± $124	$14	<0.001*
Home health agency	$148 ± $1,466	$3 ± $87	$145	<0.001*
Other	$21 ± $99	$4 ± $31	$17	<0.001*
Total pharmacy cost	$185 ± $373	$59 ± $262	$126	<0.001*
Age 13 to <18				
	N = 1,334	N = 5,336	–	–
Total annual cost, mean ± SD	$840 ± $1,351	$304 ± $640	$537	<0.001*
Total medical cost	$635 ± $1,097	$231 ± $555	$404	<0.001*
Inpatient	$187 ± $602	$43 ± $275	$143	<0.001*
Outpatient	$332 ± $596	$149 ± $354	$183	<0.001*
Emergency room	$36 ± $131	$27 ± $138	$9	<0.001*
Home health agency	$63 ± $388	$3 ± $51	$61	<0.001*
Other	$17 ± $73	$9 ± $118	$8	<0.001*
Total pharmacy cost	$205 ± $529	$73 ± $185	$132	<0.001*

DS, Down syndrome; SD, standard deviation.
* *P*-value <0.05.
[a]All costs are expressed in 2013 USD.
[b]*P* values were calculated using Wilcoxon signed-rank tests.

TABLE IV. Mean Annual Cost to Third-party Insurers Among Individuals With Ds and Matched Controls, by Age Category[a]

	Study group	Control group	Cost difference	P-Value[b]
Age 0 to <1				
	N = 1,371	N = 5,484	–	–
Total annual cost, mean ± SD	$88,502 ± $245,633	$7,638 ± $56,389	$80,864	<0.001*
Total medical cost	$86,990 ± $244,664	$7,480 ± $56,152	$79,510	<0.001*
Inpatient	$76,205 ± $233,386	$5,398 ± $55,172	$70,808	<0.001*
Outpatient	$5,962 ± $7,580	$1,744 ± $2,560	$4,218	<0.001*
Emergency room	$2,055 ± $13,739	$212 ± $1,040	$1,843	<0.001*
Home health agency	$2,420 ± $16,456	$80 ± $952	$2,340	<0.001*
Other	$348 ± $2,203	$46 ± $306	$302	<0.001*
Total pharmacy cost	$1,512 ± $18,165	$158 ± $1,099	$1,354	<0.001*
Age 1 to <3				
	N = 1,457	N = 5,828	–	–
Total annual cost, mean ± SD	$21,105 ± $72,150	$2,154 ± $22,419	$18,950	<0.001*
Total medical cost	$20,119 ± $71,237	$2,020 ± $22,298	$18,100	<0.001*
Inpatient	$12,159 ± $63,818	$970 ± $21,663	$11,189	<0.001*
Outpatient	$4,408 ± $6,706	$785 ± $1,403	$3,622	<0.001*
Emergency room	$617 ± $2,806	$187 ± $792	$430	<0.001*
Home health agency	$2,718 ± $17,241	$50 ± $786	$2,668	<0.001*
Other	$218 ± $1,343	$27 ± $496	$191	<0.001*
Total pharmacy cost	$985 ± $4,082	$135 ± $980	$850	<0.001*
Age 3 to <5				
	N = 1,407	N = 5,628	–	–
Total annual cost, mean ± SD	$12,533 ± $43,130	$1,305 ± $8,773	$11,228	<0.001*
Total medical cost	$11,938 ± $42,813	$1,163 ± $8,431	$10,775	<0.001*
Inpatient	$6,938 ± $39,747	$433 ± $6,841	$6,505	<0.001*
Outpatient	$3,165 ± $6,051	$550 ± $1,530	$2,615	<0.001*
Emergency room	$436 ± $1,778	$123 ± $560	$313	<0.001*
Home health agency	$1,224 ± $7,224	$43 ± $1,272	$1,182	<0.001*
Other	$175 ± $1,442	$15 ± $148	$160	<0.001*
Total pharmacy cost	$595 ± $2,488	$142 ± $765	$454	<0.001*
Age 5 to <13				
	N = 2,126	N = 8,504	–	–
Total annual cost, mean ± SD	$9,047 ± $34,401	$1,461 ± $26,977	$7,586	<0.001*
Total medical cost	$8,156 ± $33,705	$1,187 ± $23,942	$6,969	<0.001*
Inpatient	$4,666 ± $28,667	$569 ± $21,501	$4,097	<0.001*
Outpatient	$2,186 ± $4,183	$451 ± $1,053	$1,736	<0.001*
Emergency room	$287 ± $1,286	$103 ± $472	$184	<0.001*
Home health agency	$726 ± $5,189	$47 ± $2,334	$678	<0.001*
Other	$291 ± $4,866	$16 ± $124	$275	<0.001*
Total pharmacy cost	$891 ± $3,693	$274 ± $4,156	$617	<0.001*
Age 13 to <18				
	N = 1,334	N = 5,336	–	–
Total annual cost, mean ± SD	$7,267 ± $27,713	$1,640 ± $7,886	$5,627	<0.001*
Total medical cost	$6,118 ± $26,269	$1,284 ± $7,256	$4,834	<0.001*
Inpatient	$3,529 ± $20,794	$511 ± $6,061	$3,018	<0.001*
Outpatient	$1,782 ± $11,304	$547 ± $1,231	$1,235	<0.001*
Emergency room	$262 ± $1,081	$139 ± $654	$123	<0.001*
Home health agency	$430 ± $4,081	$22 ± $437	$408	<0.001*
Other	$115 ± $796	$64 ± $1,710	$51	<0.001*
Total pharmacy cost	$1,149 ± $4,847	$356 ± $2,202	$793	<0.001*

DS, Down syndrome; SD, standard deviation.
* *P*-value <0.05
[a]All costs are expressed in 2013 USD.
[b]P-values were calculated using Wilcoxon signed-rank tests.

TABLE V. Comparison of Patients With DS in OptumHealth[a] Compared to Estimated Total Population With DS, by Age Category

	2000			2005			2010		
Age group	Optum DS population	Estimated DS population[b]	Percent of total (%)	Optum DS population	Estimated DS population[b]	Percent of total (%)	Optum DS population	Estimated DS population[b]	Percent of total (%)
Total	2,286	75,986	(3.0)	3,062	82,897	(3.7)	3,465	88,604	(3.9)
0–4	704	21,014	(3.4)	957	23,812	(4.0)	774	25,448	(3.0)
5–9	753	19,719	(3.8)	916	20,565	(4.5)	1,182	23,528	(5.0)
10–14	510	19,267	(2.6)	753	19,541	(3.9)	916	20,382	(4.5)
15–19	319	15,986	(2.0)	436	18,979	(2.3)	593	19,246	(3.1)

DS, Down syndrome.
[a]Patients with DS in OptumHealth Reporting and Insights database were defined as any patient with a diagnosis for DS (ICD9 code 758.0x) at any point in their medical history.
[b]Data on estimated population with DS in the United States taken from de Graaf et al. [2016].

companies. We also cannot draw any conclusions based on race and ethnicity, as the database does not contain this information.

A previous study on healthcare expenditures for patients with DS raised the question of under-ascertainment due to ICD-9-CM coding [Boulet et al., 2008]; our study attempts to minimize such effects by requiring only one diagnosis (758.0x) during the continuous enrollment period. To this extent, our calculations may represent the average upper limits for patients with DS. Alternatively, by requiring only a single diagnosis, our study might have included some patients who did not have a confirmed

TABLE VI. Comparison of OptumHealth Population to Overall Population

	OptumHealth[a] 2014		U.S. population 2014	
	N	(%)	N	(%)
Age[b]				
Under 18 years	2,070,784	(20.3)	73,583,618	(23.1)
18–24 years	1,157,138	(11.3)	31,464,158	(9.9)
25–44 years	2,754,524	(27.0)	84,029,637	(26.4)
45–54 years	1,474,159	(14.4)	43,458,851	(13.6)
55–64 years	1,398,411	(13.7)	40,077,581	(12.6)
65 years and over	1,352,248	(13.3)	46,243,211	(14.5)
All	10,207,264	(100.0)	318,857,056	(100.0)
Gender[b]				
Male	5,047,371	(49.5)	156,936,487	(49.2)
Female	5,159,893	(50.6)	161,920,569	(50.8)
All	10,207,264	(100.0)	318,857,056	(100.0)
Census division[c]				
New England	921,637	(9.0)	14,680,722	(4.6)
Middle Atlantic	1,443,301	(14.1)	41,471,611	(13.0)
South Atlantic	1,685,289	(16.5)	62,514,615	(19.6)
East North Central	1,571,681	(15.4)	46,739,039	(14.7)
East South Central	439,255	(4.3)	18,806,265	(5.9)
West North Central	864,595	(8.5)	21,006,069	(6.6)
West South Central	1,029,071	(10.1)	38,451,054	(12.1)
Mountain	780,008	(7.6)	23,197,119	(7.3)
Pacific	1,203,835	(11.8)	49,834,269	(15.6)
Hawaii and Alaska	268,592	(2.6)	2,156,293	(0.7)
All	10,207,264	(100.0)	318,857,056	(100.0)

[a]Includes all beneficiaries eligible at any time between 2010 and 2014.
[b]Taken from: Annual Estimates of the Resident Population for Selected Age Groups by Sex for the United States, States, Counties, and Puerto Rico Commonwealth and Municipios: April 1, 2010 to July 1, 2014; released on June 2015; U.S. Census Bureau, Population Division. [United States Census Bureau-Population Division, 2014a].
[c]Taken from: Annual Estimates of the Resident Population: April 1, 2010 to July 1, 2014; released on December 2014; U.S. Census Bureau, Population Division. [United States Census Bureau-Population Division, 2014b].

diagnosis for DS, though this is unlikely given recent advancements in genetic testing to confirm DS.

A population-based national registry for people with DS has not yet been achieved, although efforts are underway [Oster-Granite et al., 2011]. Once this registry is populated with data on the daily costs associated with a person with DS, more accurate out-of-pocket expenses can be estimated. This can be achieved through a longitudinal, prospective, population-based cohort of caregivers who are surveyed about their monthly expenses.

In addition to medical costs, expectant couples also ask: what are the *lifetime* costs for a person with DS? Such calculations are difficult, partly due to a lack of data but primarily because of the complexity of considerations. Non-economic factors such as emotional considerations, values, demands on time, or other social circumstances are not examined in this study, though these factors are often considered to be as important issues for parents [Grosse, 2010]. However, with some lifetime savings such as deferred college and wedding expenses for people with DS, some caregivers might even have overall cost-neutral or cost savings associated with their son or daughter with DS when compared to the costs of typically developing children. As such, cost-benefit and cost-effectiveness studies, particularly those for NIPS, should be cautious in applying an overall price tag for people with DS, particularly one that is dated or based on incomplete data.

For some expectant couples, financial considerations play a role in their pregnancy decisions after receiving a prenatal diagnosis of DS. Based on our analysis of inpatient and outpatient medical costs, parents who have children with DS pay an additional $84 per month in out-of-pocket expenses when averaged over the first 18 years of life. Incremental lifetime costs, beyond the medical expenditures, are more difficult to measure due to lack of data and complexities of variables over one's lifetime.

ACKNOWLEDGMENTS

The authors thank Martha Samuelson of Analysis Group, Inc., for facilitating this research. We further thank Michael Hellstern of Analysis Group, Inc., for his assistance in formatting our paper and reviewing the final proofs.

AUTHORS' CONTRIBUTIONS

Mr. Kageleiry and Mr. Samuelson helped design the study, performed the analysis, interpreted the results, wrote sections of the initial draft, and reviewed and approved the final version of the manuscript. Dr. Skotko helped design the study, interpreted the results, wrote sections of the initial draft, and reviewed and approved the final version of the manuscript. Dr. Campbell, Dr. Duh, and Mr. Lefebvre helped design the study, interpreted the results, and reviewed and approved the final version of the manuscript.

CONFLICTS OF INTEREST

BGS serves in a non-paid capacity on the Medical and Science Advisory Board for the Massachusetts Down Syndrome Congress and the Board of Directors for Band of Angels Foundation, both non-profit organizations. He further serves on the Medical Advisory Board for the non-profit National Center for Prenatal and Postnatal Down Syndrome Diagnoses Resources. BGS occasionally gets remunerated from Down syndrome non-profit organizations for speaking engagements about Down syndrome. He has a sister with Down syndrome. He receives research support for clinical drug trials involving patients with Down syndrome from Hoffmann-La Roche, Inc. He also receives annual royalties from Woodbine House, Inc., for the publication of his book, *Fasten Your Seatbelt: A Crash Course on Down Syndrome for Brothers and Sisters*. JC is a member of the Massachusetts Down Syndrome Congress and has a son with Down syndrome. AK, DS, MSD, and PL report no conflicts of interest. The authors have no financial conflict of interests related to the content of this study.

REFERENCES

Arya R, Kabra M, Gulati S. 2011. Epilepsy in children with Down syndrome. Epileptic Disord 13:1–7.

Ball RH, Caughey AB, Malone FD, Nyberg DA, Comstock CH, Saade GR, Berkowitz RL, Gross SJ, Dugoff L, Craigo SD, Timor-Tritsch IE, Carr SR, Wolfe HM, Emig D, D'Alton ME, First, Second Trimester Evaluation of Risk Research C. 2007. First- and second-trimester evaluation of risk for Down syndrome. Obstet Gynecol 110:10–17.

Bergstralh EJ, Kosanke JL. 1995. Computerized matching of cases to controls. Technical report number 56. Accessed on: September 14, 2016. Available at: http://www.mayo.edu/research/documents/biostat-56pdf/doc-10026923

Bergstralh EJ, Kosanke JL. 2004. gmatch SAS Macro. Accessed on: September 14, 2016. Available at: http://www.mayo.edu/research/documents/gmatchsas/doc-10027248

Bianchi DW, Platt LD, Goldberg JD, Abuhamad AZ, Sehnert AJ, Rava RP, MatErnal BLood IS, Source to accurately diagnose fetal aneuploidy (MELISSA) study group. 2012. Genome-wide fetal aneuploidy detection by maternal plasma DNA sequencing. Obstet Gynecol 119:890–901.

Boulet SL, Molinari NA, Grosse SD, Honein MA, Correa-Villasenor A. 2008. Health care expenditures for infants and young children with Down syndrome in a privately insured population. J Pediatr 153:241–246.

Bull MJ, Committee on Genetics. 2011. Health supervision for children with Down syndrome. Pediatrics 128:393–406.

Creavin AL, Brown RD. 2009. Ophthalmic abnormalities in children with Down syndrome. J Pediatr Ophthalmol Strabismus 46:76–82.

Cuckle H, Benn P, Pergament E. 2013. Maternal cfDNA screening for Down syndrome—A cost sensitivity analysis. Prenat Diagn 33:636–642.

Data Resource Center for Child and Adolescent Health; Child and Adolescent Health Measurement Initiative. 2009/2010. National survey of children with special health care needs. condition-specific profile, Down syndrome. Accessed on: July 29, 2014. Available at: http://childhealthdata.org/

de Graaf G, Buckley F, Skotko BG. 2016. Estimation of the number of people with Down syndrome in the United States. Genet Med [Epub ahead of print]. http://www.nature.com/gim/journal/vaop/ncurrent/pdf/gim2016127a.pdf

Freeman SB, Torfs CP, Romitti PA, Royle MH, Druschel C, Hobbs CA, Sherman SL. 2009. Congenital gastrointestinal defects in down syndrome: A report from the atlanta and national down syndrome projects. Clin Genet 75:180–184.

Grosse SD. 2010. Sociodemographic characteristics of families with Down syndrome and the economic impacts of child disability on families. In: Urbano RC, editor. International review of research in mental retarda-

tion: Health issues among persons with down syndrome. Cambridge, MA: Academic Press.

Loftus EV, Jr., Skup M, Ozbay AB, Wu E, Guerin A, Chao J, Mulani P. 2014. The impact of moderate-to-severe Crohn's Disease on employees' salary growth. Inflamm Bowel Dis 20:1734–1738.

Miettinen OS. 1969. Individual matching with multiple controls in the case of all-or-none responses. Biometrics 25:339–355.

Nicolaides KH, Syngelaki A, Ashoor G, Birdir C, Touzet G. 2012. Noninvasive prenatal testing for fetal trisomies in a routinely screened first-trimester population. Am J Obstet Gynecol 207:374 e371–376.

Norton ME, Brar H, Weiss J, Karimi A, Laurent LC, Caughey AB, Rodriguez MH, Williams J, 3rd, Mitchell ME, Adair CD, Lee H, Jacobsson B, Tomlinson MW, Oepkes D, Hollemon D, Sparks AB, Oliphant A, Song K. 2012. Non-Invasive Chromosomal Evaluation (NICE) Study: Results of a multicenter prospective cohort study for detection of fetal trisomy 21 and trisomy 18. Am J Obstet Gynecol 207:137 e131–138.

Oster-Granite ML, Parisi MA, Abbeduto L, Berlin DS, Bodine C, Bynum D, Capone G, Collier E, Hall D, Kaeser L, Kaufmann P, Krischer J, Livingston M, McCabe LL, Pace J, Pfenninger K, Rasmussen SA, Reeves RH, Rubinstein Y, Sherman S, Terry SF, Whitten MS, Williams S, McCabe ER, Maddox YT. 2011. Down syndrome: National conference on patient registries, research databases, and biobanks. Mol Genet Metab 104:13–22.

Parsons L, Ovation Research Group. 2001. Reducing bias in a propensity score matched-pair sample using greedy matching techniques [poster]. Proceedings of the Twenty-Sixth Annual SAS® User Group International Conference; Available at: http://www2sascom/proceedings/sugi26/p214-26pdf

Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M, Parsons NB. 2014a. Burden of diabetic foot ulcers for medicare and private insurers. Diabetes Care 37:651–658.

Rice JB, Kirson NY, Shei A, Cummings AK, Bodnar K, Birnbaum HG, Ben-Joseph R. 2014b. Estimating the costs of opioid abuse and dependence from an employer perspective: A retrospective analysis using administrative claims data. Appl Health Econ Health Policy 12:435–446.

Skotko BG. 2005. Prenatally diagnosed Down syndrome: Mothers who continued their pregnancies evaluate their health care providers. Am J Obstet Gynecol 192:670–677.

Song K, Musci TJ, Caughey AB. 2013. Clinical utility and cost of noninvasive prenatal testing with cfDNA analysis in high-risk women based on a US population. J Matern Fetal Neonatal Med 26:1180–1185.

Tandon N, Balart LA, Laliberte F, Pilon D, Lefebvre P, Germain G, Prabhakar A. 2014. Impact of completing chronic hepatitis C (CHC) treatment on post-therapy healthcare cost. J Med Econ 17:862–871.

United States Bureau of Labor Statistics. Consumer Price Index. Accessed on: June 1, 2014. Available at: http://www.bls.gov/cpi/home.htm

United States Census Bureau-Population Division. American Fact Finder: Annual Estimates of the Resident Population for Selected Age Groups by Sex for the United States, States, Counties, and Puerto Rico Commonwealth and Municipios: April 1, 2010 to July 1, 2014; released on June 2015. Accessed on: September 30, 2016. Available at: http://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?src = bkmk

United States Census Bureau-Population Division. Annual Estimates of the Resident Population: April 1, 2010 to July 1, 2014: 2014 Population Estimates; released on December 2014. Accessed on: September 30, 2016. Available at: http://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?src = bkmk

Waitzman NJ, Romano PS, Scheffler RM. 1994. Estimates of the economic costs of birth defects. Inquiry 31:188–205.

Zimmermann B, Hill M, Gemelos G, Demko Z, Banjevic M, Baner J, Ryan A, Sigurjonsson S, Chopra N, Dodd M, Levy B, Rabinowitz M. 2012. Noninvasive prenatal aneuploidy testing of chromosomes 13, 18, 21, X, and Y, using targeted sequencing of polymorphic loci. Prenat Diagn 32:1233–1241.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site