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Sickle cell disease overview

Sickle cell disease (SCD) is one of the most common monogenetic disorders, both worldwide and in the United States, with an estimated prevalence of 100,000 affected Americans.[1] SCD itself is characterized by multisystem organ damage, which results in high levels of morbidity and often early mortality. Though all children and adults with SCD have ongoing health complications, the disease is phenotypically variable, with some children experiencing debilitating pain, frequent hospitalizations from acute inflammatory events, and life-long morbidity, whereas other children live less affected lives with fewer hospitalizations. The causes behind this phenotypic variability remain unclear.

Given the complexity, chronicity, and morbidity of the disease, it is not surprising that patients with SCD are especially costly, from a financial perspective, to the healthcare system. The first major study reporting healthcare costs due to SCD was from Yang and colleagues (1995).[2] In this analysis, they calculated total inpatient, outpatient, and emergency department healthcare charges on a group of adults with SCD, finding the average yearly cost per patient to be $7,699, significantly higher than comparable adults without SCD. Using Florida Medicaid data, Kauf and colleagues (2009) estimated that average costs of care per patient were $1,400/month, with costs increasing with patient age.[3] Extrapolating this data and using a 3% discount rate, these findings estimate an average lifetime cost of care of $460,000, again significantly higher than costs reported for the general population. More recent claims data estimated costs of $26,500 per year per patient with SCD, putting the incremental economic burden of SCD at $2.98 billion USD per year.[4] Recently published simulation models accounting for early death and lost work estimate $700,000 in lost lifetime income for each person born with SCD.[5]

While the above data is informative with regards to population-level, programmatic, hospital, and insurance-level costs associated with SCD, these studies do little to shed light on costs as experienced directly by patients. First, patient cost-sharing of inpatient, outpatient, and prescription drugs can vary significantly depending on the insurance plan and family income status, even within a similar insurance provider such as Medicaid.[6] Second and of equal importance, though often overlooked or ignored in cost analyses, patients and their families face financial costs of care that are not directly billed from providers, hospitals or pharmacies, yet are nonetheless directly attributable to their disease, such as transportation to and from clinic visits, lost days of school and/or work, childcare costs that would otherwise not be incurred. Recognizing these costs is important from a societal perspective, as funding and support for children with chronic diseases such as SCD should be informed as completely as possible. From a clinical, patient-level perspective, it is imperative to understand these costs for several key reasons. First, both chronic disease and new diagnoses of a major healthcare condition can place considerable financial strain on families and recognizing all sources of costs is key to properly evaluating and alleviating this financial toxicity.[7] This burden is especially important to document in the context of clinical trials, which are common in pediatric hematology-oncology and can require additional clinic visits and monitoring beyond standard-of-care management.

Second, though the literature is not as robust as in other areas of health economics, there is evidence that health care seeking behaviors are elastic to price, as discussed below. In pediatric hematologic and oncologic conditions, and SCD specifically, access to routine, preventative care and urgent/sick outpatient visits are major aspects of high-quality care, especially for the sickest and most high-risk patients. For example, current guidelines recommend that children initiating hydroxyurea, the most-important disease modifying medication in SCD, be seen monthly when starting the medication to achieve optimal dosing and monitor side effects.[8] Furthermore, there is compelling evidence that missed appointments and loss to follow up common in children and adults with SCD and as such, quantifying

and addressing barriers to outpatient care is a major component of improving health outcomes in these patients.[9,10]

Background on Price Elasticity in Healthcare

One of the first seminal studies to examine the price elasticity of demand for outpatient healthcare was performed by Manning and colleagues (1987).[11] This study took advantage of the federal government-initiated Rand Health Insurance Experiment, in which participating families from six U.S. cities were randomly assigned to different health care plans; the subset of interest for the Manning article was families enrolled in different fee-for-service plans, with coinsurance rates of 0, 25, 50, or 95%. Adjusted and unadjusted models both showed mean/predicted expenditure was negatively associated with coinsurance rate (*i.e.* those with higher copays had less outpatient expenditure), demonstrating a significant response to cost on healthcare seeking behaviors. Furthermore, the study found that this increase in expenditure was driven mostly by more frequent visits (as opposed to more expensive visits), that both patients with acute and chronic conditions showed similar price elasticity, and that the largest response to plan type occurred between free care and the 25% plan. Thus, this study offered compelling evidence that out-of-pocket costs indeed affect volume of healthcare uptake and specifically number of outpatient clinic visits. It should be noted that this randomized trial setting was especially advantageous for health economists, given that an individual's choice of insurance and associated out-of-pocket costs are often correlated with that individual's health status (*e.g.,* a healthier person may pick a plan with low deductible and high out-of-pocket costs, whereas an individual with a chronic disease may do the opposite), which creates a source of endogeneity. The randomization in the Rand Health Insurance Experiment created a truly exogenous source of price variation, allowing for an unbiased estimate of price elasticity.

More recent studies, though not in a randomized controlled setting, have offered further evidence on the price elasticity of health care. Duarte (2012) used a rich dataset from the Chilean healthcare market (a public-private healthcare insurance system, similar to the United States) to evaluate price elasticity of healthcare.[12] Specifically, he used an instrumental variable method with an unexpected, unpredictable health event (*e.g.,* appendicitis, broken arm) as the exogenous healthcare expenditure shock. Several key findings emerge. First, price elasticity is low for care for these acute health events, as expected. Second, non-emergent and outpatient services showed much higher price elasticity. Importantly, this price elasticity was driven by both intensity of visit (*i.e.* costs of services incurred at the visit) and number of visits. Interestingly, high-income individuals were actually more responsive to price than low-income individuals; he hypothesized that perhaps high-income individuals are better able to calculate out-of-pocket expenditures as compare to low-income. Though this study setting occurs in a different country with different social, political, and healthcare backdrops, it nonetheless offers interesting evidence into price elasticity of demand of outpatient healthcare services.

Brot-Goldberg and colleagues (2017) offer further evidence through the lens of a natural experiment in the United States, in which all employees of a large, self-insured firm were moved from a very generous healthcare plan (*i.e.* nearly completely free medical care with no cost sharing and a broad set of providers and covered services) to a high-deductible healthcare plan.[13] Notably, the high-deductible plan gave access to the same providers and services as the previous generous option, leaving out-of-pocket costs as the main source of variation. The dataset them allowed them to observe individual-level sociodemographic, health, and specific spending information, comparing pre- and post-health insurance plan switch timeframes. They observed that health expenditures decreased by 12.5% with the plan switch, with decreases in spending persisting during the study timeframe. Similar to previous studies, this decrease in spending was driven by reductions in quantity, where individuals simply received less medical care and fewer medical services. Importantly, these same reductions were

seen across all levels of health in this study population, offering evidence that even the sickest patients forego healthcare when faced with higher prices. Additionally, it appeared to be spot prices, the price paid at the moment of seeking care, as opposed to the total price, that most significantly drove this reduction in healthcare seeking. This implies that patients are sensitive to immediate, up-front, visible costs; though not studied in this analysis, it is reasonable to suspect that other immediate and visible costs associated with a healthcare visit, such as transportation costs, lost pay from a missed day of work, and childcare costs, would be similar barriers to healthcare access.

The above studies have focused specifically on elasticities with respect to direct costs and have not incorporated other out-of-pocket costs (*e.g.,* transportation, missed days of work, childcare costs) as measures of interest. There are relatively few studies that include these out-of-pocket costs in their analyses, with one key barrier being such data is not available in most datasets. Holdford and colleagues (2021) aimed to address this issue in via a cost questionnaire in a subset of adults with SCD.[14] Specifically, a convenience sample of adults with SCD was recruited from an urban SCD clinic in Virginia to complete an adapted Institute for Medical Technology Assessment (iMTA) Productivity Cost Questionnaire[15], which helps quantify the total financial costs by including their disease's impact on absenteeism, unpaid work, time as a resource, and effects on career and social lives, among others. This study found that such costs are key contributors to the financial burden of SCD, averaging $15,000 per person annually in absenteeism and presenteeism and an additional $40,000 per year in lost productivity, compared with estimated direct medical costs of $34,000 per year. While an important first step in documenting the indirect burden of SCD, this study excludes children with SCD (who may have different indirect costs given their reliance on caregivers) and does not attempt to document price elasticity to care. As a recently published systematic review on medical and non-medical costs of SCD in the United States noted, "non-medical cost literature is completely lacking" for patients with SCD.[16] Furthermore, data on out-of-pocket costs with respect to outpatient visits is surprisingly sparse,

especially in pediatrics. Without such data, it is impossible to quantify the effect of these costs as potential barriers to care.

Gaps in literature and research questions

There are therefore two major gaps in the health economics literature with regards to SCD. First, there is no literature I am aware of that attempts to quantify the costs on families of an outpatient clinic visit for pediatric SCD. Given that many families of children with SCD are of low socioeconomic status, such out-of-pocket costs could represent significant portions of disposable income. The first barrier in addressing such costs is a lack of cost instrument; specifically, there is no validated instrument that measures out-of-pocket costs to families of children with chronic conditions, SCD or otherwise. As such, the first aim of my project will be the creation and validation of such instrument. To create this instrument, I will first conduct a systematic review to identify published reports on the direct and out-of-pocket cost items to patients and their families for initial questionnaire construction. Next, I will establish face validity of the questionnaire by reviewing with subject experts, including both practicing hematologists who care for patients with SCD and experts in questionnaire construction and validation. With the initial questionnaire complete, I will then pilot the survey on a subset of families of children with SCD, which will provide both survey quality and feasibility data and also important initial out-of-pocket cost data.

The second major gap in literature is involves price elasticity; specifically, I am aware of no study that quantifies out-of-pocket price elasticity of outpatient care in pediatrics, SCD or otherwise. Furthermore, though time-price elasticity of demand has been used in other settings, this measure has not been used in the outpatient pediatric setting, which has different factors to consider, such as childcare, missed school, then the adult setting. The majority of care received by children with SCD (and most other chronic conditions) is outpatient and loss to follow up and missed clinic visits are frequently

encountered, leading to sub-optimal care. As such, it is key to determine what role cost plays in these missed visits. As previously discussed, direct costs have been shown in other settings to negatively impact care and it is therefore plausible that out-of-pocket costs and time spent associated with clinic visits could also have a significant and negative impact. To estimate out-of-pocket and time price elasticity of outpatient and preventative healthcare demand, I will employ two strategies.

First, I will use the data available from Children's Healthcare of Atlanta SCD Patient Database to estimate elasticity of demand. However, this database does not contain out-of-pocket costs; instead, I will use a time-price elasticity of demand, in which distance from the nearest outpatient clinic is used as our measure of time, and number of outpatient specialty clinic visits per year will be our measure of utilization. Of note, SCD patients are expected to have 4-12 specialty clinic visits per year, depending on their SCD genotype and treatment regimen. I hypothesize that increased distance from clinic (*i.e.* increased time spent per clinic visit) will result in less utilization. I plan to add the distance-from-clinic measure as the independent variable of interest in a regression model. I will include disease-specific covariates as well, such as SCD genotype, history of major complications (*e.g.*, stroke, ICU stays), and family-specific covariates, such as neighborhood poverty level, number of children in household, and number of children with SCD in household. The main outcome variables will be number of SCD visits per year and hydroxyurea use. Hydroxyurea is the main and to-date most effective disease-modifying medication offered to patients with SCD; however, its use requires frequent monitoring in clinic for side effects. As such, I hypothesize that distance from clinic will be inversely correlated with hydroxyurea use.

Second, once validated and further data collection has been obtained, I will use the instrument described above to calculate price elasticity of demand and income elasticity of demand. Price elasticity of demand will be calculated as the percentage change in number of outpatient specialty clinic visits per year per percent change in price and income elasticity of demand as percent change in visits per change

in income. Next, I will create an out-of-pocket payment index, which combines the total out-of-pocket costs with a measure of the family's disposable income. This index will then be the main independent variable of interest in my regression model, again including disease-specific and family-specific covariates. The outcome variables will again be number of SCD visits per year and hydroxyurea use.

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