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Health Care Resource Utilization and Expenditures in Persons with Autosomal Dominant Polycystic Kidney Disease

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HEALTH CARE RESOURCE UTILIZATION AND EXPENDITURES IN PERSONS WITH AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

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Dedicated

to

Amma and Appa

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ABSTRACT

Iyer, Neeraj N., Ph.D., Purdue University, December 2013. Health Care Resource Utilization and Expenditures in Persons with Autosomal Dominant Polycystic Kidney Disease. Major Professor: Joseph Thomas III.

The objectives of this study were to determine prevalence of autosomal dominant polycystic kidney disease (ADPKD), to determine all-cause health care resource utilization and all-cause health care expenditures, to determine incremental health care resource utilization, and to determine incremental health care expenditures associated with ADPKD. An observational database analysis of a privately insured population was conducted using information from a large administrative claims database. Individuals 18 years of age or older and enrolled in a tracked health plan anytime during the period from April 1, 2011 through March 31, 2012, were eligible for inclusion in the sample for determination of ADPKD prevalence. To select the sample for estimating all-cause and incremental resource utilization and expenditures associated with ADPKD, administrative claims and enrollment records from April 1, 2011 through March 31, 2012 were examined to select individuals 18 years or older with ADPKD (n=3,844) based on ICD-9-CM diagnosis codes. ADPKD patients were linked one-to-one on age and gender with individuals without ADPKD resulting in 3,844 persons in the comparison group and a total of 7,688 persons in the overall sample.

The number of individuals with ADPKD enrolled anytime during the period from April 1, 2011 through March 31, 2012, was identified and divided by the total population of covered individuals 18 years or older, during the same one year period to calculate prevalence of ADPKD. All-cause heath care resource utilization among individuals with ADPKD were estimated by counting the total number of hospitalizations, hospital days, nursing home confinements, nursing home days, outpatient visits and emergency room visits. All-cause heath care expenditures among individuals with ADPKD were estimated by summing standard price amounts from claims related to hospitals, nursing homes, outpatient services, emergency rooms, and prescription services. Incremental health care resource utilization and expenditures associated with ADPKD were estimated using regression models, adjusting for other risk factors including age, gender, comorbidities, cardiovascular disease, diabetes and geographical region.

The prevalence of autosomal dominant PKD was one in 1,786 persons or 560 cases per million population. The 95 percent confidence interval for estimated prevalence was 1,742 to 1,833. Mean annual unadjusted resource utilization of hospital days 2.0 versus 0.45, and outpatient visits 21.1 versus 9.7 was substantially higher among persons with ADPKD as compared to persons without ADPKD. Mean annual unadjusted total expenditures $23,242 versus $6,230, mean hospital expenditures $6,646 versus $1,484, mean outpatient expenditures $12,625 versus $3,225, and mean medication expenditures $3,537 versus $1,380, were also higher among ADPKD patients as compared to individuals without ADPKD. Multivariate regression models adjusting for risk factors revealed incremental mean (standard error) resource use associated with

ADPKD of 0.68 (0.090) hospital days, equal to 68 additional hospital days per 100 ADPKD patients, and 6.9 (0.28) outpatient visits, equal to 690 additional visits per 100 ADPKD patients. Mean (standard error) incremental total expenditures associated with PKD were $7,917 ($431). Mean incremental expenditures were largest for outpatient expenditures at $4,507 ($181), followed by mean incremental hospital expenditures of $2,385 ($241), and mean incremental medication expenditures of $1,456 ($71). Based on sub-group analysis by whether diagnosed with end-stage renal disease, mean incremental total expenditures were $3,053 ($374) among ADPKD patients without end-stage renal disease.

In conclusion, ADPKD was associated with considerable incremental health care resource utilization and expenditures. Significant illness burden was found even before patients reached end-stage renal disease.

INTRODUCTION

Background

Polycystic Kidney Disease

Polycystic kidney disease (PKD) is a serious systemic disease that damages the kidneys and causes significant morbidity in patients' lives (Pirson and Chauveau 1999). PKD is characterized by development of multiple cysts with gradual kidney enlargement and other sequelae including colonic diverticulitis, polycystic liver disease, intracranial aneurysms, and cysts in other tissues such as seminal vesicles, arachnoid membranes and the pancreas (Alehan, Gurakan, and Agildere 2002; Danaci et al. 1998; Grantham 2008; Nicolau et al. 2000; Pirson, Chauveau, and Torres 2002; Schievink et al. 1995; Torres, Harris, and Pirson 2007; Wijdicks, Torres, and Schievink 2000). Kidney cysts are fluid-filled sacs that result from dilatation of kidney parenchyma (Pirson and Chauveau 1999; Wilson 2004). As cyst develop and grow in size, they replace normal kidney parenchyma rendering them dysfunctional (Grantham 2008; Torres, Harris, and Pirson 2007). PKD potentially progresses to end-stage renal disease (Wilson 2004).

Literature Review

Forms of PKD

Non-genetic forms of polycystic kidney diseases are caused by chronic renal impairment, medullary sponge kidney disease, drugs and hormones (Pirson and Chauveau 1999; Wilson 2004). Most PKD cases are hereditary, and hereditary cases affect approximately 500,000 Americans (Pirson and Chauveau 1999; Wilson 2004; Polycystic Kidney Disease Foundation 2000). Autosomal dominant PKD (ADPKD) is the most common genetic form, occurring in 1 in 400 to 1 in 1000 live births and accounting for the majority of PKD cases (Grantham 2008; Pirson and Chauveau 1999; Torres, Harris, and Pirson 2007). Autosomal dominant PKD may be asymptomatic for several decades but as cysts increase over time, it becomes symptomatic and serious sequelae develop. Autosomal recessive PKD is usually diagnosed during infancy, but it is much rarer than autosomal dominant PKD and occurs in only about 1 in 20,000 live births (Grantham 2008; Pirson and Chauveau 1999). Symptom presentation is more rapid and occurs at an earlier age for persons with autosomal recessive PKD than for persons with autosomal dominant PKD, so that autosomal dominant PKD is more likely to be a long term chronic condition (Dell and Avner 2001; Pirson and Chauveau 1999; Wilson 2004).

Epidemiology

Previous estimates of ADPKD prevalence report occurrence in 1 in 400 to 1 in 1,000 persons in the United States (Iglesias et al. 1983). Dalgaard estimated the prevalence of ADPKD to be one in 1,000 persons in Copenhagen (Dalgaard 1957). Comparatively lower estimates of 1 in 1,111 was reported in France (Simon et al. 1996), 1 in 2,459 was reported in Wales (Davies et al. 1991), and 1 in 4,033 was reported in Japan (Higashihara et al. 1998). In Seychelles, the estimate of prevalence of ADPKD in Caucasian individuals was found to be one in 544 (Yersin et al. 1997). According to the Polycystic Kidney Disease Foundation, ADPKD affects approximately 500,000 individuals in the United States and that ADPKD affects more individuals as compared to cystic fibrosis, muscular dystrophy, hemophilia, Down's syndrome, sickle cell anemia, and Huntington's disease (Polycystic Kidney Disease Foundation 2000).

ADPKD often leads to end-stage renal disease, a condition whose prevalence in the United States was reported to be 1,752 per million population (United States Renal Data System 2012). In 2010, the prevalence of end-stage renal disease caused by cystic kidney disease was 85 per million population (United States Renal Data System 2012). Annual incidence rates of end-stage renal disease caused by ADPKD are 8.7 males and 6.9 females per million in the United States (Stengel et al. 2003), 7.8 males and 6.0 females per million in Europe (Stengel et al. 2003), and 5.6 males and 4.0 females per million in Japan (Wakai et al. 2004).

Pathophysiology of ADPKD

ADPKD is the most common hereditary kidney disorder (Grantham 2008). Genetic mutations in two genes have been identified for ADPKD of which polycystin 1 (PKD-1) accounts for 85 percent of the cases and polycystin 2 (PKD-2) accounts for 15 percent of the cases (Grantham 2008; Torres, Harris, and Pirson 2007; Wilson 2004). It is estimated that ADPKD has a 95 percent penetrance that is, 95 percent of those individuals detected with mutations in PKD-1 or PKD-2 gene develop the disease (Grantham 2008). The protein products of polycystin-1 and polycystin-2, are found on the epithelium of renal tubular cells (Wilson 2004). Polycystin-1 is a membrane receptor that initiates intracellular reactions through phosphorylation whereas polycystin-2 is a calcium permeable channel (Torres, Harris, and Pirson 2007; Wilson 2004). Expression of these two proteins in the epithelium of the kidney cells may be altered due to gene dose reduction or inactivation (Qian et al. 1996; Torra et al. 1999; Lantinga-van Leeuwen et al. 2004). Polycystin-1 and polycystin-2 form protein complexes and modulate several signaling pathways that control cellular functions such as proliferation, apoptosis, cell-adhesion and differentiation; disturbance in any of these four pathways initiates cystogenesis (Nauli et al. 2003; Wilson 2004; Sorenson, Padanilam, and Hammerman 1996; Trudel, D'Agati, and Costantini 1991; Saadi-Kheddouci et al. 2001; Saburi et al. 2008; Shannon et al. 2006).

Magnetic resonance imaging studies by the Consortium of Radiologic Imaging Study of PKD found that although cysts expand at the same rate in patients with either gene, more cysts were detected in patients with PKD-1 mutations (Harris et al. 2006).

Grantham and colleagues reported that those with PKD-1 mutations develop renal insufficiency approximately 15 years earlier than those with PKD-2 mutations (Grantham, Chapman, and Torres 2006). Comparing phenotypes of ADPKD, Hateboer et al. reported that PKD-2 patients experienced fewer complications and lived longer than PKD-1 patients (Hateboer et al. 1999).

Diagnosis of ADPKD

Diagnosis of ADPKD is made by positive family history and renal imaging (Masoumi et al. 2008; Torres, Harris, and Pirson 2007). For persons with positive family history, diagnosis of ADPKD is confirmed by detecting at least two cysts, in either one or both kidneys in persons younger than 30 years of age, at least two cysts in each kidney in persons 30 to 59 years of age, or at least four cysts in each kidney in persons 60 years of age or older (Ravine et al. 1994). Detection of liver cysts, pancreatic cysts, or both also supports a positive diagnosis of ADPKD (Grantham 2008). Torres et al. reported that the absence of family history, a composite of manifestations including bilateral kidney enlargement, presence of cysts in both kidneys, liver cysts and absence of symptoms indicating a different renal cystic disease, may prompt a prescriptive diagnosis for ADPKD (Torres, Harris, and Pirson 2007).

Pretorius reported that prenatal detection of ADPKD is not evident till the third trimester (Pretorius et al. 1987). However, amongst children, Gabow et al. found that cysts were detected by age 5 in approximately 60 percent of children showing presence of the PKD-1 gene (Gabow et al. 1997). The same study also reported that cysts were detected in 75 to 80 percent of children 5 to 18 years old carrying the PKD-1 gene

(Gabow et al. 1997). Fick-Brosnahan and colleagues, in a longitudinal study of disease progression in children, set the diagnostic age threshold at 12 years and classified those children with less than ten cysts as having mild disease and those having ten or more cysts as having severe disease (Fick-Brosnahan et al. 2001). Nauta reported that the probability of detectable cysts rose up to 95 percent by the age of 20 years and that cysts were 100 percent detectable by the age of 30 years in individuals carrying the PKD-1 gene (Nauta 2000).

Renal ultrasonography is commonly used as a diagnostic technique for detection of renal cysts (Elles et al. 1994; Gabow et al. 1997). Prior to widespread availability of ultrasonography, intravenous urography and nephrotomography were used as diagnostic techniques, but both methods were only sensitive towards advanced ADPKD (Grossman et al. 1983; Rosenfield et al. 1980). Nicolou et al. found that ultrasonography had good sensitivity especially in persons older than 30 years and those with ADPKD caused by PKD-1 gene mutations (Nicolau et al. 2000). However, O'Neill et al. reported that ultrasonography was not found to be useful in detecting short-term disease progression (O'Neill et al. 2005).

In a review of literature pertaining to ADPKD diagnosis, Torres et al. summarized that genetic testing was a costlier alternative diagnostic procedure compared to ultrasonography, and was used as a confirmatory procedure when sonographic scans did not provide sufficient proof of presence of renal cysts (Torres, Harris, and Pirson 2007). Genetic testing is performed by two methods: linkage or sequence analysis. Linkage analysis uses microsatellite markers for the PKD-1 and PKD-2 genes and compares test results of the patient against one or more family members, for confirmation (Torres,

Harris, and Pirson 2007). Torres and colleagues reported that linkage analysis was constrained by the "availability and willingness of sufficient family members to be tested" (Torres, Harris, and Pirson 2007). Sequence analysis or molecular testing using direct DNA analysis has been reported to be effective only up to 65 to 70 percent in detecting PKD gene mutations (Rossetti et al. 2002; Rossetti et al. 2001). Zhao et al. and Grantham also questioned the utility of genetic testing methods due to lower sensitivity compared to imaging methods (Grantham 2008; Zhao et al. 2008).

Disease Progression

Microscopic studies and analysis of cyst fluid composition have revealed that cysts may occur throughout the kidney in any segment of the nephron, including the glomeruli, proximal tubules, distal tubules and collecting ducts (Grantham 1993; Huseman et al. 1980). Torres et al. summarize that gene mutation is responsible for initiation of cysts alone but cyst enlargement is a process that is perpetuated by other intracellular processes (Torres, Harris, and Pirson 2007). Evidence indicates that gradual hyperplasia i.e. slow proliferation of epithelial cells of cysts causes structural changes in the wall of the renal tubule (Grantham 1990; Grantham, Chapman, and Torres 2006). Detailed morphometric analysis of renal cysts by Grantham revealed that proliferating cells in cysts cause an "out-pocketing" of the renal tubule wall, forming a sac-like structure (Grantham, Chapman, and Torres 2006; Grantham, Geiser, and Evan 1987). The renal tubule is part of the glomerulus or the filtration unit of the kidney, and this unit is a passage for the glomerular filtrate. Cystic sacs fill with fluid that enters the filtration

unit (Grantham, Chapman, and Torres 2006). The fluid-filled cyst separates from healthier tissue, continues proliferation and accumulates more fluid.

Some study findings indicate that growth of cysts is made possible by remodeling and expansion of blood vessels that supply oxygen and nutrients to the cyst cells (Bello-Reuss, Holubec, and Rajaraman 2001; Reed et al. 2011; Wei et al. 2006). Other studies have detected angiogenic growth factors, that promote formation of new blood vessels, in patients with ADPKD (Bello-Reuss, Holubec, and Rajaraman 2001; Fabris et al. 2006; Nichols et al. 2004; Wei et al. 2006). Grantham et al. in a review of literature stated that cysts function as autonomous bodies capable of sustaining their growth and consequently contribute to enlargement of the kidney (Grantham, Chapman, and Torres 2006).

Literature reports indicate differing rates of disease progression amongst persons with ADPKD (Churchill et al. 1984; Gabow et al. 1992; Hatfield and Pfister 1972; Johnson and Gabow 1997; O'Neill et al. 2005; Parfrey et al. 1990). Churchill and colleagues reported that although the probability of developing end-stage renal disease in ADPKD patients by age 58 was 0.53, a 95 percent confidence interval of 0.34 to 0.72 suggested that there was non-uniformity in progression to end-stage renal disease (Churchill et al. 1984). A study by Hatfield and colleagues reported that the frequency of finding a polycystic kidney during an autopsy of a person not clinically diagnosed with renal disease, was higher than the expected frequency suggested by the clinical prevalence of the disease (Hatfield and Pfister 1972). In a study of 17 families with ADPKD, Parfrey et al. found that 50 percent of ADPKD patients at age 58 years were alive and had not reached end-stage renal disease (Parfrey et al. 1990).

Factors Affecting Disease Progression in ADPKD

Studies reporting non-uniform progression towards end-stage renal disease in individuals with ADPKD, have suggested the presence of underlying factors in addition to the mutated PKD genes that may contribute to disease progression (Gabow et al. 1992). Gabow et al. in their study of 580 subjects with ADPKD, identified that the PKD-1 gene, younger age at diagnosis, male gender , hypertension, increased left ventricular mass, liver cysts in women, three or more pregnancies, gross hematuria i.e. blood in urine, urinary tract infection in men and renal volume were markers of disease progression and poor renal outcomes (Gabow et al. 1992). O'Neill et al. documented that increasing total renal volume was associated with disease progression (O'Neill et al. 2005). Johnson et al. reported that other than having the PKD gene, factors associated with higher risk of disease progression included being diagnosed after the age of 30 years, presenting hypertension before the age of 35 years, and having an episode of gross hematuria (blood in urine) before the age of 30 years (Johnson and Gabow 1997).

Chapman reported that outcome measures of renal disease progression accepted by the Food and Drug Administration include frequency or time to end-stage renal disease, doubling of serum creatinine, change in the rate of loss of renal function (serum creatinine, reciprocal of serum creatinine, or glomerular filtration rate [GFR]), change in proteinuria, protocol biopsy and death (Chapman 2008), Prior evidence has shown that cystic growth and expansion is a gradual process and ADPKD remains asymptomatic for several decades before renal dysfunction manifests itself (Chapman 2008; Chapman et al. 2003; Grantham 2008; Grantham, Chapman, and Torres 2006; Wilson 2004). Hence,

recent studies suggest using total kidney volume as a more reliable marker of disease progression and recommend its use as a surrogate marker in clinical trials of potential therapies for ADPKD (Chapman 2008; Grantham, Chapman, and Torres 2006).

Renal Manifestations of ADPKD

Renal manifestations of ADPKD are associated with both the rate and extent of cystic growth and development. A summary of literature regarding renal manifestations of ADPKD and, brief descriptions of structural and functional changes in the kidneys and resulting morbidity are presented below.

Renal Size and Volume

A longitudinal mapping of 241 patients with ADPKD using magnetic resonance imaging, found that total cyst volume and kidney volume increase as the disease progresses (Chapman et al. 2003; Grantham, Chapman, and Torres 2006). The cohort demonstrated gradual decrease in kidney function, measured by the glomerular filtration rate, with increasing kidney volumes and cyst volumes (Chapman 2008). Thomsen et al. studied 43 adults with PKD and compared their kidney volumes and kidney function to 497 persons with no evidence of kidney disease. Compared to persons with no renal disease, the mean kidney volume for PKD patients with normal kidney function was 1,212 (standard deviation ± 411) cm^3 whereas the mean kidney volume for PKD patients with severely decreased function was almost twice as high 2,053 (standard deviation ± 698) cm^3. (Thomsen et al. 1981). Franz and Reubi determined that renal volume and

glomerular filtration had a negative curvilinear association such that the rate of decline in glomerular filtration rate was gradual up to a point where the kidneys became substantially enlarged and rapid once a critical size had been reached (Franz and Reubi 1983). Fick-Brosnahan et al. in their longitudinal study of 229 patients with PKD also reported an inverse relationship between absolute kidney volume and glomerular filtration rate and suggested that the rate of renal volume growth may be a clinically significant surrogate marker of disease progression in ADPKD (Fick-Brosnahan et al. 2002).

Prior studies of ADPKD patients have reported that growing kidney volume and resultant abdominal enlargement affect posture, cause chronic lower back pain, early satiety, cause breathing trouble and sleep disturbance by impairing motion of the diaphragm, and raise concerns about body image (Grantham, Chapman, and Torres 2006; Perrone 2010). Research reports also indicate that enlarged kidneys may increase the risk of injury from use of seat-belts that may result in cyst rupture and hematuria (Amend and Galen 1973; Grantham, Chapman, and Torres 2006; Perrone 2010).

Renal Insufficiency and Failure

Development of urinary concentration defects, glomerular hyperfiltration, development of hypertension and reduction in renal blood flow occur with progression of ADPKD (Bouby et al. 1990; Bouby, Hassler, and Bankir 1999; Chapman et al. 1990; Torres, Keith, et al. 1994; Torres et al. 1991; Watson et al. 1992; Wong et al. 2004; Bankir et al. 1993). In an early longitudinal study of 346 persons with polycystic kidneys in Denmark, Dalgaard reported a positive association between presence of renal cysts and

renal insufficiency (Dalgaard 1957). Case studies, however, have reported variable observations regarding development of renal insufficiency and renal failure in ADPKD patients (Franz and Reubi 1983; Higgins 1952; Milutinovic et al. 1984; Rall and Odel 1949; Simon and Thompson 1955). Prior research findings indicate that renal parenchyma not affected by cysts compensate for the loss of glomerular filtration units to cysts (Grantham 2008; Torres and Grantham 2007). Grantham et al. summarized that despite development of cysts from childhood, compensatory mechanisms ensure that kidney function of a diseased individual may be indistinguishable from that of a normal individual (Grantham 2008).

Renal function in individuals with ADPKD declines around the fourth or fifth decade of life, with an annual rate of decline in glomerular filtration rate ranging from 4.4 to 5.9 mL/min per year (Torres and Harris 2009). Mitcheson and colleagues reported that approximately 70 percent of patients with ADPKD developed renal insufficiency if they survived to age 65 (Mitcheson, Williams, and Castro 1977). Churchill et al. found that the probability of being alive and not having renal failure was 77 percent by age 50, 57 percent by age 58, and 52 percent by age 73 (Churchill et al. 1984).

Pain

Pain is the most often reported symptom among patients with ADPKD and often leads to initial diagnosis (Thanos, Farmakis, and Davillas 1989; Demetriou et al. 2000; Segal, Spataro, and Barbaric 1977; Milutinovic et al. 1990). Bajwa et al. found that approximately 60 percent of ADPKD patients experienced flank pain with or without hematuria (Bajwa et al. 2001; Bajwa et al. 2004). Bajwa et al. studied 177 ADPKD

patients and classified patterns of pain (Bajwa et al. 2004). The most common type of pain was that of the lower back (71.3 percent), followed by abdominal pain (61.4 percent) (Bajwa et al. 2004). Of those reporting abdominal pain, the experience of pain was described as dull (49.5 percent), uncomfortable fullness (42.7 percent), stabbing pain (40.4percent), and cramping pain (33 percent) (Bajwa et al. 2004).

In children with ADPKD, pain is a common phenomenon despite the finding that hematuria was rarely reported (Bajwa et al. 2001; Bajwa et al. 2004; Fick et al. 1994; Fick et al. 1993; Fick-Brosnahan et al. 2001). On the other hand, cyst rupture or hemorrhage, infection in cysts, passage of kidney stones and pyelonephritis have been reported as common causes of pain among adults with ADPKD (Bajwa et al. 2001; Bajwa et al. 2004; Fick et al. 1994; Fick et al. 1993; Fick-Brosnahan et al. 2001). Hemorrhage from trauma to polycystic kidneys has been reported to occur in approximately 60 percent of individuals (Gabow et al. 1992; Gabow, Duley, and Johnson 1992; Dalgaard 1957). Presence of pain, hematuria and renal stones have been reported to have a positive correlation with extent of kidney enlargement (Gabow et al. 1990; Johnson and Gabow 1997).

Hypertension

Renal cyst enlargement causes alterations in renal vasculature causing diminished supply of oxygen to tissues and stimulating release of renin and activation of the renin-angiotensin-aldosterone system (Lawson, Doulton, and MacGregor 2006; Chapman et al. 1990; Doulton et al. 2006; Schrier 2009; Torres et al. 1992; Torres et al. 1991). The renin-angiotensin-aldosterone system regulates the body's mean arterial blood pressure

and activation of this pathway in persons with ADPKD results in hypertension and cystic growth (Chapman et al. 1990). A positive association between hypertension and renal size in ADPKD is a common finding across several studies (Gabow 1993; Gabow et al. 1990; Gabow, Duley, and Johnson 1992; Gabow et al. 1992; Ong and Harris 2005; Chapman 2003; Martinez and Grantham 1995; Chapman et al. 2003; Fick-Brosnahan et al. 2002; Kelleher et al. 2004; Nicolau et al. 2000; Thomsen et al. 1981; Chapman and Schrier 1991; Schrier, McFann, and Johnson 2003; Seeman et al. 2003; Grantham 1997; Seeman et al. 1997).

Kelleher et al. reported presence of hypertension, blood pressure greater than 140/90 mm Hg, was present in approximately 50 percent of patients aged 20 to 34 years with ADPKD and normal renal function and in 100 percent of patients with end-stage renal disease (Kelleher et al. 2004). In a cross-sectional study of 241 patients with ADPKD, higher mean kidney volume was observed in hypertensive patients than in the normotensive group (Chapman et al. 2003). Early diagnosis of hypertension is essential to delay development of and control risk of morbidity associated with cardiovascular disease (Iglesias et al. 1983; Ecder et al. 2000; Fick et al. 1995). However, Torres et al. report that the diagnosis of hypertension in ADPKD is often delayed (Torres, Harris, and Pirson 2007). Prior reports have shown that hypertension had occurred before the renal function decline was detected in persons with ADPKD and that hypertension was associated with faster progression to end-stage renal disease and increased mortality from cardiovascular disease (Fick et al. 1995; Gabow et al. 1990; Gabow et al. 1992).

Renal Stones

Persons with ADPKD develop kidney stones caused by calcification in cysts as well as calcification in renal cells un-affected by cysts (Grampsas et al. 2000; Torres et al. 1988; Levine and Grantham 1992; Dimitrakov and Simeonov 1994). Prior studies have found that about 20 to 36 percent of persons with ADPKD had renal stones (Dimitrakov and Simeonov 1994; Levine and Grantham 1992; Torres et al. 1988). Since Torres et al. and Dimitrakov et al. found that only 20 to 28 percent of ADPKD patients had symptomatic renal stones, it is important to note that symptoms from kidney stones remain hidden in a majority of ADPKD patients (Dimitrakov and Simeonov 1994; Torres et al. 1988). Grampsas et al. have reported that higher cyst numbers and larger cysts were observed in patients with stones compared to patients without renal stones (Grampsas et al. 2000). Patients with ADPKD-related renal stones have been reported to have flank pain, pain from urinary tract obstruction, hematuria and urinary tract infection (Masoumi et al. 2008).

Proteinuria

In persons with ADPKD, presence of proteinuria or excessive excretion of essential proteins in urine, is considered to be indicative of disease progression (Masoumi et al. 2008). Two studies have found that proteinuria is more pronounced in ADPKD patients with the PKD-1 mutation than those ADPKD patients with the PKD-2 mutation (Chapman et al. 2003; Grantham, Chapman, and Torres 2006). In a study of 270 patients with ADPKD, Chapman et al. reported that18 percent were diagnosed with proteinuria

and all patients with proteinuria presented with concomitant hypertension (Chapman et al. 1994). The authors also reported that proteinuria was associated with advanced renal functional decline, advanced disease progression, hypertension and hematuria (Chapman et al. 1994).

Extra-Renal Manifestations of ADPKD

ADPKD may be associated with polycystic liver disease, cysts in seminal vesicles, pancreas and arachnoid membrane, intracranial aneurysms and colonic diverticulitis (Danaci et al. 1998; Wijdicks, Torres, and Schievink 2000; Schievink et al. 1995; Alehan, Gurakan, and Agildere 2002; Nicolau et al. 2000; Grantham 2008; Torres, Harris, and Pirson 2007; Pirson, Chauveau, and Torres 2002). A summary of literature on extra-renal manifestations of ADPKD are presented below.

Polycystic Liver Disease

Polycystic liver disease is the most common extra-renal manifestation in adults with ADPKD (80 percent of patients), however, hepatic cysts are rare in children (Torres, Harris, and Pirson 2007). Bae and associates reported that the prevalence of liver cysts was 58 percent in 15 to 24 year olds, 85 percent in 25 to 34 year olds, and 94 percent in 35 to 46 year olds (Bae et al. 2006). Studies by Torres et al. and Telenti et al. showed that complications related to liver cysts may lead to symptoms including, dyspnoea, early satiety, gastroesophageal and mechanical lower-back pain, cyst hemorrhage, infection, torsion or rupture (Torres, Rastogi, et al. 1994; Telenti et al. 1990).

Cysts in Other Organs

Cysts in other organs of persons with ADPKD including the seminal vesicles (40 percent of men), pancreas (5 percent of ADPKD patients), and arachnoid membrane (8 percent of ADPKD patients) have been reported (Danaci et al. 1998; Wijdicks, Torres, and Schievink 2000; Schievink et al. 1995; Alehan, Gurakan, and Agildere 2002; Nicolau et al. 2000). Although reports of cysts in seminal vesicles have come from case reports (Shefi et al. 2009; Vecchi et al. 2003; Kanagarajah, Ayyathurai, and Lynne 2012) and cross-sectional studies (Torra et al. 2008) minimal clinical consequences have been found (Vecchi et al. 2003). Although pancreatic cysts have been reported in persons with ADPKD, the occurrence are mostly asymptomatic (Naitoh et al. 2005; Sakurai et al. 2001; Başar et al. 2006). Case studies by Wijdicks et al. and Abderrahim et al. reported sub-arachnoid membrane cysts and associated increased risk of subdural hematomas in ADPKD patients (Wijdicks, Torres, and Schievink 2000; Abderrahim et al. 2004).

Vascular Manifestations

Vascular manifestations of ADPKD include intracranial aneurysms and dolichoectasias, thoracic aortic and cervicocephalic artery dissections, and coronary artery aneurysms (Griffin et al. 1997; Torres et al. 2001; Qian et al. 2003). Intracranial aneurysms occur in approximately 6 percent of ADPKD patients with negative family history and 16 percent of those ADPKD patients with a positive history (Pirson, Chauveau, and Torres 2002). The incidence of rupture of intracranial aneurysms was 1 in 2,000 persons in a city-based population with ADPKD (Schievink et al. 1992), and this

rate was five-fold greater than in the general population (Ingall et al. 1989; Phillips et al. 1980). Rupture of intracranial aneurysms in ADPKD patients has a 35 percent to 55 percent risk of mortality (Chauveau et al. 1994; Schievink et al. 1992).

Cardiac Manifestations

Mitral valve prolapse is the most common valvular abnormality appearing in up to 25 percent of PKD patients on echocardiography (Hossack et al. 1988; Lumiaho et al. 2001). Among adults with ADPKD, the association between hypertension and increased risk of cardiovascular morbidity and mortality has been established (Fick et al. 1995; Gabow et al. 1990). Cadnapaphornchai reported that hypertension in children with ADPKD was associated with higher left ventricular mass index (Cadnapaphornchai et al. 2008, 2009). Children with borderline hypertension were also found to have increased left ventricular mass index as compared with affected children with lower blood pressure (Cadnapaphornchai et al. 2008).

Colonic Diverticular Disease

Colonic diverticular disease or diverticulosis is characterized by out-pocketing of the muscular wall of the colon and clinical manifestations including abdominal tenderness, fever and leukocytosis (Scheff et al. 1980). Scheff et al. in a retrospective study of individuals with PKD reported that colonic diverticula presented with complications such as sepsis resulting from rupture and death (Scheff et al. 1980). Scheff et al. also report that colonic diverticulosis is more common in patients with ADPKD and

end-stage renal disease (83 percent) than in those end-stage renal disease without ADPKD (32 percent) (Scheff et al. 1980). Similar trends were reported in two other research studies. McCune et al. found that colonic diverticulosis was present in 50 percent of ADPKD patients with end-stage renal disease versus 15 percent of patients with other causes of end-stage renal disease (McCune et al. 1992) and Lederman et al. found colonic diverticulosis in 20 percent of ADPKD patients with end-stage renal disease versus 3 percent of end-stage renal disease due to other causes (Lederman et al. 2000). Sharp et al. however, found that the occurrence of colonic diverticulosis did not differ between ADPKD patients without end-stage renal disease and the general population (Sharp et al. 1999).

Treatment of ADPKD

Medications commonly used to treat disease symptoms and complications of ADPKD include analgesics for pain, angiotensin-converting enzyme inhibitors to control hypertension, and antibiotics for cyst infection and urinary-tract infections associated with the disease (Torres, Harris, and Pirson 2007). To date, however, no clinical trial has shown benefit of renin-angiotensin-aldosterone system inhibition with anti-hypertensive medications on progression to end-stage renal disease or rate of glomerular filtration rate decline.

As cysts grow and proliferate, invasive surgical procedures including cyst drainage, renal denervation and nephropexy may be required to relieve intractable pain associated with the cysts (Badani, Hemal, and Menon 2004; Elzinga et al. 1992). No medication has been approved for controlling PKD cystogenesis. Findings from clinical

trials have provided evidence that a number of drugs including rapamycin (Walz et al. 2010), tolvaptan (Torres et al. 2011), bosutinib (National Institutes of Health 2011), pravastatin (Belibi and Edelstein 2010) and ocreotide (Ruggenenti et al. 2005) may reduce cystogenesis.

Disease Burden

Chronic kidney disease, regardless of its underlying cause, has been recognized as a source of substantial clinical and economic burden. Smith et al. reported that among enrollees of the Kaiser Permanente Northwest Region health maintenance organization, chronic kidney disease patients spent approximately $8,000 more than those without it and those with chronic kidney disease and chronic kidney disease-related comorbidities spent approximately $26,000 more on healthcare than those without chronic kidney disease (Smith et al. 2004). In an observational study of a general population, Baumeister et al. reported that persons with chronic kidney disease had approximately 68 percent higher drug costs, 60 percent higher inpatient costs, 48 percent higher drug costs and a 1.40 higher relative risk of hospitalization compared to persons without chronic kidney disease (Baumeister et al. 2010). Alexander at al. estimated all-cause health care utilization in a nationally representative population of persons with chronic kidney disease in the period from 1988 to 1994 and reported that individuals with late-stage chronic kidney disease reported higher mean number of hospitalizations (0.42 ± 0.03) than those without chronic kidney disease (0.15 ± 0.01) and mean number of annual physician visits (6.53 ± 0.38) compared to those without chronic kidney disease (3.51 ± 0.08) (Alexander et al. 2009).

Persons with chronic kidney disease incur substantial costs prior to end-stage renal disease and these expenses increase with deteriorating kidney function and onset of dialysis (Smith et al. 2004; London et al. 2002; Robbins et al. 2003). Robbins et al. reported that per-patient-per-month charges increased from $4,265 in the pre-dialysis period to $15,399 in the two to three months after dialysis initiation (Robbins et al. 2003).

PKD has been identified as the leading hereditary cause of end-stage renal disease in the United States and accounts for approximately five percent of all end-stage renal disease cases (United States Renal Data System 2011). Renal failure occurs by age 60 in approximately 50 percent of patients with ADPKD, requiring dialysis or kidney transplant (Grantham 2008). Lentine and colleagues estimated all-cause health care costs for persons with ADPKD, stratified those costs by kidney function and reported that advancing renal insufficiency was associated with higher health care expenditures (Lentine et al. 2010). However, Lentine et al. did not estimate incremental health care resource utilization or expenditures associated with ADPKD (Lentine et al. 2010).

Medical Resource Utilization and Expenditures

Studies that estimate expenditures and medical resource utilization associated with a disease, provide valuable insight regarding economic burden of the disease and indicate the potential savings that may be achieved if the disease were avoided, controlled or eliminated (Akobundu et al. 2006; Ament and Evers 1993; Lipscomb, Barnett, et al. 2009; Lipscomb, Yabroff, et al. 2009; Mushkin and Collings 1959; Rice, Hodgson, and Kopstein 1985; Rice 1994, 2000; Tarricone 2006; Wiseman and Mooney 1998). Data on health care expenditures and utilization inform public policy, allocation of scarce

resources towards prevention or treatment of a disease and assessment of financial strain a disease has on society, the health care system, stakeholders such as payers, businesses, and the government and on patients and their families (Segel 2006; Finkelstein, Fiebelkorn, and Wang 2003; Taylor and Sloan 2000; Miller et al. 1998; Thompson et al. 1998; Goetzel et al. 2004; Hodgson and Meiners 1982). Monetary values of health care events are calculated as either all-cause estimates or incremental estimates. A brief description of methods of cost estimation is presented below.

All-Cause or Sum of all Costs Approach

The all-cause approach estimates total expenditure or utilization of persons diagnosed with the disease. When estimating all-cause utilization or expenditures among persons diagnosed with the disease, all patients with a diagnosis of the disease are identified and all health care utilization as well as health care expenditures are added up, regardless of whether these costs directly relate to the disease of interest (Akobundu et al. 2006). This method is advantageous for its simplicity but has been reported to overestimate the cost of diseases which are associated with many comorbidities (Cummings et al. 2002). Akobundu et al. state that the all-cause method is better suited for making cross-country comparisons regarding burden of illness estimates rather than presenting an absolute statement about burden (Akobundu et al. 2006).

Incremental Approach

The incremental approach estimates the burden directly associated with the disease in particular. There are two methods of calculating incremental estimates: the matching method and the regression method. In the matching method persons with the disease are identified and matched with a cohort of persons without the disease. Persons with the disease are matched with those without the disease on specific demographic characteristics including age, gender and race (Balu and Thomas 2006; Birnbaum et al. 2004; Gabriel et al. 2002). Incremental burden of the disease is calculated by subtracting health care resource utilization or expenditures of persons without the disease from corresponding resource utilization or expenditures of persons with the disease. The matching method is based on the premise that the matching process accounts for all differences between the cohort with the disease and the one without, such that the only remaining difference between them is the presence of the disease (Akobundu et al. 2006). Akobundu et al. highlight that the matched control method is a simple technique of estimating costs of illness but identification of all relevant comorbid conditions as well as potential demographic variables is essential for obtaining accurate estimates (Akobundu et al. 2006).

The regression method has been used by researchers to estimates excess medical cost of treating a particular disease (Balu and Thomas 2006; Birnbaum et al. 2004; Gabriel et al. 2002; Lozano et al. 1997; Martin et al. 2000). In this method, a regression equation a adjusting for comorbidities and other relevant variables is used to estimate incremental costs associated with a disease (Lee, Meyer, and Clouse 2001; Lozano et al.

1997; Martin et al. 2000). Total costs for patients with the disease are compared to total costs among patients without the disease, and the difference is the estimated regression parameter from an equation such as:

$$\text{Cost} = \beta_0 + \beta_1 \text{Disease} + \beta_2 \text{Demographic}_1 + \beta_3 \text{Demographic}_2 + \beta_4 \text{Comorbidity}_1 + \beta_5 \text{Comorbidity}_2 + \varepsilon$$

where, "Disease" is a binary variable with a value of '1' for persons with the disease and '0' for persons without the disease, 'Demographic_1' and 'Demographc_2' representing relevant demographic characteristics that must be adjusted for, 'Comorbidity_1' and 'Comorbidity_2' representing two comorbid conditions and 'ε' is the error term. The incremental cost of the disease is given by the estimate of the parameter β_1. Controlling for comorbidities has been highlighted as a critical step of the regression method, and insufficient rigor can introduce misspecification bias into the regression parameter estimate (Akobundu et al. 2006; Lee, Meyer, and Clouse 2001). Lee et al. conclude that failing to adjust for sufficient comorbid conditions for may result in overestimation of costs or adjusting for all comorbidities may underestimate costs of illness (Lee, Meyer, and Clouse 2001). Akobundu et al. conclude that the regression method is the preferred method of cost estimation for diseases which are not associated with unobservable factors which may introduce bias (Akobundu et al. 2006).

Study Rationale

The United States Renal Data System reports annual estimates of prevalence of chronic kidney disease; however, this estimate does not provide a breakdown by cause of chronic kidney diseases. This study will provide a current description of epidemiology of ADPKD by estimating one year disease prevalence. There is limited evidence describing economic burden of ADPKD. Although one study estimated health care costs in ADPKD stratified by kidney function (Lentine et al. 2010), we found no study that assessed all-cause health care resource utilization or incremental impact of ADPKD on health care resource utilization and health care expenditures. Understanding incremental health care resource utilization and incremental expenditures associated with ADPKD would more likely give precise estimate of burden associated with the disease since the regression method will identify burden specific to ADPKD. The findings should provide valuable data on the societal impact of the disease.

Objectives

This study sought to determine the prevalence of ADPKD in a private pay population and to identify demographic and clinical characteristics of patients with PKD. Health care resource utilization and health care expenditures in persons with PKD was also assessed. The specific study objectives were to:

1. determine prevalence of ADPKD in a private-pay population,
2. determine all-cause health care resource utilization and expenditures among persons with ADPKD,

3. determine incremental health care resource utilization associated with ADPKD by categories including hospitalizations, hospital days, nursing home visits, nursing home length of stay, emergency room encounters and outpatient encounters, and
4. determine incremental health care expenditures associated with ADPKD by categories including total expenditures, hospital stay, nursing home stay, emergency room encounters, outpatient services and medication.

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METHODS

Study Design

An observational database analysis was conducted using information from a large administrative database. Individuals 18 years old or older with autosomal dominant PKD (ADPKD) were identified using International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes. Administrative claims data were used to calculate annual all-cause health care resource utilization for hospitalizations, hospital days, nursing home confinements, nursing home days, emergency department visits and outpatient visits. All-cause heath care expenditures among individuals with ADPKD were characterized based on whether they were for hospital, nursing home, outpatient, emergency room or prescription services. A one-year study interval from April 1, 2011 through March 31, 2012 was used in the analysis.

Data Source

Health insurance claims data from a large administrative claims database between April 1, 2011 and March 31, 2012 were used for the study. The database included medical and pharmacy claims for 13 million privately-insured lives covering all census regions of the United States.

Ethical Consideration

Institutional Review Board approval for the study was obtained from the Committee on the Use of Human Subjects in Research at Purdue University, West Lafayette, Indiana.

Study Sample

Analytic samples were drawn based on each study objective. The inclusion criteria and exclusion criteria for each analytic sample are described below.

Prevalence of ADPKD

Individuals 18 years of age or older and enrolled in a tracked health plan anytime during the period from April 1, 2011 through March 31, 2012, were eligible for inclusion in the sample for determination of ADPKD prevalence. No exclusion criteria were specified for this prevalence sample.

All-Cause Health Care Resource Utilization and Expenditures

Individuals 18 years of age or older, enrolled in a tracked health plan for twelve months in the period from April 1, 2011 through March 31, 2012, and having an ICD-9-CM diagnosis code for "polycystic kidney, autosomal dominant" (753.13) or for "polycystic kidney, unspecified type (753.12) were eligible for inclusion in the analytic sample. Persons having ICD-9-CM diagnosis codes for "polycystic kidney, autosomal recessive" (753.14) or "cystic kidney disease" (753.1) were excluded from the sample.

Incremental Health Care Resource Utilization and Expenditures

The sample for analysis of incremental health care utilization and expenditures used the same inclusion and exclusion criteria as the one for all-cause analysis. Individuals 18 years of age or older, enrolled in a tracked health plan for twelve months in the period from April 1, 2011 through March 31, 2012, and having an ICD-9-CM diagnosis code for “polycystic kidney, autosomal dominant” (753.13) or for “polycystic kidney, unspecified type (753.12) were eligible for inclusion in the analytic sample. Persons having ICD-9-CM diagnosis codes for “polycystic kidney, autosomal recessive” (753.14) or “cystic kidney disease” (753.1) were excluded from the analytic sample.

This sample was linked to comparison individuals without ADPKD on age and gender. To be included in the non-PKD group, an individual had to be 18 years of age or older by April 1, 2011 and enrolled in a tracked health plan for twelve months between April 1, 2011 through March 31, 2012. Exclusion criteria for the comparison group were having “polycystic kidney, autosomal recessive” (753.14) or “cystic kidney disease” (753.1), chronic kidney disease stage three to stage six (585, 585.3, 585.4, 585.5, 585.6, 585.9, 586), nephrotic syndrome (581, 581.0, 581.1, 581.2, 581.3, 581.8, 581.9, 581.81, 583.81, V13.03), diabetic kidney disease (250.4, 250.40, 250.41, 250.42, 250.43, 249.4, 249.40, 249.41), or kidney stones associated with cystic kidney disease (diagnosis code: 274.11, procedure codes: 55.03, 55.04, 59.95, 56.0, 98.5, 98.51).

Study Variables

All-Cause Health Care Resource Utilization

All-cause health care resource utilization among persons with ADPKD was estimated from patients' insurance claims during the period from April 1, 2011 through March 31, 2012, for number of hospitalizations, hospital days, nursing home confinements, nursing home days, outpatient visits and emergency room visits. Total number of hospitalizations and nursing home stays were determined by identifying and counting the number of unique confinements per patient. Claims for outpatient facilities or emergency rooms were identified by the place of service and provider category associated with the claim. Each visit to an outpatient facility or emergency room had a unique claim identification number, and multiple claims from the same visit were had a claim sequence number each. In the first step, sub-claims were collapsed such that each visit had only record. One visit at an outpatient facility or an emergency room was defined as a summation of all visits to that facility per day. For example, if a patient visited his primary physician's office three times in one day and on the same day, visited a particular laboratory twice, the resultant visit count for that day was one visit each for a physician office and for a laboratory. The total number of visits per patient for emergency rooms and outpatient facilities were counted and reported.

All-Cause Health Care Expenditures

All-cause heath care expenditures among individuals with ADPKD were characterized based on whether they are for hospital, nursing home, outpatient, emergency room, or prescription services during the one year period from April 1, 2011 through March 31, 2012. To account for pricing variation across providers or geographic regions, standard prices in the database reflected allowed payments from a single source with a consistent payment plan. The standardized prices have been used in analysis of expenditures reported in prior literature (Kimball et al. 2011; Vekeman et al. 2011).

For inpatient expenditures, standard cost of the inpatient admission as a whole were added to professional fees associated with the confinement, but billed externally. Total hospitalization costs per patient were calculated by adding expenditures from all general hospital episodes. Total nursing home expenditures per patient were calculated by summing expenditures from all nursing home confinements. In this study, sub-claims were collapsed such that each visit to an emergency room or an outpatient facility per day was represented by a single record. If there were multiple visits to the same facility on the same day, a visit-level summation of expenditures was generated to obtain one record per visit (outpatient facility or emergency room) per day. Total annual emergency room expenditures as well as total annual outpatient expenditures per patient were calculated by adding facility-specific expenditures for the patient in the specified one-year period. Total annual prescription expenditures per patient, were calculated by adding standard prices for all medication claims during the specified one year period.

Demographic Variables

Demographic variables used in the study included age, gender and geographical region. Gender was coded as female or male. Geographical region were classified into four regions including Midwest, Northeast, South and West.

Clinical Variables

Charlson Comorbidity Index

The Charlson Comorbidity Index consists of eighteen categories of comorbidity, which are defined using ICD-9 diagnosis codes. Higher comorbidity scores indicated a more severe burden of comorbidity. A modified Charlson comorbidity index developed by Romano et al. was constructed in which renal diseases were excluded in the computation of comorbidity index scores was calculated for each individual, based on claims between April 1, 2011 through March 31, 2012 (Romano, Roos, and Jollis 1993).

Cardiovascular Disease

The presence of cardiovascular disease in the sample was defined by administrative claims with corresponding ICD-9 diagnosis codes for angina pectoris, myocardial infarction, congestive heart failure or stroke/transient ischemic attack during the one year period from April 1, 2011 through March 31, 2012. The list of codes for cardiovascular disease were obtained from an online searchable 2009 ICD-9-CM and Medical Terminology dictionary (Anonymous 2009).

Diabetes

The presence of diabetes in the sample was defined by administrative claims with corresponding ICD-9 diagnosis codes for Type 1 diabetes mellitus, Type 2 diabetes mellitus or gestational diabetes during the one year period from April 1, 2011 through March 31, 2012. The list of codes for diabetes were obtained from an online searchable 2009 ICD-9-CM and Medical Terminology dictionary (Anonymous 2009).

Statistical Analysis

Data were analyzed using SAS for Unix Version 9.2 and STATA for Unix version 12. An *a priori* alpha level of 0.05 was used in all statistical analysis. Frequency distributions were developed and Chi-square tests were used to assess statistical differences between persons with or without ADPKD on demographic variables and clinical variables including age, gender, geographical region, Charlson Comorbidity Index (Charlson et al. 1987), cardiovascular disease and diabetes. Multivariate models in this study were adjusted for geographical region because of prior reports of variation in health care utilization and spending in different health care markets, above and beyond observable differences in demographics or disease severity (Philipson et al. 2010). Statistical analyses for each objective are explained in the sections below.

Prevalence of ADPKD

The number of individuals 18 years or older with ICD-9 diagnosis codes for “polycystic kidney, autosomal dominant” (753.13) or for “polycystic kidney, unspecified

type" (753.12), and enrolled anytime during the period from April 1, 2011 through March 31, 2012, were identified and divided by the total population of covered individuals 18 years or older, during the same one year period. A 95 percent confidence interval of the estimated prevalence was constructed.

All-Cause Health Care Resource Utilization

All-cause heath care resource utilization among individuals with ADPKD were characterized by number of hospitalizations, hospital days, nursing home confinements, nursing home days, outpatient visits and emergency room visits, during the one year period from April 1, 2011 through March 31, 2012. Unadjusted means, medians and 95 percent confidence intervals were computed for each utilization category. Wilcoxon Mann Whitney tests were used to detect differences between individuals with ADPKD and those without ADPKD, for each resource utilization variable.

All-Cause Health Care Expenditures

All-cause heath care expenditures among individuals with ADPKD were characterized for hospitals, nursing homes, outpatient services, emergency rooms, and prescription services during the one year period from April 1, 2011 through March 31, 2012. To account for pricing variation across providers or geographic regions, the database included standard prices that reflected allowed payments from a single source with a consistent payment plan. Unadjusted means, medians and 95 percent confidence intervals were computed for each expenditure category. Wilcoxon Mann Whitney tests

were used to detect differences between individuals with ADPKD and those without ADPKD, for each expenditure variable.

Incremental Health Care Resource Utilization Associated with ADPKD

Each individual with ADPKD was linked one-to-one based on age and gender with comparison individuals without PKD for estimation of incremental annual health care resource utilization associated with ADPKD. A systematic approach based on examination of data distributional characteristics and assessment of fit of alternative models was used to select a multivariate model for analysis. Residuals of ordinary least squares regression models with untransformed and models with log transformed utilization and expenditure variables were examined for violation of assumptions. P-values lower than 0.05 for each Kolmogorov-Smirnov test were used to assess whether residuals were normally distributed (D'Agostino and Stephens 1986). Glejser tests were used to investigate whether residuals were significantly associated with independent variables (Glejser 1969). Generalized linear models were also developed and tested for model fit. Presence of overdispersion of dependent variables was assessed using Vuong tests (Long and Freese 2006; Vuong 1989), and likelihood ratio tests and the z-test for alpha were used to determine comparative fit of alternative generalized linear models (Long and Freese 2006; Vuong 1989; Cameron and Trivedi 1986)

Individual regression models were developed to estimate independent association between ADPKD and utilization of health services such that individual models were developed for hospitalizations, hospital days, nursing home confinements, nursing home days, outpatient visits, and for emergency room visits. A binary predictor variable for

ADPKD was included in each model and covariates in each model included age, gender, co-morbidity index score, cardiovascular disease, diabetes and geographical region, to adjust for those risk factors. The general regression model developed for estimating incremental health care resource utilization is shown below:

$$\text{Resource Utilization} = \beta_0 + \beta_1\,\text{ADPKD} + \beta_2\,\text{Age} + \beta_3\,\text{Gender} + \beta_4\,\text{Cardiovascular Disease} + \beta_5\,\text{Diabetes} + \beta_6\,\text{Geographical Region (Midwest)} + \beta_7\,\text{Geographical Region (West)} + \beta_8\,\text{Geographical Region (South)} + \varepsilon$$

where, "Resource Utilization" is the dependent variable for a type of health care resource utilization including hospitalizations, hospital days, nursing home confinements, nursing home days, outpatient visits, or emergency room visits. "ADPKD" is a binary variable with a value of '1' for persons with ADPKD and '0' for persons without ADPKD. 'Age' is a continuous variable that represents the age of the individual. "Gender" is a binary variable with a value of '1' for males and '0' for females. "Cardiovascular Disease" is a binary variable with a value of '1' for persons with cardiovascular disease and '0' for persons without cardiovascular disease. "Diabetes" is a binary variable with a value of '1' for persons with diabetes and '0' for persons without diabetes. "Geographical Region (Midwest)", Geographical Region (West) and Geographical Region (South) are dummy variables for geographical region. 'ε' is the error term and incremental resource utilization associated with the disease is the estimate of the parameter β_1, which is the regression coefficient of the independent variable "ADPKD".

Incremental Health Care Expenditures Associated with ADPKD

For analysis of incremental health care expenditures associated with ADPKD, regression models similar to those developed for analysis of incremental resource utilization were developed. A systematic approach, similar to that used for selecting a model for estimating incremental resource utilization, based on examination of data distributional characteristics and assessment of fit of alternative models, was used to select a multivariate model for analysis of incremental expenditures. Individual regression models were developed to estimate independent association between ADPKD and total expenditures, hospital expenditures, nursing home expenditures, outpatient expenditures, emergency room expenditures, and medication expenditures. A binary predictor variable for ADPKD was included in each model. Covariates in each model included age, gender, co-morbidity index, cardiovascular disease, diabetes and geographical region, to adjust for any differences between the ADPKD group and the comparison group without ADPKD. The formula for the general regression model developed for estimating incremental health care expenditures is given below:

$$\text{Expenditure Category} = \beta_0 + \beta_1\,\text{ADPKD} + \beta_2\,\text{Age} + \beta_3\,\text{Gender} + \beta_4\,\text{Cardiovascular Disease} + \beta_5\,\text{Diabetes} + \beta_6\,\text{Geographical Region (Midwest)} + + \beta_7\,\text{Geographical Region (West)} + \beta_8\,\text{Geographical Region (South)} + \varepsilon$$

where, “Expenditure Category” is the dependent variable for a type of health care expenditure including total expenditures, hospital expenditures, nursing home

expenditures, outpatient expenditures, emergency room expenditures, or medication expenditures. "ADPKD" is a binary variable with a value of '1' for persons with ADPKD and '0' for persons without ADPKD. 'Age' is a continuous variable that represents the age of the individual. "Gender" is a binary variable with a value of '1' for males and '0' for females. "Cardiovascular Disease" is a binary variable with a value of '1' for persons with cardiovascular disease and '0' for persons without cardiovascular disease. "Diabetes" is a binary variable with a value of '1' for persons with diabetes and '0' for persons without diabetes. "Geographical Region (Midwest)", "Geographical Region (West)", and "Geographical Region (South)" are dummy variables for geographical region. 'ε' is the error term and incremental expenditure associated with the disease is the estimate of the parameter β_1, which is the regression coefficient of the independent variable "ADPKD".

Sub-Group Analysis by whether Diagnosed with End-Stage Renal Disease

Sub-group analysis examined incremental resource utilization and expenditures associated with ADPKD across two sub-groups. ADPKD cases with a diagnosis of end-stage renal disease (ICD-9-CM code 586.6) and their linked comparison observations were one sub-group and cases without end-stage renal disease and their linked comparison observations formed the other sub-group. Individual regression models, as described for the overall analysis, were developed to estimate incremental resource utilization and expenditures by category for each sub-group adjusting for risk factors including age, gender, co-morbidity index, cardiovascular disease, diabetes and geographical region.

Notes

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RESULTS

Prevalence of ADPKD

Figure 1 shows the sample selection procedure and results for selection of the sample for determining prevalence of ADPKD. There were 10,500,664 persons at least 18 years old and enrolled during the period from April 1, 2011 through March 31, 2012. Of those10,500,664 persons, 5,878 individuals satisfied sample selection criteria of being at least 18 years old, enrolled anytime during the 12-month period from April 1, 2011 through March 31, 2012 and having an ICD-9-CM diagnosis code for "polycystic kidney, autosomal dominant" (753.13) or for "polycystic kidney, unspecified type (753.12). The prevalence of autosomal dominant PKD was one in 1,786 persons or 560 cases per million population. The 95 percent confidence interval for estimated prevalence was 1,742 to 1,833.

Demographic Characteristics of Prevalence Sample

Table 1 shows characteristics of the prevalence sample and compares it to the total population covered by the administrative database. In the prevalence sample, 81.9 percent of individuals with ADPKD were 35 years of age older. The proportion of females with ADPKD (53%) was higher than males with ADPKD (47%). The proportion of females in the total population was lower (50.2%) than the prevalence sample. There

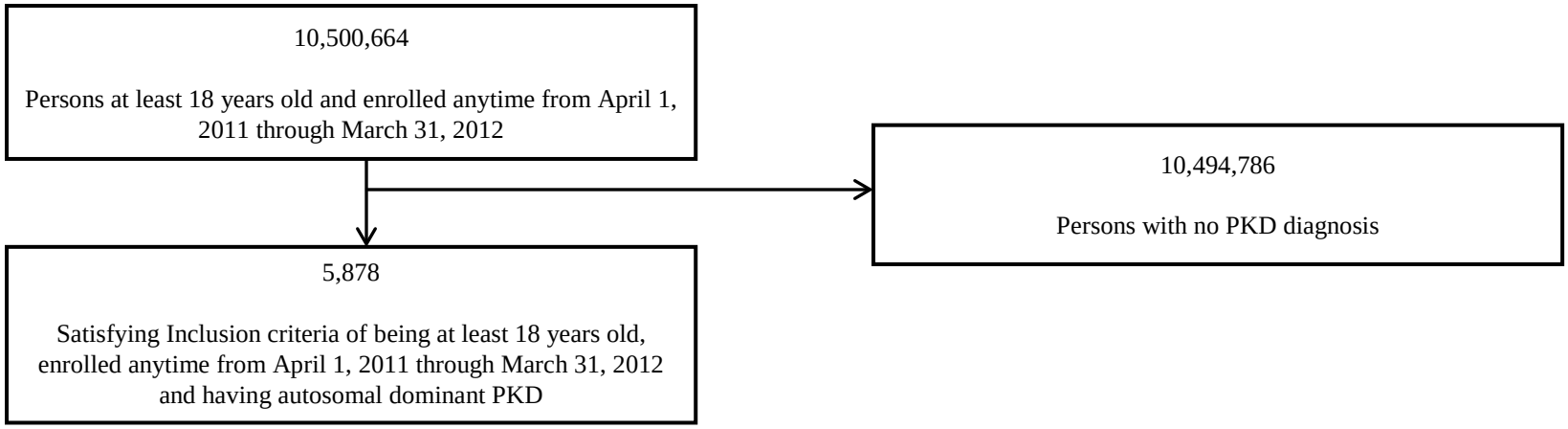

Figure 1. Sample Selection Results to Determine ADPKD Prevalence

Table 1. Demographic Characteristics of Prevalence Sample

Characteristic	With ADPKD (n=5,878) Number (Percent)	Total Covered Population (n=10,494,786) Number (Percent)	p-value[a]
Age			
Under 35	1,062 (18.1)	3,546,924 (33.8)	<0.001
35 to 44	1,206 (20.5)	2,271,320 (21.6)	0.036
45 to 54	3,060 (52.0)	4,083,630 (38.9)	<0.001
65 and over	550 (9.4)	591,912 (5.6)	<0.001
Gender			
Female	3,116 (53.0)	5,271,621 (50.2)	<0.001
Male	2,762 (47.0)	5,222,341 (49.8)	<0.001
Missing/Unknown	-	824 (0.0)	-
Region			
Midwest	1,550 (26.4)	2,722,158 (25.9)	0.45
Northeast	607 (10.3)	1,046,279 (10.0)	0.36
South	2,760 (47.0)	4,914,171 (46.8)	0.84
West	960 (16.3)	1,805,781 (17.2)	0.075
Missing/Unknown	-	6,398 (0.1)	-

[a] The p-value is based on z-test for two population proportions

was no difference in the proportions of individuals with ADPKD versus the proportion of individuals in the population by geographical region.

All-Cause Resource Utilization and Expenditures

Sample Characteristics

Figure 2 shows the sample selection procedure and results for selection of the sample for determining all-cause resource utilization and expenditures as well as for determining incremental resource utilization and expenditures. Out of 10,500,664 persons covered in the database, 4,020 individuals satisfied sample selection criteria of being at least 18 years old, enrolled continuously for the 12-month period from April 1, 2011 through March 31, 2012 and having a diagnosis for autosomal dominant PKD. After excluding 115 individuals who either had a diagnosis of autosomal recessive PKD or unspecified cystic kidney disease, and 61 persons who had no medical claim information, a total of 3,844 individuals remained in the ADPKD group. The individuals with a diagnosis for ADPKD were linked one-to-one with individuals without ADPKD, resulting in 3,844 persons in the comparison group and a total of 7,688 persons in the sample for determining all-cause resource utilization and expenditures and determining incremental resource utilization and expenditures. Sample characteristics are described in each of the sections below.

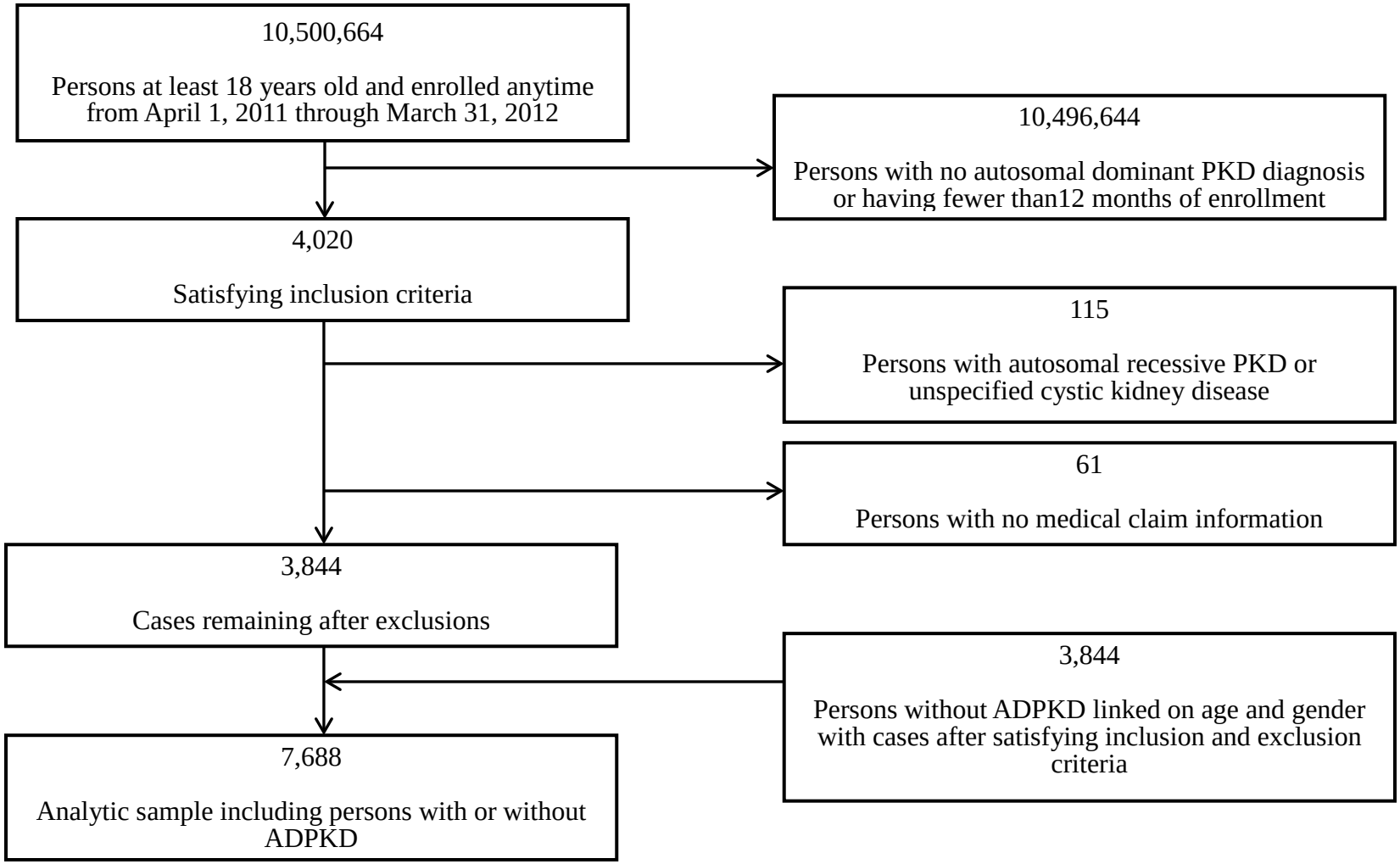

Figure 2. Sample Selection Results to Determine All-Cause and Incremental Health Care Resource Utilization and Expenditures

Age

Table 2 shows that approximately 55 percent of the sample was between 45 to 64 years old. Since persons with ADPKD were linked one-to-one on age with a comparison sample of persons without ADPKD, no significant differences were observed on age between persons with ADPKD and those without ADPKD. The mean age of the sample was 49.15 years with a standard deviation of 13.67.

Gender

Table 3 shows sample distribution based on gender. The proportion of females with ADPKD was higher (53.2%) than males with ADPKD (46.8%). Since persons with ADPKD were linked one-to-one on gender with a comparison sample of persons without ADPKD, no significant gender differences were observed between person with ADPKD and those without ADPKD.

Charlson comorbidity Index

Table 4 describes the distribution of the study sample and compares persons with ADPKD and those without ADPKD with respect to Charlson Comorbidity Index scores. Fifty-three percent of the sample had a Charlson comorbidity score of zero indicating that they did not have any of the comorbid conditions listed in the Charlson Comorbidity Index, other than renal diseases, which were excluded from the algorithm for calculating the scores. Approximately, 19 percent of the sample had a score of one and 11 percent of

the sample had a score of two. Individuals with a score of three or more constituted 17.1 percent of the sample.

Among individuals with ADPKD, 44.2 percent had a Charlson comorbidity score of zero indicating that they did not have any of the comorbid conditions listed in the Charlson Comorbidity Index. In comparison, a significantly higher proportion of individuals in the comparison group without ADPKD (62.5%) had Charlson Comorbidity Index scores greater than zero indicating that persons with ADPKD had more comorbidities compared to persons without ADPKD. Significantly higher proportions were observed for individuals in the ADPKD group for each level of Charlson Comorbidity Index score above zero, compared to the those individuals without ADPKD, for a Charlson score of '1' (20.3 percent vs. 17.3 percent, $p=0.003$), for a Charlson score of '2' (12.1 percent vs. 9.3 percent, $p=0.003$), for a Charlson score of '3' (8.1 percent vs. 4.7 percent, $p<0.001$), for a Charlson score of '4' (5.0 percent vs. 2.3 percent, $p<0.001$), for a Charlson score of '5' (3.1 percent vs. 1.3 percent, $p<0.001$), and also for a Charlson score of '6 or more' (7.2 percent vs. 2.6 percent, $p<0.001$).

Cardiovascular Disease

The sample distribution based on presence of cardiovascular disease is shown in Table 5. Cardiovascular disease was present 19.4 percent of the overall sample. Among persons with ADPKD, a total of 983 persons or 25.6 percent had a diagnosis of cardiovascular disease. This proportion was significantly higher than for persons without ADPKD, among whom 510 persons or 13.3 percent had cardiovascular disease.

Diabetes

The sample distribution based on presence of diabetes is shown in Table 5. Diabetes was present in a total of 926 persons or 19.4 percent of the overall sample. Among persons with ADPKD, 14.1 percent had a diagnosis of diabetes, which was significantly higher than among persons without ADPKD, where 10.0 percent had with diabetes.

Geographical Region

Table 6 shows the distribution of the sample by geographical region. The sample was divided into four regions including the Midwest, Northeast, South and West. The largest proportion of the sample was from the South (44.9 percent), followed by the Midwest (27.2 percent) and the West (17.4 percent). Among persons with ADPKD, a total of 1,777 persons or 46.2 percent were from the South. The proportion of individuals from the comparison group without ADPKD from the South was not significantly different, 43.7 percent. Similarly, there were no differences observed in the proportion of ADPKD patients by geographical region when compared to the proportion of persons without ADPKD from the Midwest, Northeast or the West.

ADPKD Complications

The presence of specific ADPKD complications including liver cysts, kidney stones, urinary tract infection or cerebral aneurysm during the period from April 1, 2011 through March 31, 2012 were detected using ICD-9-CM diagnosis codes reported in

Table 2. Distribution of Study Sample by Age (n=7,688)

Age	Number (n=7,688)	Percent
Under 35	1,242	16.2
35 to 44	1,496	19.5
45 to 54	2,086	27.1
55 to 64	2,118	27.5
65 and over	746	9.7

The mean age ± standard deviation of the sample was 49.15 ± 13.67.

Table 3. Distribution of Study Sample by Gender (n=7,688)

Gender	Number (n=7,688)	Percent
Female	4,094	53.2
Male	3,594	46.8

Table 4. Distribution of Total Study Sample and Distribution of Persons with or without ADPKD by Charlson Comorbidity Index

Charlson Comorbidity Index	Total Sample (n=7,688) Number (Percent)	With ADPKD (n=3,844) Number (Percent)	Without ADPKD (n=3,844) Number (Percent)	p-value[a]
0	4,103 (53.4)	1,700 (44.2)	2,403 (62.5)	<0.001
1	1,447 (18.8)	781 (20.3)	666 (17.3)	0.003
2	823 (10.7)	464 (12.1)	359 (9.3)	0.003
3	491 (6.4)	312 (8.1)	179 (4.7)	<0.001
4	280 (3.6)	192 (5.0)	88 (2.3)	<0.001
5	169 (2.2)	120 (3.1)	49 (1.3)	<0.001
6 or more	375 (4.9)	275 (7.2)	100 (2.6)	<0.001

[a] The p-value is based on Chi-square tests

Table 5. Distribution of Total Study Sample and Distribution of Persons with or without ADPKD by Presence of Cardiovascular Disease and Presence of Diabetes

	Total Sample (n=7,688)	With ADPKD (n=3,844)	Without ADPKD (n=3,844)	
Disease	Number (Percent)	Number (Percent)	Number (Percent)	p-value[a]
Cardiovascular disease	1,493 (19.4)	983 (25.6)	510 (13.3)	<0.001
Diabetes	926 (12.0)	542 (14.1)	384 (10.0)	<0.001

[a] The p-value is based on Chi-square tests

Table 6. Distribution of Total Study Sample and Distribution of Persons with or without ADPKD by Geographical Region

	Total Sample (n=7,688)	With ADPKD (n=3,844)	Without ADPKD (n=3,844)	
Region	Number (Percent)	Number (Percent)	Number (Percent)	p-value[a]
Midwest	2,101 (27.2)	1,008 (26.2)	1,093 (28.4)	0.063
Northeast	801 (10.4)	419 (10.9)	382 (10.0)	0.190
South	3,455 (44.9)	1,777 (46.2)	1,678 (43.7)	0.092
West	1,327 (17.4)	640 (16.7)	687 (17.9)	0.190

[a] The p-value is based on Chi-square tests

Table 7. Number of Complications among Persons with ADPKD[a]

Number of Complications	Number (n=3,844)	Percent
0	2,937	76.4
1	776	20.1
2	127	3.3
3	7	0.2
4	0	0

[a] Number of ADPKD complications, including liver cysts, kidney stones, urinary tract infection or cerebral aneurysm, ranging from 0 (no ADPKD complication) to 4 (up to four ADPKD complications) during the study period from April 1, 2011 to March 31, 2012

Table 8. Disease Complications among Persons with ADPKD[a]

	Absence of Complication	Presence of Complication
ADPKD Complication	Number (Percent)	Number (Percent)
Liver cysts	3,747 (97.5)	97 (2.5)
Kidney stones	3,532 (91.9)	312 (8.1)
Urinary tract infection	3,238 (84.2)	606 (15.6)
Cerebral aneurysm	3,808 (99.1)	36 (0.9)

[a] A diagnosis of a complication during the study period from April 1, 2011 to March 31, 2012

medical claims. Table 7 shows the number of complications among persons with ADPKD. There were 2,937 persons or 76.4 percent of persons with ADPKD who did not did not have any ADPKD complications. There were 776 persons or 20.1 percent of ADPKD patients who had at least one ADPKD complication. Individuals with two or more ADPKD complications constituted only 3.5 percent of the sample.

The frequencies of persons with specific ADPKD complications are reported in Table 8. A total of 606 persons or 15.6 percent of persons with ADPKD were diagnosed with urinary tract infection in the one year study period. Urinary tract infection was the most common ADPKD complication observed followed by kidney stones (8.1 percent) and liver cysts (2.5 percent). Less than one percent of the persons with an ADPKD diagnosis had a diagnosis of cerebral aneurysm.

End-Stage Renal Disease

The presence of end-stage renal disease among persons with ADPKD was identified based on the ICD-9-CM diagnosis code (586.6) coding for end-stage renal disease. Out of 3,844 persons with ADPKD, 644 had end-stage renal disease whereas the remaining 3,200 persons with ADPKD had not reached end-stage renal disease.

Unadjusted Annual Health Care Resource Utilization

Mean unadjusted annual health care utilization for persons with or without ADPKD is reported in Table 9. Mean annual unadjusted hospitalizations among individuals with ADPKD were 0.24 (95 percent C.I.: 0.21 to 0.26). Mean annual

unadjusted hospital days among individuals with ADPKD were 2.0 (95 percent C.I.: 1.6 to 2.5). Among individuals with ADPKD, mean annual unadjusted nursing home confinements were 0.011 (95 percent C.I.: 0.0077 to 0.015) and the mean annual unadjusted nursing home length of stay was 0.33 (95 percent C.I.: 0.18 to 0.49). Mean annual unadjusted outpatient visits among individuals with ADPKD were 21.1 (95 percent C.I.: 20.3 to 21.9). Mean annual unadjusted emergency room visits among individuals with ADPKD were 1.0 (95 percent C.I.: 0.93 to 1.1).

Compared to individuals with ADPKD, significantly lower mean unadjusted hospitalizations, mean unadjusted hospital days and mean unadjusted outpatient visits were observed among those without ADPKD. Mean annual unadjusted hospitalizations among individuals without ADPKD were 0.0085 (95 percent C.I.: 0.074 to 0.096). Mean annual unadjusted hospital days among individuals without ADPKD were 0.45 (95 percent C.I.: 0.27 to 0.62). Mean annual unadjusted outpatient visits among individuals without ADPKD were 9.7 (95 percent C.I.: 9.3 to 10.0). No significant difference in the mean unadjusted nursing home confinements, nursing home length of stay or emergengy room visits were observed between person with ADPKD and those without ADPKD. Mean annual unadjusted nursing home confinements among individuals without ADPKD were 0.0031 (95 percent C.I.: 0.0013 to 0.0048) and the mean annual unadjusted nursing home length of stay was 0.071 (95 percent C.I.: 0.021 to 0.012). Mean annual unadjusted emergency room visits among individuals without ADPKD were 0.68 (95 percent C.I.: 0.61 to 0.76).

All-cause health care resource utilization by age, gender and ADPKD complications are reported in Tables A1 to A8 under Appendix A.

Unadjusted Annual Health Care Expenditures

Table 10 provides mean unadjusted annual health care expenditures for individuals with ADPKD and those without ADPKD. Mean annual unadjusted inpatient expenditures among individuals with ADPKD were $6,646 (95 percent C.I.: $5,685 to $7,608). Mean annual unadjusted nursing home expenditures among individuals with ADPKD were $252 (95 percent C.I.: $131 to $373). Among individuals with ADPKD, mean annual unadjusted outpatient expenditures were $12,625 (95 percent C.I.: $11,550 to $13,701) and the mean annual unadjusted emergency room expenditures were $174 (95 percent C.I.: $157 to $191). Mean annual unadjusted medication expenditures among individuals with ADPKD were $3,537 (95 percent C.I.: $3,324 to $3,751). Mean annual unadjusted total health care expenditures among individuals with ADPKD were $23,242 (95 percent C.I.: $21,590 to $24,895).

Compared to individuals with ADPKD, significantly lower mean annual unadjusted hospital expenditures, nursing home expenditures, outpatient expenditures, and medication expenditures were observed among individuals without ADPKD. Mean annual unadjusted inpatient expenditures among individuals without ADPKD were $1,484 (95 percent C.I.: $1,234 to $1,734). Mean annual unadjusted nursing home expenditures among individuals without ADPKD were $41 (95 percent C.I.: $13 to $69). Among individuals without ADPKD, mean annual unadjusted outpatient expenditures were $3,225 (95 percent C.I.: $2,797 to $3,653) and mean annual unadjusted medication expenditures were $1,380 (95 percent C.I.: $1,234 to $1,525). Significant difference was also observed in the mean annual adjusted total health care expenditures between persons

Table 9. Unadjusted Annual Health Care Resource Utilization among Persons with ADPKD and those without ADPKD

Health Care Resource Category	With ADPKD (n=3,844) Mean (95% CI)	Without ADPKD (n = 3,844) Mean (95% CI)
Hospitalizations	0.24 (0.21 to 0.26)	0.085 (0.074 to 0.096)
Hospital days	2.0 (1.6 to 2.5)	0.45 (0.27 to 0.62)
Nursing home confinements	0.011 (0.0077 to 0.015)	0.0031 (0.0013 to 0.0048)
Nursing home length of stay	0.33 (0.18 to 0.49)	0.071 (0.021 to 0.12)
Outpatient visits	21.1 (20.3 to 21.9)	9.7 (9.3 to 10.0)
Emergency room visits	1.0 (0.93 to 1.1)	0.68 (0.61 to 0.76)

Table 10. Unadjusted Annual Health Care Expenditures in Dollars among Persons with ADPKD and those without ADPKD

Health Care Expenditure Category	With ADPKD (n=3,844) Mean (95% CI)	Without ADPKD (n = 3,844) Mean (95% CI)
Inpatient expenditures	6,646 (5,685 to 7,608)	1,484 (1,234 to 1,734)
Nursing home expenditures	252 (131 to 373)	41 (13 to 69)
Outpatient expenditures	12,625 (11,550 to 13,701)	3,225 (2,797 to 3,653)
Emergency room expenditures	174 (157 to 191)	100 (89 to 111)
Medication expenditures	3,537 (3,324 to 3,751)	1,380 (1,234 to 1,525)
Total health care expenditures	23,242 (21,590 to 24,895)	6,230 (5,668 to 6,791)

with ADPKD and those without ADPKD, such that expenditures among individuals with ADPKD were thrice as high $23,242 (95 percent C.I.: $21,590 to $24,895) compared to individuals without ADPKD $6,230 (95 percent C.I.: $5,668 to $6,791).

All-cause health care resource utilization by age, gender and ADPKD complications are reported in Tables B1 to B8 under Appendix B.

Incremental Annual Health Care Resource Utilization Associated with ADPKD

Data distributional characteristics were examined and sequential assessment of potential regression techniques was conducted to select an appropriate model, for analysis of incremental resource utilization associated with ADPKD. The models were examined in sequence beginning with ordinary least squares regression on the untransformed dependent variables, followed by ordinary least squares regression on the log transformed dependent variables, generalized linear models and zero-inflated generalized linear models. Residuals of ordinary least squares regression models with untransformed and models with log transformed utilization and expenditure variables, showed violation of assumptions of normality and constant variance. P-values lower than 0.05 for each Kolmogorov-Smirnov test showed that residuals for each ordinary least squares regression model were not normally distributed (D'Agostino and Stephens 1986). Results of each Glejser test showed p-values lower than 0.05, confirming that residuals were significantly associated with independent variables (Glejser 1969). Therefore, generalized linear models were developed and tested for model fit.

Medical resource utilization and expenditure variables in this study had a high number of observations with zeros. Overdispersion of each resource utilization variable

evidenced by p-values less than 0.05 for Vuong tests, suggested a need for a zero-inflated generalized linear model.(Long and Freese 2006; Vuong 1989) Significant likelihood ratio tests, shown by p-values less than 0.05 indicated that for each dependent variable, zero-inflated negative binomial models were more suitable than zero-inflated Poisson models.(Long and Freese 2006; Vuong 1989; Cameron and Trivedi 1986)

Results from multivariate zero-inflated negative binomial regression models for each health care resource utilization type are reported in Table 11. For nursing home confinements, results from regression models were not available since the number of nursing home confinements were so low that models did not converge. ADPKD was associated with more outpatient visits as reflected in a mean of 6.9 (0.28), $p<0.05$ incremental outpatient visits. Although ADPKD was associated with incrementally more hospitalizations, 0.087 (0.011), $p<0.05$, the impact of ADPKD on hospital resource utilization may be better reflected in the mean incremental hospital days, 0.68 (0.090), $p<0.05$. Emergency room visits were also incrementally greater among persons with ADPKD, 0.29 (0.055), $p<0.05$.

Incremental Annual Health Care Expenditures Associated with ADPKD

Individual regression models were developed to estimate incremental health care expenditures associated with autosomal dominant ADPKD. A binary predictor variable for ADPKD was included in each model and covariates in each model included age, gender, co-morbidity index score, cardiovascular disease, diabetes and geographical region, to adjust for these risk factors. P-values lower than 0.05 for each Kolmogorov-

Table 11. Annual Incremental Health Care Resource Utilization Associated with ADPKD (n=7,688)[a]

Resource Utilization Category	ADPKD Marginal Effect[b] (SE)	Age Marginal Effect[c] (SE)	Gender Marginal Effect[b] (SE)	Comorbidity Index Marginal Effect[c] (SE)	Cardiovascular Disease Marginal Effect[b] (SE)	Diabetes Marginal Effect[b] (SE)	Midwest Marginal Effect[b] (SE)	West Marginal Effect[b] (SE)	South Marginal Effect[b] (SE)
Hospitalizations	0.087** (0.011)	-0.0017** (0.00042)	-0.023 (0.012)	0.063** (0.0082)	0.076* (0.034)	-0.0047 (0.018)	0.0071 (0.017)	-0.019 (0.019)	-0.019 (0.017)
Hospital days	0.68** (0.090)	-0.012** (0.0028)	0.15 (0.081)	0.41** (0.050)	0.42** (0.11)	-0.34* (0.11)	0.0022 (0.13)	-0.20 (0.15)	-0.18 (0.12)
Nursing home confinements	NA	NA	NA	NA	NA	NA	NA	NA	NA
Nursing home days	0.028 (0.018)	0.0024* (0.00091)	-0.019 (0.012)	0.0084* (0.0042)	0.021 (0.014)	-0.0061 (0.012)	0.0082 (0.017)	-0.0094 (0.019)	-0.018l (0.019)
Outpatient visits	6.9** (0.28)	0.10** (0.010)	-3.8** (0.28)	2.9** (0.11)	1.0* (0.11)	-0.91* (0.42)	-2.2** (0.49)	-1.3* (0.52)	-1.9** (0.46)
Emergency room visits	0.29** (0.055)	-0.0045* (0.0022)	-0.21** (0.054)	0.045 (0.023)	0.22* (0.088)	0.15 (0.087)	0.038 (0.096)	0.16 (0.10)	-0.026 (0.087)

[a]Results from zero-inflated negative binomial regression models. The dependent variables for models are listed in the columns and the independent variables in the rows. The marginal effects are estimated at the starting value for each independent variable fixed at the observed mean value for the entire sample (persons with or without ADPKD), that is, proportion with PKD 50%, age at 49.14 years, proportion of males at 0.46, Charlson Comorbidity Index at 1.14, proportion of cardiovascular disease 19.4%, proportion of diabetes 12.04%, proportion of Midwest 27.3%, proportion of West 17.3% and proportion of South 44.9%.

[b] Marginal effects for dichotomous variables are change in the expected value of the dependent variable for the discrete change from 0 to 1 of the independent variable, that is, from no ADPKD to ADPKD and woman to man.

[c] Marginal effects for continuous variables are change in the expected value of the dependent variable for a unit change in the independent variable, given a specific starting value for the independent variable.

*p <0.05, **p<0.001 based on z-test.

NA – Results were not available since the number of nursing home confinements were so low that models did not converge

Smirnov test showed that residuals for each ordinary least squares regression model were not normally distributed (D'Agostino and Stephens 1986). Results of each Glejser test showed p-values lower than 0.05, confirming that residuals were significantly associated with independent variables (Glejser 1969). Medical expenditure variables in this study had a high number of observations with zeros. Overdispersion of each health care expenditure variable evidenced by p-values less than 0.05 for Vuong tests, suggested a need for a zero-inflated generalized linear model.(Long and Freese 2006; Vuong 1989) Significant likelihood ratio tests, shown by p-values less than 0.05 indicated that for each dependent variable, zero-inflated negative binomial models were more suitable than zero-inflated Poisson models.(Long and Freese 2006; Vuong 1989; Cameron and Trivedi 1986) Results from multivariate zero-inflated negative binomial regression models for each health care expenditure type are reported in Table 12. The mean incremental expenditures for outpatient expenditures associated with ADPKD, $4,507 (181), $p<0.05$, accounted for the largest incremental expenditure. Hospital expenditures had the second largest incremental effect associated with ADPKD, $2,385 ($241), $p<0.05$. As shown in Table 12, significant incremental expenditures associated with ADPKD were also found for medication expenditures, $1,456 ($71), $p<0.05$ and emergency room expenditures, $62 ($7), $p<0.05$. The mean estimate of incremental total health care expenditures associated with ADPKD was $7,917 ($431), $p<0.05$.

Table 12. Annual Incremental Health Care Expenditures in Dollars Associated with ADPKD (n=7,688)[a]

Health Care Expenditure Category	ADPKD Marginal Effect[b] (SE)	Age Marginal Effect[c] (SE)	Gender Marginal Effect[b] (SE)	Comorbidity Index Marginal Effect[c] (SE)	Cardiovascular Disease Marginal Effect[b] (SE)	Diabetes Marginal Effect[b] (SE)	Midwest Marginal Effect[b] (SE)	West Marginal Effect[b] (SE)	South Marginal Effect[b] (SE)
Hospital expenditures	2,385** (241)	-25* (8)	1 (215)	991** (76)	1,167** (279)	-250 (285)	3 (374)	-803 (420)	-544 (356)
Nursing home expenditures	22 (14)	1* (0.61)	-5 (7)	5 (2)	18 (11)	4 (8)	4 (12)	-6 (13)	-7 (13)
Outpatient expenditures	4,507** (181)	26** (7)	-1,100** (168)	1,923** (74)	428 (260)	-1,135** (263)	140 (296)	515 (320)	1,028** (279)
Emergency room expenditures	62** (7)	-1** (0.31)	-36** (7)	11** (3)	53** (11)	9 (12)	35* (13)	37* (14)	19 (12)
Medication expenditures	1,456** (71)	30** (2)	-97 (68)	629** (29)	47 (102)	224* (105)	170 (120)	97 (131)	292* (113)
Total health care expenditures	7,917** (431)	48** (11)	-1,237** (297)	3,562** (131)	1,604** (455)	-1,228* (465)	267 (525)	-449 (568)	419 (494)

[a]Results from zero-inflated negative binomial regression models. The dependent variables for models are listed in the columns and the independent variables in the rows. The marginal effects are estimated at the starting value for each independent variable fixed at the observed mean value for the entire sample (persons with or without autosomal dominant ADPKD), that is, proportion with ADPKD 50%, age at 49.14 years, proportion of males at 0.46, Charlson Comorbidity Index at 1.14, proportion of cardiovascular disease 19.4%, proportion of diabetes 12.04%, proportion of Midwest 27.3%, proportion of West 17.3% and proportion of South 44.9%.

[b] Marginal effects for dichotomous variables are change in the expected value of the dependent variable for the discrete change from 0 to 1 of the independent variable, that is, from no ADPKD to ADPKD and woman to man.

[c] Marginal effects for continuous variables are change in the expected value of the dependent variable for a unit change in the independent variable, given a specific starting value for the independent variable.

*p <0.05, **p<0.001 based on z-test.

NA – Results were not available since the number of nursing home confinements were so low that models did not converge

Sub-Group Analysis by whether Diagnosed with End-Stage Renal Disease

Unadjusted Annual Health Care Resource Utilization by whether Diagnosed with End-Stage Renal Disease

Among 3,844 persons with ADPKD, 644 had a diagnosis of end-stage renal disease and 3,200 persons with ADPKD had not been diagnosed with end-stage renal disease. Unadjusted resource utilization among persons with ADPKD by whether diagnosed with end-stage renal disease is reported in Table 13.

Mean annual unadjusted hospitalizations were more than three times higher among ADPKD patients with end-stage renal disease 0.56 (95 percent C.I.: 0.49 to 0.64). as compared to ADPKD patients without end-stage renal disease 0.17 (95 percent C.I.: 0.15 to 0.19), $p < 0.05$. Individuals with ADPKD and end-stage renal disease had more than four times greater mean annual unadjusted hospital days 5.7 (95 percent C.I.: 3.7 to 7.8) as compared to ADPKD patients without end-stage renal disease 1.3 (95 percent C.I.: 0.94 to 1.7), $p < 0.05$. Mean annual unadjusted outpatient visits were approximately three times as great among individuals with ADPKD and end-stage renal disease 44.6 (95 percent C.I.: 41.6 to 47.7) as compared to those with ADPKD but without end-stage renal disease 16.3 (95 percent C.I.: 15.7 to 16.9), $p < 0.05$.

Unadjusted Annual Health Care Expenditures by whether Diagnosed with End-Stage Renal Disease

Table 14 compares mean unadjusted annual health care expenditures for individuals with ADPKD and end-stage renal disease and those with ADPKD but without end-stage renal disease. Mean annual unadjusted hospital expenditures were five times

Table 13. Unadjusted Annual Health Care Resource Utilization among Persons with ADPKD by whether Diagnosed with End-Stage Renal Disease (ESRD)[a]

	No ESRD (n=3,200)	ESRD (n=644)
Utilization Category	Mean (95% CI)	Mean (95% CI)
Hospitalizations	0.17 (0.15 to 0.19)	0.56 (0.49 to 0.64)
Hospital days	1.3 (0.94 to 1.7)	5.7 (3.7 to 7.8)
Nursing home confinements	0.0094 (0.0054 to 0.013)	0.023 (0.010 to 0.036)
Nursing home days	0.30 (0.13 to 0.47)	0.50 (0.14 to 0.85)
Outpatient visits	16.3 (15.7 to 16.9)	44.6 (41.6 to 47.7)
Emergency room visits	1.1 (0.96 to 1.2)	1.0 (0.78 to 1.2)

[a] A diagnosis of ICD-9-CM code 585.6 during the study period from April 1, 2011 to March 31, 2012

Table 14. Unadjusted Annual Health Care Expenditures in Dollars among Persons with ADPKD by whether Diagnosed with End-Stage Renal Disease (ESRD)[a]

	No ESRD (n=3,200)	ESRD (n=644)
Expenditure Category	Mean (95% CI)	Mean (95% CI)
Inpatient expenditures	3,974 (3,280 to 4,668)	19,927 (15,471 to 24,384)
Nursing home expenditures	189 (90 to 288)	566 (33 to 1,100)
Outpatient expenditures	5,352 (4,977 to 5,727)	48,767 (43,431 to 54,103)
Emergency room expenditures	176 (157 to 196)	194 (153 to 234)
Medication expenditures	2,439 (2,234 to 2,644)	8,995 (8,381 to 9,610)
Total health care expenditures	12,131 (11,174 to 13,089)	78,451 (71,168 to 85,733)

[a] A diagnosis of ICD-9-CM code 585.6 during the study period from April 1, 2011 to March 31, 2012

higher for individuals with ADPKD and end-stage renal disease $19,927 (95 percent C.I.: $15,471 to $24,384) as compared to individuals with ADPKD but without end-stage renal disease $3,974 (95 percent C.I.: $3,280 to $4,668), p <0.05. Mean annual unadjusted expenditures from nursing homes were three-fold higher for the patients with ADPKD and end-stage renal disease $566 (95 percent C.I.: $33 to $1,100) than for those ADPKD patients without end-stage renal disease $189 (95 percent C.I.: $90 to $288), p <0.05.The unadjusted mean annual outpatient expenditures were nine times higher among individuals with ADPKD and end-stage renal disease $48,767 (95 percent C.I.: $43,431 to $54,103) than for ADPKD patients without end-stage renal disease $5,352 (95 percent C.I.: $4,997 to $5,727), p <0.05. The mean annual unadjusted medication expenditure for individuals with ADPKD and end-stage renal disease $8,995 (95 percent C.I.: $8,381 to $9,610) were approximately four times higher when compared to individuals with ADPKD but without end-stage renal disease $2,439 (95 percent C.I.: $2,234 to $2,644), p<0.05. Mean unadjusted expenditures among individuals with ADPKD and end-stage renal disease $78,451 (95 percent C.I.: $71,168 to $85,733) were 6.5 times higher compared to ADPKD patients without end-stage renal disease $12,131 (95 percent C.I.: $11,174 to $13,089), p <0.05.

Incremental Annual Health Care Resource Utilization
by whether Diagnosed with End-Stage Renal Disease

Table 15 shows incremental health care resource utilization associated with ADPKD, based on results of zero-inflated negative binomial models by whether diagnosed with end-stage renal disease. Significant incremental, mean (standard error) hospitalizations, 0.35 (0.052), p<0.05 and hospital days, 2.5 (0.42), p<0.05 were

associated with ADPKD in the sub-group with end-stage renal disease. There were also significant incremental hospitalizations, 0.065 (0.028), $p<0.05$ associated with ADPKD in the sub-group without end-stage renal disease and significant incremental hospital days, 0.50 (0.091), $p<0.05$ associated with ADPKD in the sub-group without end-stage renal disease.

For the sub-group with end-stage renal disease, incremental outpatient visits were 24.0 (1.2), $p<0.05$, which were several times higher than the incremental outpatient visits associated with ADPKD for the subgroup without end-stage renal disease, 4.4 (0.41), $p<0.05$. In contrast, the sub-group analysis revealed that there were not significant incremental emergency room visits associated with ADPKD in the sub-group with end-stage renal disease, but that the sub-group without end-stage renal disease did have significant incremental emergency room visits associated with ADPKD, 0.32 (0.058), $p<0.05$.

Incremental Annual Health Care Expenditures
by whether Diagnosed with End-Stage Renal Disease

Results from sub-group analyses of incremental expenditures associated with ADPKD are also reported in Table 16. The ADPKD sub-group with end-stage renal disease had mean incremental total expenditures associated with ADPKD $42,547 ($2,102), $p<0.05$, that were much higher than those for the sub-group with ADPKD but without end-stage renal disease $3,053 ($374), $p<0.05$.

Similar relationships were seen in comparison across the sub-group with end-stage renal disease and the sub-group without end-stage renal disease, for incremental hospital expenditure $9,430 ($1,179), $p<0.05$ versus $1,365 ($207), $p<0.05$; outpatient

expenditures $26,539 ($1,373) p<0.05 versus $1,247 ($119), p<0.05; and medication expenditures $5,933 ($342), p<0.05 versus $824 ($61), p<0.05 respectively. However, incremental emergency room expenditures associated with ADPKD were of similar magnitude for the sub-group with end-stage renal disease $67 ($22), p<0.05 and the sub-group without end-stage renal disease $63 ($8), p<0.05.

Table 15. Adjusted Annual Incremental Health Care Resource Utilization Associated with ADPKD by whether Diagnosed with End-Stage Renal Disease[a]

Resource Utilization Category	ADPKD Marginal Effect[b] (SE)	Age Marginal Effect[c] (SE)	Gender Marginal Effect[b] (SE)	Comorbidity Index Marginal Effect[c] (SE)	Cardiovascular Disease Marginal Effect[b] (SE)	Diabetes Marginal Effect[b] (SE)	Midwest Marginal Effect[b] (SE)	West Marginal Effect[b] (SE)	South Marginal Effect[b] (SE)
Hospitalizations									
ESRD[d]	0.35** (0.052)	-0.0043 (0.0023)	-0.067 (0.048)	0.093** (0.019)	0.097 (0.063)	-0.034 (0.061)	-0.018 (0.078)	-0.052 (0.092)	-0.13 (0.075)
No-ESRD[e]	0.065* (0.028)	-0.0018** (0.00050)	-0.0073 (0.030)	0.048* (0.019)	0.070 (0.087)	0.0039 (0.026)	0.022 (0.031)	-0.0092 (0.020)	-0.0098 (0.018)
Hospital days									
ESRD[d]	2.5** (0.42)	-0.044* (0.017)	-0.28 (0.33)	0.71** (0.15)	0.57 (0.42)	-0.99* (0.47)	-1.0 (0.63)	-1.7* (0.70)	-1.4* (0.62)
No-ESRD[e]	0.50** (0.091)	-0.011** (0.0028)	0.23* (0.090)	0.39** (0.059)	0.33* (0.13)	-0.18 (0.12)	0.22 (0.14)	-0.0056 (0.15)	-0.0079 (0.12)
Nursing home confinements									
ESRD[d]	NA	NA	NA	NA	NA	NA	NA	NA	NA
No-ESRD[e]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Nursing home days									
ESRD[d]	NA	NA	NA	NA	NA	NA	NA	NA	NA
No-ESRD[e]	0.018 (0.013)	0.0015 (0.00072)	-0.022 (0.013)	0.0033 (0.0023)	0.013 (0.0098)	-0.013 (0.014)	0.0042 (0.010)	-0.0098 (0.012)	-0.015 (0.014)

Table 15. Continued

Resource Utilization Category	ADPKD Marginal Effect[b] (SE)	Age Marginal Effect[c] (SE)	Gender Marginal Effect[b] (SE)	Comorbidity Index Marginal Effect[c] (SE)	Cardiovascular Disease Marginal Effect[b] (SE)	Diabetes Marginal Effect[b] (SE)	Midwest Marginal Effect[b] (SE)	West Marginal Effect[b] (SE)	South Marginal Effect[b] (SE)
Outpatient visits									
ESRD[d]	24.0** (1.2)	0.010 (0.05)	-3.6** (1.0)	3.0** (0.34)	0.63 (1.3)	-0.43 (1.4)	-2.3 (1.9)	-0.97 (2.1)	-2.1 (1.8)
No-ESRD[e]	4.4** (0.41)	0.091** (0.012)	-3.9** (0.26)	2.4** (0.11)	0.57 (0.41)	-0.85* (0.41)	-2.7** (0.45)	-1.6* (0.49)	-2.3** (0.42)
Emergency room visits									
ESRD[d]	0.12 (17.2)	-0.022 (1.4)	0.12 (7.8)	-0.023 (3.9)	0.30 (14.0)	0.083 (9.9)	0.25 (10.6)	0.51 (25.5)	0.22 (5.3)
No-ESRD[e]	0.32** (0.058)	-0.0031 (0.0024)	-0.28** (0.059)	0.061* (0.027)	0.19 (0.10)	0.14 (0.098)	-0.018 (0.10)	0.094 (0.10)	-0.082 (0.094)

[a]Analysis based on zero-inflated negative binomial regression models. The dependent variables for models are listed in the columns and the independent variables in the rows. The marginal effects are estimated at the starting value for each independent variable fixed at the observed mean value for the entire sample (persons with or without autosomal dominant ADPKD), that is, proportion with ADPKD 50%, age at 49.14 years, proportion of males at 0.46, Charlson Comorbidity Index at 1.14, proportion of cardiovascular disease 19.4%, proportion of diabetes 12.04%, proportion of Midwest 27.3%, proportion of West 17.3% and proportion of South 44.9%.

[b] Marginal effects for dichotomous variables are change in the expected value of the dependent variable for the discrete change from 0 to 1 of the independent variable, that is, from no ADPKD to ADPKD and woman to man.

[c] Marginal effects for continuous variables are change in the expected value of the dependent variable for a unit change in the independent variable, given a specific starting value for the independent variable.

[d] 644 individuals with ADPKD with end-stage renal disease linked with 644 comparison observations

[e] 3,200 individuals with ADPKD without end-stage renal disease linked with 3,200 comparison observations

$^{*}p < 0.05$, $^{**}p < 0.001$ based on z-test.

NA – Results were not available since the number of nursing home confinements were so low that models did not converge

Table 16. Adjusted Annual Incremental Health Care Expenditures in Dollars Associated with ADPKD by whether Diagnosed with End-Stage Renal Disease[a]

Health Care Expenditure Category	ADPKD Marginal Effect[b] (SE)	Age Marginal Effect[c] (SE)	Gender Marginal Effect[b] (SE)	Comorbidity Index Marginal Effect[c] (SE)	Cardiovascular Disease Marginal Effect[b] (SE)	Diabetes Marginal Effect[b] (SE)	Midwest Marginal Effect[b] (SE)	West Marginal Effect[b] (SE)	South Marginal Effect[b] (SE)
Hospital expenditures									
ESRD[d]	9,430** (1,179)	-148* (49)	-149 (977)	1,765** (317)	1,868 (1,221)	-745 (1,207)	-3,638* (1,826)	-5,873* (2,108)	-4,992* (1,748)
No-ESRD[e]	1,365** (207)	-17* (7)	-42 (195)	727** (69)	880* (257)	-8 (269)	527 (335)	-11 (371)	23 (318)
Nursing home expenditures									
ESRD[d]	88 (58)	-1 (2)	67 (48)	19 (13)	76 (44)	41 (37)	30 (49)	130 (105)	37 (48)
No-ESRD[e]	9 (6)	0.84* (0.38)	-10 (6)	2 (1)	8 (5)	-5 (5)	4 (6)	-3 (6)	-7 (7)
Outpatient expenditures									
ESRD[d]	26,539** (1,373)	-51 (47)	-1,873* (913)	2,582** (336)	-67 (1,236)	-998 (1,270)	-538 (1,741)	830 (1,891)	874 (1,655)
No-ESRD[e]	1,247** (119)	11* (5)	-1,066** (122)	1,103** (52)	35 (187)	-656* (194)	-434* (209)	105 (226)	301 (197)
Emergency room expenditures									
ESRD[d]	67*	-2*	-17	3	44	25	54	75	58
(22)	(1)	(20)	(6)	(26)	(28)	(41)	(43)	(38)	
No-ESRD[e]	63**	-1**	-41**	14**	56**	4	34*	34*	14
	(8)	(0.33)	(8)	(3)	(13)	(13)	(14)	(15)	(13)

Table 16. Continued

Health Care Expenditure Category	ADPKD Marginal Effect[b] (SE)	Age Marginal Effect[c] (SE)	Gender Marginal Effect[b] (SE)	Comorbidity Index Marginal Effect[c] (SE)	Cardiovascular Disease Marginal Effect[b] (SE)	Diabetes Marginal Effect[b] (SE)	Midwest Marginal Effect[b] (SE)	West Marginal Effect[b] (SE)	South Marginal Effect[b] (SE)
Medication expenditures									
ESRD[d]	5,933** (342)	20 (13)	115 (266)	537** (86)	-191 (339)	742* (364)	-141 (502)	-609 (553)	84 (478)
No-ESRD[e]	824** (61)	23** (2)	-143* (61)	568** (28)	7 (97)	166 (98)	90 (107)	102 (117)	228* (100)
Total health care expenditures									
ESRD[d]	42,547** (2,102)	-78 (74)	-942 (1,478)	4,908** (522)	2,409 (1,907)	-1,816 (2,063)	-5,172 (2,789)	-5,294 (3,045)	-5,326* (2,644)
No-ESRD[e]	3,053** (374)	20* (8)	-1,320** (238)	2,475** (108)	1,415** (375)	-602 (385)	151 (415)	-7 (448)	540 (390)

[a]Analysis based on zero-inflated negative binomial regression models. The dependent variables for models are listed in the columns and the independent variables in the rows. The marginal effects are estimated at the starting value for each independent variable fixed at the observed mean value for the entire sample (persons with or without autosomal dominant ADPKD), that is, proportion with ADPKD 50%, age at 49.14 years, proportion of males at 0.46, Charlson Comorbidity Index at 1.14, proportion of cardiovascular disease 19.4%, proportion of diabetes 12.04%, proportion of Midwest 27.3%, proportion of West 17.3% and proportion of South 44.9%.

[b] Marginal effects for dichotomous variables are change in the expected value of the dependent variable for the discrete change from 0 to 1 of the independent variable, that is, from no ADPKD to ADPKD and woman to man.

[c] Marginal effects for continuous variables are change in the expected value of the dependent variable for a unit change in the independent variable, given a specific starting value for the independent variable.

[d] 644 individuals with ADPKD with end-stage renal disease linked with 644 comparison observations

[e] 3,200 individuals with ADPKD without end-stage renal disease linked with 3,200 comparison observations

*p <0.05, **p<0.001 based on z-test.

NA – Results were not available since the number of nursing home confinements were so low that models did not converge

Notes

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SUMMARY AND CONCLUSIONS

Background

Polycystic kidney disease is the most common hereditary kidney disorder (Pirson and Chauveau 1999; Wilson 2004). It is characterized by growth and development of multiple fluid filled sacs known as cysts that cause gradual kidney damage and significant morbidity (Grantham 2008; Pirson and Chauveau 1999; Torres, Harris, and Pirson 2007; Wilson 2004). PKD is characterized by gradual kidney enlargement and other sequelae including colonic diverticulitis, polycystic liver disease, intracranial aneurysms, and cysts in other tissues such as seminal vesicles, arachnoid membranes and the pancreas (Alehan, Gurakan, and Agildere 2002; Danaci et al. 1998; Grantham 2008; Nicolau et al. 2000; Pirson, Chauveau, and Torres 2002; Schievink et al. 1995; Torres, Harris, and Pirson 2007; Wijdicks, Torres, and Schievink 2000). As cysts develop and grow in size, they impinge upon kidney parenchyma, ultimately rendering the kidneys dysfunctional, and the condition eventually progresses to end-stage renal disease (Grantham 2008; Torres, Harris, and Pirson 2007; Torres and Grantham 2007; Wilson 2004).

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic form of PKD, occurring in 1 in 400 to 1 in 1,000 live births and it affects

approximately 500,000 Americans (Grantham 2008; Pirson and Chauveau 1999; Torres, Harris, and Pirson 2007). ADPKD may be asymptomatic for several decades but as cysts increase in size and number, symptoms and serious sequelae develop. Autosomal recessive PKD is much rarer than ADPKD and it occurs in only about 1 in 20,000 live births (Grantham 2008; Pirson and Chauveau 1999). Symptom presentation is more rapid and occurs at an earlier age for persons with autosomal recessive PKD than for persons with ADPKD, so that ADPKD is more likely to be a long term chronic condition (Dell and Avner 2001; Pirson and Chauveau 1999; Wilson 2004).

This study provides a current description of the epidemiology of ADPKD by estimating its one year prevalence. There is limited evidence describing economic burden of ADPKD. Only one study was found that estimated all-cause health care costs for persons with ADPKD (Lentine et al. 2010) and the reported mean annual unadjusted all-cause total health care expenditures ranged from $26,521 at baseline to $140,139 at the advanced kidney disease level (Lentine et al. 2010). No study was found that assessed incremental health care resource utilization or incremental health care expenditures associated with ADPKD. Additional evidence regarding the burden of ADPKD may offer valuable input in understanding the societal impact of the disease.

Objectives

The specific objectives for this study were to

1. determine prevalence of ADPKD in a private-pay population,
2. determine all-cause health care resource utilization and expenditures among persons with ADPKD,

3. determine incremental health care resource utilization associated with ADPKD by categories including hospitalizations, hospital days, nursing home visits, nursing home length of stay, emergency room encounters and outpatient encounters, and
4. determine incremental health care expenditures associated with ADPKD by categories including total expenditures, hospital stay, nursing home stay, emergency room encounters, outpatient services and medication.

Methods

Health insurance claims data from a large administrative database between April 1, 2011 and March 31, 2012 were used to conduct an observational database analysis. The database included medical and pharmacy claims for 13 million privately-insured lives covering all census regions of the United States. To account for pricing variation across providers or geographic regions, standard prices in the database reflected allowed payments from a single source with a consistent payment plan. The study was approved by the Institutional Review Board of Purdue University.

Sample

Individuals 18 years of age or older and enrolled in a tracked health plan anytime during the period from April 1, 2011 through March 31, 2012, were eligible for inclusion in the sample for determination of ADPKD prevalence. No exclusion criteria were specified for this prevalence sample.

Persons age 18 years or older, enrolled in a tracked health plan during the twelve-month period from April 1, 2011 through March 31, 2012, and having a diagnosis for "polycystic kidney, autosomal dominant" (753.13) or for "polycystic kidney, unspecified type (753.12) were selected for inclusion in the sample for determining all-cause health care resource utilization and expenditures as well as incremental health care resource utilization and expenditures associated with ADPKD. Persons having ICD-9-CM diagnosis codes for "polycystic kidney, autosomal recessive" (753.14) or "cystic kidney disease" (753.1) were excluded from the ADPKD group because of their differing clinical presentation and prognosis. Each individual in the ADPKD group was linked one-to-one on age and gender with an individual without ADPKD. The comparison group without ADPKD consisted of individuals who satisfied all inclusion criteria for the ADPKD group but did not have a diagnosis for ADPKD. Exclusion criteria for the non-ADPKD group were a diagnosis for autosomal recessive PKD, cystic kidney disease, chronic kidney disease ranging from stage 3 to stage 6, nephrotic syndrome, diabetic kidney disease, or kidney stones associated with cystic kidney disease. Renal diseases were excluded from the comparison group so as to avoid potential confounding from associated resource utilization and expenditures from those renal diseases. Demographic variables including year of birth, gender, and geographic region were extracted from eligibility and claims files. A modified Charlson Comorbidity Index developed by Romano et al. was constructed for the sample, in which renal diseases were excluded in the computation of comorbidity index scores (Romano, Roos, and Jollis 1993).

Analysis

Data were analyzed using SAS for Unix Version 9.2 and STATA for Unix version 12. Frequency distributions were developed to describe the sample and Chi-square tests were used to assess statistical differences between persons with ADPKD and those without ADPKD on, demographic variables and clinical variables. To estimate one-year prevalence of ADPKD, the number of individuals 18 years or older with ICD-9 diagnosis codes for "polycystic kidney, autosomal dominant" (753.13) or for "polycystic kidney, unspecified type" (753.12), and enrolled anytime during the period from April 1, 2011 through March 31, 2012, were identified and divided by the total population of covered individuals 18 years or older, during the same one year period. A 95 percent confidence interval of the estimated prevalence was constructed. Health care resource utilization by specific categories was calculated for each individual and health care expenditures by specific categories were computed by adding standard prices from insurance claims. Unadjusted means and 95 percent confidence intervals for utilization and expenditure in each category were also computed, and Wilcoxon Mann Whitney tests were used to detect differences between the groups.

Individual regression models were developed to estimate independent association between ADPKD and utilization of health services such that individual models were developed for hospitalizations, hospital days, nursing home confinements, nursing home days, outpatient visits and emergency room visits. A binary predictor variable for ADPKD was included in each model and covariates in each model included age, gender, co-morbidity index score, cardiovascular disease, diabetes and geographical region, to

adjust for these risk factors. Similar regression models for health care expenditures were developed, with the predictor variable and covariates described above, with individual models for total expenditures, hospital expenditures, nursing home expenditures, outpatient expenditures, emergency room expenditures, and medication expenditures. Sub-group analysis examined incremental resource utilization and expenditures associated with ADPKD by whether diagnosed with end-stage renal disease. ADPKD cases with a diagnosis of end-stage renal disease (ICD-9-CM code 585.6) and their linked comparison individuals were one sub-group and cases without end-stage renal disease and their linked comparison individuals formed the other sub-group. Individual regression models, as described for the overall analysis, were developed to estimate incremental resource utilization and expenditures by category for each sub-group adjusting for risk factors.

Results and Discussion

Demographic Characteristics of Prevalence Sample

In the prevalence sample, 81.9 percent of individuals with ADPKD were 35 years of age older. The proportion of females with ADPKD (53%) was higher than for males with ADPKD (47%).

Prevalence of ADPKD

From 10,500,664 persons at least 18 years old and enrolled during the period from April 1, 2011 through March 31, 2012, there were 5,878 individuals having an ICD-9-

CM diagnosis code for “polycystic kidney, autosomal dominant” (753.13) or for “polycystic kidney, unspecified type (753.12). The number of ADPKD patients (5,878) was divided by the number of all covered individuals (10,500,664) to calculate the one-year prevalence of the disease. The prevalence of ADPKD was one in 1,786 persons or 560 cases per million population. The 95 percent confidence interval for estimated prevalence was between 1,833 to 1,742 persons.

The only prior estimate of prevalence of ADPKD in the United States was reported to be between one in 400 persons to one in 1,000 persons (Iglesias et al. 1983). The prevalence of ADPKD in the United States estimated in this study, one in 1,786 persons, was lower than the ADPKD prevalence estimate reported by Iglesias and colleagues (one in 400 to one in 1,000). Five other studies have estimated prevalence of ADPKD in populations outside the United States (Davies et al. 1991; Higashihara et al. 1998; Simon et al. 1996; Yersin et al. 1997; Dalgaard 1957). The prevalence of ADPKD in the current study, one in 1,786 persons, was lower than the estimated prevalence in Seychelles, one in 544 (Yersin et al. 1997), in Copenhagen, one in 1,000 (Dalgaard 1957), and in France, one in 1,111 (Simon et al. 1996). However, the current prevalence estimate was higher than the estimated ADPKD prevalence in Wales, one in 2,459 (Davies et al. 1991) and Japan, one in 4,033 (Higashihara et al. 1998).

Some reasons for variation in prevalence estimates across studies may include differences between the samples used to calculate prevalence, differences in diagnostic techniques available during each study period or differing case identifying approaches used across studies. The study by Iglesias et al. estimated ADPKD prevalence during a 45-year study period between January 1, 1935 and December 31, 1980, from clinical and

autopsy records of all residents of Olmsted County in Minnesota (Iglesias et al. 1983). Yersin et al. estimated prevalence in Seychelles by requesting all doctors employed in the national health system to refer all presumed or confirmed cases and by examining the family members of all confirmed cases (Yersin et al. 1997). Dalgaard estimated prevalence from annual reports and autopsy records of maternity clinics of one hospital in Copenhagen, between 1911 to 1953 (Dalgaard 1957). The prevalence estimate from France was based on a survey of individuals and their families from one region in France (Simon et al. 1996). The study by Davies et al. estimated prevalence in Wales using a renal patient data repository from four nephrology clinics (Davies et al. 1991).

In contrast, the current study estimated one-year prevalence using insurance claims records of privately-insured individuals across all census regions in the United States. A diagnosis of ADPKD was identified by presence of ICD-9-CM diagnosis codes. The prevalence of ADPKD obtained in this study may have been lower because administrative data was limited to privately insured patients only, autopsy records were not examined. However, an estimate from a broader population such as the one reported in this current study is an improvement over the previously available U.S. prevalence estimate (Iglesias et al. 1983) which sampled the population of a single U.S. county.

The findings on prevalence of ADPKD may help in understanding disease epidemiology relative to other diseases, and may inform decisions for allocation of resources by public institutions for research directed towards ADPKD. Availability of updated epidemiological data regarding ADPKD may be useful for patient advocacy groups to provide current disease-related information to patients, payers and providers, and also in attempts to raise awareness regarding the disease.

All-Cause Resource Utilization and Expenditures

Sample Characteristics

Out of 10,500,664 persons at least 18 years old and enrolled during the 12-month period from April 1, 2011 through March 31, 2012, there were 4,020 individuals who had a diagnosis for ADPKD. After excluding 115 individuals who either had a diagnosis of autosomal recessive ADPKD or unspecified cystic kidney disease, and 61 persons who had no medical claim information, a total of 3,844 individuals remained in the ADPKD group. The individuals with an ADPKD diagnosis were linked one-to-one with 3,844 individuals without ADPKD. The final sample size for determining all-cause health care resource utilization and expenditures was 7,688. The sample was 53 percent female, with a mean age ± standard deviation of 49.15 ± 13.67. Approximately 55 percent were between 45 and 64 years old. A significantly higher proportion of individuals in the ADPKD group had Charlson Comorbidity Index scores greater than zero (55.8% versus 37.5%, $p<0.05$). The cohort with ADPKD also had proportionally higher diagnosis of cardiovascular disease (25.6% versus 13.3%, $p<0.05$) and diabetes (14.1% versus 10.0%, $p<0.05$) than those without ADPKD. Among individuals with ADPKD, 20.1 percent patients had at least one ADPKD complication. Urinary tract infection was the most common ADPKD complication (15.6 %), followed by kidney stones (8.1%) and liver cysts (2.5%). Out of 3,844 persons with ADPKD, 644 had reached end-stage renal disease.

Unadjusted Annual Health Care Resource Utilization

Mean annual unadjusted hospitalizations were three times higher among individuals with ADPKD (0.24) as compared to those without ADPKD (0.085), $p<0.05$. Individuals with ADPKD had four times greater mean annual unadjusted hospital days (2.0) as compared to individuals without ADPKD (0.45), $p<0.05$. Mean annual unadjusted outpatient visits were more than twice as great among individuals with ADPKD (21.1) as compared to those without ADPKD (9.7), $p<0.05$.

Findings from this study are consistent with findings from prior studies that reported higher resource utilization in persons with chronic kidney diseases compared to individuals without chronic kidney disease (Alexander et al. 2009; Baumeister et al. 2010; Khan et al. 2002). However, differences were observed between some types of all-cause resource utilization among ADPKD patients compared to corresponding resource utilization among patients with chronic kidney disease in general. The estimate of all-cause mean hospitalizations among ADPKD patients found in this study, 0.24 (95 percent C.I.: 0.21 to 0.26), was higher than all-cause mean (± standard deviation) hospitalizations among patients with early stages of chronic kidney disease (stage 1 or stage 2), 0.19 ± 0.01 but lower than all-cause mean hospitalizations among persons with late-stage chronic kidney disease (stage 3 or stage 4), 0.42 ± 0.03, reported by Alexander et al. (Alexander et al. 2009). When compared to results from a study by Khan and colleagues, the estimate of all-cause annual mean hospitalizations reported in the current study, 0.24 (95 percent C.I.: 0.21 to 0.26), was lower than the 0.96 all-cause annual mean hospitalizations among a small retrospective cohort of persons with chronic kidney

disease from an outpatient nephrology clinic (Khan et al. 2002). The all-cause annual mean hospital days, 2.0 (95 percent C.I.: 1.6 to 2.5), among persons with ADPKD observed in the current study were lower than the 6.6 all-cause mean hospital days among chronic kidney disease patients reported by Khan et al. (Khan et al. 2002).

Unadjusted Annual Health Care Expenditures

Mean annual unadjusted hospital expenditures were more than four times higher among individuals with ADPKD ($6,646) as compared to individuals without ADPKD ($1,484), $p<0.05$. Mean annual unadjusted expenditures from nursing homes were also six-fold higher for the cohort with ADPKD ($252) as compared to the cohort without ADPKD ($41), $p<0.05$. Unadjusted mean annual outpatient expenditures were almost four times higher among individuals with ADPKD ($12,625) than for individuals without ADPKD ($3,225), $p<0.05$. Mean annual unadjusted medication expenditures for individuals with ADPKD ($3,537) were approximately 2.5 times higher when compared to individuals without ADPKD ($1,380), $p<0.05$. Mean annual unadjusted total health care expenditures among individuals with ADPKD ($23,242) were more than three and one-half times as high as for individuals without ADPKD ($6,230), $p<0.05$.

Similar to current study findings, where persons with ADPKD had higher health care expenditure than persons without ADPKD, prior studies have reported higher health care expenditures in persons with chronic kidney disease compared to individuals without chronic kidney disease (Smith et al. 2004; Baumeister et al. 2010). However, differences were observed between some types of all-cause health care expenditure among ADPKD patients compared to corresponding all-cause health care expenditures among patients

with chronic kidney disease in general. All-cause mean annual total health care expenditures associated with ADPKD $23,242 (95 percent C.I.: $21,590 to $24,895) was lower than the total health care expenditures of $37,330 among individuals with chronic kidney disease, reported by London et al. (London et al. 2002). However, the all-cause mean medication expenditures among individuals with ADPKD, $3,537 (95 percent C.I.: $3,324 to $3,751), were more than twice the all-cause mean medication expenditures of $1,503 among individuals with chronic kidney disease, reported by London and colleagues (London et al. 2002).

London et al. estimated health care expenditures using billed amounts for each service whereas in the current study, standard prices were used to calculate health care expenditures. Billed amounts for medical services may differ across regions whereas standard prices adjust for geographic variation in provider pricing. Therefore, differences in all-cause health care expenditures between the study by London et al. and the current study may be due to the type of cost estimates used to estimate expenditures.

Incremental Annual Health Care Resource Utilization Associated with ADPKD

The sample of 7,688 persons used to determine all-cause health care resource utilization and expenditures was also used for estimation of incremental resource utilization associated with ADPKD. ADPKD was associated with many more outpatient visits as reflected in a mean of 6.9 (0.28), $p<0.05$ incremental outpatient visits. Although ADPKD was associated with incrementally more hospitalizations, 0.087 (0.011), $p<0.05$, the impact of ADPKD on hospital resource utilization may be better reflected in the mean

incremental hospital days, 0.68 (0.090), $p<0.05$. Emergency room visits were also incrementally greater among persons with ADPKD, 0.29 (0.055), $p<0.05$.

To our knowledge, no prior study has estimated incremental health care resource utilization associated with ADPKD. However, some prior studies estimated incremental health care resource utilization associated with persons with chronic diseases of the kidneys (Baumeister et al. 2010; Smith et al. 2004). Higher resource utilization associated with having chronic kidney disease were reported by Smith. et al. and Baumeister et al., which was consistent with the current finding of higher resource utilization associated with having ADPKD. Smith et al. reported that persons with stage 2 chronic kidney disease had 7.5 incremental outpatient visits, those with stage 3 chronic kidney disease had 3.5 incremental outpatient visits and those with stage 4 chronic kidney disease had 10.2 incremental outpatient visits per year compared to those without chronic kidney disease. In comparison, a mean of 6.9 (0.28), $p<0.05$ incremental outpatient visits associated with ADPKD were estimated in the current study. Smith et al. also reported that persons with stage 2 chronic kidney disease had 0.29 incremental hospitalizations, those with stage 3 chronic kidney disease had 0.17 incremental hospitalizations and those with stage 4 chronic kidney disease had 0.70 incremental hospitalizations per year when compared to those without chronic disease. In comparison, estimated mean incremental hospitalizations of 0.087 (0.011), $p<0.05$ associated with ADPKD found in the current study, were lower than any of the estimates reported by Smith et al.

Regression models used by Smith et al. to estimate incremental health care resource utilization in chronic kidney disease were adjusted for age and gender only, whereas in the current study, multivariate regression equations adjusted for age, gender,

co-morbidity index score, cardiovascular disease, diabetes and geographical region. Lower incremental resource utilization estimates in the current study, compared to those presented by Smith et al., may be related to adjustment of those risk factors that may have inflated resource utilization estimates in the Smith et al. study.

Baumeister et al. conducted a study in a general population in the city of Augsburg in Germany and reported that chronic kidney disease was associated with 3.7 additional mean annual incremental outpatient visits (Baumeister et al. 2010), which was lower than the 6.9 (0.28), $p<0.05$ mean incremental outpatient visits associated with ADPKD in the current study. However, the study by Baumeister et al. reported higher 4.6 mean annual incremental hospital days (Baumeister et al. 2010), compared to the 0.68 mean incremental hospital days found in the current study. Both, the study by Baumeister et al. as well as the current study, used multivariate regression to estimate incremental resource utilization adjusted for age, gender and comorbidities. However, Baumeister et al. studied a cohort of patients with chronic kidney disease over a ten-year period whereas the current study estimated utilization over a one-year period only, which may explain observed differences in incremental resource utilization estimates between the two studies.

The studies by Smith et al. and by Baumeister et al. estimated incremental resource utilization associated with chronic kidney diseases regardless of disease etiology whereas this current study focused on estimating incremental resource utilization associated specifically with ADPKD (Baumeister et al. 2010; Smith et al. 2004). Therefore, observed differences in incremental resource utilization estimates between

previous reports and estimates found in this current study may also be due to differences in composition of study samples.

Incremental Annual Health Care Expenditures Associated with ADPKD

The same sample of 7,688 persons used to determine incremental health care resource utilization was also used for estimation of incremental expenditures associated with ADPKD. The mean incremental total health care expenditure associated with ADPKD was $7,917 ($431), $p<0.05$. The mean incremental outpatient expenditures associated with ADPKD, $4,507 ($181), $p<0.05$, accounted for the largest incremental expenditure. Hospital expenditures were the second largest incremental expenditure associated with ADPKD, $2,385 ($241), $p<0.05$. Incremental expenditures associated with ADPKD for medication expenditures were $1,456 ($71), $p<0.05$ and incremental emergency room expenditures were $62 ($7), $p<0.05$.

Smith et al. estimated incremental health care expenditures associated with each stage of chronic kidney disease (Smith et al. 2004). According to Smith et al., mean annual incremental outpatient expenditures associated with stage 2 chronic kidney disease was $4,646, associated with stage 3 chronic kidney disease was $3,194, and associated with stage 4 chronic kidney disease was $3,549 (Smith et al. 2004). In comparison, mean incremental outpatient expenditures associated with ADPKD in the current study were $4,507 ($181), $p<0.05$. Smith et al. also reported that mean annual incremental total health care expenditures associated with stage 2 chronic kidney disease was $22,552, incremental expenditures associated with stage 3 chronic kidney disease was $14,179, and incremental expenditures associated with stage 4 chronic kidney

disease was $22,821 (Smith et al. 2004). In comparison, the current study estimated a lower mean incremental total health care expenditures of $7,917 ($431), $p<0.05$, associated with ADPKD.

Both, the study by Smith et al. as well as the current study, used standard prices to calculate health care expenditures that reflected allowed payments from a single source with a consistent payment plan. However, Smith et al. only adjusted for age and gender only whereas in the current study, multivariate regression equations adjusted for age, gender, co-morbidity index score, cardiovascular disease, diabetes and geographical region. Lower incremental expenditure estimates in the current study, compared to those presented by Smith et al., might be due to adjustment for those risk factors. Also, the study by Smith et al. estimated incremental expenditures associated with chronic kidney diseases regardless of disease etiology whereas this current study focused on estimating incremental expenditures associated specifically with ADPKD (Smith et al. 2004). Therefore, observed differences in incremental resource expenditures estimates between the study by Smith et al. and estimates found in this current study may also be due to differences in composition of the sample across studies.

The current study findings indicate that ADPKD is associated with significant incremental health care expenditures even after adjusting for age, gender, co-morbidities, cardiovascular disease, diabetes and geographical region. Quantifying the specific health care expenditure components such as incremental expenditures from hospitals, nursing homes, outpatient visits, emergency room visits and medications provide valuable insight regarding economic burden associated with ADPKD. These incremental

expenditure estimates indicate the potential savings that may be achieved if ADPKD were better treated or controlled.

Sub-Group Analysis by whether Diagnosed with End-Stage Renal Disease

Among 3,844 persons with ADPKD, 644 had a diagnosis of end-stage renal disease and 3,200 persons with ADPKD had not been diagnosed with end-stage renal disease. Significant incremental, mean (standard error) hospitalizations, 0.35 (0.052), $p<0.05$ and hospital days, 2.5 (0.42), $p<0.05$ were associated with ADPKD in the sub-group with end-stage renal disease. There were also significant incremental hospitalizations, 0.065 (0.028), $p<0.05$ and hospital days, 0.50 (0.091), $p<0.05$ associated with ADPKD in the sub-group without end-stage renal disease. Although the magnitude of estimated incremental hospitalizations and hospital days were greater in the sub-group with end-stage renal disease as compared to estimates from the model including all persons regardless of end-stage renal disease status, ADPKD was still associated with significant incremental hospitalizations and hospital days in the sub-group containing only persons without end-stage renal disease. The magnitude of the estimates of incremental hospitalizations in the group without end-stage renal disease, 0.065 (0.028), $p<0.05$ were similar to those from the model including everyone regardless of end-stage renal disease status, 0.087 (0.011), $p<0.05$. The same was true for the magnitude of the incremental hospital days estimate among those without end-stage renal disease, 0.50 (0.091), $p<0.05$, as compared to that from the model for all individuals regardless of end-stage renal disease status 0.68 (0.090), $p<0.05$.

Although the sub-group with end-stage renal disease had several times higher incremental outpatient visits 24.0 (1.2), $p<0.05$ associated with ADPKD as compared to the estimates for all individuals with ADPKD regardless of end-stage renal disease status, 6.9 (0.28), $p<0.05$; the ADPKD sub-group without end-stage renal disease had mean incremental outpatient visits, 4.4 (0.41), $p<0.05$ close in magnitude to those from the inclusive sample. In contrast, the sub-group analysis revealed that there were not significant incremental emergency room visits associated with ADPKD in the sub-group with end-stage renal disease, but that the sub-group without end-stage renal disease did have significant incremental emergency room visits 0.32 (0.058), $p<0.05$ associated with ADPKD and of similar magnitude to that from the model for all individuals regardless of end-stage renal disease status, 0.29 (0.055), $p<0.05$.

The ADPKD sub-group with end-stage renal disease had mean incremental total expenditures associated with ADPKD $42,547 ($2,102), $p<0.05$, that were much higher than those for the sample including all persons with ADPKD regardless of end-stage renal disease status $7,917 ($431), $p<0.05$. Although the sub-group without end-stage renal disease had lower incremental mean total expenditures $3,053 ($374), $p<0.05$ associated with ADPKD than for the group including everyone regardless of end-stage renal disease status $7,917 ($431), $p<0.05$, the incremental expenditures were still large. Similar relationships were seen in comparison across the sub-group with end-stage renal disease, the sub-group without end-stage renal disease and the overall sample, for incremental hospital expenditure $9,430 ($1,179), $p<0.05$, $1,365 ($207), $p<0.05$, and $2,385 ($241), $p<0.05$; outpatient expenditures $26,539 ($1,373) $p<0.05$, $1,247 ($119), $p<0.05$, and $4,507 ($181), $p<0.05$; and medication expenditures $5,933 ($342), $p<0.05$,

$824 ($61), p<0.05, and $1,456 ($71), p<0.05 respectively. However, incremental emergency room expenditures associated with ADPKD were of similar magnitude for the sub-group with end-stage renal disease $67 ($22), p<0.05, the sub-group without end-stage renal disease $63 ($8), p<0.05, and the overall group incorporating all individuals regardless of end-stage renal disease status $62 ($7), p<0.05.

Prior studies have found declining renal function is associated with increased risks of adverse outcomes including health care resource utilization and health care expenditures (Go et al. 2004; Smith et al. 2004; Lentine et al. 2010). Mean annual all-cause total health care expenditures reported by Lentine et al. were $26,521 at early stages of renal function decline among individuals with ADPKD and all-cause expenditures rose to $140,139 when ADPKD patients reached end-stage renal disease (Lentine et al. 2010). The current study found that mean all-cause health care expenditures were higher for the ADPKD sub-group with end-stage renal disease $78,451 (95 percent C.I.: $71,168 to $85,733) than for the ADPKD sub-group without end-stage renal disease $12,131 (95 percent C.I.: $11,174 to $13,089). The current study also found that mean incremental total health care expenditures associated with ADPKD were higher for the ADPKD sub-group with end-stage renal disease $42,547 ($2,102) than for the ADPKD sub-group without end-stage renal disease $3,053 ($374).

Although both, the study by Lentine et al. as well as the current study, reported higher all-cause health care expenditures among ADPKD patients who reached advanced stages of renal disease, compared to those ADPKD patients who had not reached end-stage renal disease, expenditure estimates in the current study differed from expenditures reported by Lentine et al. Whereas Lentine et al. derived costs for all medical services

and medications from charges reported on claims paid by a large national health insurance provider (Lentine et al. 2010), the current study used standard prices that reflected allowed payments from a single source with a consistent payment plan.

A diagnosis of ADPKD without end-stage renal disease was associated with considerable incremental inpatient expenditures, outpatient expenditures and medication expenditures, and total health care expenditures. The finding that the economic burden of ADPKD was present even before end-stage renal disease was reached indicates that early intervention in treating or controlling ADPKD may offer significant savings.

Study Limitations

A limitation of this study was that ICD-9-CM codes were used to identify individuals with ADPKD. Also the comorbidities used for the Charlson Comorbidity Index were identified using ICD-9-CM codes. Use of diagnostic codes in claims to identify diagnosis is known to be imperfect due to variations in coding (Romano and Mark 1994). However, the set of codes used in this study to identify ADPKD have been utilized in prior studies (Lentine et al. 2010; Perrone et al. 2005). Since the database used for the study consisted of claims information from privately insured individuals, this study is generalizable only to the privately insured population. However, when compared to the only other estimate of U.S. prevalence of ADPKD that was limited to one county in Minnesota, the current study provides an estimate using a sample spanning all U.S. census regions.

Conclusions

Prevalence of ADPKD in a private-pay population was one in 1,786 persons or 560 cases per million population. The study findings indicate that ADPKD is associated with significant incremental health care resource utilization and incremental health care expenditures even after adjusting for age, gender, co-morbidities, cardiovascular disease, diabetes and geographical region. Incremental resource utilization (standard error) from outpatient visits were large, 6.9 (0.28). Significant incremental resource utilization associated with ADPKD for hospitalizations, 0.087 (0.011), hospital days, 0.68 (0.090) and emergency room visits, 0.29 (0.055) was also found. Considerable incremental expenditures from hospital expenditures $2,385 ($241), incremental medication expenditures $1,456 ($71), and substantially high incremental outpatient expenditures, $4,507 ($181) associated with ADPKD were also observed.

Sub-group analysis of incremental resource utilization and expenditures by whether diagnosed with end-stage renal disease revealed substantially higher incremental burden for patients with ADPKD and diagnosed with end-stage renal disease. However, a diagnosis of ADPKD without end-stage renal disease was associated with significant incremental inpatient expenditures, outpatient expenditures and medication expenditures. These findings indicate that considerable illness burden is associated with ADPKD even before patients reach end-stage renal disease.

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APPENDICES

Appendix A

All-Cause Resource Utilization by Age, Gender and ADPKD Complications

Table A1. Unadjusted Annual Health Care Resource Utilization among Persons with ADPKD by Age

Utilization Category	Under 35 (n=621) Mean (95% CI)	35 to 44 (n=748) Mean (95% CI)	45 to 54 (n=1,043) Mean (95% CI)	55 to 64 (n=1,059) Mean (95% CI)	65 and over (n=373) Mean (95% CI)
Hospitalizations	0.20 (0.16 to 0.25)	0.16 (0.11 to 0.22)	0.25 (0.20 to 0.30)	0.26 (0.21 to 0.30)	0.34 (0.27 to 0.40)
Hospital days	2.1 (0.87 to 3.3)	1.2 (0.20 to 2.1)	1.6 (1.0 to 2.2)	2.3 (1.4 to 3.2)	4.3 (1.8 to 6.9)
Nursing home confinements	0	0.0013 (-0.0013 to 0.0040)	0.0048 (0.00059 to 0.0090)	0.016 (0.0072 to 0.025)	0.059 (0.030 to 0.088)
Nursing home days	0	0.057 (-0.055 to 0.17)	0.12 (-0.029 to 0.28)	0.44 (0.14 to 0.74)	1.7 (0.48 to 2.9)
Outpatient visits	13.1 (11.9 to 14.3)	17.8 (15.8 to 19.7)	21.3 (19.8 to 22.9)	23.4 (23.8 to 26.9)	27.5 (25.2 to 30.3)
Emergency room visits	1.1 (0.89 to 1.4)	1.0 (0.80 to 1.3)	0.99 (0.82 to 1.2)	1.1 (0.91 to 1.3)	0.91 (0.67 to 1.1)

Table A2. Unadjusted Annual Health Care Resource Utilization among Persons with ADPKD by Gender

	Female (N=2,047)	Male (N=1,797)
Utilization Category	Mean (95% CI)	Mean (95% CI)
Hospitalizations	0.23 (0.20 to 0.26)	0.24 (0.21 to 0.28)
Hospital days	1.9 (1.3 to 2.5)	2.2 (1.5 to 2.9)
Nursing home confinements	0.0092 (0.0047 to 0.014)	0.014 (0.0077 to 0.021)
Nursing home days	0.37 (0.12 to 0.62)	0.29 (0.12 to 0.45)
Outpatient visits	21.8 (20.7 to 22.9)	20.2 (19.1 to 21.4)
Emergency room visits	1.1 (0.99 to 1.3)	0.96 (0.82 to 1.1)

Table A3. Unadjusted Annual Health Care Resource Utilization among Persons with ADPKD by ADPKD Complication – Liver Cysts[a]

	No Liver Cysts (n=3,747)	Liver Cysts (n=97)
Utilization Category	Mean (95% CI)	Mean (95% CI)
Hospitalizations	0.22 (0.20 to 0.25)	0.70 (0.43 to 0.96)
Hospital days	1.9 (1.5 to 2.4)	6.5 (1.3 to 11.7)
Nursing home confinements	0.011 (0.0077 to 0.015)	0.010 (-0.010 to 0.030)
Nursing home days	0.33 (0.18 to 0.49)	0.17 (-0.17 to 0.52)
Outpatient visits	20.7 (20.0 to 21.6)	32.7 (26.7 to 38.7)
Emergency room visits	1.0 (0.95 to 1.2)	1.2 (0.51 to 1.9)

[a] A diagnosis of liver cysts during the study period from April 1, 2011 to March 31, 2012

Table A4. Unadjusted Annual Health Care Resource Utilization among Persons with ADPKD by ADPKD Complication – Kidney Stones[a]

	No Kidney Stones (n=3,532)	Kidney Stones (n=312)
Utilization Category	Mean (95% CI)	Mean (95% CI)
Hospitalizations	0.22 (0.20 to 0.24)	0.44 (0.31 to 0.57)
Hospital days	1.9 (1.5 to 2.4)	3.4 (1.3 to 5.5)
Nursing home confinements	0.011 (0.0076 to 0.016)	0.0096 (-0.0012 to 0.020)
Nursing home days	0.35 (0.18 to 0.52)	0.099 (-0.042 to 0.24)
Outpatient visits	20.8 (19.9 to 21.6)	24.4 (22.2 to 26.7)
Emergency room visits	1.0 (0.90 to 1.1)	1.7 (1.2 to 2.1)

[a] A diagnosis of kidney stones during the study period from April 1, 2011 to March 31, 2012

Table A5. Unadjusted Annual Health Care Resource Utilization among Persons with ADPKD by ADPKD Complication – Urinary Tract Infection (UTI)[a]

	No UTI (n=3,238)	UTI (n=606)
Utilization Category	Mean (95% CI)	Mean (95% CI)
Hospitalizations	0.18 (0.16 to 0.20)	0.54 (0.44 to 0.64)
Hospital days	1.6 (1.1 to 2.0)	4.7 (3.0 to 6.4)
Nursing home confinements	0.0074 (0.0040 to 0.010)	0.034 (0.017 to 0.051)
Nursing home days	0.23 (0.091 to 0.38)	0.84 (0.28 to 1.4)
Outpatient visits	19.3 (18.5 to 20.1)	30.5 (28.3 to 32.7)
Emergency room visits	1.0 (0.87 to 1.1)	1.5 (1.2 to 1.7)

[a] A diagnosis of urinary tract infection during the study period from April 1, 2011 to March 31, 2012

Table A6. Unadjusted Annual Health Care Resource Utilization among Persons with ADPKD by ADPKD Complication – Cerebral Aneurysm[a]

	No Cerebral Aneurysm (n=3,808)	Cerebral Aneurysm (n=36)
Utilization Category	Mean (95% CI)	Mean (95% CI)
Hospitalizations	0.23 (0.21 to 0.25)	1.0 (0.53 to 1.5)
Hospital days	2.0 (1.5 to 2.5)	7.7 (1.2 to 14.2)
Nursing home confinements	0.011 (0.0078 to 0.015)	0
Nursing home days	0.33 (0.18 to 0.49)	0
Outpatient visits	20.9 (20.1 to 21.7)	33.5 (21.8 to 45.1)
Emergency room visits	1.0 (0.95 to 1.2)	1.4 (0.057 to 2.8)

[a]A diagnosis of cerebral aneurysm during the study period from April 1, 2011 to March 31, 2012

Table A7. Unadjusted Annual Health Care Resource Utilization among Persons with ADPKD by ADPKD Complication – Any Complication[a]

Utilization Category	No Complication (n=2,934) Mean (95% CI)	At Least One ADPKD Complication (n=910) Mean (95% CI)
Hospitalizations	0.16 (0.14 to 0.18)	0.48 (0.40 to 0.56)
Hospital days	1.5 (0.99 to 1.9)	4.0 (2.7 to 5.2)
Nursing home confinements	0.0078 (0.0041 to 0.011)	0.024 (0.012 to 0.035)
Nursing home days	0.26 (0.097 to 0.42)	0.57 (0.19 to 0.95)
Outpatient visits	18.8 (17.9 to 19.7)	28.4 (26.7 to 30.1)
Emergency room visits	0.94 (0.83 to 1.0)	1.4 (1.2 to 1.7)

[a] A diagnosis for any one of four ADPKD complications including liver cysts, kidney stones, urinary tract infection or cerebral aneurysm during the study period from April 1, 2011 to March 31, 2012

Table A8. Unadjusted Annual Health Care Resource Utilization among Persons with ADPKD by Number of ADPKD Complications[a]

	0 (n=2,934)	1 (n=776)	2 (n=127)	3 (n=7)	4 (n=0)
Utilization Category	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Hospitalizations	0.16 (0.14 to 0.18)	0.41 (0.34 to 0.49)	0.78 (0.57 to 0.99)	2.6 (-0.14 to 5.3)	0
Hospital days	1.5 (0.99 to 1.9)	3.2 (2.0 to 4.4)	8.0 (2.6 to 13.4)	12.8 (-2.4 to 28.1)	0
Nursing home confinements	0.0078 (0.0041 to 0.011)	0.024 (0.011 to 0.037)	0.023 (-0.0031 to 0.050)	0	0
Nursing home days	0.26 (0.097 to 0.42)	0.62 (0.18 to 1.1)	0.28 (-0.11 to 0.67)	0	0
Outpatient visits	18.8 (17.9 to 19.7)	27.8 (25.9 to 29.7)	30.2 (26.6 to 33.7)	58.6 (9.2 to 108.0)	0
Emergency room visits	0.94 (0.83 to 1.0)	1.4 (1.1 to 1.6)	1.8 (1.1 to 2.5)	2.6 (0.65 to 4.5)	0

[a]Number of ADPKD complications, including liver cysts, kidney stones, urinary tract infection or cerebral aneurysm, ranging from 0 (no ADPKD complication) to 4 (up to four ADPKD complications), during the study period from April 1, 2011 to March 31, 2012

Appendix B

All-Cause Expenditures by Age, Gender and ADPKD Complications

Table B1. Unadjusted Annual Health Care Expenditures in Dollars among Persons with ADPKD by Age

Expenditure Category	Under 35 (n=621) Mean (95% CI)	35 to 44 (n=748) Mean (95% CI)	45 to 54 (n=1,043) Mean (95% CI)	55 to 64 (n=1,059) Mean (95% CI)	65 and over (n=373) Mean (95% CI)
Inpatient expenditures	6,152 (2,781 to 9,522)	2,991 (1,840 to 4,141)	7,116 (5,275 to 8,957)	8,126 (6,244 to 10,008)	9,290 (6,797 to 11,782)
Nursing home expenditures	0	40 (-38 to 119)	106 (-31 to 243)	385 (61 to 709)	1,128 (391 to 1,865)
Outpatient expenditures	4,583 (3,700 to 5,465)	8,978 (6,964 to 10,992)	14,605 (12,214 to 16,996)	17,300 (14,899 to 19,701)	14,525 (11,153 to 17,896)
Emergency room expenditures	209 (167 to 251)	171 (142 to 201)	201 (153 to 249)	164 (139 to 189)	129 (85 to 172)
Medication expenditures	1,989 (1,326 to 2,652)	2,236 (1,837 to 2,636)	3,700 (3,313 to 4,087)	4,774 (4,363 to 5,186)	4,759 (4,184 to 5,333)
Total health care expenditures	12,933 (9,056 to 16,809)	14,417 (11,791 to 17,044)	25,729 (22,267 to 29,190)	30,751 (27,206 to 34,296)	29,830 (25,263 to 34,398)

Table B2. Unadjusted Annual Health Care Expenditures in Dollars among Persons with ADPKD by Gender

	Female (n=2,047)	Make (n=1,797)
Expenditure Category	Mean (95% CI)	Mean (95% CI)
Inpatient expenditures	6,058 (4,747 to 7,370)	7,317 (5,904 to 8,730)
Nursing home expenditures	218 (83 to 353)	290 (81 to 500)
Outpatient expenditures	12,206 (10,786 to 13,626)	13,104 (11,467 to 14,740)
Emergency room expenditures	201 (172 to 229)	155 (136 to 174)
Medication expenditures	3,185 (2,902 to 3,486)	3,939 (3,616 to 4,262)
Total health care expenditures	21,869 (19,702 to 24,037)	24,806 (22,276 to 27,336)

Table B3. Unadjusted Annual Health Care Expenditures in Dollars among Persons with ADPKD by ADPKD Complication – Liver Cysts[a]

	No Liver Cysts (n=3,747)	Liver Cysts (n=97)
Expenditure Category	Mean (95% CI)	Mean (95% CI)
Inpatient expenditures	6,247 (5,315 to 7,178)	22,095 (9,790 to 34,400)
Nursing home expenditures	256 (131 to 380)	108 (-107 to 324)
Outpatient expenditures	12,339 (11,275 to 13,403)	23,697 (12,490 to 34,903)
Emergency room expenditures	178 (160 to 196)	232 (129 to 334)
Medication expenditures	3,490 (3,274 to 3,707)	5,363 (4,080 to 6,646)
Total health care expenditures	22,511 (20,889 to 24,132)	51,496 (32,894 to 70,098)

[a] A diagnosis of liver cysts during the study period from April 1, 2011 to March 31, 2012

Table B4. Unadjusted Annual Health Care Expenditures in Dollars among Persons with ADPKD by ADPKD Complication – Kidney Stones[a]

	No Kidney Stones (n=3,532)	Kidney Stones (n=312)
Expenditure Category	Mean (95% CI)	Mean (95% CI)
Inpatient expenditures	6,345 (5,340 to 7,351)	10,058 (6,796 to 13,319)
Nursing home expenditures	265 (134 to 397)	103 (-38 to 245)
Outpatient expenditures	12,610 (11,466 to 13,754)	12,803 (9,981 to 15,625)
Emergency room expenditures	160 (146 to 175)	394 (254 to 534)
Medication expenditures	3,563 (3,340 to 3,785)	3,253 (2,479 to 4,028)
Total health care expenditures	22,944 (21,202 to 24,687)	26,612 (21,564 to 31,660)

[a] A diagnosis of kidney stones during the study period from April 1, 2011 to March 31, 2012

Table B5. Unadjusted Annual Health Care Expenditures in Dollars among Persons with ADPKD by ADPKD Complication – Urinary Tract Infection (UTI)[a]

	No UTI (n=3,238)	UTI (n=606)
Expenditure Category	Mean (95% CI)	Mean (95% CI)
Inpatient expenditures	5,298 (4,342 to 6,254)	13,851 (10,572 to 17,130)
Nursing home expenditures	160 (65 to 255)	742 (163 to 1,322)
Outpatient expenditures	11,794 (10,637 to 12,952)	17,068 (14,211 to 19,924)
Emergency room expenditures	152 (137 to 167)	325 (248 to 402)
Medication expenditures	3,370 (3,142 to 3,598)	4,433 (3,847 to 5,019)
Total health care expenditures	20,776 (19,093 to 22,479)	36,420 (31,332 to 41,507)

[a] A diagnosis of urinary tract infection during the study period from April 1, 2011 to March 31, 2012

Table B6. Unadjusted Annual Health Care Expenditures in Dollars among Persons with ADPKD by ADPKD Complication – Cerebral Aneurysm[a]

	No Cerebral Aneurysm (n=3,808)	Cerebral Aneurysm (n=36)
Expenditure Category	Mean (95% CI)	Mean (95% CI)
Inpatient expenditures	6,308 (5,373 to 7,243)	42,474 (16,233 to 68,714)
Nursing home expenditures	254 (132 to 377)	0
Outpatient expenditures	12,416 (11,354 to 13,477)	34,839 (10,974 to 58,703)
Emergency room expenditures	178 (160 to 196)	284 (118 to 450)
Medication expenditures	3,544 (3,329 to 3,759)	2,863 (1,610 to 4,116)
Total health care expenditures	22,701 (21,080 to 24,322)	80,459 (41,355 to 119,564)

[a]A diagnosis of cerebral aneurysm during the study period from April 1, 2011 to March 31, 2012

Table B7. Unadjusted Annual Health Care Expenditures in Dollars among Persons with ADPKD by ADPKD Complication – Any Complication[a]

Expenditure Category	No Complication (n=2,934) Mean (95% CI)	At Least One ADPKD Complication (n=910) Mean (95% CI)
Inpatient expenditures	4,820 (3,845 to 5,796)	12,535 (9,999 to 15,071)
Nursing home expenditures	174 (69 to 278)	504 (118 to 891)
Outpatient expenditures	11,400 (10,209 to 12,591)	16,578 (14,165 to 18,991)
Emergency room expenditures	142 (127 to 158)	298 (243 to 353)
Medication expenditures	3,377 (3,138 to 3,616)	4,055 (3,585 to 4,526)
Total health care expenditures	19,914 (18,171 to 21,657)	33,972 (29,901 to 38,042)

[a] A diagnosis for any one of four ADPKD complications including liver cysts, kidney stones, urinary tract infection or cerebral aneurysm during the study period from April 1, 2011 to March 31, 2012

Table B8. Unadjusted Annual Health Care Expenditures in Dollars among Persons with ADPKD by Number of ADPKD Complications[a]

	0 (n=2,934)	1 (n=776)	2 (n=127)	3 (n=7)	4 (n=0)
Expenditure Category	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Inpatient expenditures	4,820 (3,845 to 5,796)	10,316 (7,926 to 12,707)	23,666 (13,359 to 33,972)	56,534 (981 to 112,097)	0
Nursing home expenditures	174 (69 to 278)	549 (99 to 999)	261 (-95 to 618)	0	0
Outpatient expenditures	11,400 (10,209 to 12,591)	16,433 (13,769 to 19,098)	14,668 (10,607 to 18,729)	67,251 (-22,748 to 152,249)	0
Emergency room expenditures	142 (127 to 158)	250 (213 to 286)	571 (249 to 894)	652 (-47 to 1,353)	0
Medication expeditures	3,377 (3,138 to 3,616)	4,022 (3,498 to 4,547)	3,969 (2,985 to 4,952)	9,306 (1,976 to 16,637)	0
Total health care expenditures	19,914 (18,171 to 21,657)	31,572 (27,359 to 35,785)	43,136 (30,980 to 55,292)	133,744 (14,296 to 253,191)	0

[a]Number of ADPKD complications, including liver cysts, kidney stones, urinary tract infection or cerebral aneurysm, ranging from 0 (no ADPKD complication) to 4 (up to four ADPKD complications), during the study period from April 1, 2011 to March 31, 2012

VITA

VITA

Neeraj N. Iyer was born to Mr. R. Neelakantan Iyer and Mrs. Rajalakshmi N. Iyer on March 12, 1983 in Pune, India. After finishing high school from St. Vincent's High School, in 1999, he joined St. Vincent's Junior college, Pune to pursue preparation for a career in the science and technology field. He then pursued a Bachelor's degree in Pharmacy from Pune University starting in 2001. After obtaining his Bachelor's degree, he worked as a Consultant, Marketing Intelligence with Concordas Informatics India. Pvt. Ltd in Mumbai from December 2005 to June 2006. He then joined Purdue University in August 2006 to pursue a doctoral degree in Pharmacy Administration.

Neeraj received his first degree from Purdue University in August 2010 when he graduated with a Masters in Pharmacy Administration. While at Purdue University, he was involved in various research projects, presentations and publications. He was the finalist for the Best Presentation Award, for the Wiederholt Consortium for Research on Administrative Pharmacy, at the Midwest Social and Administrative Pharmacy Conference, Iowa City, IA in June 2010. He received the Kienly Award for Excellence in Teaching, awarded to outstanding teaching assistants in the College of Pharmacy in November 2011. Neeraj also received the Teaching Award, awarded by the Committee for the Education of Teaching Assistants (CETA), for excellence in teaching in April 2012. He has been an active member of the International Society for

Pharmacoeconomics and Outcomes Research (ISPOR) and received the ISPOR Distinguished Service Award, May 2010. He also represented the Purdue University Student chapter at the International Society for Pharmacoeconomics and Outcomes Research as President. During his doctoral studies, Neeraj completed a summer internship at Pfizer Inc. in the Specialty Care Outcomes research group in summer 2011.

Neeraj's research interests are in the field of health economics and outcomes research and upon graduation he looks forward to build his career in the same field.