HSR Health Services Research

DOI: 10.1111/j.1475-6773.2011.01301.x
RESEARCH ARTICLE

Managed Care and the Diffusion of Endoscopy in Fee-for-Service Medicare

Lee Rivers Mobley, Sujha Subramanian, Julia Koschinsky, H. E. Frech, Laurel Clayton Trantham, and Luc Anselin

Objective. To determine whether Medicare managed care penetration impacted the diffusion of endoscopy services (sigmoidoscopy, colonoscopy) among the fee-for-service (FFS) Medicare population during 2001–2006.

Methods. We model utilization rates for colonoscopy or sigmoidoscopy as impacted by both market supply and demand factors. We use spatial regression to perform ecological analysis of county-area utilization rates over two time intervals (2001–2003, 2004–2006) following Medicare benefits expansion in 2001 to cover colonoscopy for persons of average risk. We examine each technology in separate cross-sectional regressions estimated over early and later periods to assess differential effects on diffusion over time. We discuss selection factors in managed care markets and how failure to control perfectly for market selection might impact our managed care spillover estimates.

Results. Areas with worse socioeconomic conditions have lower utilization rates, especially for colonoscopy. Holding constant statistically the socioeconomic factors, we find that managed care spillover effects onto FFS Medicare utilization rates are negative for colonoscopy and positive for sigmoidoscopy. The spatial lag estimates are conservative and interpreted as a lower bound on true effects. Our findings suggest that managed care presence fostered persistence of the older technology during a time when it was rapidly being replaced by the newer technology.

Key Words. Endoscopy utilization, spatial regression analysis, Medicare population trends, managed care spillovers, cost-effectiveness

BACKGROUND

More than 100,000 new cases of colorectal cancer (CRC) were detected in 2010, and more than 50,000 people died from CRC. Survival rates are 90 percent if diagnosed early, yet only 39 percent of CRC cases are diagnosed at an early stage (ACS, 2010). Medicare has covered CRC screening since 1998, but use has been low, as only about 50 percent of beneficiaries had received a CRC test during 1998–2005 (Schenck et al. 2009). Similarly, as of 2005, only half of adults older than age 50 had been screened in the past 10 years (Shapiro et al. 2008). CRC remains the second leading cause of cancer death in the United States, and there is concern over the low compliance with screening recommendations (Klabunde et al. 2008; Holden et al. 2010).

The most recent American Cancer Society (ACS) guidelines for CRC screening recommend four procedures that can both *detect and prevent* CRC (barium enema, sigmoidoscopy, colonoscopy, and CT colonography) (ACS, 2008). The American College of Gastroenterology and the Centers for Medicare & Medicaid Services (CMS) view colonoscopy as the "gold standard" (Rex et al. 2009; Neugut and Lebwohl 2010; CMS 2011); however, the U.S. Preventive Services Task Force does not (USPSTF, 2007). The USPSTF recommends that choice among methods should be customized to patients or practice settings, because none of the various test modalities could be identified as superior in cost-effectiveness analysis, tests were not uniformly accessible and posed various risks to patients, and tests were not uniformly acceptable to all patients (Pignone et al. 2002a,b; USPSTF, 2002; Whitlock et al. 2008).

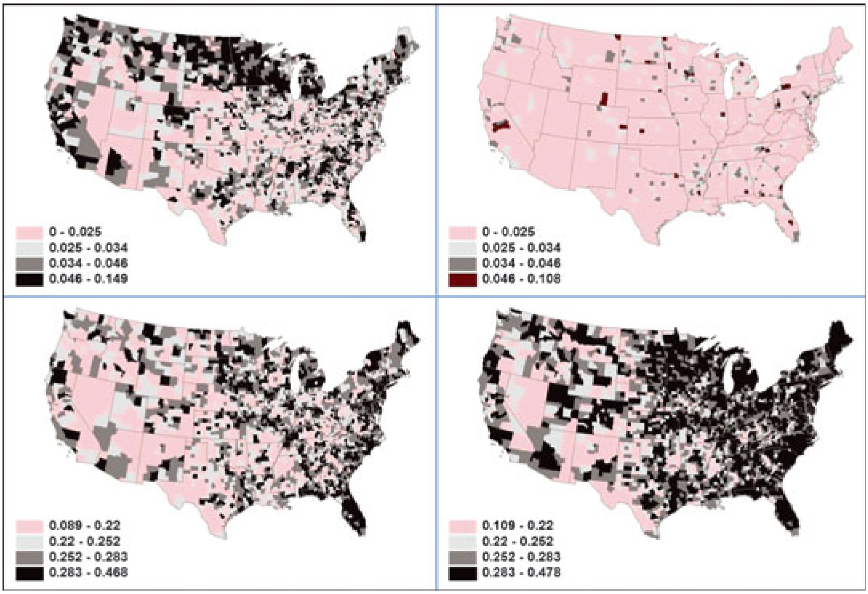
The USPSTF recommends CRC screening for people aged 50 or older because they have higher prevalence of this disease, which can be prevented through routine screening and more effectively treated following early detection. While CRC screening was lower than national guidelines, three nationally representative studies found dramatic increases in endoscopy use over the period 2000–2005 for both the age 50+ and age 65+ populations (Shih, Zhao, and Elting 2006; Shapiro et al. 2008; Doubeni et al. 2010). Several factors that likely contributed to the increase include the expansion of Medicare coverage in 2001 for screening colonoscopy in people of average risk (Cooper and Koroukian 2004), media coverage of colonoscopy, and changes in physician and patient preferences (Shapiro et al. 2008). Colonoscopy use increased steadily, whereas sigmoidoscopy use declined during 1998–2005 (Shapiro et al. 2008), which is consistent with our Medicare population data used here (Figure 1).

Colonoscopy procedures are more complex and cost more to perform than sigmoidoscopy procedures. Medicare reimbursement rates, which are

---

Address correspondence to Lee Rivers Mobley, Ph.D., RTI International, Discovery and Analytical Sciences, 3040 Cornwallis Road, Research Triangle Park, NC 27709-2194; e-mail: lmobley@rti.org. Sujha Subramanian, Ph.D., is with RTI International, Social, Statistical, and Environmental Sciences, Waltham, MA. Julia Koschinsky, Ph.D., and Luc Anselin, Ph.D., are with the Arizona State University, GeoDa Center for Geospatial Analysis and Computation, Tempe, AZ. H. E. Frech, Ph.D., is with the University of California, Economics Department, Santa Barbara, CA. Laurel Clayton Trantham is with the University of North Carolina-Chapel Hill, Gillings School of Global Public Health, Chapel Hill, NC.

Figure 1: Expansion of Colonoscopy and Contraction of Sigmoidoscopy Procedure Utilization over Time among Fee-for-Service (FFS) Medicare Beneficiaries, 2001--2006



Notes. The maps in the four panels of this figure display sigmoidoscopy use rates in the top row, and colonoscopy use rates in the bottom row. Moving left to right, the early period is defined as 2001--2003 and the late period is 2004--2006. Rates are defined as the sum of utilization in the 3 years divided by the average Medicare FFS population in the 3 years. Utilization was defined from extracts of 100 percent of Medicare claims files, 2001--2006. Use rate categories were defined identically in early and late periods to reveal changes in prevalence of use over time.

cost-based, were (in 2007 dollars) $650 for colonoscopy and $350 for sigmoidoscopy (AHRQ, 2007). Private insurers pay more, and there are significant profit margins on endoscopy services, especially in outpatient settings (Luchtefeld and Kim 2006); thus, physician groups have formed to offer these services in competition with hospital outpatient departments (Berenson, Bodenheimer, and Pham 2006). Sigmoidoscopy was the incumbent endoscopy procedure, whereby the provider inserts a thin, lighted tube into the rectum to examine the lower third of the colon while the more recent colonoscopy procedure involves a longer, flexible tube to examine the entire colon. Most polyps and some cancers can be found and removed during either procedure, although polyp removal involves additional training and equipment and sigmoidoscopy providers may not be equipped to do so (ACS

2008). Colonoscopy involves more intensive advance preparation on the part of the patient (to cleanse the upper colon) and poses greater risk of perforation, because the tube goes beyond a sharp bend separating the lower and upper colon, and also poses risks associated with the ingestion of dehydrating laxatives and fasting for several days.

Colonoscopy is considered superior by some experts because precancerous lesions in the upper colon cannot be detected and removed by sigmoidoscopy (Loeve et al. 2000a,b; O'Leary et al. 2003; Brenner 2008; Rex et al. 2009). However, the superior efficacy of colonoscopy versus sigmoidoscopy has been questioned in recent studies (Baxter and Rabeneck 2010; Neugut and Lebwohl 2010). The lack of a body of evidence regarding superior comparative or cost-effectiveness advantages for colonoscopy over sigmoidoscopy have escalated focus in the United States on whether the extra cost of colonoscopy is worthwhile for improving population health, as the vast majority are not in the high-risk category (Neugut and Lebwohl 2010; Subramanian, Bobashev, and Morris 2010; Goodwin et al. 2011).

Given the lack of consensus among experts regarding which test is "best" and the higher procedure costs, it is surprising that the diffusion of colonoscopy has been so rapid. Although reasons are not apparent, some have conjectured that the expansion of Medicare reimbursement of colonoscopy to cover average-risk persons was intended to reduce access barriers to CRC screening, and it was expected to reduce disparities among minorities and whites (Shih, Zhao, and Elting 2006). At about this same time, Medicare was promoting use of managed care plans and the promise of managed care to improve disease management and preventive services utilization and to slow escalating health care costs resulting from poor management and prevention (Greenwald et al. 2004; Hurley and Retchin 2006; Pope et al. 2006). Managed care plans can control costs by assessing the cost-effectiveness of various treatment options and disseminating information and guidelines regarding the preferred protocols for preventive health services. During this period of uncertainty regarding which cancer screening modality was best, managed care plans had an opportunity to exert influence on their providers and constituents.

In this paper, we assess empirically whether managed care prevalence seemed to have had any influence over the diffusion of colonoscopy relative to sigmoidoscopy among fee-for-service (FFS) Medicare beneficiaries following Medicare coverage expansion in 2001. We focus on these two endoscopic procedures, which are near-perfect substitutes from a payments perspective. That is, for average-risk Medicare-insured persons aged 65+ during this time period, based on screening recommendations and Medicare reimbursement rates, payments over a 10-year interval were about the same for colonoscopy and sigmoidoscopy. Screening guidelines recommend annual home fecal occult blood testing (FOBT) with sigmoidoscopy every 5 years, OR colonoscopy every 10 years, for persons of average risk (ACS 2008), and two sigmoidoscopies in 10 years cost about the same as a single colonoscopy (AHRQ 2007).

In addition, beneficiaries were required to pay 20–25 percent of the procedure costs out-of-pocket, during this period, with the higher rate for services provided outside of hospitals (MLN, 2006). From the patient's perspective, out-of-pocket costs at the point of service are lower for sigmoidoscopy, patient time costs per procedure are lower, and procedure risks are lower. So while near-perfect substitutes from a planning perspective, patients and their providers would likely view colonoscopy as having higher out-of-pocket and time costs, and greater risk, with perhaps greater efficacy to prevent cancer.

Managed Care Plans and Endoscopy Use

Spillover effects from managed care have been variously defined as changes in practice patterns, costs, or the diffusion of new technology relative to what might occur in markets with little managed care influence (Miller and Luft 1994; Baker 2003). Changes in practice patterns can spill over to people who are not insured by the managed care plans (such as our FFS Medicare population), but who are seen by the physicians who are affected by the information the plans disseminate. Also, Medicare beneficiaries may compare treatment options with and be influenced by the care patterns received by their peers who are in managed care plans. These behavioral spillovers among people are not expected to be contained within county boundaries, generating spatial spillovers across people in adjacent counties. In this way, managed care plans can impact the way medicine is practiced in their markets, impacting adherence to screening guidelines by market participants, *whether or not they are enrolled in managed care plans.*

If endoscopic CRC screening is cost-effective, one might expect that managed care plans would encourage its utilization. However, there is very little empirical evidence regarding CRC screening modalities among Medicare managed care (MMC) constituents, because MMC plans are not required to collect or publish utilization data; the only existing study found that MMC enrollees were more likely to use FOBT than endoscopy, as compared to their peers in FFS Medicare (Schneider et al. 2008). There is some limited evidence regarding managed care *spillover effects* on the utilization of endoscopy in FFS Medicare in 1999, where modest positive impacts on various CRC screening modalities were found (Koroukian et al. 2005).

The major contribution of this paper is to assess whether MMC penetration impacted the diffusion of endoscopy services among the FFS Medicare population during 2001–2006. Medicare policy expanded in 2001 to cover the newer, more expensive procedure that had no strong evidence of cost-effectiveness advantages for persons of average risk. This topic is timely to inform ongoing health care reform efforts aimed at improving preventive care services utilization and ultimately slowing the growth in national health care expenditures.

METHODS

In this cross-sectional study design, the outcome measures are county-level utilization rates of two CRC screening modalities (sigmoidoscopy and colonoscopy) utilized by the FFS Medicare beneficiary population over two intervals, 2001–2003 and 2004–2006, residing in all counties in the continental United States. Two time periods allow for comparisons over time that can inform us regarding diffusion of the newer relative to the older technology. We assess ecological spillover effects from MMC directly, by including MMC penetration as an explanatory variable, along with other statistical control variables needed to reduce potential selection effects that might impact the MMC spillovers estimate.

Selection Effects

Medicare Part B insurance to cover outpatient and preventive care is discretionary, and in the past decade, many poorer elderly could not afford this coverage. In an effort to encourage MMC plan enrollment by low-income seniors who lacked preventive care or management, CMS subsidized the MMC plans during this period so that low-income seniors could obtain Part B benefits at no additional cost (Greenwald et al. 2004; Pope et al. 2006). Wealthier individuals were required to give up their very popular MediGap supplemental insurance plans if they elected to join MMC plans, so elderly with lower socioeconomic status (SES) were more likely to join MMC than wealthier individuals (AHIP, 2005; Atherly and Thorpe 2005). Therefore, FFS Medicare covers the relatively wealthier beneficiaries in

MMC-penetrated markets, and since higher-income beneficiaries have been shown to prefer colonoscopy procedures relative to other CRC modalities (Phillips et al. 2007), FFS utilization of colonoscopy would appear relatively higher in MMC-penetrated markets than in unpenetrated markets. These income dynamics portend a selection bias on the spillover effect from MMC onto FFS constituents, which is toward higher utilization of colonoscopy. Because of these selection issues, it is important to control statistically for aspects of elderly SES so that a reliable estimate of the MMC spillover effect can be identified.

As noted by Baker (2003) in his seminal work on this topic, studying managed care spillovers, defined broadly as impacts on the structure and functioning of the health care system in highly penetrated markets, requires careful empirical model design to eliminate potential selection bias. It is important to include in cross-sectional studies (such as this one) comprehensive controls for all factors that may be associated with performance or entry by managed care organizations in the health markets being studied, to avoid omitted variables bias in the spillover parameter estimate that would be induced by selection effects. We included a comprehensive set of variables (described below) to allow interpreting the managed care penetration effect as a spillover effect on the FFS utilization rate outcomes. To further reduce endogeneity problems caused by potential selection bias in contemporaneous data, we lagged the MMC penetration rate 2 years.

To identify the full set of confounding factors that are needed to control statistically for potential selection effects, we developed a conceptual model of the ecological predictors of endoscopy utilization (the outcome), based on economic factors. Both supply and demand factors determine endoscopy use rates in small areas (Tangka et al. 2005). Adoption (purchase) of endoscopy equipment and acquiring the necessary training to use it will depend on the expected return on investment, which is a function of market conditions. Observed utilization rates will depend on various factors:

1. market size (density), which affects pace of return on investment;
2. socioeconomic status, acculturation, and educational attainment of the treatment population; and
3. health market conditions, such as
   i. prevalence of managed care plans,
   ii. prevalence of endoscopy providers and service diffusion (lack of specialization) among them, and
   iii. importance of Medicare as a market demand segment.

We expect that counties with greater poverty over the past decade, or with lower elderly educational attainment or English language ability, would be less viable and unattractive to investors, thus characterized by smaller supply of endoscopy, resulting in lower utilization rates. Demand (willingness) and ability to pay out-of-pocket expenses is also expected to be lower among poorer, less educated or informed individuals. As investment in sigmoidoscopy is cheaper (both procedure costs and training requirements are lower), and because costs to the patient are lower, then all else equal, sigmoidoscopy use rates are expected to be higher than colonoscopy use rates in less viable markets.

Managed care has been known to slow the adoption of newer technology and favor treatments with greater cost-effectiveness (Miller and Luft 1994; Baker 2003). In urban areas where managed care is more prevalent, managed care plans can impact the diffusion of newer technology by directly impacting the decision whether to invest in endoscopy equipment. Thus, we might expect markets with higher managed care penetration to have lower utilization of colonoscopy and higher utilization of sigmoidoscopy. Our focus is therefore on testing the hypothesis that, in areas where MMC was more prevalent, there were negative spillovers on colonoscopy and positive spillovers on sigmoidoscopy use rates.

Data

The study population is the entire Medicare FFS population aged 65+ and residing in the continental United States, each year during 2001–2006. Alaska and islands are excluded because spatial continuity is a fundamental premise of the spatial regression analysis that we employ. Study outcomes are county-area utilization rates for sigmoidoscopy or colonoscopy procedures. We included all persons each year with traditional FFS Medicare coverage (both Parts A and B coverage for at least 11 months of the year). We used extracts of 100 percent of Medicare Part B/physician carrier files for all claims with endoscopy procedure codes, and we calculated the number of beneficiaries who had received any endoscopy service in the year, by county. We then summed the counts of beneficiaries who had used any annual endoscopy over 3 years (2001–2003, 2004–2006) and divided this sum by the average FFS population size (from the 100 percent denominator file) over the 3 years. Using only the physician carrier file, we avoided duplication that might have been obtained from using in addition hospital or outpatient facility files, reasoning that physician claims would be filed for every procedure regardless of the delivery location. Counting persons with "any endoscopy" in the year (rather than actual number of procedures per person) also controlled for possible errors from duplication in claims or service use. We used annual data beginning in 2001, the first year that both types of endoscopy were covered by FFS Medicare, and for every year thereafter through 2006. We used 3-year rates because screening recommendations are defined for time intervals; thus, annual rates would be sparse and noisy. Two sequential rates were used to allow assessment of any diffusion effects over time.

In addition, we used 100 percent Medicare population demographic information from the Medicare denominator file and other factors describing local market conditions from the U.S. Census and the CMS Geographic Service Area Files. Table 1 presents the descriptions and data sources for the variables, and Table 2 presents their sample statistics. The ecological variables reflect aggregate conditions in counties across the continental United States.

To develop the explanatory variables describing demand (population) factors, we used the 100 percent Medicare denominator files to construct area proportions representing race or ethnicity, and sex. As there are no data describing SES in the Medicare files, we used several census variables, including population density, proportion of elderly with poor or no English language ability, and proportion of elderly with a graduate or professional degree. We used annual county data from 1990 to 2000 and 1995 to 2005 to calculate average 10-year poverty rate in each county, thus calibrated to the early and late screening intervals in the analysis. The MMC penetration rate was derived using the CMS Geographic Service Area File, defined as the proportion of Medicare eligibles in the county that were enrolled in MMC plans. Other statistical control variables reflecting health status included proportions of the Medicare beneficiary population by age group; with end-stage renal disease; or who were disabled as their original reason for Medicare entitlement.

All endoscopy providers in our 100 percent claims files were used to define endoscopy provider specialization indices. We used the market share of each unique provider of endoscopy services delivered to FFS Medicare beneficiaries in the county, then summed and squared the market shares, creating a quasi-Herfindahl index(we did not have information regarding which providers practiced together in groups) of market concentration. A higher index number reflects greater concentration of services among fewer providers, but we wanted the opposite measure, which effectively deals with the

Table 1: Variables Used in Modeling: All Data Used in Modeling Are Aggregated to Reflect Proportions in Counties, County-Specific Indices, Per-Capita Densities, or County Averages

Variable Name	*Variable Description*	*Source*
Dependent variables		
Colonoscopy or sigmoidoscopy 3-year utilization rate in county	Proportion of FFS-insured beneficiaries with any annual colonoscopy (sigmoidoscopy) use, summed over the 3 years and divided by the average number of FFS beneficiaries in the 3 years, by county	Extracts of 100% of Medicare claims for all endoscopy use 2001–2006 and 100% Medicare denominator files 2001–2006
Independent variables		
AGE groups: <65 (omitted reference), 65–74, 75–84, 85+	Proportion of beneficiaries in each age group	100% Medicare denominator files, 2001–2006
ESRD*	Proportion of beneficiaries with end-stage renal disease	
Disabled original reason*	Proportion of beneficiaries with disability as original reason for entitlement	
Female	Proportion of beneficiaries who were female	
Race/ethnicity	Proportion of beneficiaries by race or ethnicity category: Asian, African American, Hispanic, Native American	
Population density	Population per square mile in 2001 and in 2004	Census annual county population estimates
Little or no English language ability	Elderly (age 65+)	Census of population, 2000
Graduate or professional degree	Elderly (age 65+)	
Medicare importance	Medicare enrollment as a proportion of local population, 2002 and 2005	CMS/ORDI state data compendium: http://www.cms.gov/DataCompendium/16_2008DataCompendium.asp#TopOfPage
10-Year average poverty	Average 1990–2000 and 1995–2005 of county poverty rates (proportion)	http://rtispatialdata.rti.org

continued

Table 1. *Continued*

Variable Name	*Variable Description*	*Source*
MMC penetration	Proportion of beneficiaries in MMC plans in 1998 and 2001(lagged to reduce endogeneity)	CMS Geographic Service Area Files, with enrollees by plan by county
Lack of specialization endoscopy provider index	Diffusion index defined from unique endoscopy provider shares of county markets, in 2001 and 2004	100% Medicare denominator files, 2001–2006

Notes. *Included in analysis but excluded from reported statistics and results tables.
CMS, Centers for Medicare & Medicaid Services; FFS, fee-for-service; ESRD, end-stage renal disease; MMC, Medicare managed care.

Table 2: Sample Statistics for County-Level Variables

Years	*2001–2003*		*2004–2006*	
Variables	*Mean*	*SD*	*Mean*	*SD*
Sample Size	*3,099 Counties*		*3,099 Counties*	
Outcome				
Colonoscopy use rate	0.252	0.049	0.279	0.045
Sigmoidoscopy use rate	0.037	0.018	0.018	0.009
Age <65 (omitted reference group)	0.162	0.060	0.177	0.063
Age 65–74	0.449	0.037	0.441	0.039
Age 75–84	0.289	0.035	0.283	0.037
Age 85+	0.100	0.024	0.099	0.025
Female	0.553	0.028	0.548	0.028
Asian	0.002	0.007	0.003	0.008
African American	0.073	0.127	0.074	0.128
Hispanic	0.010	0.034	0.009	0.031
Native American	0.007	0.038	0.009	0.048
Population density	239.3	1671.0	243.2	1686.2
Little or no English language ability, elderly (age 65+)	0.143	0.147	0.143	0.147
Graduate or professional degree, elderly (age 65+)	0.044	0.028	0.044	0.028
Medicare importance in area	0.141	0.020	0.148	0.020
10-Year average poverty rate	0.148	0.067	0.141	0.057
Index of nonspecialization of endoscopy providers	0.020	0.046	0.019	0.047
Medicare managed care (MMC) penetration	0.048	0.089	0.043	0.090

missing data for counties with no service providers. We converted the Herfindahl into a "dispersion" index, which reflects lack of specialization. We took the reciprocal of the county-specific Herfindahl series, then converted this into an index by dividing the series by the maximum value for the series in that year. We then assigned “0” to areas with missing data (no providers); thus, the index reflects diffusion of services provision among many separate physicians. The larger the measure, the less specialized/more dispersed are these services among available providers, and no dispersion (“0”) reflects no providers.

Statistical Analysis

Spatial correlation across adjacent areas in public goods or preventive health care services subject to resource constraints is fairly common (Brueckner 1998, 2003; Brueckner and Saavedra 2001; Mobley et al. 2006). When people share information and resources across county boundaries, adjacent county outcomes will be spatially correlated. Ignoring these misspecification problems is equivalent to falsely assuming that observations (county utilization rates) are statistically independent, which is a standard assumption under ordinary least squares (OLS) regression. This can lead to either efficiency bias, parameter bias, or both (Anselin 1988, 2006; Anselin, Le Gallo, and Jayet 2008). Recent papers have shown that ignoring spatial spillovers can yield highly inflated estimates of the marginal impact of living in rural poverty on preventive care service utilization by the elderly (Mobley et al. 2006) and misleading antitrust prescriptions (Mobley, Frech, and Anselin 2009). As we show below, ignoring spatial spillovers in this paper could result in inflated effect estimates for MMC spillover effects.

Because the decision regarding whether to establish endoscopy services in a county may be affected by prevalence of these services in adjacent counties, we expect there will be spatially correlated errors in the models. We used the residuals from OLS regression as diagnostics to test for spatial correlation and then determine the form of spatial regression that best fits the data, using a Lagrange Multiplier test (Anselin 1988; Mobley 2003). We found significant spatial correlation in the OLS regression residuals and determined that the spatial lag model is a better fit to these data than the spatial error model. We used the spatial lag model specification1 to perform small area, ecological analysis of the predictors of sigmoidoscopy and colonoscopy use rates in U.S. counties over an early (2001–2003) and later (2004–2006) time period.

We incorporate the lag model within a seemingly unrelated regression (SUR) framework (Anselin 1988). The SUR framework allows us to estimate separate regression equations for each service type (colonoscopy or sigmoidoscopy) at each time period, pooling the two equations over time for each service type. The SUR approach correlates the error terms for observations (counties) across time (the two equations), and we find that this significantly improves the efficiency of the effect estimates (Zellner 1962). The spatial SUR model allows for spatially correlated error terms within each equation and across equations, with separate parameter estimates for each time period. To assess diffusion effects, we performed parameter-specific Wald tests (Anselin 1988, 1990) to test for the stability of parameters across time.

RESULTS

We present findings from the spatial SUR models in Table 3, and we highlight the parameter estimates that are statistically significant at the 5 percent level or better in bold font. Table 4 contains misspecified OLS results for comparison. Asterisks indicate parameter estimates that changed significantly over time, based on Wald tests.

The spatial lag parameter estimate is large and positive (ranging from 0.481 to 0.574 across models) and statistically significant. A positive spatial lag effect indicates that competition for scarce resources and information spillovers cross county boundaries; thus, adjacent counties are impacted by the same market forces. This spatial correlation across adjacent counties means that observations are not independently distributed, and an OLS model is misspecified. In error processes with spatial lag, this results in multiplier bias on the OLS estimates (see bottom of Table 3 for size of multiplier bias), and in these data OLS parameter estimates are inflated to about double the actual magnitude of effect via the spatial multiplier bias (Mobley, Frech, and Anselin 2009). This multiplier bias can be demonstrated by comparing the misspecified OLS results in Table 4 to the lag model results in Table 3. Thus, using OLS estimates for policy prescriptions, one would profess larger spillover effects at work than are actually present.

Regarding our main hypothesis, we find that areas with higher MMC penetration have significantly higher sigmoidoscopy use and significantly lower colonoscopy use. The MMC spillover estimate for colonoscopy in the early period is −0.029 (versus −0.051 from the misspecified OLS model), while the estimate for sigmoidoscopy is 0.06 (versus 0.017 from the OLS model).

Table 3: Spatial SUR Predictors of Medicare FFS Endoscopy Utilization Rates in Counties, 2001–2003 and 2004–2006

Time Interval	*Colonoscopy Utilization Rate*				*Sigmoidoscopy Utilization Rate*			
	2001–2003		*2004–2006*		*2001–2003*		*2004–2006*	
	Estimate	*p-Value*	*Estimate*	*p-Value*	*Estimate*	*p-Value*	*Estimate*	*p-Value*
Population/demographics								
Age 65–74 (ref <65)	**0.099**	.000	**0.086**	.000	0.006	.483	−0.007	.126
Age 75–84 (ref <65)	**0.155**	.000	**0.104***	.000	0.017	.119	−0.011*	.077
Age 85+ (ref <65)	**−0.324**	.000	**−0.281**	.000	−0.008	.595	−0.001	.864
Female	**0.120**	.000	**0.159**	.000	**0.030**	.012	**0.024**	.001
Asian	−0.119	.270	−0.134	.128	−0.042	.287	−0.009	.645
African American	**0.015**	.050	0.010	.114	8.297	.976	0.001	.357
Hispanic	**−0.105**	.000	**−0.122**	.000	**−0.020**	.026	0.001	.892
Native American	**−0.112**	.000	**−0.097**	.000	−0.008	.237	−0.005	.113
Population density	7.480	.869	−4.735	.910	−3.127	.058	−8.568	.360
Little or no English	−0.007	.159	**−0.012**	.009	**−0.004**	.035	**−0.002***	.031
Graduate or professional	**0.254**	.000	**0.219**	.000	**0.077**	.000	**0.018**	.001
Medicare importance	**0.198**	.000	**0.116***	.001	0.002	.872	0.002	.819
10-Year average poverty	**−0.057**	.001	**−0.084**	.000	**−0.012**	.050	**−0.010**	.014
Market competition								
Index of nonspecialization of endoscopy providers	**0.044**	.014	0.026	.111	**0.038**	.000	**0.022***	.000
Medicare managed care (MMC) penetration	**−0.029**	.000	**−0.018**	.005	**0.006**	.039	**0.005**	.001
Spatial lag	**0.546**	.000	**0.545**	.000	**0.609**	.000	**0.481***	.000
Average spatial multiplier effect	**2.2**		**2.2**		**2.6**		**1.9**	

Notes. Area prevalence of end-stage renal disease (ESRD) and disability as original reason for entitlement among those aged 65+ were included in the modeling as comorbidity adjusters but not presented in this table for parsimony. Effect estimates significant at the 5% level or better are highlighted in bold font.

*Denotes significant change over time in coefficient estimate at 5% level, based on Wald test.

FFS, fee-for-service; SUR, seemingly unrelated regression.

Table 4: Misspecified OLS Model of Medicare FFS Endoscopy Utilization Rates in Counties, 2001–2003 and 2004–2006

	Colonoscopy Utilization Rate				Sigmoidoscopy Utilization Rate			
	2001–2003		*2004–2006*		*2001–2003*		*2004–2006*	
Time Interval	*Estimate*	*p-Value*	*Estimate*	*p-Value*	*Estimate*	*p-Value*	*Estimate*	*p-Value*
Population/demographics								
Age 65–74	**0.100**	.002	0.035	.238	−0.010	.354	−**0.012**	.047
Age 75–84	**0.280**	.000	**0.196**	.000	**0.041**	.013	−**0.014**	.071
Age 85+	−**0.583**	.000	−**0.502**	.000	−0.001	.942	0.002	.848
Female	**0.142**	.002	**0.186**	.000	−0.002	.889	**0.027**	.001
Asian	−**0.245**	.012	−**0.284**	.000	−0.006	.871	0.009	.719
African American	**0.049**	.000	**0.042**	.000	**0.013**	.000	**0.006**	.000
Hispanic	−**0.165**	.000	−**0.213**	.000	−**0.026**	.003	−0.002	.678
American Indian	−**0.124**	.000	−**0.100**	.000	**0.015**	.051	−**0.006**	.076
Population density	**0.000**	.010	**0.000**	.057	**0.000**	.017	0.000	.707
Little or no English	−0.009	.136	−**0.015**	.009	−**0.006**	.003	−**0.003**	.013
Graduate or professional	**0.276**	.000	**0.234**	.000	**0.080**	.000	**0.019**	.005
Medicare importance	**0.352**	.000	**0.147**	.001	0.009	.573	0.013	.129
10-Year average poverty	−**0.135**	.000	−**0.195**	.000	−**0.052**	.000	−**0.020**	.000
Index of nonspecialization of endoscopy providers	**0.089**	.000	**0.071**	.000	**0.041**	.000	**0.020**	.001
Medicare managed care (MMC) penetration	−**0.051**	.000	−**0.039**	.000	**0.017**	.000	**0.013**	.000

Notes. Area prevalence of ESRD and disability as original reason for entitlement among those aged 65+ were included in the modeling as comorbidity adjusters but not presented in this table. Effect estimates significant at the 5% level or better are highlighted in bold font.
ESRD, end-stage renal disease; FFS, fee-for-service; OLS, ordinary least squares.

The MMC penetration variable standard deviation is twice the magnitude of the mean (see Table 2), so large changes (larger than 10 percent) are actually consistent with our data. If we interpret the lag estimates in terms of elasticities, we find that a 10 percent increase in MMC penetration in the early period is associated with about a 6 percent decrease in the colonoscopy use rate, and about an 8 percent increase in the sigmoidoscopy use rate. In the later period, the colonoscopy elasticity effect is a 3 percent decrease, while the sigmoidoscopy effect is a 12 percent increase. For both screening modalities, the *changes over time* in the MMC spillover effect estimates are not statistically significant, based on the Wald tests. However, for both, the MMC spillover effect is statistically significant and large enough to be economically meaningful.

The various statistical controls for market factors generally have significant parameter estimates and are of the expected sign. In particular, markets with higher 10-year poverty rates show slightly lower sigmoidoscopy use and much lower colonoscopy use. This suggests that sigmoidoscopy can survive in less viable markets as compared to colonoscopy, and increasingly so over time.

We recognize that we may not have been able to control completely for socioeconomic factors responsible for selection bias. In this case, our estimate of the MMC spillover effect on colonoscopy use is conservative and may be construed as a lower bound on the true effect. To see this, because selection effects related to the MMC spillovers tend to increases utilization of colonoscopy, and the actual spillover effect is negative, then the bias is toward the null, resulting in a smaller negative effect estimate than may actually be the case.

To test whether our selection theory is valid, we added an additional socioeconomic control variable (a measure of dual eligibility among the FFS elderly) as a robustness check. Although the dual eligibility measure is not a reliable indicator of all FFS elderly in poverty or enrolled in Medicaid, it is correlated at >80 percent (simple Pearson) with area 10-year poverty, and it more specifically represents the FFS population. These results (available from the authors upon request) confirm our selection theory. Adding dual eligibility for the FFS beneficiaries to the model as an additional control variable (which was highly significant) resulted in a slightly larger magnitude, negative spillover effect for colonoscopy. However, in terms of the elasticities associated with a 10 percent increase in MMC penetration, the effects were not noticeably different. For the sigmoidoscopy model, there was no significant dual eligibility effect and the spillover estimates were not affected.

A more direct approach to deal with selection bias would be the use of an instrumental variables (IV) estimator. We could not find very reliable instruments, but exploratory work with IV models suggested potential selection bias from omitted variables was much smaller than the bias from ignoring spatial lags. As it is not possible to control for both spatial spillovers and selectivity using a single estimator, we opted for the spatial estimator because the spatial multiplier bias appears to be larger than any remaining selection bias. We can only reduce the selection bias by lagging MMC penetration, not completely eliminate it. Remaining selection bias probably leads to conservative estimates (underestimates) of the magnitude of spillover effects from MMC penetration on endoscopy use.

Discussion and Conclusion

Evidence from the nationally representative National Health Interview Survey suggests that the number of endoscopy procedures performed on those privately insured and those enrolled in Medicare was approximately the same and that a similar proportion of each group used endoscopy for CRC screening, with increasing utilization of colonoscopy relative to sigmoidoscopy for both groups (Shapiro et al. 2008). It would be enlightening to study the role of the spread of managed care on the diffusion of these two competing procedures for the entire insured population in the United States. However, no data are available to do that. We do have excellent data to study this phenomenon in the Medicare population, which is the focus of this paper.

We use county-level ecological analysis with spatial regression to assess whether MMC penetration had any impact on the rate of use of colonoscopy or sigmoidoscopy among the FFS Medicare-insured population. Any impact from MMC on FFS Medicare would be interpreted as a spillover effect, acting through managed care's influence on both providers and constituents in their markets.

As MMC plans are all provided by private insurance companies that also offer plans for other consumers in the same markets (Pope et al. 2006), and because trends in endoscopy use among Medicare and private populations have been similar, the Medicare market may provide useful, albeit indirect evidence about the managed care impact across the entire U.S. insurance market. Conversely, what we observe for the Medicare market may reflect larger forces at work than simply the influence of MMC plans on Medicare constituents' behavior.

This is the first study to examine managed care's impact on the relative diffusion of these two competing endoscopy technologies. We find evidence that markets with worse socioeconomic conditions are less viable for colonoscopy than sigmoidoscopy. Holding constant statistically the confounding influences of socioeconomic factors, this study provides the first evidence to date regarding the role that MMC plans have played in the diffusion of colonoscopy following benefits expansion to cover it in 2001.

We find that counties with greater MMC penetration had lower colonoscopy use, but higher sigmoidoscopy use, and that these spillover effects did not change significantly over time. Counties with 10 percent higher MMC penetration than average saw about 3–6 percent lower colonoscopy rates and 8–12 percent higher sigmoidoscopy rates over 2001–2006. Thus, MMC plans may have played an important role in sustaining the practice of sigmoidoscopy and slowing down the diffusion of colonoscopy.

During the period we study, colonoscopy technology transitioned from being a "gold standard" promoted by the American College of Gastroenterology (Rex et al. 2009) to one increasingly questioned by the mounting evidence base, especially in the face of considerable risks posed to older persons from the procedure itself (Whitlock et al. 2008). Now that rising budget deficits are looming, economists are questioning the cost-effectiveness of colonoscopy and providing more evidence against it (Subramanian, Bobashev, and Morris 2010; Goodwin et al. 2011). Perhaps in this time of increased cost-consciousness, managed care practices will return to positions of influence and imbue more constraint on the diffusion of cost-increasing technologies.

ACKNOWLEDGMENTS

Joint Acknowledgment/Disclosure Statement: This work was supported by a National Cancer Institute grant (1R01CA126858). The content is solely the responsibility of the authors and does not necessarily represent the official views of RTI International, Arizona State University, The University of California at Santa Barbara, the University of North Carolina at Chapel Hill, the National Cancer Institute, or the National Institutes of Health.

Disclosures: None.

Disclaimers: None.

Note

1. The spatial lag model includes the average of neighboring values of the dependent variable, treated as an endogenous explanatory variable:

$$Y = \rho WY + X\beta + \varepsilon$$

where WY is the spatial autoregressive and X is the regressive component of the model, ρ is the spatial autoregressive "lag" parameter, and ε is the vector of regression disturbances (i.i.d). Y is the vector of observations on the dependent variable, X is the matrix of exogenous variables, and W is an $N \times N$ matrix (by convention, W is row-standardized and does not define an observation as its own neighbor). The term WY is the spatial lag of Y.

References

Agency for Healthcare Research and Quality (AHRQ). 2007. "Technology Assessment: Cost-effectiveness of DNA Stool Testing to Screen for Colorectal Cancer" [accessed October 2010]. Available at http://www.cms.gov/determinationprocess/downloads/id52TA.pdf

American Cancer Society (ACS). 2008. "New Guidelines to Prevent and Detect Colon Cancer" [accessed March 2011]. Available at http://www.cancer.org/AboutUs/DrLensBlog/post/2008/03/05/New-Guidelines-To-Prevent-And-Detect-Colon-Cancer.aspx

American Cancer Society (ACS). 2010. "Cancer Prevention and Early Detection Facts and Figures" [accessed July 2011]. Available at: http://www.cancer.org/Research/CancerFactsFigures/CancerPreventionEarlyDetectionFactsFigures/cped-2010

America's Health Insurance Plans (AHIP). 2005. *Low-Income and Minority Beneficiaries in Medicare Advantage Plans, 2002.* AHIP Center for Policy and Research. [accessed July 2011]. Available at: http://www.ahipresearch.org/pdfs/medicareadvantage051005_full.pdf.

Anselin, L. 1988. *Spatial Econometrics: Methods and Models.* Dordrecht, The Netherlands: Kluwer Academic.

———. 1990. "Spatial Dependence and Spatial Structural Instability in Applied Regression Analysis." *Journal of Regional Science* 30: 185–207.

———. 2006. "Spatial Econometrics." In *Palgrave Handbook of Econometrics: Volume 1, Econometric Theory*, edited by T. C. Mills, and K. Patterson, pp. 901–60. Basingstoke: Palgrave Macmillan.

Anselin, L., J. Le Gallo, and H. Jayet. 2008. "Spatial Panel Econometrics." In *The Econometrics of Panel Data, Fundamentals and Recent Developments in Theory and Practice*, 3rd Edition, edited by L. Matyas, and P. Sevestre, pp. 627–62. Berlin: Springer-Verlag.

Atherly, A., and K. E. Thorpe. 2005. *Value of Medicare Advantage to Low-Income and Minority Medicare Beneficiaries.* Atlanta, GA: Emory University Rollins School of

Public Health [accessed March 16, 2011]. Available at http://c0540862.cdn.cloudfiles.rackspacecloud.com/Ken_Thorpe_MA_Report.pdf.

Baker, L. 2003. "Managed Care Spillover Effects." *Annual Review of Public Health* 24 (1): 435–56.

Baxter, N., and L. Rabeneck. 2010. "Is the Effectiveness of Colonoscopy 'Good Enough' for Population-Based Screening?" *Journal of the National Cancer Institute* 102 (2): 70–1.

Berenson, R., T. Bodenheimer, and H. Pham. 2006. "Specialty-Service Lines: Salvos in the New Medical Arms Race." *Health Affairs* 25 (5): w337–43.

Brenner, H. 2008. "Efficacy, Effectiveness and Cost-Effectiveness of Endoscopic Screening Methods." *Zeitschrift fur Gastroenterologie* 46 (suppl 1): S20–2.

Brueckner, J. 1998. "Testing for Strategic Interaction among Local Governments: The Case of Growth Controls." *Journal of Urban Economics* 44 (3): 438–67.

———. 2003. "Strategic Interaction among Governments: An Overview of Empirical Studies." *International Regional Science Review* 26 (2): 175–88.

Brueckner, J., and L. Saavedra. 2001. "Do Local Governments Engage in Strategic Property-Tax Competition?" *National Tax Journal* 54: 203–29.

Centers for Medicare & Medicaid Services (CMS). 2011. Colorectal Cancer Screening Overview [accessed March 2011]. Available at http://www.cms.gov/colorectalcancerscreening/

Cooper, G. S., and S. M. Koroukian. 2004. "Geographic Variation among Medicare Beneficiaries in the Use of Colorectal Carcinoma Screening Procedures." *American Journal of Gastroenterology* 99 (8): 1544–50.

Doubeni, C., A. Laiyemo, A. Young, C. Klabunde, G. Reed, T. Field, and R. Fletcher. 2010. "Primary Care, Economic Barriers to Health Care, and Use of Colorectal Cancer Screening Tests among Medicare Enrollees over Time." *Annals of Family Medicine* 8 (4): 299–307.

Goodwin, J., A. Singh, N. Reddy, T. Tiall, and Y. Kuo. 2011. "Overuse of Screening Colonoscopy in the Medicare Population." *Archives of Internal Medicine* [accessed May 9, 2011]. Available at http://archinte.ama-assn.org/cgi/content/short/archinternmed.2011.212

Greenwald, L., G. Pope, W. Anderson, L. Mobley, N. West, S. Bernard, J. Kautter, and E. Root. 2004. "Medicare Preferred Provider Organization (PPO) Case Study and Implementation Report." Final Report. Prepared for the Centers for Medicare & Medicaid Services (RTI Project Number 0207964.005) [accessed April 18, 2010]. Available at http://www.cms.hhs.gov/DemoProjectsEvalRpts/downloads/PPO_Implementation_Report.pdf

Holden, D. J., R. Harris, D. S. Porterfield, D. E. Jonas, L. C. Morgan, D. Reuland, M. Gilchrist, M. Viswanathan, K. N. Lohr, and B. Lyda-McDonald. 2010. Enhancing the Use and Quality of Colorectal Cancer Screening [accessed March 25, 2011]. Agency for Healthcare Research and Quality (AHRQ) Publication No. 10-E002. Available at http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=erta190.

Hurley, R. E., and S. M. Retchin. 2006. "Medicare and Medicaid Managed Care: A Tale of Two Trajectories." *American Journal of Managed Care* 12: 40–4.

Klabunde, C., D. Lanier, H. Meissner, E. Breslau, and M. Brown. 2008. "Improving Colorectal Cancer Screening through Research in Primary Care Settings." *Medical Care* 46 (9 suppl 1): S1–4.

Koroukian, S., D. Litaker, A. Dor, and G. Cooper. 2005. "Use of Preventive Services by Medicare Fee-for-Service Beneficiaries Does Spillover from Managed Care Matter?" *Medical Care* 43 (5): 445–52.

Loeve, F., M. L. Brown, R. Boer, M. van Ballegooijen, G. J. van Oortmarssen, and J. D. Habbema. 2000a. "Endoscopic Colorectal Cancer Screening: A Cost Saving Analysis." *Journal of the National Cancer Institute* 92: 557–63.

Loeve, F., M. Brown, R. Boer, J. Dik, and F. Habbema. 2000b. "Re: Improving the Cost-Effectiveness of Colorectal Cancer Screening." [Commentary]. *Journal of the National Cancer Institute* 92: 1691–2.

Luchtefeld, M. A., and D. G. Kim. 2006. "Colonoscopy in the Office Setting Is Safe, and Financially Sound … for Now." *Diseases of the Colon and Rectum* 49 (3): 377–81; discussion 381–2.

Miller, R. H., and H. S. Luft. 1994. "Managed Care Plan Performance Since 1980: A Literature Analysis." *Journal of the American Medical Association* 271: 1512–9.

MLN. 2006. "Non-Application of Deductible for Colorectal Cancer Screening Tests" [accessed March 23, 2010]. MLN Matters Number: MM5127. Available at http://www.cms.hhs.gov/MLNMattersArticles/downloads/MM5127.pdf

Mobley, L. 2003. "Estimating Hospital Market Pricing: An Equilibrium Approach Using Spatial Econometrics." *Regional Science and Urban Economics* 33 (4): 489–516.

Mobley, L. R., H. Frech, and L. Anselin. 2009. "Spatial Interaction, Hospital Pricing and Hospital Antitrust." *International Journal of the Economics of Business* 16 (1): 1–17.

Mobley, L. R., E. D. Root, L. Anselin, N. Lozano-Gracia, and J. Koschinsky. 2006. "Spatial Analysis of Elderly Access to Primary Care Services." *International Journal of Health Geographics* 5 [accessed May 15, 2006]. Available at http://www.ij-healthgeographics.com/content/5/1/19

Neugut, A., and B. Lebwohl. 2010. "Colonoscopy vs Sigmoidoscopy Screening: Getting It Right." *Journal of the American Medical Association* 304 (4): 461–2.

O'Leary, B., J. Olynyk, M. Neville, and C. Platell. 2003. "Cost-Effectiveness of Colorectal Cancer Screening: Comparison of Community-Based Flexible Sigmoidoscopy with Fecal Occult Blood Testing and Colonoscopy." *Journal of Gastroenterology and Hepatology* 19 (1): 38–47.

Phillips, K. A., S. Y. Liang, U. Ladabaum, J. Haas, K. Kerlikowske, D. Lieberman, R. Hiatt, M. Nagamine, and S. L. Van Bebber. 2007. "Trends in Colonoscopy for Colorectal Cancer Screening." *Medical Care* 45 (2): 160–7.

Pignone, M., M. Rich, S. M. Teutsch, O. Berg, and K. N. Lohr. 2002a. "Screening for Colorectal Cancer in Adults at Average Risk: A Summary of the Evidence for the U.S. Preventive Services Task Force." *Annals of Internal Medicine* 137: 132–41.

Pignone, M., S. Saha, T. Hoerger, and J. Mandelblatt. 2002b. "Cost-Effectiveness Analyses of Colorectal Cancer Screening: A Systematic Review for the U.S. Preventive Services Task Force." *Annals of Internal Medicine* 137: 96–104.

Pope, G., L. M. Greenwald, J. Kautter, E. A. Olmstead, and L. R. Mobley. 2006. "Medicare Preferred Provider Organization Demonstration: Plan Offerings and Beneficiary Enrollment." *Health Care Financing Review* 27 (3): 96–109.

Rex, D. K., D. A. Johnson, J. C. Anderson, P. S. Schoenfeld, A. Burke, and J. M. Inadomi. 2009. "American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2009." *American Journal of Gastroenterology* 104 (3): 739–50.

Schenck, A. P., S. C. Peacock, N. Klabunde, P. Lapin, J. F. Coan, and M. L. Brown. 2009. "Trends in Colorectal Cancer Test Use in the Medicare Population, 1998–2005." *American Journal of Preventive Medicine* 37 (1): 1–7.

Schneider, C., M. Rosenthal, C. G. Gatsonis, J. Zheng, and A. M. Epstein. 2008. "Is the Type of Medicare Insurance Associated with Colorectal Cancer Screening Prevalence and Selection of Screening Strategy?" *Medical Care* 46 (9 suppl 1): S84–90.

Shapiro, J., L. Seeff, T. Thompson, M. Nadel, C. Klabunde, and S. Vernon. 2008. "Colorectal Cancer Test Use from the 2005 National Health Interview Survey." *Cancer Epidemiology, Biomarkers and Prevention* 17 (7): 1623–30.

Shih, Y. T., L. Zhao, and L. S. Elting. 2006. "Does Medicare Coverage of Colonoscopy Reduce Racial/Ethnic Disparities in Cancer Screening among the Elderly?" *Health Affairs* 25 (4): 1153–62.

Subramanian, S., G. Bobashev, and R. Morris. 2010. "When Budgets Are Tight, There Are Better Options Than Colonoscopies for Colorectal Cancer Screening." *Health Affairs* 29 (9). Web exclusive [accessed October 2010]. Available at http://content.healthaffairs.org/cgi/content/abstract/hlthaff.2008.0898v1

Tangka, F., N. Molinari, S. Chattopadhyay, and L. Seeff. 2005. "Market for Colorectal Cancer Screening by Endoscopy in the United States." *American Journal of Preventive Medicine* 29 (1): 54–60.

U.S. Preventive Services Task Force. 2002. "Screening for Colorectal Cancer: Recommendation and Rationale." *Annals of Internal Medicine* 137: 129–31.

U.S. Preventive Services Task Force (USPSTF). 2007. "Screening for Colorectal Cancer." In *Pocket Guide to Clinical Preventive Services, 2007: Recommendations of the U.S. Preventive Services Task Force*, pp. 32–5. Rockville, MD: Agency for Healthcare Research and Quality.

Whitlock, P., J. S. Lin, E. Liles, T. L. Beil, and R. Fu. 2008. "Screening for Colorectal Cancer: A Targeted, Updated Systematic Review for the U.S. Preventive Services Task Force." *Annals of Internal Medicine* 149 (9): 638–58.

Zellner, A. 1962. "An Efficient Method of Estimating Seemingly Unrelated Regressions and Tests for Aggregation Bias." *Journal of the American Statistical Association* 57: 348–68.

Supporting Information

Additional supporting information may be found in the online version of this article:

Appendix SA1: Author Matrix.