Demographic shifts associated with implementation of evidence-based guidelines for ovarian conservation in patients with endometrioid endometrial cancer

Beryl L Manning-Geist ,[1] Eric Rios-Doria ,[1] Emeline M Aviki,[1,2] Qin Zhou,[3] Alexia Iasonos,[3] Nadeem R Abu-Rustum ,[1,2] Carol L Brown,[1,2] Jennifer J Mueller [1,2]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ijgc-2022-003661).

For numbered affiliations see end of article.

Correspondence to
Dr Jennifer J Mueller, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA; muellerj@mskcc.org

Received 27 April 2022
Accepted 22 June 2022
Published Online First 13 July 2022

To cite: Manning-Geist BL, Rios-Doria E, Aviki EM, *et al. Int J Gynecol Cancer* 2022;**32**:1141–1146.

HIGHLIGHTS

⇒ Evidence-based guidelines increase ovarian conservation in endometrial cancer patients under age 50.
⇒ Standardized ovarian conservation guidelines decrease uptake disparities across demographic groups.
⇒ Insurance type is not associated with patient pursuit of ovarian conservation.

ABSTRACT

Objective In 2018, evidence-based surgical guidelines were introduced to identify appropriate patients with low-grade endometrioid endometrial cancer for ovarian conservation. We sought to identify trends and demographic shifts associated with guideline implementation.

Methods We identified women treated for endometrioid endometrial cancer at our institution from January 2010 to June 2021. Eligibility criteria included age ≤50 years, normal-appearing ovaries on preoperative imaging, no family history of hereditary breast and ovarian cancer syndrome or Lynch syndrome, and no hormone receptor-positive malignancy. Trends in ovarian conservation were examined with the Cochran-Armitage trend test or in a logistic regression model. Associations between ovarian conservation and clinicodemographic factors before and after guideline implementation were compared using Wilcoxon rank-sum and Fisher's exact tests.

Results Of 420 women ≤50 years of age undergoing surgery for endometrioid endometrial cancer, 355 (85%) met the criteria for ovarian conservation—267 (75%) before and 88 (25%) after guideline implementation. Median patient age was 45 years (range 25–50); 62% were non-Hispanic White, 10% Hispanic White, 8% non-Hispanic Black, 0% Hispanic Black, and 20% Asian. Patients were significantly more likely to choose ovarian conservation after (48%) compared with before guideline implementation (21%) (p<0.001). Pre-guidelines, non-Hispanic White women were less likely to elect for ovarian conservation (12%) compared with non-Hispanic Black, Asian, or Hispanic White women (28%) (p=0.002). Similarly, older women were less likely to elect for ovarian conservation compared with younger women (p<0.001). There were no differences by obesity (p=0.68), marital status (p=0.86), or insurance (p=0.89). Post-guidelines, there were no differences in ovarian conservation between non-Hispanic White women (36%) and non-Hispanic Black, Asian, or Hispanic White women (50%) (p=0.56). Older women were still less likely to elect for ovarian conservationcompared with younger women (p<0.001).

Conclusions After guideline implementation, ovarian conservation increased and uptake disparities across demographic groups decreased.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Ovarian conservation does not increase recurrence rates or cancer-specific mortality in well-selected women with early-stage, low-grade endometrial cancer; despite this, however, <20% of premenopausal women undergo ovarian conservation during surgery for endometrial cancer.

WHAT THIS STUDY ADDS

⇒ Incorporation of evidence-based guidelines for ovarian conservation in low-risk endometrial cancer patients increased rates of ovarian conservation and decreased uptake disparities across demographic groups.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings demonstrate the benefits of ovarian conservation guidelines in low-risk endometrial cancer patients

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in the USA, with an estimated 65 950 new cases in 2022.[1] Approximately 12–21% of newly diagnosed cases occur in premenopausal women, and population trends suggest that the burden of premenopausal disease will continue to increase.[2–5] The treatment of young women with endometrial cancer can be challenging, particularly regarding ovarian conservation. Surgery for endometrial

Preoperative variables	Intraoperative variables
○ Age 50 years or younger ○ Strong desire to preserve hormonal or reproductive function ○ Normal-appearing ovaries on preoperative imaging ○ Grade 1 or 2 disease ○ Intact MMR and p53 on pre-operative biopsy (D&C preferred) ○ No history suggestive of hereditary breast-ovarian cancer or Lynch syndrome ○ No personal history of ER/PR positive malignancy ○ Patient counseled on risks/benefits, and documentation of this in EMR	○ Normal-appearing ovaries on intraoperative inspection ○ No metastatic disease appreciated on intraoperative inspection

Figure 1 Institutional criteria for ovarian conservation. D&C, dilation and curettage; EMR, electronic medical record; ER, estrogen receptor; MMR, mismatch repair; PR, progesterone receptor.

cancer has historically included hysterectomy, bilateral salpingo-oophorectomy, and lymph node assessment.[6 7] However, oophorectomy and induction of surgical menopause is associated with increased risk of heart disease, decreased bone density, impaired cognitive function, and increased all-cause mortality for premenopausal women.[8–13] In addition, evidence suggests that ovarian conservation does not increase recurrence rates or cancer-specific mortality in well-selected women with early-stage, low-grade endometrial cancer; however, despite this, <20% of premenopausal women undergo ovarian conservation during surgery for endometrial cancer.[14]

Table 1 Clinicodemographic characteristics (n=355)

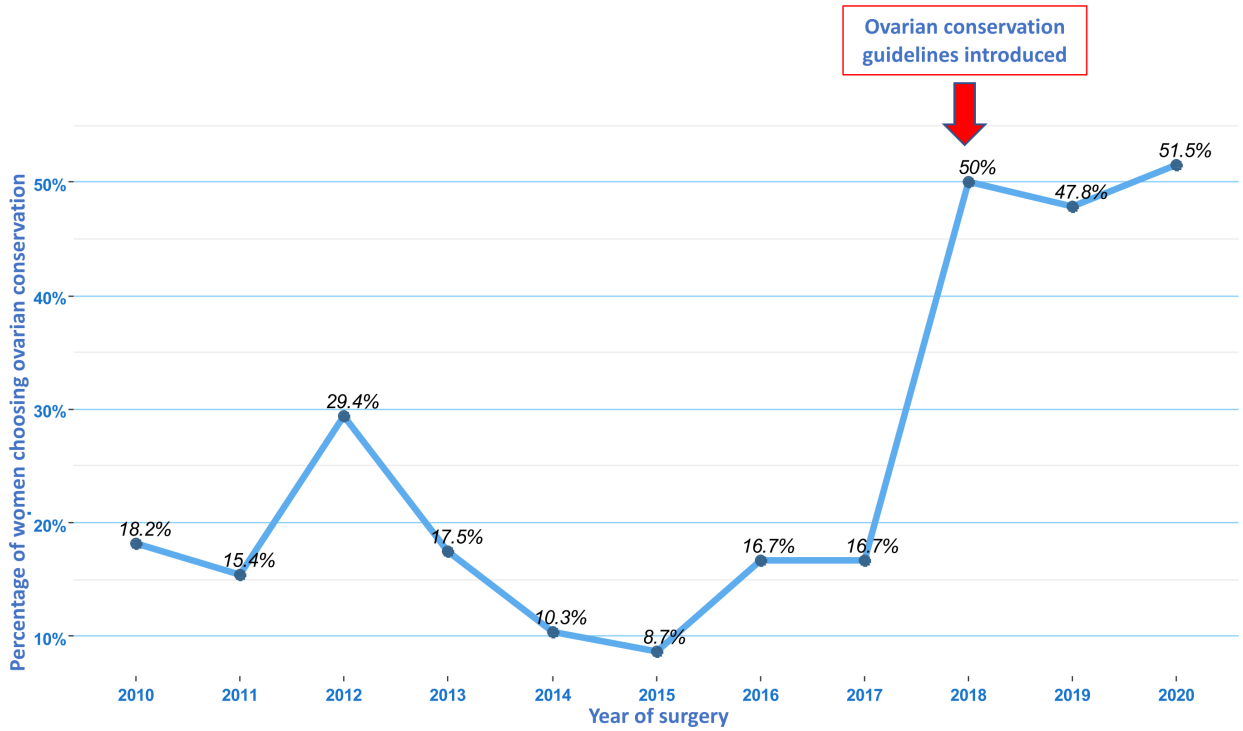
Characteristic	Overall n (%)
Race/ethnicity (n=295)	
Non-Hispanic White	183 (62%)
Non-Hispanic Black	24 (8%)
Asian/Indian sub-continent	59 (20%)
Hispanic White	29 (10%)
Hispanic Black	0 (0%)
Missing*	60
Body mass index (n=340)	
Normal (<25 kg/m^2)	103 (30%)
Overweight (25–30 kg/m^2)	66 (19%)
Obese (≥30 kg/m^2)	171 (50%)
Missing	15
Insurance (n=228)	
Commercial	202 (89%)
Medicaid/Medicare	16 (7%)
Self-pay	10 (4%)
Missing	127
Marital status (n=297)	
Partnered	190 (64%)
Single/divorced/widowed	107 (36%)
Missing	58

*Missing data included patients who declined to self-identify race and/or ethnicity and patients without available data.

While much research has focused on fertility-sparing uterine conservation, research on ovarian conservation in premenopausal women with early-stage, low-grade endometrial cancer is lacking.[5 15–17] In 2018, our service introduced institutional evidence-based guidelines for ovarian conservation in women undergoing surgery for endometrioid endometrial cancer in order to provide these women with consistent standardized recommendations. These guidelines were developed using the published evidence base in conjunction with institution-level data. Under these guidelines, women 50 years of age or younger with mismatch repair proficient low-grade endometrioid endometrial cancer who desire preservation of hormonal function, have normal-appearing ovaries on preoperative imaging, have no family history of hereditary breast and ovarian cancer or Lynch syndromes, and have no personal history of hormone receptor-positive malignancy could be offered ovarian conservation, with the understanding that bilateral oophorectomy remained the standard of care and could be recommended if final pathology revealed additional risk factors. Prior to guideline implementation, ovarian conservation was offered at the surgeon's discretion, and National Comprehensive Cancer Network guidelines on ovarian conservation in low-grade endometrioid cancer had not yet been introduced. Here, we report trends over time and demographic shifts in ovarian conservation uptake before and after implementation of these institutional guidelines.

METHODS

Women with endometrioid endometrial cancer diagnosed between January 2010 and June 2021 who underwent surgery at Memorial Sloan Kettering Cancer Center were identified (n=456) from a retrospective database that includes patients treated from 2010 to 2016 as well as a prospectively maintained database that has been in place since 2017. Women with a known diagnosis of a secondary malignancy such as colon, cervical, or ovarian cancer (n=19), women with suspected advanced disease (n=13), women with prior bilateral salpingo-oophorectomy (n=3), and women with streak ovaries (n=1) were excluded.



	N = 22[1]	N = 26[1]	N = 17[1]	N = 40[1]	N = 29[1]	N = 23[1]	N = 42[1]	N = 30[1]	N = 40[1]	N = 46[1]	N = 33[1]	p-value[2]
No ovarian conservation	18 (82%)	22 (85%)	12 (71%)	33 (82%)	26 (90%)	21 (91%)	35 (83%)	25 (83%)	20 (50%)	24 (52%)	16 (48%)	<0.001
Ovarian conservation	4 (18%)	4 (15%)	5 (29%)	7 (18%)	3 (10%)	2 (8.7%)	7 (17%)	5 (17%)	20 (50%)	22 (48%)	17 (52%)	

Figure 2 Trends over time in patients choosing ovarian conservation (n=355). [1]Statistics presented: n (%). [2]Statistical tests performed: χ^2 test of independence, Cochran-Armitage p value reported.

Medical records from preoperative visits were reviewed for clinicodemographic factors as well as pathology and radiology information. Race and ethnicity were self-reported as Hispanic White, non-Hispanic White, Hispanic Black, non-Hispanic Black, or Asian/Indian subcontinent (hereafter referred to as Asian). Women who would qualify for ovarian conservation by institutional guidelines implemented in 2018 were identified (n=355) (Figure 1). Rates of ovarian conservation among women who would qualify were measured before and after implementation of institutional guidelines. Trends for choosing ovarian conservation over time were examined with the Cochran-Armitage trend test. As the data abstraction cut-off date was June 1, 2021, trend-related analyses covered 2010–2020. In addition, to explore whether a trend in pursuit of ovarian conservation over time could be related to a shift in clinicodemographic factors, a logistic model was built with ovarian conservation (yes/no) as the outcome and surgery year as a continuous variable. Each clinicodemographic factor was dichotomized and examined with a logistic model that included interaction term with year of surgery.

After examining trends over time, clinicodemographic factors were evaluated for association with pursuit of ovarian conservation before and after guideline implementation. Variables of interest included age (<40 or ≥40 years), body mass index classification (normal, overweight, obese), self-identified race/ethnicity, marital status (partnered vs single/divorced/widowed), and payer status (commercial, Medicare/Medicaid, self-pay) before and after guideline implementation, which were compared using Wilcoxon rank-sum and Fisher's exact tests. The Institutional Review Board at Memorial Sloan Kettering Cancer Center approved this study.

RESULTS

Of 420 women identified per study parameters, 355 (85%) met the criteria for ovarian conservation—267 (75%) before and 88 (25%) after guideline introduction. Median patient age was 45 years (range 25–50). The majority of women were non-Hispanic White (62%, n=183/295), had a body mass index considered overweight or obese (70%, n=237/340), were partnered (64%, n=190/297), and had commercial insurance (89%, n=202/228) (Table 1). Among the 355 patients, 298 (84%) patients had stage IA, seven (2%) stage IB, eight (2%) stage II, three (1%) stage IIIA, 15 (4%) stage IIIC, and one (0.3%) stage IV disease; 23 (6%) had unknown disease stage.

Among the 355 women who met institutional guideline criteria for ovarian conservation, 98 (28%) chose this approach. Over time, women were significantly more likely to pursue ovarian conservation. Between 9–29% of women per year elected for ovarian conservation prior to guideline implementation, which increased to 48–52% after guideline implementation (p<0.001) (Figure 2). A logistic model was built to explore whether this trend in increased rates of ovarian conservation was associated with differences in other clinicodemographic variables. This model demonstrated no

Table 2 Association of clinicodemographic variables with ovarian conservation

Characteristic	Before guideline implementation			After guideline implementation		
	No ovarian conservation, n=211	Ovarian conservation, n=56	*P value	No ovarian conservation, n=46	Ovarian conservation, n=42	*P value
Median age, years (range)	46 (27–50)	40 (26–50)	**<0.001**	47 (31–50)	40 (25–50)	**<0.001**
Race			**0.002**			0.56
Non-Hispanic White	127 (88%)	17 (12%)		25 (64%)	14 (36%)	
Non-Hispanic Black	13 (68%)	6 (32%)		3 (60%)	2 (40%)	
Asian	29 (66%)	15 (34%)		8 (53%)	7 (47%)	
Hispanic White	17 (89%)	2 (11%)		4 (40%)	6 (60%)	
Missing	25	16		6	13	
Body mass index			0.68			0.19
Normal (<25 kg/m^2)	56 (76%)	18 (24%)		11 (38%)	18 (62%)	
Overweight (25–30 kg/m^2)	40 (77%)	12 (23%)		9 (64%)	5 (36%)	
Obese (≥30 kg/m^2)	104 (81%)	25 (19%)		24 (57%)	18 (43%)	
Missing	11	1		2	*	
Insurance			0.89			
Commercial	120 (78%)	33 (22%)		29 (59%)	20 (41%)	
Medicaid/ Medicare	9 (90%)	1 (10%)		5 (83%)	1 (17%)	
Self-pay	6 (86%)	1 (14%)		1 (33%)	2 (67%)	
Missing	76	21		11	19	
Marital status			0.86			0.45
Partnered	123 (83%)	25 (17%)		26 (62%)	16 (38%)	
Single/ divorced/ widowed	67 (82%)	15 (18%)		13 (52%)	12 (48%)	
Missing	21	16		7	14	

*Statistical tests performed: Wilcoxon rank-sum test; Fisher's exact test. P value not provided if certain level counts <5.

interaction effects between clinicodemographic variables and year of surgery (online supplemental table 1).

Before guideline implementation (2010–2018), 12% of non-Hispanic White women (n=17), 11% of Hispanic White women (n=2), 32% of non-Hispanic Black women (n=6), and 34% of Asian women (n=15) chose ovarian conservation (p=0.002). Women >40 years of age were less likely to choose ovarian conservation (13%, n=25) compared with women ≤40 years (44%, n=31) (p<0.001). There were no differences in ovarian conservation rates by body mass index classification (p=0.68), marital status (p=0.86), or payer type (p=0.53) (Table 2).

After guideline implementation (2018–2020), there were no differences in rates of ovarian conservation by race; 36% of non-Hispanic White women (n=14), 60% of Hispanic White women (n=6), 40% of non-Hispanic Black women (n=2), and 47% of Asian women (n=7) chose ovarian conservation (p=0.56). Women >40 years of age continued to be less likely to choose ovarian conservation (32%, n=18) compared with women ≤40 years (75%, n=24) (p<0.001). There were again no differences in ovarian conservation rates by body mass index classification (p=0.19), marital status (p=0.45), or payer type (p>0.99) (Table 2).

DISCUSSION

Summary of Main Results

In our study, the implementation of institutional ovarian conservation guidelines for women undergoing surgery for endometrioid endometrial cancer was associated with a significant increase in rates of ovarian conservation. Prior to guideline implementation in 2018, 21% (56/267) of women chose ovarian conservation, which was higher than that of reported rates of 5.7–16.4% in women with stage I endometrioid adenocarcinoma diagnosed from 2000 to 2014.[18] Our rate increased to 48% (42/88) after guideline implementation.

Results in the Context of Published Literature

National Comprehensive Cancer Network guidelines recommend bilateral oophorectomy as part of surgical staging, independent of age, for patients with endometrial cancer. In February 2018, however, guideline updates introduced ovarian conservation as an option in select premenopausal women with early-stage endometrial cancer, normal-appearing ovaries, and no family history of breast/ovarian cancer or Lynch syndrome.[6] Following these guidelines, our service introduced a similar framework to guide ovarian

conservation in patients with endometrial cancer (Figure 1). These institutional guidelines were also developed and implemented because of emerging data suggesting similar oncologic outcomes in women with endometrial cancer who had undergone ovarian conservation instead of oophorectomy, which complemented well-established data documenting harms associated with premenopausal oophorectomy.[11 14 19–21] After 4 years of implementation, we sought to evaluate if and how our institutional guidelines altered patterns of care.

To contextualize the possible impact of these increasing rates of ovarian conservation, a study of bilateral oophorectomy compared with ovarian conservation in women <50 years of age who had undergone hysterectomy for benign disease reported that eight patients would need to undergo bilateral oophorectomy to cause one all-cause death, and 33 would need to undergo bilateral oophorectomy to cause one death from heart disease.[11] While our patient population differs in that all hysterectomies at our institution were performed for malignancy, women with low-grade endometrial cancer are generally considered to be at low risk for oncologic recurrence but high risk for cardiovascular comorbidities.[22] For example, among women diagnosed with all stages of low-grade endometrial cancer from 1973 to 1988 captured by the Surveillance, Epidemiology, and End Results database, 42.1% died from cardiovascular causes compared with 7.2% from endometrial cancer.[23]

In addition to increasing rates of women undergoing ovarian conservation, we also observed demographic shifts among women pursuing ovarian conservation. Comparing rates of ovarian conservation before and after guideline implementation, 12% versus 36% of non-Hispanic White women, 11% versus 60% of Hispanic White women, 34% versus 40% of non-Hispanic Black women, and 34% versus 47% of Asian women underwent ovarian conservation. In our study and large national database studies, younger women and non-Hispanic Black women were more likely to choose ovarian conservation.[24] After guideline introduction, while younger women remained more likely to pursue ovarian conservation, we no longer observed differences in patterns of care by race or ethnicity. The specific factors underlying these differences in patterns of care prior to guideline introduction are beyond the scope of this study; however, this study and others suggest that clinical practice guidelines may mitigate variations in care.[25]

Strength and Weaknesses

The strengths of this study include the early adoption of ovarian conservation guidelines for women ≤50 years of age undergoing surgery for endometrial cancer that paralleled the introduction of national guidelines for ovarian conservation. This generated a relatively large sample size, which allowed for the further investigation of interactions between guideline introduction and shifts in ovarian conservation by clinicodemographic factors. Many of the limitations of this study are inherent in its retrospective, single-institution design. While we sought to limit biases in the design of this study by identifying patients from rigorously maintained institutional databases and including only women who had undergone hysterectomy at our institution, it is possible that additional variables that may have influenced pursuit of ovarian conservation were unaccounted for. In addition, determining the association of ovarian conservation with certain clinicodemographic factors, including payer status and race/ethnicity, is limited by sample size or by missing data. For example, marital status was missing for 58 patients. This variable was self-reported, and assessment on the association between marital status and ovarian conservation is limited by data available in the prospectively maintained database. Finally, it is possible that the trends observed were unique to this institution and may not be generalizable to other patient populations. For example, this study preferentially included younger patients with endometrioid histology who ultimately underwent surgery. Thus, this study group should be considered to have lower risk disease compared with the average patient with endometrial cancer.

Implications for Practice and Future Research

Despite the above limitations, our findings may facilitate future studies, including systematic reviews, meta-analyses, and qualitative studies, to help us better understand patient decision-making in this setting, as well as continued refinement of endometrial cancer management guidelines. Furthermore, the demographic shifts in ovarian conservation observed after guideline implementation support the adoption of ovarian conservation guidelines across other institutions.

CONCLUSIONS

Evidence-based guidelines can improve quality and consistency of care.[26 27] Here, we report increased rates of ovarian conservation after implementation of evidence-based institutional guidelines for women ≤50 years of age undergoing surgery for endometrioid endometrial cancer. Furthermore, our findings suggest that the implementation of clinical practice guidelines may lead to decreased variations in care across demographics.

Author affiliations
[1]Gynecology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York, USA
[2]Department of Obstetrics & Gynecology, Weill Cornell Medical College, New York, New York, USA
[3]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York, USA

Contributors Conceptualization: BLM-G, JJM. Data curation: BLM-G. Formal analysis: QZ, AI. Methodology: BLM-G, JJM. Roles/writing - original draft: BMG. Writing - review & editing: all authors. JJM is responsible for the overall content as the guarantor.

Funding This research was funded in part by the NIH/NCI Cancer Center Support Grant P30 CA008748.

Competing interests Outside the submitted work, Dr Abu-Rustum reports research funding paid to the institution from GRAIL.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the IRB of Memorial Sloan Kettering Cancer Center (protocol #17-546). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs
Beryl L Manning-Geist http://orcid.org/0000-0002-5556-0457
Eric Rios-Doria http://orcid.org/0000-0002-5494-8775
Nadeem R Abu-Rustum http://orcid.org/0000-0001-9689-1298
Jennifer J Mueller http://orcid.org/0000-0003-0365-7510

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Supplementary Table 1: Clinicodemographic Factors

Characteristic	Interaction in Logistic Model Pv[1]	Cochran Armitage Pv[2]	2010[3]	2011[3]	2012[3]	2013[3]	2014[3]	2015[3]	2016[3]	2017[3]	2018[3]	2019[3]	2020[3]
Age<45	0.45	**<0.001**											
OVconserv=No			7(64%)	11(79%)	2(33%)	9(64%)	10(77%)	10(83%)	16(70%)	6(60%)	9(36%)	9(35%)	4(24%)
OVconserv=Yes			4(36%)	3(21%)	4(67%)	5(36%)	3(23%)	2(17%)	7(30%)	4(40%)	16(64%)	17(65%)	13(76%)
Age>45		**0.002**											
OVconserv=No			11(100%)	11(92%)	10(91%)	24(92%)	16(100%)	11(100%)	19(100%)	19(95%)	11(73%)	15(75%)	12(75%)
OVconserv=Yes			0(0%)	1(8.3%)	1(9.1%)	2(7.7%)	0(0%)	0(0%)	0(0%)	1(5.0%)	4(27%)	5(25%)	4(25%)
Race													
White	0.67	**0.014**											
OVconserv=No			11(85%)	16(84%)	7(78%)	22(85%)	17(100%)	11(92%)	20(100%)	14(100%)	9(64%)	13(65%)	10(59%)
OVconserv=Yes			2(15%)	3(16%)	2(22%)	4(15%)	0(0%)	1(8.3%)	0(0%)	0(0%)	5(36%)	7(35%)	7(41%)
Non-White		0.09											
OVconserv=No			3(60%)	5(100%)	4(57%)	9(75%)	7(70%)	7(88%)	10(67%)	5(56%)	9(75%)	7(44%)	6(55%)
OVconserv=Yes			2(40%)	0(0%)	3(43%)	3(25%)	3(30%)	1(12%)	5(33%)	4(44%)	3(25%)	9(56%)	5(45%)
BMI													
Normal	0.87	**0.005**											
OVconserv=No			4(67%)	4(67%)	3(60%)	8(89%)	7(88%)	6(100%)	12(80%)	7(88%)	6(46%)	5(38%)	3(30%)
OVconserv=Yes			2(33%)	2(33%)	2(40%)	1(11%)	1(12%)	0(0%)	3(20%)	1(12%)	7(54%)	8(62%)	7(70%)
Overweight/ Obese		**<0.001**											

Characteristic	Interaction in Logistic Model Pv[1]	Cochran Armitage Pv[2]	2010[3]	2011[3]	2012[3]	2013[3]	2014[3]	2015[3]	2016[3]	2017[3]	2018[3]	2019[3]	2020[3]
OVconserv=No			14(88%)	16(89%)	9(75%)	22(79%)	15(88%)	14(88%)	23(85%)	18(82%)	13(52%)	19(58%)	11(55%)
OVconserv=Yes			2(12%)	2(11%)	3(25%)	6(21%)	2(12%)	2(12%)	4(15%)	4(18%)	12(48%)	14(42%)	9(45%)
Insurance													
Commercial	0.45	**0.041**											
OVconserv=No			9(75%)	15(83%)	6(55%)	23(79%)	14(88%)	9(90%)	20(83%)	13(100%)	12(55%)	13(54%)	14(64%)
OVconserv=Yes			3(25%)	3(17%)	5(45%)	6(21%)	2(12%)	1(10%)	4(17%)	0(0%)	10(45%)	11(46%)	8(36%)
Medicaid/Selfpay		0.20											
OVconserv=No			1(100%)	0(NA%)	0(NA%)	1(100%)	2(100%)	4(80%)	3(100%)	2(67%)	2(100%)	5(62%)	1(100%)
OVconserv=Yes			0(0%)	0(NA%)	0(NA%)	0(0%)	0(0%)	1(20%)	0(0%)	1(33%)	0(0%)	3(38%)	0(0%)
Marital Status													
Partnered	0.08	0.12											
OVconserv=No			9(69%)	12(80%)	7(64%)	19(90%)	19(95%)	12(92%)	22(81%)	12(92%)	12(71%)	13(59%)	11(65%)
OVconserv=Yes			4(31%)	3(20%)	4(36%)	2(9.5%)	1(5.0%)	1(7.7%)	5(19%)	1(7.7%)	5(29%)	9(41%)	6(35%)
Single / Widowed / Divorced		**<0.001**											
OVconserv=No			5(100%)	9(100%)	4(80%)	13(72%)	5(83%)	7(88%)	10(100%)	6(100%)	8(53%)	7(50%)	5(50%)
OVconserv=Yes			0(0%)	0(0%)	1(20%)	5(28%)	1(17%)	1(12%)	0(0%)	0(0%)	7(47%)	7(50%)	5(50%)

[1] This pvalue is obtained through logistic model with interaction between surgery year and corresponding variable.
[2] This pvalue is obtained using Cochran-Armitage trend test.
[3] Statistics presented: n(%)