



# Optimizing outcomes in colorectal surgery: cost and clinical analysis of robotic versus laparoscopic approaches to colon resection

Kevin J. Hancock<sup>1</sup> · V. Suzanne Klimberg<sup>1</sup> · Omar Nunez-Lopez<sup>1</sup> · Aakash H. Gajjar<sup>1,2</sup> · Guillermo Gomez<sup>1</sup> · Douglas S. Tyler<sup>1</sup> · Laila Rashidi<sup>3</sup>

Received: 3 June 2020 / Accepted: 25 January 2021 / Published online: 25 February 2021  
© The Author(s), under exclusive licence to Springer-Verlag London Ltd. part of Springer Nature 2021

## Abstract

The use of robotics in colorectal surgery has been steadily increasing, however, reported longer operative times and increased cost has limited its widespread adoption. We investigated the cost of elective colorectal surgery based on type of anatomic resection and the impact of a standardized protocol for robotic colectomies. A retrospective review was conducted of 279 elective colectomies at a single institution between 2013 and 2017. Clinical outcomes and detailed cost data were compared based on open, laparoscopic, or robotic surgical approach and stratified by anatomic resection. Robotic, laparoscopic and open colectomy rates were 35, 34 and 31%, respectively. While total costs were similar in robotic and laparoscopic surgery, anatomic resection stratification showed that low anterior resection (LAR) was significantly cheaper (\$14,093 vs \$17,314). When a standardized surgical protocol was implemented for robotic colectomies, significant reductions in operative times, length of stay, total cost, and operative cost were observed. Robotic surgery may be most cost effective for elective LAR compared to laparoscopic or open approaches. A standardized surgical protocol for robotic surgery may help reduce costs by reducing operative times, operating rooms expenditure, and lengths of stay.

**Keywords** Colorectal · Robotic · Minimally invasive · Cost · Standardized surgical protocol

## Introduction

Minimally invasive colorectal surgery has been shown to improve clinical outcomes compared to open surgery [1]. Robotic surgery is an emerging technology that has been shown to be as safe as laparoscopic surgery with oncologic equivalence [2–4]. Institutions and payers debate the use of this technology, as robotic surgery is usually shown to be more expensive and many studies fail to show significant improvements in short-term clinical outcomes, especially in its early phase of adoption.

The cost of using the robot for colorectal surgery compared to laparoscopy is routinely under scrutiny as most

retrospective, large database studies have found robotic surgery to be more expensive than laparoscopic surgery [5, 6]. However, smaller single-institution studies have published data demonstrating robotic and laparoscopic surgery to have similar hospital costs and charges [7, 8]. Furthermore, we have previously demonstrated that significant reductions in length of stay, conversion to open surgery rate, and total hospital cost occur for surgeons performing a high volume of robotic surgery defined as at least 30 cases/year [9].

Historically, minimally invasive laparoscopy went through a transformation of acceptance in colorectal surgery. In terms of economic viability, laparoscopic versus open colectomy has been debated with varying results in single-institution and large database studies [10–14]. Laparoscopic technology has been increasingly more accepted as national database studies are starting to show significant cost reductions in colon and rectal resections with this technique [15, 16].

For oncologic resection efficacy, laparoscopic surgery for both colon and rectal surgery has been shown equally effective as open surgery in the Colorectal Cancer Laparoscopic or Open Resection (COLOR II) trial [17]. For robotic

✉ Laila Rashidi  
lailarashidi58@gmail.com

<sup>1</sup> Department of Surgery, University of Texas Medical Branch, 301 University Dr, Galveston, TX 77555, USA

<sup>2</sup> PRiSMA Proctology Surgical Medicine & Associates, PLLC, Houston, TX, USA

<sup>3</sup> Department of Surgery, Multicare Health System, 3124 19th St. Suite 220, Tacoma, WA 98405, USA

surgery, the first randomized trial comparing robotic and laparoscopic oncologic equivalency is the Robotic vs Laparoscopic Resection for Rectal Cancer (ROLARR) trial [18]. The preliminary pathologic outcomes were similar to laparoscopy for rectal cancer with long-term data still accruing. A retrospective national database study by Sun et al. has shown significantly reduced conversion rates for rectal cancer resection with robotic surgery [3]. While robotic colorectal surgery clinical outcomes and oncologic equivalency are being shown as comparable to laparoscopy, a major remaining inhibitor to acceptance is cost.

To optimize and streamline robotic approaches to colorectal procedures at our institution, we implemented a standardized surgical protocol (SSP) that includes a dedicated OR team and sequential operative steps. Using this approach, we hypothesized that robotic surgery is not more expensive than laparoscopy alone in colorectal surgery. Towards this aim, we compare the impact of robotic surgery in terms of type of surgery, anatomic stratification, implementation of SSP, detailed costs and clinical outcomes at a single center on the performance of colectomies.

## Materials and methods

### Patients

A retrospective review was conducted on all patients undergoing elective colon and rectal resections at University Texas Medical Branch from 2013 to 2017. Using an IRB-approved protocol, clinical, demographic, and patient-level cost data were abstracted from medical records for all patients using electronic health record (EHR) system (Epic™, Madison, WI).

### Surgery

Procedures were grouped based on surgical approach (open, laparoscopic, robotic) and stratified by anatomic resection (right colectomy, low anterior resection, and total colectomy). Robotic colon and rectal resections were performed on da Vinci® Si or Xi platform (Intuitive Surgical, Inc. Sunnyvale, CA) by four different surgeons for benign disease, colon/rectal cancer, or polyp(s) unresectable by endoscopy. All four surgeons were considered experienced in robotic surgery. Surgical approach was based on surgeon preference with indication of previous diverticulitis chosen specifically for robotic approach. The cohort of patients was initially identified by a combination of Current Procedural Terminology (CPT™, American Medical Association, Chicago) code and procedure descriptions as coded within the EHR. Laparoscopic, open and robotic approaches were then refined using an algorithm of key terms and identifying common

supplies unique to each approach. Stratification of patient approach was kept to the final operative approach (i.e., if a laparoscopic approach was converted to open, that procedure is classified as open). Data were limited to the following categories: right colectomy, low anterior resection (LAR) and total colectomy. LAR includes sigmoid and rectum excisions as one group. Only rectopexies that included a bowel resection were included in the LAR category in our data. Complex total proctocolectomies and abdominal perineal resections were excluded as very few are performed entirely robotically.

### Total direct cost and operating room analysis

Costs included in the analysis were operative time, recovery room time, hospital length of stay, surgical supplies, robotic instruments, anesthesia, operating room and hospital medication, and nursing. Hospital length of stay includes both intensive care unit and floor hospital care. Total direct cost does not include pre-operative antibiotics, pathology, readmission costs, robotic service contracts and depreciation of robotic equipment. The total direct costs included fees for all operating room supplies, conversion factor for cost of operative time, as well as pre- and post-operative hospital management costs. Hospital costs across the system averaged \$3500/day and was used in the calculation of average total direct costs. The supply costs were defined as cost of surgical instruments and supplies. For all predictors, univariate analysis by the Kruskal–Wallis non-parametric equality of populations rank test was performed. All statistical tests were two-sided, and a p value less than 0.05 was considered statistically significant. All statistical analyses were performed with STATA® (14.0 for Mac OS X, College Station, TX).

### Outcome measures

Outcome measures included mean operative time, conversion to open surgery, return of bowel function, length of stay, complications, and 30-day all cause readmissions. Operative time was recorded as the time from skin incision to skin closure. Complications of any type were included and were obtained through the EMR where International Classification of Diseases (ICD9 and ICD10) codes were recorded in the patient's record during or after surgery.

### Standardized surgical protocol

A Standardized Surgical Protocol (SSP) was implemented in August 2016 for all robotic operations and included a dedicated team of operating room staff, standard instrument use, routine use of sequential operative steps, and participation of two surgeons during operations when warranted. Outcome

measures of this subgroup are identical to the anatomical stratification including total cost, operating room cost, mean operative time, conversion to open surgery, return of bowel function, length of stay, complications and 30 day all cause readmission.

## Results

### Patients

We identified 279 cases that met inclusion criteria. Average age was  $60 \pm 15$  years and 54% (151) were males. Of these cases, 56% of the patients had prior abdominal surgery. The majority of patients were American Society of Anesthesiologists (ASA) physical status classification 2 or 3 with 15 patients being classification 4. Cancer was the most common indication for surgery (54%). Other indications for surgery include polyps not amenable to endoscopic resection or polyps incompletely excised in 21 percent of the cases. Benign entities that were mostly diverticular disease accounted for 25 percent of the cases.

### Surgery

Robotic, laparoscopic and open approach rates were 35, 34 and 31 percent, respectively. Right colectomy was the most common operation in robotic and laparoscopic subgroup 56%, and 55%, respectively.

### Total direct cost analysis

When averaged for all cases, total costs were similar in robotic and laparoscopic approaches (\$13,529 vs \$13,039,  $p=0.78$ ) (Table 1). However, when total cost was stratified by anatomic resection, robotic approach was more expensive for right colectomy (\$12,016 vs \$10,993,  $p=0.31$ ) but significantly less expensive for LAR (\$14,093 vs \$17,314,  $p=0.048$ ).

### Outcome measures

Length of stay was not significantly different between robotic and laparoscopic surgery (5.63 vs 5.41 days,  $p=0.77$ ) and neither was return of bowel function (3.02 vs 3.10,  $p=0.27$ ) (Table 2). Readmission rates were significantly less with robotic approach as compared to laparoscopic (4.1 vs 10.6%,  $p=0.04$ ). Operating room supply costs were not significantly different by robotic or laparoscopic approach (\$2,060 vs \$2,027,  $p=0.61$ ). Overall operative time was not significant between robotic and laparoscopic approach (293 vs 276 min,  $p=0.27$ ). In anatomical approach analysis, operative time was significantly shorter for robotic LAR vs laparoscopic (311 vs 366 min,  $p=0.04$ ) and significantly longer for robotic right hemicolectomy vs laparoscopic (272 vs 220 min,  $p=0.04$ ).

**Table 1** Cost by anatomic resection and surgical approach

	Right colectomy	Low anterior resection	Total colectomy	Total average cost
Laparoscopic	10,993	17,314	14,907	13,039
Open	19,222	22,753	25,498	21,168
Robotic	12,016	14,093	19,631	13,529

**Table 2** Robotic and laparoscopic colectomy costs and clinical outcomes

Procedure type	All			Low anterior resection			Right colectomy		
	Robotic surgery	Laparoscopic surgery	<i>p</i> value	Robotic surgery	Laparoscopic surgery	<i>p</i> value	Robotic surgery	Laparoscopic surgery	<i>p</i> value
Total cost	13,529	13,039	0.78	14,093	17,314	0.048	12,016	10,993	0.31
OR Supply cost	2060	2027	0.61	2611	2930	0.33	2737	2613	0.56
Nursing cost	3002	3054	0.92	3783	3870	0.95	2519	2747	0.56
Readmission rate (%)	4.1	10.6	0.04	5.7	20.7	0.04	1.8	7.7	0.02
LOS (days)	5.63	5.41	0.77	5.26	6.27	0.34	5.49	4.46	0.14
Return of bowel function (days)	3.02	3.10	0.79	2.71	3.40	0.28	3.33	3.02	0.44
OR time (min)	293	276	0.27	311	366	0.04	272	220	0.002

## Standardized surgical protocol

After implementation of SSP for robotic procedures, operative time was significantly reduced (279 vs 431 min,  $p \leq 0.01$ ) (Table 3). Total cost and OR cost were significantly reduced (\$12,489 vs \$10,174),  $p \leq 0.04$ ; \$3,936 vs \$2,622,  $p \leq 0.04$ ). In addition, length of stay and conversion to open rates were significantly reduced (6.8 vs 3.4 days,  $p \leq 0.04$ ; 9% vs 2%,  $p \leq 0.01$ ). Complication rates and 30-day readmission rates were not significantly different after SSP. Patient gender, age, and operation type were not significantly different but patient diagnosis was significantly different with more colectomies for diverticulosis being performed after SSP was implemented.

## Discussion

Robotic surgery continues to be a debated surgical platform for colorectal surgery with studies reaching different conclusions on cost, conversion rates, oncologic usefulness and short-term clinical outcomes. While clinical and procedural outcome advantages of robotic colorectal surgery have been observed in multi-institutional studies, only single-institution studies have exhibited some implications at cost advantages. Our retrospective, single-institution study found that compared to laparoscopy, the robotically performed LAR group had significantly reduced cost, operative time, and

readmission rate. The robotic right colectomy group had significant longer operative times. In addition, implementing a standard surgical protocol for robotic surgery is indicative of reducing operative time, conversion to open surgery rates, and total cost.

Retrospective review of National Surgical Quality Improvement Program (NSQIP) data has shown reductions in left side robotic colectomy conversion to open rates and length of stay but longer operative times compared to laparoscopy [19]. The patients of our robotic LAR cohort also had reduced lengths of stay and this likely contributed to reduced overall cost of hospital admission. This reduced total cost is also likely aided by the decreased OR supply cost. We hypothesize the shorter operative times for our robotic LAR cohort were because all of our surgeons were considered past the initial learning curve of robotic surgery. The learning curve of robotic colorectal surgery is considered at least 15–25 cases and the number of cases being performed nationwide is increasing [20, 21]. We have previously demonstrated high-volume surgeons have reduction in total cost, operative time, and conversion to open surgery rates compared to low-volume surgeons [9]. Just as acceptance of laparoscopy took time, robotic surgery is potentially at the beginning of its widespread adoption and its full advantages are not evident on a national scale.

While there are several published procedural operative steps for minimally invasive and robotic colorectal surgery, there are no studies documenting combining this with the

**Table 3** Standardized surgical protocol patient characteristic, cost and outcomes

	Before ssp <i>n</i> = 27	After ssp <i>n</i> = 71	<i>p</i> value
Gender— <i>n</i> (%)	Male 15 (56%) Female 12 (44%)	Male 37 (52%) Female 34 (48%)	0.7
Age (years)	58 (30–91)	58 (22–88)	0.99
Diagnosis— <i>n</i> (%)	Cancer 15 (56%) Neoplasm 9 (33%) Diverticulitis 1 (4%) Other benign 2 (7%)	Cancer 37 (52%) Neoplasm 3 (4%) Diverticulitis 26 (37%) Other benign 5 (7%)	$\leq 0.01$
Operation— <i>n</i> (%)	RC 11 (41%) LAR 11 (41%) APR 2 (7%) TAC 3 (11%)	RC 13 (18%) LAR 48 (68%) APR 5 (7%) TAC 5 (7%)	0.07
Operative time—min	431	279	$< 0.01$
LOS—days	6.8 (2–27)	3.4 (1–27)	$< 0.04$
Complications, any— <i>n</i> (%)	12 (44%)	13 (19%)	0.08
Conversion— <i>n</i> (%)	9 (33%)	2 (3%)	$< 0.01$
30 day readmit— <i>n</i> (%)	3 (11%)	6 (8%)	0.3
Total cost	12,489	10,174	$\leq 0.04$
OR cost	3936	2622	$\leq 0.04$

RC right colectomy, LAR low anterior resection, APR abdominalperineal resection, TAC total abdominal colectomy

same OR team for analysis of cost and clinical outcomes [22]. The outcomes of our robotic LAR could be heavily influenced by our SSP implementation and lead to significant reductions in robotic surgery operative time, total cost, OR cost, length of stay, and conversion to open surgery rates when compared to prior use of SSP. Other studies have shown that individual consumable items add exponentially to the OR cost [7]. Our SSP likely reduces the opening of these items without absolute need, therefore reducing total and OR cost. Also, operative time is likely reduced with advancement further on learning curve and the utilization of methodical operative steps. Also, more cases of LAR were in SSP group where robotic surgery is thought to be more advantageous.

Our data concur with other previous studies including the meta-analysis by Solaini et al. that right colectomy takes longer and is more expensive robotically than laparoscopic [23]. Right colectomies are thought to be quicker laparoscopic mainly because of the anatomy of that location. However, when considering the anatomy for rectal cancer resections, total mesorectal resection is much more difficult because of limited space to navigate compared to the abdominal cavity for right colectomies. The only randomized trial comparing laparoscopic versus robotic resection of rectal cancer did not look at the outcome of operative time [18]. To decrease operative time and make robotic resections other than LAR more cost effective, a SSP will likely need to be used to reduce docking times and opening of unnecessary supplies. The conversion to open rates of this study was similar to those observed in the ROLARR trial. In addition, after SSP implementation, conversion rates were considered significantly reduced. While conversion rate reduction may not be attributed to standard instrument usage alone, the learning curve of the group was certainly increasing as well. Therefore, it may be reasonable to think that the value of robotic surgery may be more evident in single-institution trials where expertise is more mature than in multi-institutional trials where expertise is less well known. This is one of the first single-institution studies showing that robotic LAR surgery has an economic advantage with similar if not improved clinical outcomes.

This is a single-institution study with a relatively small but comparable sample size to existing single-institution trials. While a large sample size and multicenter inclusion would provide more data, detailed financial information can be hard to obtain. This study did not include cost of readmissions and variable costs associated with surgeon's volume that we have previously analyzed in the Providence Health System Hospitals. The robot acquisition (0.6–2.5 million dollars) and maintenance cost/contract (100–170 thousand dollars) is not included, as in most studies because it is hard to assign the appropriate cost per case with multiple specialties using the robot [24, 25]. We also did not compare

cancer resection outcomes, such as node acquisition, margins and circumferential radial margins, although previous studies have not shown inferiority with robotic surgery [26]. This study does not account for experience with specific case numbers although all colorectal surgeons were past their learning curve.

## Conclusion

We found that elective robotic colorectal surgery is most cost effective for left-sided colon and rectal resection. Implementation of a SSP is indicative of reducing robotic colorectal surgery costs.

**Author contributions** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by LR and ON-L. The first draft of the manuscript was written by KH and SK and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Funding** This research was supported in part by the National Institutes of Diabetes and Digestive and Kidney Disease of the National Institutes of Health (grant number T32DK007639).

## Compliance with ethical standards

**Conflict of interest** All of the authors declare that they have no conflicts of interest or financial ties to disclose.

## References

1. Juo Y-Y, Hyder O, Haider AH et al (2014) Is minimally invasive colon resection better than traditional approaches? *JAMA Surg* 149(2):177–184. <https://doi.org/10.1001/jamasurg.2013.3660>
2. Miller PE, Dao H, Paluoi N et al (2016) Comparison of 30 day postoperative outcomes after laparoscopic vs robotic colectomy. *J Am Coll Surg* 223(2):369–373. <https://doi.org/10.1016/j.jamcollsurg.2016.03.041>
3. Sun Z, Kim J, Adam MA et al (2016) Minimally invasive versus open low anterior resection: equivalent survival in a national analysis of 14,033 patients with rectal cancer. *Ann Surg* 263:1152–1168. <https://doi.org/10.1097/SLA.0000000000001388>
4. Trinh BB, Jackson NR, Hauch AT et al (2014) Robotic versus laparoscopic colorectal surgery. *JLS* 18:e2014.00187. <https://doi.org/10.4293/JLS.2014.00187>
5. Al-Mazrou AM, Baser O, Kiran RP (2018) Propensity score-matched analysis of clinical and financial outcomes after robotic and laparoscopic colorectal resection. *J Gastrointest Surg* 22:1043–1051. <https://doi.org/10.1007/s11605-018-3699-8>
6. Yeo HL, Isaacs AJ, Abelson JS et al (2016) Comparison of open, laparoscopic, and robotic colectomies using a large national database: outcomes and trends related to surgery center volume. *Dis Colon Rectum* 59:535–542. <https://doi.org/10.1097/DCR.0000000000000580>
7. Hollis RH, Cannon JA, Singletary BA et al (2016) Understanding the value of both laparoscopic and robotic approaches compared

- to the open approach in colorectal surgery. *J Laparoendosc Adv Surg Tech* 26(11):850–856. <https://doi.org/10.1089/lap.2015.0620>
8. Vasudevan V, Reusche R, Wallace H, Kaza S (2016) Clinical outcomes and cost-benefit analysis comparing laparoscopic and robotic colorectal surgeries. *Surg Endosc* 30:5490–5493. <https://doi.org/10.1007/s00464-016-4910-1>
  9. Bastawrous A, Baer C, Rashidi L, Neighorn C (2018) Higher robotic colorectal surgery volume improves outcomes. *Am J Surg* 215:874–878. <https://doi.org/10.1016/j.amjsurg.2018.01.042>
  10. Liberman MA, Phillips EH, Carroll BJ et al (1996) Laparoscopic colectomy vs traditional colectomy for diverticulitis. *Surg Endosc* 10:15–18. <https://doi.org/10.1007/s004649910002>
  11. Bergamaschi R, Arnaud JP (1997) Immediately recognizable benefits and drawbacks after laparoscopic colon resection for benign disease. *Surg Endosc* 11:802–804. <https://doi.org/10.1007/s004649900457>
  12. Senagore AJ, Duepre HJ, Delaney CP et al (2002) Cost structure of laparoscopic and open sigmoid colectomy for diverticular disease. *Dis Colon Rectum* 45(4):485–490. <https://doi.org/10.1007/s10350-004-6225-x>
  13. Delaney CP, Chang E, Senagore AJ, Broder M (2008) Clinical outcomes and resource utilization associated with laparoscopic and open colectomy using a large national database. *Ann Surg* 247:819–824. <https://doi.org/10.1097/SLA.0b013e31816d950e>
  14. Shabbir A, Roslani AC, Wong K-S et al (2009) Is laparoscopic colectomy as cost beneficial as open colectomy? *ANZ J Surg* 79:265–270. <https://doi.org/10.1111/j.1445-2197.2009.04857.x>
  15. Keller DS, Senagore AJ, Lawrence JK et al (2014) Comparative effectiveness of laparoscopic versus robot-assisted colorectal resection. *Surg Endosc* 28:212–221. <https://doi.org/10.1007/s00464-013-3163-5>
  16. Vaid S, Tucker J, Bell T et al (2012) Cost analysis of laparoscopic versus open colectomy in patients with colon cancer: results from a large nationwide population database. *The Am Surg* 78(6):635–641
  17. Bonjer HJ, Deijen CL, Abis GA et al (2015) A randomized trial of laparoscopic versus open surgery for rectal cancer. *N Engl J Med* 372:1324–1332. <https://doi.org/10.1056/NEJMoa1414882>
  18. Jayne D, Pigazzi A, Marshall H et al (2017) Effect of robotic-assisted vs conventional laparoscopic surgery on risk of conversion to open laparotomy among patient undergoing resection for rectal cancer. *JAMA* 318(16):1569–1580. <https://doi.org/10.1001/jama.2017.7219>
  19. Bhamra AR, Obias V, Welch KB et al (2016) A comparison of laparoscopic and robotic colorectal surgery outcomes using the american college of surgeons national surgical quality improvement program (ACS NSQIP) database. *Surg Endosc* 30:1576–1584. <https://doi.org/10.1007/s00464-015-4381-9>
  20. Bokhari MB, Patel CB, Ramos-Valadez DI et al (2011) Learning curve for robotic-assisted laparoscopic colorectal surgery. *Surg Endosc* 25:855–860. <https://doi.org/10.1007/s00464-010-1281-x>
  21. Damle A, Damle RN, Flahive JM (2017) Diffusion of technology: trends in robotic-assisted colorectal surgery. *Am J Surg* 214:820–824. <https://doi.org/10.1016/j.amjsurg.2017.03.020>
  22. Salem JF, Gummadi S, Marks JH (2018) Minimally invasive surgical approaches to colon cancer. *Surg Oncol Clin N Am* 27:303–318. <https://doi.org/10.1016/j.soc.2017.11.005>
  23. Solaini L, Bazzocchi F, Cavaliere D et al (2018) Robotic versus laparoscopic right colectomy: an updated systematic review and meta-analysis. *Surg Endosc* 32:1104–1110. <https://doi.org/10.1007/s00464-017-5980-4>
  24. Shih Y-CT, Shen C, Hu JC (2017) Do robotic surgical systems improve profit margins? A cross-sectional analysis of California hospitals. *Value in Health* 20:1221–1225. <https://doi.org/10.1016/j.jval.2017.05.010>
  25. Zelhart M, Kaiser AM (2018) Robotic versus laparoscopic versus open colorectal surgery: towards defining criteria to the right choice. *Surg Endosc* 32:24–28. <https://doi.org/10.1007/s00464-017-5796-2>
  26. Valverde A, Goasguen N, Oberlin O et al (2017) Robotic versus laparoscopic rectal resection for sphincter-saving surgery: pathological and short-term outcomes in a single-center analysis of 130 consecutive patients. *Surg Endosc* 31(10):4085–4091. <https://doi.org/10.1007/s00464-017-5455-7>

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.