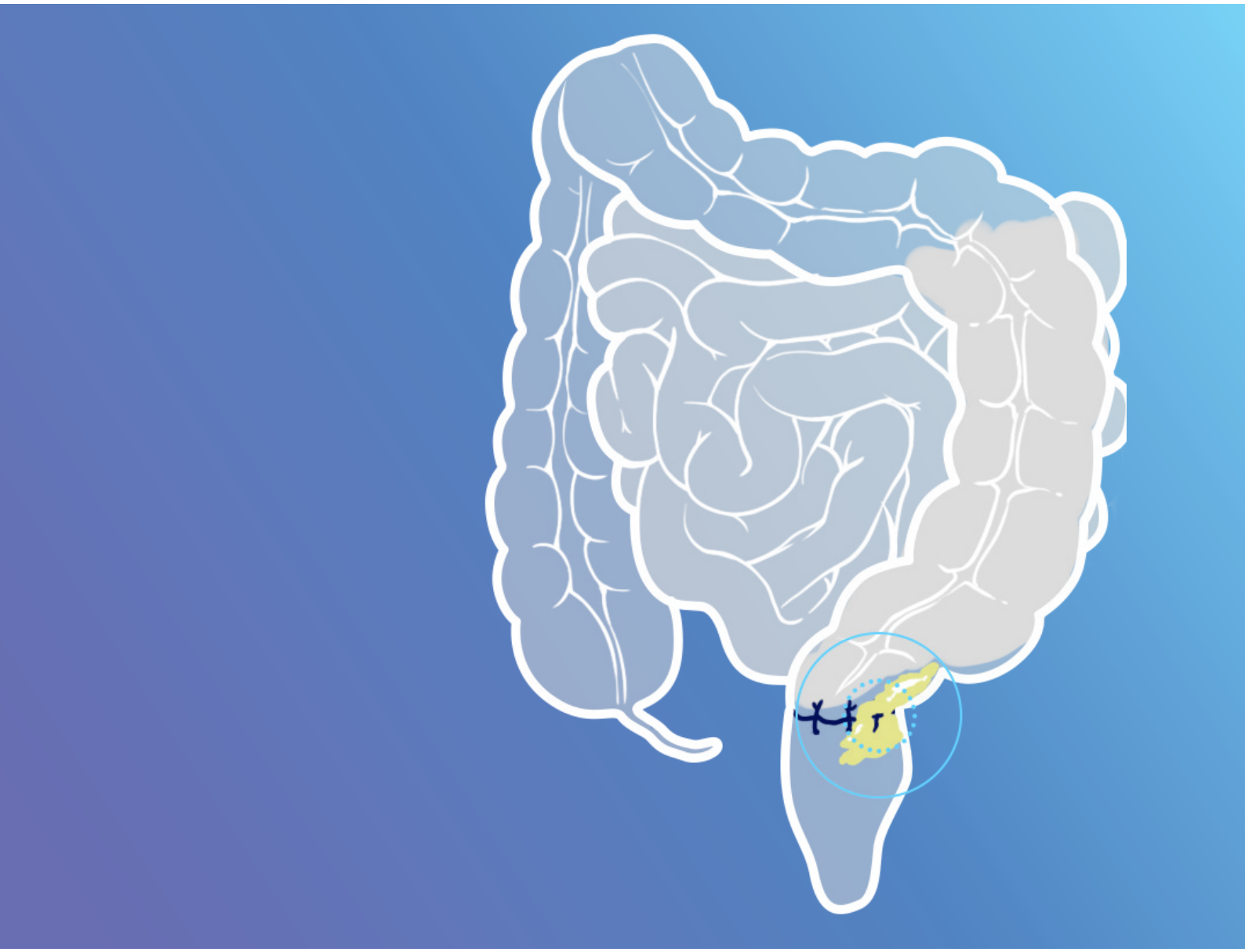

Introduction to Colorectal Anastomotic Leakage.

FluidAI

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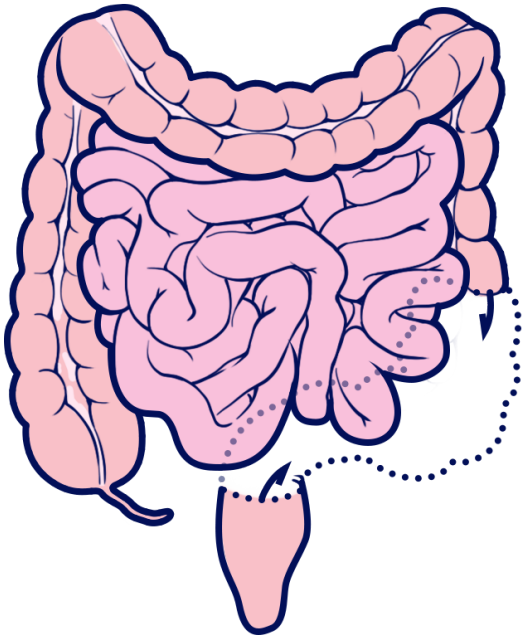
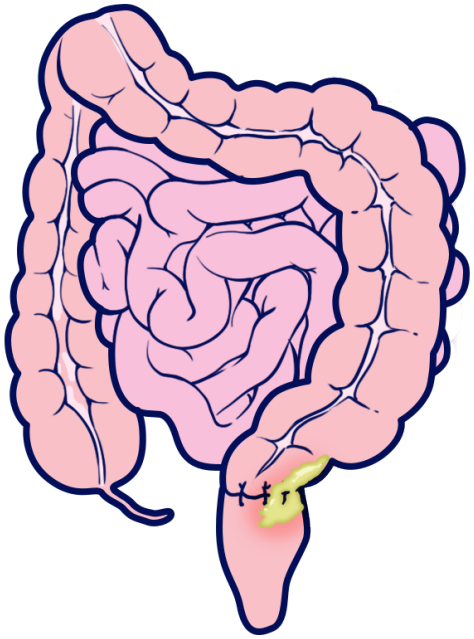
INTRODUCTION

Colorectal surgery is defined as a surgical procedure involving large and/or small bowel resection and reconstruction. Classic colorectal procedures are described by the level of resection (proximal, middle, or distal) and the method of reconstruction utilized (i.e., creation of stoma vs anastomosis).

Lower anterior resection (LAR)



Anastomotic leak



Colorectal procedures are conducted to help treat various pathologies including (but not limited to) colorectal cancer (CRC), mechanical bowel obstruction, recurrent diverticulitis, familial adenomatous polyposis, and inflammatory bowel diseases (IBD) such as ulcerative colitis, Crohn's disease, and indeterminate colitis[1]. Additionally, colorectal procedures may be done in response to injury, ischemic colitis, refractory constipation, rectal prolapse and proctological disorders[1].

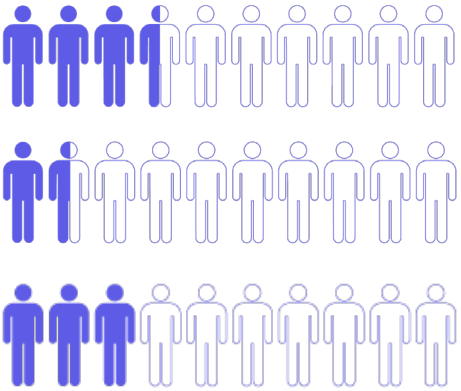
Most colorectal procedures involve the resection of a target pathology followed by the restoration of gastrointestinal continuity through the creation of an anastomosis. An anastomosis can be defined as a hand-sewn or stapled connection between two tubular structures[2]. As with any surgical intervention, the creation of an anastomosis does not come without risk. Some of the main postoperative complications associated with the creation of an intestinal anastomosis following colorectal surgery include surgical site infection, bleeding, stenosis, fistula formation, ileus, and anastomotic leakage/dehiscence. If not managed properly, such complications can lead to sepsis, septic shock, or even death. Of those complications, anastomotic leakage (AL) is considered a major source of morbidity and mortality with rates equivalent to 20–35% and 2–16.4% respectively[3].

Despite advances in surgical techniques, the incidence of AL has not changed significantly in recent decades and was reported in literature to vary from 2.8% to as high as 30%[3]. Anastomotic leakage is associated with additional intervention, prolonged hospital stays, and hospital readmission.

Morbidity
up to 35%

Mortality
up to 16.4%

Incidence
up to 30%



This series of articles will provide a comprehensive review of published evidence pertaining to anastomotic leaks, culminating with a white paper that unites this information in a single document. Here, a thorough discussion on the definition, grading system, and consequences of anastomotic leaks is provided. Subsequent reports will outline risk factors, prevention methods, diagnostic techniques, current approaches for treatment and effective management, and long-term outcomes associated with anastomotic leakage after colorectal surgery. Additionally, this discussion will introduce a novel medical device (Stream™ Platform) developed by FluidAI (formally NERv Technology Inc.), intended for the early detection of anastomotic leakage. This technology can allow for timely therapeutic action to diminish the postoperative mortality, morbidity, cost, and high complication rates that are associated with anastomotic leaks.

TERMINOLOGY

Anastomotic leakage (AL) is used synonymously with **anastomotic leak, anastomotic insufficiency, anastomotic failure, anastomotic defect, anastomotic breakdown, suture insufficiency, suture line disruption, and anastomotic dehiscence.**

Definition and AL Grading Systems

In attempting to accurately capture the incidence of anastomotic leaks – and by extension, develop better detection and treatment – defining both the complication itself, and various degrees of severity, is imperative. Unfortunately, a universally accepted definition and grading system continue to be lacking, leading to variability in the reported incidence of anastomotic leakage (which ranges in the literature widely – from 2.8-30%)[3,4,5]. Thus, the reported incidence continues to vary depending on the clinician/ research group's definition of leakage.

Additional factors adding to the variability in estimates include differences in the anastomotic site, institutional and individual differences in operative technique, preoperative factors, intraoperative factors, and postoperative factors. Each of these will be outlined further below, or in a subsequent article[6,7].

Various groups such as the United Kingdom Surgical Infection Study Group (SISG) (1991) and the International Study Group of Rectal Cancer (ISGRC/ ISREC) (2010) published guidelines for defining and grading AL. The Clavien-Dindo (CD) surgical complication severity scale was also proposed for the grading/classification of AL (Grade I, II, IIIa, IIIb, IVa, IVb, V). While each of these guidelines is an important starting place, none have yet been widely accepted. In an early review conducted by *Bruce et al*. (2001), 29 different definitions of lower gastrointestinal leakage were reported across 49 studies[8]. Further, consensus-based surveys conducted by *Adams et al.* and *Van Rooijen et al*. in 2013 and 2017, respectively, continued to demonstrate no uniform definition of AL (and beyond this, that significant heterogeneity still exists)[9]. A more recent systematic review of 2938 abstracts and 1382 full-text articles showed that only 347 articles highlighted a definition of AL – and that this definition varied significantly across studies[10]. The lack of a widely accepted definition results in highly variable incidence rates and prevents the proper comparison of data across various studies and centers.

Clinical Grading Systems

United Kingdom Surgical Infection Study Group- 1991[11]

Verbatim Definition

"This is defined as a leak of luminal contents from a surgical join between two hollow viscera."

Clinical Leak

Defined as the leak of luminal contents through the wound or at the drain site, or the collection of such content at the anastomosis resulting in one of the following symptoms/findings: fever, abscess, septicaemia, metabolic disturbance and/or multiple-organ failure.

Subclinical leak

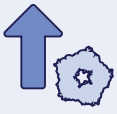
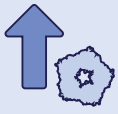
This is usually detected via imaging and is defined as the leak of luminal contents from an anastomosis into an adjacent localised area. Patients that present with subclinical leaks have no clinical symptoms or signs of leakage.

International Study Group of Rectal Cancer- 2010[7]

Verbatim Definition

"A communication between the intra- and extraluminal compartments owing to a defect of the integrity of the intestinal wall at the anastomosis between the colon and rectum or the colon and anus. Because of its similar clinical impact, a leakage originating from the suture or staple line of a neorectal reservoir (e.g. J-pouch or transverse coloplasty) should also be considered as an anastomotic leakage. Furthermore, we recommend considering a pelvic abscess in the proximity of the anastomosis as anastomotic leakage".

Graphic summary: International Study Group of Rectal Cancer- 2010[12]

	Grade A	Grade B	Grade C
Therapeutic intervention	No therapeutic intervention 	Antibiotics, drainage 	Surgical intervention/ ICU admission 
Cllnical symptoms	No clinical signs/symptoms 	Mild/moderate discomfort 	Severe disccomfort 
Leukocytosis status	No clinical signs/symptoms 	Leukocytosis 	Leukocytosis 
Serum C-reactive protein level	Normal serum C-reactive protein level 	Increased serum C-reactive protein 	Increased serum C-reactive protein 
Leakage	Small, contained leak 	Abcess formation 	Considerable leakage at the anastomotic site with fluid collections 

International Study Group of Rectal Cancer- 2010[12]

Grade A

Defined as an AL requiring no active therapeutic intervention. This grade of anastomotic leakage is not associated with clinical signs/symptoms or abnormal laboratory tests. Radiological evaluation may show a small, contained leak. Contents from the drain (if present) are usually serous however, some patients may present with turbid or feculent contents.

Grade B

Defined as an AL requiring active therapeutic intervention (administration of antibiotics, interventional drainage, or transanal drainage). Such leaks are usually managed without operative reintervention. Clinical symptoms associated with grade B leaks include mild/moderate discomfort with abdominal/pelvic pain, leukocytosis, elevated serum C-reactive protein (CRP), and turbid/purulent rectal or vaginal discharge. Radiological evaluation conducted on these patients show leakage of the endoluminally administered contrast agent at the anastomosis. CT scans may also reveal abscess formation.

Grade C

Defined as an AL requiring re-laparotomy. This can include performing a Hartmann's procedure or creating a protective ileostomy. Clinical symptoms associated with grade C leaks include severe discomfort, leukocytosis, elevated serum CRP, abdominal pain, fever, purulent/fecal drainage, and signs of sepsis/ peritonitis (abdominal wall rigidity, tenderness to palpation, tachycardia, hemodynamic instability, leukopenia, hypothermia, organ failure, etc.). Radiological evaluation conducted on these patients reveals considerable leakage at the anastomotic site with fluid collection(s).

Due to the urgent need of for a broadly accepted definition, the Italian Society of Surgery (SIC) (2020) and other reputable study groups published multiple international studies utilizing the Delphi method to establish a recommended general definition of AL[13,14,15]. Today, the ISGRC/ ISREC definition is the most recommended universal definition for colorectal anastomotic leakage.

CONSEQUENCES OF LEAKS

Colorectal anastomotic leakage is considered the bane of intestinal surgery and is one of the most feared complications due to the associated clinical and economic burden.

AL can impose a significant burden on patients, healthcare providers, and hospitals.

Increased morbidity

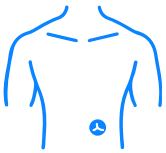
A large number of research articles report that AL results in high morbidity. A prospective multicenter international study conducted by the European Society of Coloproctology in 2015 reported a 30-day morbidity rate of 38.0% in AL patients who underwent a right hemicolectomy or ileocecal resection[16]. Another study conducted by *Alves et al.* reported an overall morbidity rate of 35% in AL patients[17]. Additionally, *McArdle et al.* and *Branagan et al.* reported that the 30-day mortality is 12.1% and 24.7% higher in AL when contrasted to non-anastomostic leak (nAL) patients, respectively[18,19].

Increased mortality

Overall, the reported mortality rate in patients that present with AL varies between 6-39%[20]. A study conducted by *Bakker et al.* showed that the mortality rate in patients with AL was 13.3% higher than the reported rate in their non-leaking counterparts[21]. Another study compromised of 28,271 patients reported that the mortality rate was 16% higher in AL patients[22]. A meta-analysis with a cohort of 154,981 patients revealed that anastomotic leakage has a significantly negative impact on overall survival[23].

Increased rate of secondary postoperative complications

AL (specifically grade B and C leaks) is associated with the need for a change in patient management and in particular, the need for antibiotic administration, interventional drainage, endoscopic management, ICU admission, increased length of stay or reoperation to prevent sepsis and peritonitis[24]. Such interventions can have a devastating impact on the patient's postoperative course. Perioperative analysis by *Kube et al*. showed that AL is associated with secondary postoperative complications[25]. These include pneumonia, pulmonary complications, cardiac complications, renal complications, wound infection, abscess formation, enterocutaneous fistula, complete rupture of the operation wound, sepsis, peritonitis, and multi-organ failure. *Kube et al*. showed that the rates of the above complications were significantly higher ($p < 0.05$) in AL patients when contrasted to nAL with an incidence of 62.7% in AL and 19.9% in patients without AL[25]. Additionally, a retrospective analysis of data from more than 600 US hospitals revealed that AL patients had a higher postoperative infection rate (0.8–1.9 times increase) compared with patients without leaks[26].



Increased risk of permanent stoma

The risk of permanent stoma after clinical leakage is reported in literature to vary between 10-100%[27]. A retrospective analysis of 1,442 patients revealed that the overall rate of permanent stoma among patients with anastomotic leakage was measured at 65%[28]. Such intervention can highly impact a patient's overall satisfaction and quality of life[29].

Higher reoperation rate

According to literature, AL leads to secondary complications and results in an increased risk of reoperation by more than 10-fold[42]. One study of 600 patients reported a significantly higher reoperation rate of 91.7% vs 5.4% in patients that presented with a leak and those that did not respectively[43]. Other research articles reported a reoperation rate of 50 -60% in patients with anastomotic leakage[44].

50%-60% reoperation rate in AL patients

Poor Health-related Quality of Life (HRQoL)

Anastomotic Leakage is a severe complication associated with ICU admission, increased LOS, and reoperation. Such interventions can have a profound impact on a patient's quality of life. A case-matched study conducted by *Marinatou et al.* utilized several validated questionnaires to compare the short-term and long-term HRQoL in AL and non-AL patients[30]. 12 months after surgery, the Medical Outcomes Study Short Form, European Organization of Research and Treatment of Cancer Quality of Life Questionnaire, and Gastrointestinal Quality of Life Index Questionnaire revealed that anastomotic leak patients had a significant reduction in physical function, social function, emotional function, and general health perception[36]. AL patients also reported role limitations due to physical health and emotional problems. Another study by *Cristofaro et al.* revealed that leakage was an independent predictor of quality of life and highly impacted the patient-surgeon satisfaction level[31]. Additionally, patients with AL of lower rectal anastomoses showed a 33% reduction in their neorectal capacity, significant tenesmus, and incontinence. Such impaired anorectal function had severe implications on the patient's HRQoL as identified by *Nesbakken et al*[32].

Extended Length of Stay (LOS)

Length of stay has been used as an indicator of the quality of care. ERAS protocols have been developed to enhance postoperative recovery and reduce LOS without affecting patient outcome. Multiple research articles reported an increase in LOS due to AL. Retrospective analysis conducted on data collected from more than 600 hospitals throughout the US showed that the mean LOS of patients with AL was 2.4 times higher (23 vs 9.7) than patients without leakage[33]. Another retrospective study including 8597 patients that underwent elective resection showed that the mean LOS for AL patients was 2.7-2.9 times higher than non-leaking patients[34]. A more recent analysis of 337 patients who underwent low anterior resection (LAR) in a Brazilian center revealed that the average length of hospitalization for AL patients was 39.6 days and 7.5 days for non-leaking patients[35]. This is equivalent to a 5.3-fold increase in the average length of patient stay. Lastly, a study conducted by *Hammond et al.* reported that the total LOS of AL per 1,000 patients was 9,500 days longer in AL patients (LOS was measured at 26,300 days in AL patients vs 16,800 days in nAL)[26].

Increased hospitalization cost

AL is associated with a higher total cost due to prolonged hospitalization, the need for further diagnostic workup, and re-intervention. In fact, a study conducted by *Braga et al.* revealed that an anastomotic leak is regarded as one of the most expensive postoperative complications as shown in a single-center randomized trial[36]. The overall cost of AL per patient was reported to vary between € 37,609- 71,940. 60% of such added cost was attributed to the increased LOS, while 40% of the cost was tied to the resources used to diagnose and treat the anastomotic leak[37]. Other studies conducted by *Ashraf et al.* and *Hammond et al*. to evaluate the burden of AL reported that the annual direct healthcare cost associated with AL in the UK alone was equivalent to £1.1–3.5 million, while the mean cost of AL in the US was calculated at over $72,905 per patient[26, 38, 39]. This was 2.9-times higher than the cost observed in patients without AL. Finally, according to a study published by *Hammond et al.* the difference in cost of AL and nAL per 1,000 patients was equivalent to $28.6 million[26].

Increased readmission rates

Reduced hospital readmissions are used as a marker of the quality of care provided by hospitals. Readmissions are associated with an economic burden, poor patient satisfaction, poor patient outcomes, and have also recently been tied to hospital reimbursement[40]. AL is regarded as one of the most common causes for postoperative readmission, and therefore, early identification and treatment is paramount to reducing readmission in these patients. A retrospective analysis of 6,174 patients revealed that the 30-day readmission rate of patient with AL was equivalent to 29% whereas the readmission rate in patients that did not present with leakage was measured at 13%[26]. Furthermore, the overall readmission cost and length of stay upon readmission was 1.9 times and 1.8 times higher respectively for AL patients versus patients without a leak[41].

Increased ICU admission

AL is associated with life threatening intra-abdominal peritonitis, sepsis, and multiorgan failure requiring the need for ICU admission for organ support in the postoperative period[45]. In fact, one study reported that the unplanned ICU admission rate associated with AL was 30.3%[46]. Another study of 323 patients highlighted that admission to intensive care was required in 22.9% of patients that presented with leakage[47].

Poor oncological outcome and poor prognosis

In patients who underwent resection for colorectal cancer, an association between anastomotic leak and increased risk of cancer recurrence and poor oncologic prognosis has been noted in the literature. It is hypothesized that the elevated inflammatory markers (such as C-reactive protein (CRP)) associated with AL stimulate tumour proliferation and neoangiogenesis which leads to higher recurrence rates and reduces the overall survival/disease-free survival[48]. One study reported a 9.2 increase in local recurrence rate in patients that presented with leakage[49]. Similarly, *Merkel et al*. analyzed the data from 940 colorectal patients and concluded that the rate of locoregional recurrence in anastomotic leak patients was 9.5% higher than in non-leaking patients[50]. Another study by *Law et al.* highlighted that AL is regarded as an independent factor for an increased local tumor recurrence rate after curative resection in colorectal patients (hazard ratio: 2.55, 95% CI: 1.07-6.06, p = 0.034)[51]. A much larger meta-analysis including 78,434 colorectal cancer patients revealed similar results showing that AL was associated with increased local recurrence [RR= 1.90] after curative resection[52].

Clearly, developing innovative methods of detecting anastomotic leaks is critical in improving patient care and reducing surgical mortality. To address this important gap in surgical care, FluidAI (formally NERv Inc.) has developed a novel technology, Stream™ Platform, with real-time monitoring capabilities for AL. In brief, Stream™ Platform is a portable system designed for use by medical practitioners to continuously measure the pH and electrical conductivity of drainage fluid from patients during post-operative recovery. Using the predictive power of these parameters, the burden of anastomotic leaks (including mortality and healthcare system costs) can be significantly reduced. This technology, and its value in the surgical landscape, will continue to be explored in subsequent reports, as more comprehensive details are provided on other important considerations in colorectal surgery (including risk factors, prevention methods, diagnostic techniques, current approaches for treatment and effective management, and long-term outcomes).

Real-Time Monitoring for Anastomotic Leaks **Stream™ Platform**

by FluidAI

Interested in the technology?

For more information, please contact **info@fluidai.md**

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