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Wounds in Genome: How Early Life Colibactin Producing Escherichia coli May Seed Primary Colorectal Cancer Onset

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Abstract. The prevalence of early-onset colorectal cancer during the previous 20 years (EOCRC diagnosed before 50 years of age) has doubled in several countries, and its causes are still mostly unknown. There is mounting evidence that early life exposure to colibactin, a genotoxin generated by Escherichia coli strains containing the polyketide synthase (pks) island, can be mutagenic. The discovery and chemistry of colibactin and the experimental evidence that it leaves a distinctive mutational signature (SBS88/ID18) are summarized in this article. These markers were enriched in early onset illness (3.3 times more common in patients diagnosed before 40 than those older than 70) and imprinted early in tumor formation according to a seminal 2025 analysis of 981 colorectal cancer genomes from 11 nations. The emerging prevalence conundrum, translational techniques (ClbP inhibition, anti-adhesion, engineered neutralization, and probiotic safety), and the safety and effectiveness of therapies are then reviewed, along with clinical prevalence investigations that include data from Iraq. E. Coli that produces colibactin provides a unique, mechanistically defined link between a gut microbe and human cancer as well as the new "windows of opportunity" model of exposure. Lastly, we list the main information gaps, which include the early-stage prevalence conundrum, population coverage, timing and acquisition of exposure, causal proof in people, and the safety and effectiveness of therapies. Colibactin-producing E. coli provides a plausible method for prevention as well as a rare, mechanistically specific connection between a gut bacterium and human cancer.

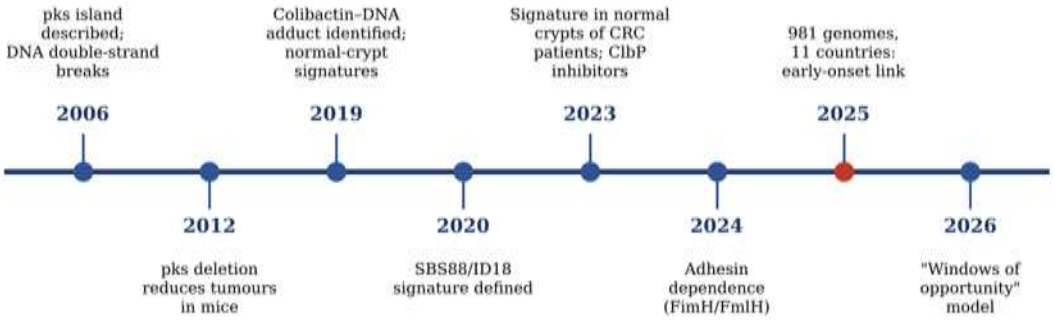
Keywords: Escherichia bacteria, colibactin, pks island, early-onset colorectal cancer, mutational markers, SBS88, and gut microbiome

1. Introduction

Geographically, the prevalence of colorectal cancer (CRC) varies, and the incidence of early CRC, which affects people under 50, has changed over time. Over the past 20 years, CRC has increased in many nations; the causes of this increase are uncertain [1]. This has drawn attention to exposures that may have an early impact, including gut microbiota products. In 2006, commensal and extraintestinal pathogenic E. coli belonging to phylogenetic group B2 began to possess a genomic island expressing large modular poylogenetic synthases and nonribosomal peptides. DNA double strand breaks are caused by contact with bacteria that express this cluster, which triggers the DNA damage checkpoint and results in cell cycle arrest [2]. In 2012, azoxymethane-treated IL10-deficient mice were monocolonized with E. coli NC101, providing the first proof of tumor promotion in vivo. Mucosa-associated pks + E. coli were detected in a significant proportion of individuals with inflammatory bowel illness and colorectal cancer [3]. Promoted invasive carcinoma removing the pks island decreased tumor multiplicity and invasion without changing inflammation.

Reviews of the role of pks+ E.coli in colon carcinogenesis are available [4]. Here we review the most recent advances centred on the 2025 genomic evidence linking colibactin exposure to early onest disease and we highlight the gaps that should drive the next generation of studies. The figure 1 places the key milestones on a timeline. Exposure to early onest disease, and we highlight the gaps that should drive the next generation oe studies the (figure 1) places the milestones on a timeline. This is a narrative rather than a systematic review, sources were identified through web searches of journal and database records up to October2026 and conference abstracts and preprints are flagged whrer they are cited.

(Figure 1). Key milestones in research on colibactin producing E. coli and colorectal cancer [1– 3, 5–9].



2. Colibactin from gene cluster to DNA lesion

The pks island encodes a nonribosomal peptide synthetase polyketide synthase assembly pathway that produces colibactin. Periplasmic peptidase C1Bp eliminates an N-myristoyl-D asparagine "prodrug" scaffold from a bigger precursor, precursor, precolibactin, during the last stage of biosynthesis.
Releasing the active genotoxin. The active species is thought to alkylate two adenine residues on opposite DNA strand through electrophilic cyclopropane groups producing interstrand cross links [10]. Diract chemical evidence came from DNA adductomics, a covalent colibactin DNA adduct was identified in human cells treated with colibactin producing E.coli and the same metabolite formed in mice colonized by these bacteria suggesting a potential biomarker of expousure [5]. The pathway is shown in figure2.

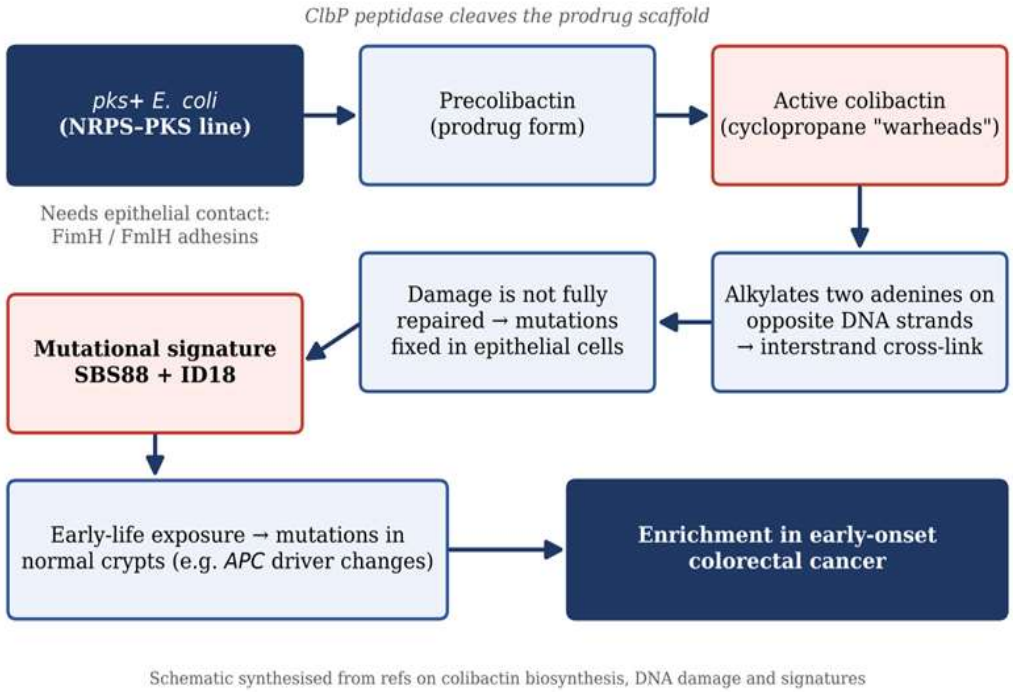


Figure 2. simplified schematic of colibactin production by pks + E.coli, DNA damage and the resulting mutational signature [5,6,8,10].

Colibactin is unstable and its genotoxic effects depend on cell contact and on inflammation [10].
Colibactin-driven colon cancer is dependent on bacterial adherence to epithelial cells, which is mediated by the type 1 pilus adhesin Fm1H, as demonstrated by Jans and colleagues in 2024. Additionally, they found that in the probiotic strain Nissle 1917, allelic flipping of FimH significantly affects genotoxic potential and can result in a genotoxic gain of function [8]. Together, these findings explain why carrying the pks island is necessary but not sufficient for harm.

3. A Mutational Fingerprint of Bacterial Exposure

The key step from association to mechanism was the identification of a colibactin specific mutation signature. Pleguezuelos-Manzano and colleagues exposed human intestinsl organoids to pks+ E.coli by repeated luminal injection over five months. Whole genome sequencing found a unique signal in a subset of 5,875 human cancer genomes that was not present in organoids exposed to isogenic pks mutant bacteria, predominantly CRC [6]. It has two components, a single base substitution signature (SBS88) and a small indel signature (ID18) marked by single deletions at homopolymer runs [6,7].

An independent approach mapped colibactin induced double strand breaks in infected human cells found enrichment of an AT rich hexameric motif and showed that this motif and the break locicoincided with mutational hotspots in colorectal cancer genomes [11].

The signature is not confined to tumours. Whole genome sequencing of hunderds of normal colonic crypts from 42 individual showed that some mutational processes occur only in some people, some crypts from 42 individuals showed that some mutational processes occur only in some people some crypts or certain periods of life [12 colibactin dependent signatures in normal crypts have been reported to accumulate mainaly before 10 years [10,12]. In a study of 30 CRC patients, the pks+ signature was present in 76.6% of cancer crypts and 70.6% of crypts adjacent to the tumour and 50% of distant normal crypts and in 23 of 30 tumours. The signatures were compatible with many clonal driver mutations, supporting a role in early tumourigenesis [7].

4. The 2025 turning point, colibactin and early onset disease

The decisive epidemiological step was made in 2025, Diaz – Gay and their group analysed 981 CRC genomes from 11 countries and found no major difference in microsatellite unstable cancer but clear variation in mutation burden and signatures among the 802microsatellite stable cases. SBS88 and ID18 carried higher mutation loads in countries with higher CRC incidence were enriched in Early onset malignancies were marked early in the development of cancer and were 3.3 times more common in individuals diagnosed before 40 than in those over 70.

They were also associated with early driver mutationsin APC. The authors concluded that early life mutagenic exposure to colibactin producing bacteria may contribute to the rising incidence of early onset CRC [1]. The inference is indirect since the signature records past mutagenesis rather than the presence of the bacteria themselves.

The inference is indirect, since the signature record past mutagenesis rather than the presence of the bacteria themselves.

Mechanistic work is beginning to explain why the signature is enriched in younger patients. A 2025 conference abstract reported that human CRC organoids co-cultured with pks+ E.coli for three months acquired SBS-pks signature and shifted towards proliferative intestinal stem cell states

The authors proposed that younger, replication and repair proficient cells overcome colibactin induced DNA damage response stress, whereas older cells exit through cell cycle arrest and apoptosis, producing the observed enrichment in young onset disease [13]. These data are preliminary and await full publication. In 2026 synthesis further suggested that when host barriers and microbial ecology momentarily allow interaction between pks + E. coli and the eithelium, colibactin mutagenesis takes place in distinct temporal windows. These periods may occur during the early stages of gut development or inflammatory diseases, which share the proliferation of facultative anaerobes, impaired epithelial defenses, and dynamic oxygen gradients.

The authors note that the signatures are detectable in about 12% of CRC [9].

Table 1 summarizes the principal studies that connect colibactin to DNA damage, mutational signatures and early onset disease

Study	Design	Key finding
Nougayrède et al., 2006 [2]	Infection of eukaryotic cells with *E. coli* carrying the *pks* island	Contact causes DNA double-strand breaks, checkpoint activation and cell-cycle arrest.
Arthur et al., 2012 [3]	*Il10*-deficient mice, azoxymethane model	*pks* deletion decreased tumour multiplicity and invasion without altering inflammation.
Wilson et al., 2019 [5]	DNA adductomics in human cells and mice	Colibactin alkylates DNA through an electrophilic cyclopropane; the adduct is a potential exposure biomarker.
Pleguezuelos-Manzano et al., 2020 [6]	Organoid exposure for five months; 5,876 cancer genomes	Distinct signature absent with *pks*-mutant bacteria; detected predominantly in CRC.
Dziubańska-Kusibab et al., 2020 [11]	Mapping of colibactin-induced double-strand breaks	AT-rich motif enriched in colorectal cancers; break loci matched mutational hotspots.
Chen et al., 2023 [7]	Crypts from 30 CRC patients	Signature in 76.7% of cancer crypts and 50% of distant normal crypts; compatible with driver mutations.
Díaz-Gay et al., 2025 [1]	981 CRC genomes, 11 countries	SBS88/ID18 enriched in early-onset CRC (3.3 times more common under 40 than over 70) and imprinted early.

5. Clinical and Regional Evidence

Prevalence studies broadly support an association but results differ from one to another. In Malaysia pks+E.coli was detected in 16.7% of CRC patients and 4.3% of healthy controls. And the isolated caused cytopathic effects in colon epithelial and carcinoma cell lines [14]. A Japanese Studies of 414 CRC patients usung droplet PCR found pks+E.coli more abundant in stage 0 – I tumors than in normal mucosa or in stage II - IV tumors, high abundance was associated with shallower tumors depth and absence of lymph node metastasis leading the authors to suggest a role in initiation rather than progression [15].

In Iraq, Hussein and his group test 88 clinical Enterobactriaceae isolates and found 11 (12.5%) have pks + , 7*E.coli*, (8 %), 2 *Klebsiella pneumoniae* and 2 *Enterobacter aerogenes* (2.25%). Selected pks + isolates produced reduced cell numbers, enlarged nuclei fragmentation in Hela a cells consistent with a genotoxic insult [16].

Because theses isolate came from clinical specimens rather than CRC cohorts, they show that colibactin capable bacteria circulate locally but cannot yet inform CRC risk in Iraq patients. Table 2 and figure 3 bring together the prevalence data from these studies. The denominators differ so the values should not be compared directly.

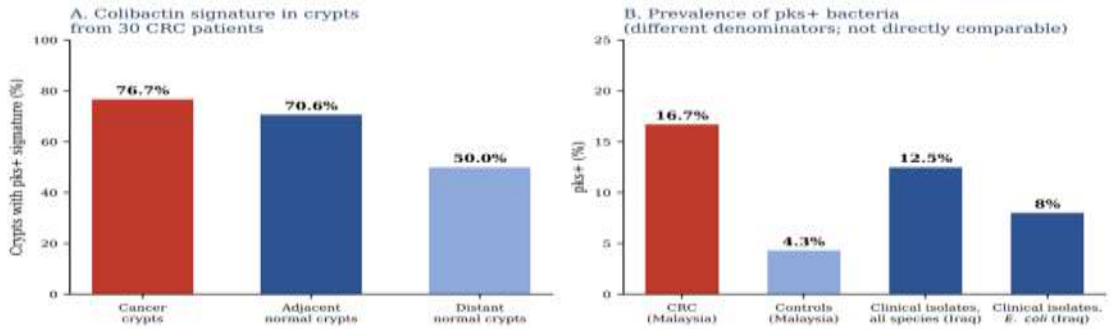


Figure (3). (A)proportion of crypts showing the pks+signature in 30 patients [7]. (B) prevalence of pks+ bacteria in Malaysian CRC patients and healthy controls [14] and among Iraqi clinical Enterobacteriaceae isolates [16].

Table 2: Reported prevalence and abundance of colibactin related markers.

Setting / study	Sample	Result
Malaysia [14]	48 CRC patients; 23 healthy controls (mucosal tissue)	*pks*+ *E. coli* in 16.7% of CRC patients vs 4.3% of controls.
Japan [15]	413 CRC patients (droplet digital PCR)	*pks*+ *E. coli* more abundant in stage 0–I than in stage II–IV tumours.
EPICC cohort [7]	30 CRC patients (crypt sequencing)	*pks*+ signature in 76.7% of cancer, 70.6% of adjacent and 50% of distant normal crypts.
Iraq [16]	88 clinical Enterobacteriaceae isolates	11 (12.5%) *pks*+: 7 *E. coli* (8%), 2 *K. pneumoniae* and 2 *E. aerogenes* (2.25% each).

6. Translational Strategies

6.1 Exposure biomarkers

The colibactin DNA adduct and the SBS88 /ID 18 signature are respectively a chemical and a genomic record of exposure [1,5]. Both are currently resrarch tools and neither has been validated for population screening.

6.2 Blocking Colibactin Production

Attractive drug target is a C1Bp. Boron based compound that bind the C1Bp actice site suppressed the genotoxic activity of colibactin producing E.coli in cell and in mice and in CRC mouse model colonized by such bacteria. Tumors number fell 3.5- fold in animals receiving the compound in drinking water [17].

A later series of boronic acid inhibitors designed to mimic precolibactin inhibited C1Bp covalently and reproduced the phenotype of a C1Bp deletion mutation, blocked colibactin 's genotoxic effects in human cells, and did not impair growth of representative gut bacteria at concentarations well above. A later series of boronic acid inhibitors to mimic precolibactin inhibited C1Bp covalently reproduced the phenotype of phenotype of a clbP deletion mutation blocked colibactin's genotoxic effects in human cells, and did not impair growth of representative gut bacteria at concentration well above those needed for c1Bp inhibition, those authers also reported that an earlier pair of computationally identified inhibitors had minimal effect on C1bp in their handss [10]. A discrepancy that underlines the need for independent replication.

6.3 Anti adhesion and engineered neutralization

Because epithelial binding is required for colibactin driven tumour development; anti adhesive therapies targeting FimH and Fm1H are a rational alternative [8]. In 2024 preprint described displaying C1bs the enzyme that protects pks+ bactria from their own toxin. On the surface of engineered bacteria. This outperformed secreted C1bs and a small molecule inhibitor in cell lines and colon organoids and suppressed tumourigenesis in mouse models and this work has not yet been reviewed [18].

6.4 Probiotic Safety

The widely used probiotic E.coli Nissle in 1917 carries the pks island. Experimental work indicates that its genotoxicity cannot be dissociated from its probiotic activity [19] and a 2024 review concluded that conflicting findings demand further research to clarify its safety [20]. The finding that FimH variation can switch on genotoxicity in this strain adds urgency [8].

7. Key Knowledge Gaps and Priorities for Future Research

Table 3 summarises the main gaps that, in our assessment, should be addressed by new studies, with the evidence that motivates each and the study designs that could close it.

Table 3: Principal knowledge gaps and priority studies on colibactin-producing E. coli and colorectal cancer.

#	Knowledge gap	Why it matters (evidence)	Priority studies
1	Timing and duration of exposure	The duration and timing of the colibactin insult are still poorly understood but are probably significant predictors of the risk of colorectal cancer [10]. Direct testing of the "windows of opportunity" model is still necessary. The duration and timing of the colibactin insult are still poorly understood but are probably significant predictors of the risk of colorectal cancer [10]. Direct testing of the "windows of opportunity" model is still necessary. [9].	Longitudinal child cohorts with serial stool quantification of *pks* genes, linked to later mutational profiling of normal colonic crypts.
2	Acquisition and persistence of *pks*+ *E. coli* in early life	Where, when and how children acquire colibactin-producing strains, and which host or dietary factors let them persist, have not been mapped (a gap identified by this review rather than quantified in the cited studies).	Birth cohorts with strain tracking; mother–infant transmission studies; links to mucus-barrier maturation and diet.
3	Causal proof in humans	The signature records past mutagenesis; it does not show that the bacteria are present at diagnosis. Evidence in patients is therefore associative, supported by organoid and mouse experiments [3,6].	Paired metagenomics and whole-genome sequencing of normal mucosa; organoid transformation screens; adduct-based exposure measurement [5].
4	Population coverage, including Iraq and the wider region	Signature load varies between countries [1]. To our knowledge, Iraqi data come mainly from screening of clinical isolates, not CRC cohorts [16].	Multicentre Iraqi case–control studies: tissue/stool *pks* PCR plus signature analysis in early-onset cases.
5	Prevalence–stage paradox and inconsistent prevalence	*pks*+ *E. coli* was more abundant in stage 0–I than in stage II–IV tumours [15], and case–control prevalence differs between studies (for example 16.7% vs 4.3% in Malaysia) [14].	Standardised quantitative methods (e.g. droplet digital PCR), stage-stratified and spatially mapped sampling, prospective designs.
6	Host and ecological modifiers	Colibactin effects depend on inflammation and epithelial adhesion [3,8]; production in a complex community differs markedly from monoculture [10].	Conventional-microbiota animal models rather than monocolonisation; test diet, inflammation and co-resident genotoxic taxa.
7	Safety and efficacy of interventions	ClbP inhibitors have been tested only preclinically [10,17]; engineered neutralisation is at preprint stage [18]; safety of the *pks*+ probiotic Nissle 1917 is disputed [19,20].	Pharmacokinetic, resistance and microbiome-impact studies; first-in-human trials; routine *pks* screening of probiotic strains.
8	Clinical utility for screening and prevention	Whether exposure markers should alter screening age or surveillance for at-risk people is untested; the 2025 genomic study itself calls for further research on targeted prevention [1].	Risk-prediction modelling, cost-effectiveness analysis and prospective screening trials.

8. Conclusions and Outlook

Colibactin producing E.coli now stands as one of the best characterized links between a gut microbe and human cancer, with a defined molecule a defined DNA lesion and a defined mutational signature. Since 2025, a plausible link to the rise of early onset CRC [1]. Evidence remains largely inferential for humans yet. The next advances will require longitudinal early life cohorts standardized detection of pks+ bacteria and of the name in the same individuals. Inclusion of under represented regions such as Iraq and rigorous testing of interventions from C1bp inhibitors to safer probiotics. If exposure can be measured can and modified the colibactin offers a rare opportunity for primary prevention of a cancer that increasingly affects the young.

References

1. Díaz-Gay M, dos Santos W, Moody S, Kazachkova M, Abbasi A, Steele CD, et al. Geographic and age variations in mutational processes in colorectal cancer. Nature. 2025;643(8070):230–40. doi:10.1038/s41586-025-09025-8
2. Nougayrède JP, Homburg S, Taieb F, Boury M, Brzuszkiewicz E, Gottschalk G, et al. Escherichia coli induces DNA double-strand breaks in eukaryotic cells. Science. 2006;313(5788):848–51. doi:10.1126/science.1127059
3. Arthur JC, Perez-Chanona E, Mühlbauer M, Tomkovich S, Uronis JM, Fan TJ, et al. Intestinal inflammation targets cancer-inducing activity of the microbiota. Science. 2012;338(6103):120–3. doi:10.1126/science.1224820
4. Sadeghi M, Mestivier D, Sobhani I. Contribution of pks+ Escherichia coli (E. coli) to colon carcinogenesis. Microorganisms. 2024;12(6):1111. doi:10.3390/microorganisms12061111
5. Wilson MR, Jiang Y, Villalta PW, Stornetta A, Boudreau PD, Carrá A, et al. The human gut bacterial genotoxin colibactin alkylates DNA. Science. 2019;363(6428):eaar7785. doi:10.1126/science.aar7785
6. Pleguezuelos-Manzano C, Puschhof J, Rosendahl Huber A, van Hoeck A, et al. Mutational signature in colorectal cancer caused by genotoxic pks+ E. coli. Nature. 2020;580(7802):269–73. doi:10.1038/s41586-020-2080-8
7. Chen B, Ramazzotti D, Heide T, Spiteri I, Fernandez-Mateos J, James C, et al. Contribution of pks+ E. coli mutations to colorectal carcinogenesis. Nat Commun. 2023;14(1). doi:10.1038/s41467-023-43329-5
8. Jans M, Kolata M, Blancke G, D'Hondt A, Gräf C, Ciers M, et al. Colibactin-driven colon cancer requires adhesin-mediated epithelial binding. Nature. 2024;635(8038).
9. Windows of opportunity for genotoxic E. coli in colorectal cancer initiation. J Appl Microbiol. 2026. doi:10.1093/jambio/lxag192 [author list to be added]
10. Volpe MR, Velilla JA, Daniel-Ivad M, et al. A small molecule inhibitor prevents gut bacterial genotoxin production. Nat Chem Biol. 2023;19:159–67. doi:10.1038/s41589-022-01147-8
11. Dziubańska-Kusibab PJ, Berger H, Battistini F, Bouwman BAM, Iftekhar A, Katainen R, et al. Colibactin DNA-damage signature indicates mutational impact in colorectal cancer. Nat Med. 2020;26(7):1063–9. doi:10.1038/s41591-020-0908-2
12. Lee-Six H, Olafsson S, Ellis P, Osborne RJ, Sanders MA, Moore L, et al. The landscape of somatic mutation in normal colorectal epithelial cells. Nature. 2019;574(7779):532–7. doi:10.1038/s41586-019-1672-7
13. Abstract 2856: Pks+ E. coli trigger intestinal stem cell plasticity and early onset colorectal cancer [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2025; Part 1; 2025 Apr 25–30; Chicago, IL. Philadelphia (PA): AACR; 2025. doi:10.1158/1538-7445.AM2025-2856 [author list to be added]
14. Iyadorai T, Mariappan V, Vellasamy KM, Wanyiri JW, Roslani AC, et al. Prevalence and association of pks+ Escherichia coli with colorectal cancer in patients at the University Malaya Medical Centre, Malaysia. PLoS One. 2020;15(1).
15. Pks-positive Escherichia coli in tumor tissue and surrounding normal mucosal tissue of colorectal cancer patients. Cancer Sci. 2024;115(4):1184–95. [author list to be added]
16. Hussein MT, Al-Qaysi SAS, Rathi MH, Hussein QI, Moussa TAA. Prevalence and characterization of some colibactin genes in clinical Enterobacteriaceae isolates from Iraqi patients. Baghdad Sci J. 2020;17(3 Suppl):1113.
17. Cougnoux A, Delmas J, Gibold L, Faïs T, Romagnoli C, Robin F, et al. Small-molecule inhibitors prevent the genotoxic and protumoural effects induced by colibactin-producing bacteria. Gut. 2016;65(2):278–85.
18. Li J, Yang S, Wang Z, et al. In situ neutralization of the genotoxicity of pathogenic gut bacteria with the polyketide synthase island. Research Square [Preprint]. 2024. doi:10.21203/rs.3.rs-5286472/v1
19. Olier M, et al. Genotoxicity of Escherichia coli Nissle 1917 strain cannot be dissociated from its probiotic activity. Gut Microbes. 2012;3:501–9.
20. Falzone L, Lavoro A, Candido S, Salmeri M, Zanghì A, Libra M. Benefits and concerns of probiotics: an overview of the potential genotoxicity of the colibactin-producing Escherichia coli Nissle 1917 strain. Gut Microbes. 2024;16(1):2397874. doi:10.1080/19490976.2024.2397874