Title	Author	Year	Method	Patients	Results
Long-term Expansion of Epithelial Organoids From Human Colon, Adenoma, Adenocarcinoma and Barrett's Epithelium [37]	Sato et al	2011	Proof of concept	20 colon cancer, 5 normal colon, 5 Barrett's esophagus	Able to culture benign colon tissue, colonic adenocarcinoma and metaplastic Barrett's esophageal tissue for 6 months with phenotypic and genetic stability
Directed differentiation of human pluripotent stem cells into intestinal tissue in vitro [51]	Spence et al	2011	Proof of concept	2 human embryonic stem cell line and 4 pluripotent stem cell lines.	Generated ability to create embryonic stem cell and induced pluripotent stem cell derived hind gut
Functional Repair of CFTR by CRISPR/Cas9 in Intestinal Stem Cell Organoids of Cystic Fibrosis Patients [81]	Schwank	2013	Genetic Manipulation	2 pediatric Cystic Fibrosis patients	Patient derived organoids showed phenotypic changes associated with CF including non-responsiveness to forksolin treatment. Following CRISPR/Cas9 insertion of wild-type CFTR gene, organoids showed forksolin-induced swelling when treated and could be modulated through use of CFTR inhibitor.
Rapidly Derived Colorectal Cancer Cultures Recapitulate Parental Cancer Characteristics and Enable Personalized Therapeutic Assays [58]	Ashley	2014	Characterization	45 colorectal cancer patients	Patient derived organoids were cultured and 6 individual lines were compared using immunostaining to show similarity in goblet cell percentage between patient tissue and organoid. These lines were subsequently used to perform drug testing with 5-flurouracil, staurosporine and camptothecin.
Adult Stem Cells in the Small Intestine Are Intrinsically Programmed With Their Location-Specific Function [55]	Middendorp	2014	Characterization	Biopsies	Organoids were derived from duodenum, jejunum and ileum and shown to have location specific gene expression
Many inflammatory bowel disease risk loci include regions that regulate gene expression in immune cells and the intestinal epithelium [96]	Mokry	2014	Characterization	4 patients total; 1 patient with UC who had samples collected from cecum, descending colon and sigmoid; 2 patients with normal colon and 1 patient with Crohn's disease.	ChIP-seq was performed on the samples. Findings support involvement of DNA regulatory elements in the immune and epithelial cells of IBD
Sequential Cancer Mutations in Cultured Human Intestinal Stem Cells [45]	Drost	2015	Genetic Manipulation	1 normal colon specimen obtained during resection for sigmoid colon cancer	Utilizing CRISPR/Cas9, the most common mutations in CRC were introduced into normal colon organoids, APC knockout, P53 knockout, SMAD4 knockout and a G12D mutation in KRAS leading to constitutive activation. These organoids developed aneuploidy over prolonged culture and became highly metastatic.
Modeling colorectal cancer using CRISPR-Cas9–mediated engineering of human intestinal organoids [47]	Matano	2015	Genetic Manipulation	3 normal colon specimens, 4 adenoma specimens derived from 3 patients, 10 CRC specimens derived from 7 patients	Utilizing CRISPR/Cas9, the most common mutations in CRC were introduced into normal colon organoids, APC knockout, P53 knockout, SMAD4 knockout and a **G12V** mutation in KRAS leading to partial constitutive activation. Unlike the prior experiment, these cells lacked metastatic potential without induced aneuploidy.
Intestinal organoids: A model of intestinal fibrosis for evaluating anti-fibrotic drugs [54]	Rodansky	2015	Pharmacologic Treatment	1 line of human embryonic stem cells differentiated to human intestinal organoids.	Human intestinal organoids were characterized with immunofluorescence staining to contain myofibroblast. The cells were treated with TGFβ leading to an increase in fibrogenic activation with an increase in the fibroblast population. Spironolactone was added to culture and shown to reverse TGFβ mediated induction of fibrosis.
Prospective derivation of a Living Organoid Biobank of colorectal cancer patients [59]	van de Wetering	2015	Proof of concept/Pharmacologic Treatment	22 tumor organoids from 20 CRC patients and 19 normal adjacent tissue organoids from 20 CRC patients	Organoid cultures were successfully derived from clinical specimens about 90% of the time. These organoids underwent genetic and transcriptomic characterization. A drug screen was performed testing 83 different compounds including: 25 drugs in clinical use, 10 chemotherapeutic agents, 29 drugs undergoing clinical trial and 29 experimental compounds. They subsequently attempted to detect genetic signatures leading to pharmacologic resistance.
Development of an enhanced human gastrointestinal epithelial culture system to facilitate patient-based assays [40]	VanDussen	2015	Proof of concept	65 patient biopsies	Using a 2D-monoloayer transwell system, VanDussen and colleagues showed the ability to perform adherence assays with bacteria to assess host-bacterial interactions.
Human Colorectal Cancer Organoids: A Tractable Platform for Modeling Patient Tumors and Testing Chemotherapeutic Efficacy [62]	Costacurta	2016	Pharmacologic Treatment	9 CRC and 9 normal adjacent organoids	Organoids showed similar histology to primary tissue from which they were derived. 5-FU was used to treat both the organoids showing varying sensitivities between patients and between cancer and normal organoids.
A Colorectal Tumor Organoid Library Demonstrates Progressive Loss of Niche Factor Requirements during Tumorigenesis [60]	Fujii	2016	Proof of concept	55 organoids derived from 52 CRCs in 43 patients as well as 41 normal colonic organoids	Organoids were derived from colon cancers, rectal cancers, metastatic colorectal cancer as well as histological subtypes including poorly differentiated adenocarcinoma, mucinous adenocarcinoma and neuroendocrine tumors. In comparison to parental tissues, organoids showed similar histology and gene expression.
Large variety in a panel of human colon cancer organoids in response to EZH2 inhibition [70]	Koppens	2016	Pharmacologic Treatment	20 organoid lines derived from 20 CRCs	20 organoid lines were treated with the EZH2 inhibitor GSK126. There results showed varying efficacies of GSK126 based on the given patient tumor.

Colonic Organoids Derived from Human Pluripotent Stem Cells for Modeling Colorectal Cancer and Drug Testing [63]	Crespo	2017	Pharmacologic Treatment	2 IPSC and organoid lines derived from 2 FAP patients	2 iHIO lines derived from skin fibroblast and 2 organoid lines from colonic adenomas were generated from 2 FAP patients. They also tested normal colonic epithelia and showed that Geneticin, an aminoglycoside antibiotic is capable of decreasing epithelial proliferation and WNT activity in FAP organoids but not normal tissue.
Personalized Proteome Profiles of Healthy and Tumor Human Colon Organoids Reveal Both Individual Diversity and Basic Features of Colorectal Cancer [76]	Cristobal	2017	Proof of Concept	7 CRC organoids and 7 normal organoids derived from 7 patients with CRC	Proteomic and transcriptomic profiling was performed on the 14 organoid lines and the primary tissue showing concordant results. They highlighted changes in the Wnt/Beta-catenin pathway.
Genetic dissection of colorectal cancer progression by orthotopic transplantation of engineered cancer organoids [50]	Fumagali	2017	Genetic Manipulation	2 normal human colon organoids, one from a patient with CRC and 1 from a healthy donor	CRISPR/Cas9 knockout was performed of key elements in the adenoma-carcinoma sequence including APC, P53 and SMAD4 as well as activating mutations of KRAS. Organoids were implanted orthotopically in the cecum of mice and shown to have metastatic potential to lung and liver. They showed P53 acts a a gatekeeper to the emergence of CIN and progression to metastasis.
Engineered human pluripotent-stem-cell-derived intestinal tissues with a functional enteric nervous system [53]	Workman	2017	Proof of Concept	2 embryonic stem cell lines and 3 IPSC lines	Using directed differentiation, Workman and colleagues developed a human IPSC derived neural crest cell line and IHIOs which when combined self-organized into induced human intestinal organoids with a functional ENS. Using PHOX2B mutations, they were able to recapitulate the phenotypic changes of Hirschsprung's disease in vitro
Lesion- specific gene expression in the epithelial cells of Crohn's dis ease by comparing small intestinal organoids from active and inactive lesion in the same patient. [97]	Hibiya	2018	Characterization	3 inflamed ileal organoids and 3 normal organoids from 3 patients with Crohn's Disease	Microarray gene expression profiling was performed showing 7 significantly upregulated genes and 3 downregulated genes between the inflamed and uninflamed organoids
Low dose Naltrexone for induction of remission in inflammatory bowel disease patients [104]	Mitchell	2018	Pharmacologic Treatment	2 organoids derived from non-inflamed intestinal biopsies of IBD patients	Organoids were treated with LPS and showed upregulated GRP78 expression indicative of endoplasmic reticulum stress. They were then treated with naloxone which showed reduction of levels consistent with human trials.
PRDM1 silences stem cell-related genes and inhibits proliferation of human colon tumor organoids	Liu	2018	Genetic Manipulation	2 organoids derived from CRC resection specimens	In this study Liu and colleagues assessed organoid proliferation and formation following upregulation through lentiviral transduction. In this study, they showed that PRDM1 overexpression results in down-regulation of the intestinal stem cell compartment and proliferation of tumor organoids
Organoid modeling of the tumor immune microenvironment [73]	Neal	2019	Characterization	100 surgical resections of varying tumor types, 20 of which were CRC	Neal et al showed that these organoids recapitulated the histology of their primary tumor. There culturing methodology preserved associated stroma and integrated immune elements including tumor-infiltrating lymphocytes, macrophages, T cells, B-cells and natural killer cells. They showed there cultures recapitulated the T cell repertoire of original tumors
Intra-tumour Diversification in Colorectal Cancer at the Single-Cell Level [77]	Roerink	2018	Characterization	3 CRC patients from which 4-6 organoid lines were derived per tumor as well as matched normal colon from patients	Each organoid under went genomic, transcriptomic and epigenomic sequencing which showed significant intra-tumoral heterogeneity in both genome, transcriptome and epigenetics. These organoids were then exposed to chemotherapeutic agents in vitro with many clones showing significant resistance to commonly used agents.
Single Cell Analysis of Crohn's Disease Patient-Derived Small Intestinal Organoids Reveals Disease Activity-Dependent Modification of Stem Cell Properties [89]	Suzuki	2018	Characterization	1 normal colon organoid, 1 active Crohn's disease organoid,1 Crohn's disease remission organoid	Through single-cell analysis, Suzuki and colleagues showed that active CD has a unique intestinal stem cell transcriptome consisting of SMOC2-LGR5 expression
Patient-derived organoids model treatment response of metastatic gastrointestinal cancers [61]	Vlachogiannis	2018	Pharmacologic Treatment	Numerous metastatic gastrointestinal cancer biopsies, 15 from metastatic CRC	Vlachoginnis and colleagues showed that the organoids shared morphologic similarities to original patient biopsies. Genomic sequencing was performed showing significant overlap with parental tissue. Using these organoids, a drug-screening assay was performed using 55 drugs in phase 1 to 3 clinical trials. They showed that there was 88% positive predictive valuable and 100% negative predictive value in forecasting response to targeted agents or chemotherapy in patients.
Plocabulin Displays Strong cytotoxic activity in a personalized colon cancer Patient-Derived 3D organoid Assay [68]	Costales-Carrera	2019	Pharmacologic Treatment	Organoids were derived from 3 patients with CRC	Costales-Carrera showed that plocabulin has potent cytotoxic activity in human tumor organoids when compared to SN38, the active derivative of irinotecan.
Transcriptional profiling of intestinal epithelial organoids derived from paediatric Crohn's disease patients [86]	Dotti	2017	Characterization	organoids from pediatric and adult Crohn's Disease patients	Dotti and colleagues showed that CD harbors lasting alterations in the epithelial compartment

A rectal cancer organoid platform to study individual response to chemoradiation [67]	Ganesh	2019	Pharmacologic Treatment	65 rectal cancer organoids from 41 patients and 51 normal rectal cancer organoids	Ganesh and colleagues treated 21 rectal cancer organoids with 5-FU and FOLFOX yielding varying dose responses. These findings correlated to recorded clinical response to therapy. They then radiated 19 rectal cancer tumoroids. They showed that tumoroids that delayed resistance to radiation were derived from patients following radiation and surgery or had minimal response to radiation. They also showed successful endoluminal implantation of organoids that developed progression to invasive disease and metastasis to lungs and liver
Lactobacillus rhamnosus GG prevents epithelial barrier dysfunction induced by interferon-gamma and fecal supernatants from irritable bowel syndrome patients in human intestinal enteroids and colonoids [108]	Han	2019	Characterization	Unknown number of healthy human colon organoids	Han and colleagues used microinjection techniques to inject fluorescent dye into the lumen of organoids to ass epithelial barrier function. They subsequently injected INF-gamma into the lumen and showed a significant decrease in barrier integrity. They subsequently showed that the presence of lactobacillus rhamnosus, a common probiotic preserves epithelial barrier function when treated with IFN-gamma. They subsequently injected fecal supernatants from healthy controls and IBS patients into the organoids and showed that the microbiota of IBS patients significantly decreases epithelial barrier function and is rescued by lactobacillus rhamnosus.
Establishment of an in vitro system to evaluate the therapeutic effect of the investigational drug on ulcerative colitis using human colonic organoids [102]	Nishimura	2019	Pharmacologic Treatment	3 colonic organoids from histologically normal tissue of patients undergoing colonoscopy for IBD	Nishimura and colleagues exposed normal human colonoids to inflammatory stimuli consisting of flagellin, IL-1B and TNF-alpha. They showed that after 12 weeks of culturing the transcriptome showed similar upregulation to that of inflamed ulcerative colitis tissue. The organoids were subsequently treated with KAG-308, a selective agonist against prostaglandin E2 receptor 4 (EP4). This treatment lead to a reduction in the inflammatory signature and promoted cellular regeneration.
Advancing IL-22-based therapies for inflammatory bowel diseases with human intestinal organoids [105]	Patnaude	2019	Pharmacologic Treatment	3 normal and 3 UC organoids	Patnaude cultured organoids and treated them with IL-22. IL-22 treatment led to increased stem cell survival, cell proliferation and production of anti-microbial peptides. It also increased membrane mucus.
Leveraging Human Intestinal Organoids to Advance Il-22-Based Therapies for Ulcerative Colitis [106]	Patnaude	2019	Pharmacologic Treatment	3 normal and 3 UC organoids	Patnaude cultured organoids and treated them with IL-22. IL-22 treatment led to increased stem cell survival, cell proliferation and production of anti-microbial peptides. It also increased membrane mucus.
The interleukin 22 transcriptional programme is activated in human colonic inflammation and associated to anti-TNFalpha primary non-response in Crohn's [107]	Pavlidis	2019	Pharmacologic Treatment	4 normal organoids	Pavlidis and colleagues treated normal colon organoids with IL-22 and other cytokines related to IBD pathogenesis: TNF-alpha, IL-18A and IFN-gamma. They showed that IL-22 signatures were the second highest group of transcriptional signatures upregulated in human colon-organoids treated with the above cytokines. They also showed that enrichment of IL-22 signatures was associated with primary non-response to anti-TNF therapy.
3D bioengineered tissue model of the large intestine to study inflammatory bowel disease [91]	Roh	2019	Characterization	Normal human colon organoids	Roh and colleagues developed a novel 3D system that allowed co-culture of human organoids with associated macrophages in an apical-basal orientation. They showed the ability for this model to allow leukocyte migration and pro-inflammatory cytokine secretion. Their model recapitulated epithelial injury when treated with TNF-alpha.
3D model for CAR-mediated cytotoxicity using patient-derived colorectal cancer organoids [80]	Schnalzger	2019	Pharmacologic Treatment	Human CRC organoids and normal human organoids	Schnalzger and colleagues developed a novel platform for testing CAR-mediated therapies against CRC. Using this technique they demonstrated that CAR-NK-92 cytotoxicity could be directed against tumor organoids. They also showed that near-quantitative eradication of tumor cells could be achieved in the absence of death to tumor-antigen negative cells
TP53 mutation in human colonic organoids acquires resistance to in vitro long-term inflammation [74]	Tsuchiya	2019	Characterization	3 normal human colon organoids	Tsuchiya and colleagues mutated TP53 in normal human organoids and characterized them compared to non-mutated organoids over 60 week period with and without inflammatory stimuli. They showed that TP53 mutations lead to increased cell proliferation and stemness even in the setting of long-term inflammation.

Integrated chromatin and transcriptomic profiling of patient-derived colon cancer organoids identifies personalized drug targets to overcome oxaliplatin resistance [78]	Tung	2019	Pharmacologic Treatment	4 metastatic CRC human organoids; 3 liver metastases and 1 omental	Tung and colleagues treated CRC organoids with three standard chemotherapy agents, 5-FU, oxaliplatin and SN-38 (the active metabolite of irinotectan). They subsequently performed chromatin and transcriptomic profiling of the organoids and identified chromatin regions and gene expressions associated with response to chemotherapy in resistant cells. They discovered two genes FGFR! and OXTR which when inhibited lead to improved treatment response to oxaliplatin in one organoid line.
MEK inhibitors activate Wnt signalling and induce stem cell plasticity in colorectal cancer [65]	Zhan	2019	Pharmacologic Treatment	5 CRC human organoids	Zhan and colleagues showed that MEK1/2 inhibitors activate Wnt signaling in CRC and increase LGR5 and intestinal stemness signatures. They also show that MEK1/2 inhibition leads to transcriptomic signatures consistent with cancer relapse. Subsequently they show that combination therapy with MEK1/2 inhibitors and Wnt inhibitors reduce tumor growth.
Patient-Derived Colorectal Cancer Organoids Upregulate Revival Stem Cell Marker Genes following Chemotherapeutic Treatment [72]	Engel	2020	Pharmacologic Treatment	10 CRC human organoids	Engel and colleagues treated human CRC organoids with varying amounts of 5-FU and showed that revival stem cell markers correlate with chemoresistace.
Somatic inflammatory gene mutations in human ulcerative colitis epithelium [100]	Nanki	2020	Characterization	170 normal organoid lines from 55 patients with Ulcerative Colitis and 16 healthy control patients. They also established 18 colitis-associated-cancer lines	Nanki and colleagues showed that IL-17 signaling is a key pathway that drives somatic evolution in colitis. IL-17A drove a pro-apoptotic response in normal colonic organoids and loss of function mutations in positive regulators of IL-17 signaling were enriched in UC epithelium.
Patient-Derived Organoids Predict Chemoradiation Responses of Locally Advanced Rectal Cancer [66]	Yao	2020	Pharmacologic Treatment	96 rectal cancer organoids from treatment naïve patients with locally advanced rectal cancer	Yao and colleagues showed that the organoids recapitulated the genomic profile of their parental tumors. They treated the organoids with combinatorial therapy with irradiation, 5-FU and irinotecan. They showed that the results obtained in combinatorial treatment of the organoids were consistent with the response seen in the patient from which they were derived.