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EDITORIAL

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ORIGINAL ARTICLE**Retrospective Study**

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Observational Study

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Gene, genetics and genetic medicines in gastroenterology: Current status and its future

Ashok Kumar, Yajnadatta Sarangi, Payal Kaw

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Abstract

The etiopathogenesis of gastrointestinal diseases is varied in nature. Various etiogenic factors described are infective, inflammatory, viral, bacterial, parasitic, dietary and lifestyle change. Rare causative agents are immunological, and others associated as idiopathic, are undiagnosed by all possible means. Some of the rare diseases are congenital in nature, passing from the parent to the child. Many of the undiagnosed diseases are now being diagnosed as genetic and the genes have been implicated as a causative agent. There is a search for newer treatments for such diseases, which is called genomic medicine. Genomic medicine is an emerging medical discipline that involves the use of genomic information about an individual. This is used both for diagnostic as well as therapeutic decisions to improve the current health domain and pave the way for policymakers for its clinical use. In the developing era of precision medicine, genomics, epigenomics, environmental exposure, and other data would be used to more accurately guide individual diagnosis and treatment. Genomic medicine is already making an impact in the fields of oncology, pharmacology, rare, infectious and many undiagnosed diseases. It is beginning to fuel new approaches in certain medical specialties. Oncology is at the leading edge of incorporating genomics, as diagnostics for genetic and genomic markers are increasingly included in cancer screening, and to guide tailored treatment strategies. Genetics and genetic medicine have been reported to play a role in gastroenterology in several ways, including genetic testing (hereditary pancreatitis and hereditary gastrointestinal cancer syndromes). Genetic testing can also help subtype diseases, such as classifying pancreatitis as idiopathic or hereditary. Gene therapy is a promising approach for treating gastrointestinal diseases that are not effectively treated by conventional pharmaceuticals and surgeries. Gene therapy strategies include gene addition, gene editing, messenger RNA therapy, and gene silencing. Understanding genetic determinants, advances in genetics, have led to a better understanding of the genetic factors that contribute to human disease. Family-member risk stratification and

genetic diagnosis can help identify family members who are at risk, which can lead to preventive treatments, lifestyle recommendations, and routine follow ups. Selecting target genes helps identify the gene targets associated with each gastrointestinal disease. Common gastrointestinal diseases associated with genetic abnormalities include-inflammatory bowel disease, gastroesophageal reflux disease, non-alcoholic fatty liver disease, and irritable bowel syndrome. With advancing tools and technology, research in the search of newer and individualized treatment, genes and genetic medicines are expected to play a significant role in human health and gastroenterology.

Key Words: Genes; Genetics; Clinical genetic testing; Germline mutation; Somatic mutation; Targeted therapy; Pharmacogenetics; Genetic medicine; Gastroenterology; Gastrointestinal diseases

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Core Tip: With advancements in genetics, there are emerging trends in better understanding of diseases and diagnosis of many undiagnosed gastrointestinal disorders. This aids in the search for newer medicines, which are pivotal to the progress of precision medicine. Genetic analysis enables accurate diagnosis, risk stratification, and individualized treatment by identifying germline mutations, somatic alterations, and epigenetic changes. It also plays a crucial role in predicting treatment response and guiding targeted therapies. Gene therapy, gene editing, and clustered regularly interspaced short palindromic repeats-associated protein systems represent promising tools for managing many complex gastrointestinal disorders and also are an aid to the conventional treatment and has a very promising future.

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INTRODUCTION

Advances in molecular biology and genetics have revolutionized our understanding of health and disease across medical disciplines, and gastroenterology is no exception. Many gastrointestinal (GI) disorders are directly or indirectly associated with genetic influences; some are known, and many are unknown. From inherited syndromes like Lynch syndrome and familial adenomatous polyposis (FAP) to complex disorders such as inflammatory bowel disease (IBD) and colorectal cancer (CRC), genetics plays a pivotal role in the initiation, progression, and response to treatment[1-4]. Now we are in the era of precision medicine, which tailors' disease prevention, diagnosis, and treatment to the individual characteristics of each patient. Unlike the traditional "one-size-fits-all" model, precision medicine aims to deliver the right treatment to the right person at the right time, thereby improving outcomes and minimizing unnecessary interventions[5]. The precision medicine model involves large databases of diseases of various etiological factors including genetics, multi-omics, environmental and social factors which are critically analyzed with the use of artificial intelligence (AI) and forms the basis of preventive, diagnostic and therapeutic medicine. Genetic medicine includes genetic testing, molecular diagnostics, pharmacogenomics and gene therapy, which are currently used in many diseases, including gastroenterological disorders. However, the progress also possesses several challenges, including ethical concerns, high costs, and limited equitable access for the general population. This article explores the current applications of genes, genetics, and genetic medicines in gastroenterology, and also how the future innovations are likely to shape these.

Search methods

A comprehensive literature search was conducted using PubMed/MEDLINE databases using the search terms genes, genetics, precision medicine, omics, genetic testing, pharmacogenomics, targeted therapy, gene therapy, gene editing, and bullion operators like "and, or, and not". We included only those publications relevant to disorders of gastro GI tract (GIT). Secondary sources retrieved from these publications were identified through manual searches and assessed for relevance. The results are discussed in detail.

GENETIC BASIS OF GI DISORDERS

Genetic basis of gastroenterological disorders and their classification

Genetic alterations in GIT disorders can be broadly classified into germline mutations, somatic mutations, and epigenetic changes. Germline mutations are inherited and present in the egg or sperm, thus passed on to offspring. Somatic mutations, on the other hand, are acquired genetic alterations that occur after conception in non-germline cells and are

Table 1 Different types of epigenetic changes and their impact on gene[6-9]

Mechanism	How it works	Effect on genes with example
DNA methylation[6]	Addition of methyl groups (-CH ₃) to DNA (usually at CpG islands)	<i>MLH1</i> silenced: Leads to microsatellite instability increased mutation rate
Histone modification[7]	Acetylation, methylation, phosphorylation of histone proteins	<i>CDH1</i> (E-cadherin) silenced by H3 acetylation in promoter regions of cytokine genes (<i>e.g.</i> , TNF- α) leads to increased transcription
Chromatin remodeling [8]	Changing the physical structure of chromatin	Loss of <i>ARID1A</i> failure of chromatin remodeling improper gene silencing or activation. Progression of HCC, CRC
Non-coding RNAs (<i>e.g.</i> , miRNA, lncRNA)[9]	Bind to mRNA or DNA to regulate expression	CRC (miR-21, miR-135b, lncRNA <i>HOTAIR</i>); gastric cancer (miR-148a, miR-21, lncRNA <i>MALAT1</i> , circPVT1); inflammatory bowel disease (miR-155, miR-21, lncRNA <i>IFNG-AS1</i>); HCC (miR-122, miR-221/222, lncRNA <i>HULC</i>); celiac disease (miR-449a)

miRNA: MicroRNA; lncRNA: Long non-coding RNA; CH₃: Methyl group; mRNA: Messenger RNA; TNF- α : Tumor necrosis factor alpha; CRC: Colorectal cancer; HCC: Hepatocellular carcinoma; circPVT1: Circular RNA plasmacytoma variant translocation 1.

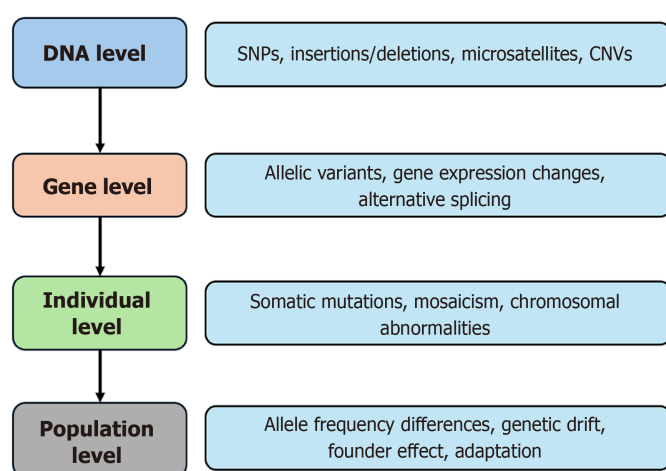


Figure 1 Genetic variation at different levels. SNP: Single nucleotide polymorphism; CNV: Copy number variation.

not inherited. These mutations commonly contribute to the pathogenesis of sporadic GI cancers and other non-hereditary GIT disorders. Epigenetic changes, including DNA methylation, histone modifications, and regulation by non-coding RNAs, alter gene expression without modifying the DNA sequence and play a significant role in both benign and malignant GIT conditions. Epigenetics refers to heritable changes in gene expression that do not involve changes to the DNA sequence itself. These modifications regulate when, where, and how much a gene is expressed, and are frequently influenced by environmental factors, aging, disease processes, or developmental stages, playing a significant role in both benign and malignant conditions of the GIT. Different types of epigenetic changes with examples are described in Table 1 [6-9]. Genetic variation occurs at multiple levels. It can be observed at the DNA level (*e.g.*, single nucleotide polymorphisms, insertions, deletions), at the gene level (different alleles, altered gene expression, or splicing variants), at the individual level (somatic mutations, mosaicism, or chromosomal abnormalities), and at the population level (differences in allele frequencies, genetic drift, founder effects, or adaptation) (Figure 1).

Another form of genetic variation is mosaicism, which occurs when a postzygotic genetic variant exists in only a portion of the body's cells, meaning two or more genetically distinct cell populations within the same individual, all originating from a single zygote. Similarly, genetic disorders can be classified as monogenic, caused by mutations in a single gene, while others are polygenic, involving complex interactions among multiple genes (Table 2). Disorders of the GIT can be classified as hereditary, inflammatory, malignant and metabolic (Figure 2).

Functional classification of genes

Numerous genes implicated in these disorders are involved in key biological processes such as DNA repair, cell adhesion, maintenance of structural integrity, bile acid synthesis and transport, immune regulation, mucosal barrier function and nutrient absorption. Table 3[10-16] provides a functional classification of these genes and highlights their specific associations with various GI disorders, helping to illustrate the complexity and diversity of the genetic contributions to GIT pathology.

Table 2 Different genetic pathway disorders, its mechanism of action in gastrointestinal tract

Genetic pathway disorder	Mechanism	Examples
Monogenic disorders	Mutations in a single gene that often follow Mendelian inheritance patterns	Hereditary hemochromatosis (<i>HFE</i> gene), Wilson disease (<i>ATP7B</i> gene), alpha-1 antitrypsin deficiency
Polygenic and multifactorial disorders	Involve multiple genes and environmental interactions	Inflammatory bowel disease (over 200 loci have been identified), celiac disease (<i>HLA-DQ2</i> and <i>HLA-DQ8</i>)
Cancer predisposition syndromes	Inherited mutations in tumor suppressor genes or DNA repair genes increase GI cancer risk	Lynch syndrome (HNPCC) (<i>MLH1</i> , <i>MSH2</i>), familial adenomatous polyposis (<i>APC</i>) gene
Mosaicism	Two or more genetically distinct cell populations within the same individual, derived from a single zygote	Mosaic <i>APC</i> gene mutations may cause attenuated forms of FAP. Very early changes in IBD

GI: Gastrointestinal; FAP: Familial adenomatous polyposis; HNPCC: Hereditary non-polyposis colorectal cancer; IBD: Inflammatory bowel disease.

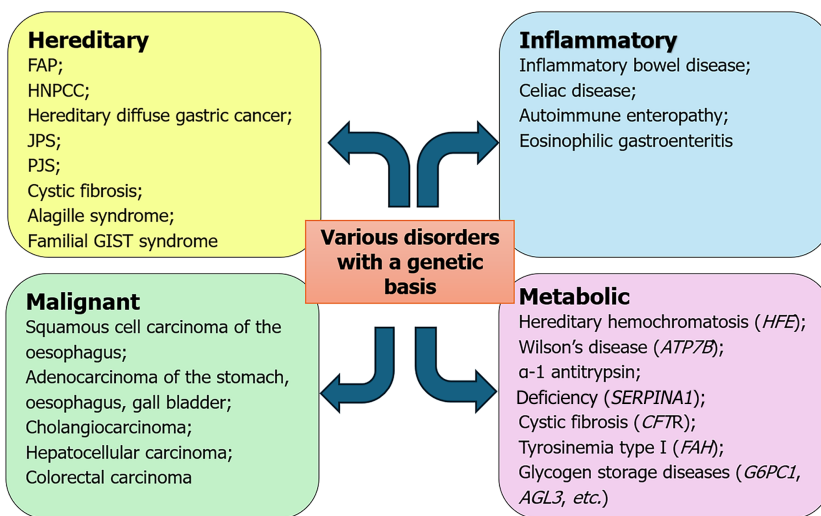


Figure 2 Disorders of gastrointestinal tract. FAP: Familial adenomatous polyposis; HNPCC: Hereditary non-polyposis colorectal cancer; JPS: Juvenile polyposis syndrome; PJS: Peutz-Jeghers syndrome; GIST: Gastrointestinal stromal tumor.

Different genetic pathways in pathogenesis of disorders of GIT

Advances in genomics have elucidated several critical pathways that contribute to the pathogenesis, progression, and treatment response of these disorders. Chronic inflammation in IBD can culminate in colitis-associated CRC through sequential genetic alterations involving *TP53*, chromosomal instability, microsatellite instability, and promoter hypermethylation of tumor suppressor genes like *CDH1* and *p16*. Furthermore, recent evidence has linked mutational signatures like *APOBEC*/activation-induced cytidine deaminase-mediated changes and epigenetic reprogramming to tumor evolution and immune evasion. Understanding these genetic pathways is critical for early diagnosis, risk stratification, and development of targeted therapies in GI diseases. Some of the key genetic pathways and mechanisms involved in GI diseases are shown in Table 4[17-32].

CLINICAL GENETIC TESTING

Clinical genetic testing plays a pivotal role in the screening, diagnosis, prognostication, and prediction of GI and hepatopancreatic biliary (HPB) disorders (Figure 3).

Clinical genetic testing can be classified based on the origin of the mutation as well as the clinical purpose of the test (Table 5). Based on origin, tests are categorized into germline variation testing, which detects inherited mutations present in every cell of the body, somatic variation testing, which identifies acquired mutations confined to specific tissues (commonly in tumors) and mosaicism testing, which detects mosaicism in both inherited and acquired diseases like FAP and IBD[33]. Genetic testing can be categorized by purpose into various types: Diagnosis, prognostication, prediction of treatment response, and guiding targeted therapy.

Germline genetic testing

Germline genetic testing involves the analysis of inherited DNA changes that are present in every cell of the body. These

Table 3 Classification of genes based on their function and their association with gastrointestinal disorders[10-16]

Genes	Function	Associated disorders
Genes involved in DNA repair and genomic stability[10]		
<i>MLH1, MSH2, MSH6, PMS2, EPCAM</i>	Mismatch repair (MMR) system	Lynch syndrome colorectal, gastric, pancreatic cancer
<i>MUTYH</i>	Base excision repair	<i>MUTYH</i> -associated polyposis
<i>BRCA1/BRCA2, ATM, PALB2</i>	Double-strand break repair	Familial pancreatic and gastric cancers
<i>TP53</i>	Tumor suppressor, DNA damage response	CRC, gastric, pancreatic, hepatocellular carcinoma
Genes involved in cell adhesion and structural integrity[11]		
<i>CDH1</i>	E-cadherin (cell-cell adhesion)	Hereditary diffuse gastric cancer
<i>CTNNA1</i>	Catenin alpha-1 (adherens junctions)	HDGC
<i>SMAD4, BMPR1A</i>	TGF- β pathway mediators	Juvenile polyposis syndrome, pancreatic cancer
Genes regulating inflammation and immune response[12]		
<i>NOD2</i>	Innate immunity, bacterial sensing	Crohn's disease
<i>IL23R, IL10, IL12B</i>	Cytokine signaling	IBD susceptibility
<i>IRGM, ATG16 L1</i>	Autophagy genes	Crohn's disease
<i>HLA-DQA1/HLA-DQB1</i>	Antigen presentation	Celiac disease
<i>TLR4, TLR9</i>	Pattern recognition receptors	Functional dyspepsia, IBD
Genes involved in bile acid transport and cholestasis[13]		
<i>ABCB11</i>	Bile salt export pump	PFIC2, BRIC
<i>ABCC2 (MRP2)</i>	Bile excretion	Dubin-Johnson syndrome
<i>ATP8B1</i>	Phospholipid transporter	PFIC1
<i>TJP2</i>	Tight junction protein	PFIC4
Genes in neuronal/gut motility and enteric nervous system[14]		
<i>RET, EDNRB, GDNF</i>	ENS development	Hirschsprung's disease
<i>SCN5A</i>	Sodium channel in ICCs/ENS	IBS with constipation
<i>NEUROG3</i>	Enteroendocrine differentiation	Congenital malabsorptive diarrhoea
Genes affecting nutrient absorption and metabolism[15]		
<i>LCT</i>	Lactase enzyme	Lactose intolerance
<i>SAR1B</i>	Chylomicron transport	Chylomicron retention disease
<i>SLC26A3</i>	Cl ⁻ /HCO ₃ ⁻ exchange	Congenital chloride diarrhea
<i>SLC5A1 (SGLT1)</i>	Glucose transport	Glucose-galactose malabsorption
Genes in oncogenic signaling and growth factors[15]		
<i>KRAS, NRAS</i>	MAPK signaling	CRC, pancreatic cancer
<i>BRAF</i>	Downstream of <i>KRAS</i>	CRC (<i>BRAF V600E</i> in MSI tumors)
<i>PIK3CA</i>	PI3K/AKT pathway	CRC, gastric cancer
<i>EGFR, HER2 (ERBB2)</i>	Receptor tyrosine kinases	Gastric, colorectal cancers
<i>FGFR2, IDH1/IDH2</i>	Growth factor pathways	Cholangiocarcinoma
Genes related to epigenetic and transcriptional regulation[16]		
<i>ARID1A</i>	Chromatin remodeling	Biliary cancer, CRC, gastric
<i>MLH3, MSH3</i>	Mismatch repair (minor MMR genes)	Polyposis syndromes
<i>TET2, DNMT3A</i>	DNA methylation regulation	CRC and inflammatory epigenetic signatures

MMR: Mismatch repair; CRC: Colorectal cancer; HDGC: Hereditary diffuse gastric cancer; TGF- β : Transforming growth factor-beta; IBD: Inflammatory

bowel disease; PFIC: Progressive familial intrahepatic cholestasis; BRIC: Benign recurrent intrahepatic cholestasis; ENS: Enteric nervous system; ICCs: Interstitial cells of Cajal; IBS: Irritable bowel syndrome; Cl⁻: Chloride ion; HCO₃⁻: Bicarbonate ion; MAPK: Mitogen activated protein kinase; MSI: Microsatellite instability; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B.

Table 4 Genetic pathways, genes, and gastrointestinal disorders[17-32]

Pathway	Key genes	Associated disorders	Mechanism/role	Ref.
Wnt/ β -catenin	<i>APC, CTNNB1, AXIN2</i>	Colorectal cancer, hepatocellular carcinoma (HCC), familial adenomatous polyposis	Controls cell proliferation and differentiation; mutation leads to uncontrolled growth	Li <i>et al</i> [17]
NF- κ B	<i>NFKB1, TNFAIP3, IKK complex</i>	IBD (Crohn's, UC), gastric cancer, colorectal cancer	Regulates inflammation, cell survival, immunity; chronic activation promotes inflammation and tumorigenesis	Peng <i>et al</i> [18]
TGF- β /SMAD	<i>TGFBR2, SMAD4</i>	Juvenile polyposis, CRC, pancreatic cancer	Controls growth inhibition and apoptosis; mutations cause evasion of tumor suppression	Hata and Chen[19]
JAK/STAT	<i>JAK2, STAT3, STAT1</i>	IBD, colitis-associated cancer	Regulates immune cell signaling and cytokine responses	Hu <i>et al</i> [20]
MAPK/ERK	<i>KRAS, BRAF, EGFR</i>	CRC, pancreatic cancer, gastric cancer	Regulates cell proliferation and survival; mutations oncogenic signaling	Guo <i>et al</i> [21]
PI3K/AKT/mTOR	<i>PIK3CA, PTEN, AKT1, MTOR</i>	CRC, gastric cancer, IBD	Promotes cell growth, metabolism, and angiogenesis; dysregulation contributes to tumor growth and inflammation	Glaviano <i>et al</i> [22]
Mismatch repair	<i>MLH1, MSH2, MSH6, PMS2</i>	Lynch syndrome, CRC, gastric cancer	Repairs DNA replication errors; loss leads to microsatellite instability (MSI)	Li[23]
P53 pathway	<i>TP53</i>	CRC, esophageal, gastric, HCC	Controls cell cycle arrest, apoptosis, DNA repair; mutations common in late cancer stages	Harris and Levine[24]
Hedgehog signaling	<i>PTCH1, GLI1</i>	Gastric cancer, GI developmental disorders	Controls tissue patterning and stem cell maintenance	Briscoe and Théron[25]
Notch signaling	<i>NOTCH1, DLL1, HES1</i>	Colitis, CRC, esophageal cancer	Regulates differentiation, especially goblet cells; dysregulation affects intestinal homeostasis	Kopan[26]
Autophagy pathway	<i>ATG16 L1, IRGM</i>	Crohn's disease, IBD-associated cancer	Maintains intracellular bacterial clearance and mucosal homeostasis	Yu <i>et al</i> [27]
Immune checkpoint pathway	PD-L1, <i>CTLA4</i>	MSI-high CRC, gastric cancer, IBD	Immune evasion in cancer; dysregulated tolerance in autoimmune GI diseases	He and Xu[28]
ER stress/UPR	<i>XBPI1, IRE1, PERK</i>	IBD, Paneth cell dysfunction, CRC	Regulates response to unfolded proteins; chronic ER stress leads to inflammation and epithelial damage	Chen <i>et al</i> [29]
IL-23/Th17 pathway	<i>IL23R, STAT3, RORC</i>	Crohn's disease, UC, CRC	Inflammatory cytokine signaling driving chronic inflammation	Bunte and Beikler[30]
Apoptosis/FAS-FASL	<i>FAS, BAX, CASP8</i>	Colitis-associated cancer, gastric cancer	Regulates programmed cell death; evasion supports tumor survival	Waring and Müllbacher[31]
DNA repair pathways (base/nucleotide excision)	<i>OGG1, XPA, POLB</i>	CRC, gastric cancer	Repair oxidative and chemical DNA damage; defects genomic instability	Kumar <i>et al</i> [32]

NF- κ B: Nuclear factor kappa-B; TGF- β : Transforming growth factor-beta; JAK: Janus tyrosine kinase; STAT: Signal transducer and activator of transcription; MAPK: Mitogen-activated protein kinase; ERK: Extracellular regulated protein kinases; PI3K: Phosphatidylinositol 3-kinase; AKT: Protein kinase B; mTOR: Mammalian target of rapamycin; UPR: Unfolded protein response; ER: Endoplasmic reticulum; IL: Interleukin; Th: T helper; HCC: Hepatocellular carcinoma; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CRC: Colorectal cancer; GI: Gastrointestinal; MSI: Microsatellite instability.

mutations are passed from parent to offspring and can predispose individuals to a range of hereditary conditions, including cancers, metabolic disorders, and autoimmune diseases, particularly those affecting the GI and HPB systems. Germline testing is typically performed using DNA extracted from saliva, blood, or buccal swabs and targets mutations that are present in all somatic and germ cells. It is especially valuable when evaluating individuals at a young age or during childhood, where early detection has significant clinical implications. Techniques such as sanger sequencing, next-generation sequencing (NGS), and multiplex gene panels are commonly used for this purpose. Germline testing plays a

Table 5 Various types of clinical genetic testing

Classification	Type	Purpose
Mutation origin	Germline testing	Detects inherited mutations; used for familial risk, carrier status, and predisposition
	Somatic testing	Identifies acquired mutations in specific tissues (<i>e.g.</i> , tumors); guides cancer therapy
	Mosaicism testing	Identify mosaicism in FAP, IBD
Clinical purpose	Diagnostic testing	Confirms or rules out a specific genetic disorder in symptomatic individuals
	Prognostic testing	Predicts disease course, severity, or likelihood of complications
	Predictive/screening	Identifies asymptomatic individuals at risk of developing a genetic disorder
	Carrier testing	Identifies individuals who carry one copy of a gene mutation (relevant for recessive conditions)
	Pharmacogenetic testing	Assesses genetic variants affecting drug metabolism and response
	Somatic/tumor profiling	Detects actionable mutations in cancer cells to guide targeted therapy and prognosis
	Newborn screening	Early identification of treatable genetic disorders in neonates

FAP: Familial adenomatous polyposis; IBD: Inflammatory bowel disease.

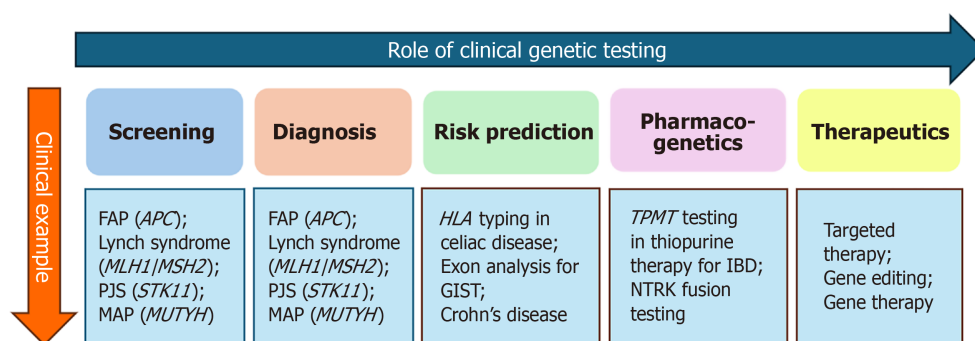


Figure 3 Role of clinical genetic testing. FAP: Familial adenomatous polyposis; PJS: Peutz-Jeghers syndrome; MAP: *MUTYH*-associated polyposis; GIST: Gastrointestinal stromal tumor; IBD: Inflammatory bowel disease; NTRK: Neurotrophic tyrosine receptor kinase.

critical role in confirming diagnoses, guiding screening strategies, prognostication and informing cascade testing in families. It is also instrumental in identifying at-risk offspring, optimizing pharmacogenetic decisions, and supporting reproductive planning in affected families. Many genetic tests currently available for screening are summarized in Table 6.

Somatic mutation profiling

Somatic genetic testing has emerged as a cornerstone of precision medicine, particularly in oncology, by detecting non-inherited, tissue-specific genetic alterations acquired during a person's lifetime. These somatic mutations distinct from germline mutations are most commonly found in tumors and are instrumental in guiding diagnosis, prognosis, and therapy selection. While somatic testing is predominantly used in malignant conditions, its utility is expanding into non-malignant, complex diseases. Disorders such as Celiac disease and Crohn's disease, although primarily immune-mediated and polygenic in origin, can exhibit somatic epigenetic changes and mucosal genetic alterations that influence disease progression, therapeutic response, and relapse risk.

Techniques of genetic testing

Genetic testing involves the analysis of DNA, or in some cases RNA transcribed from DNA, to identify variations associated with disease or an increased risk of disease. The foundation of genetic testing lies in the concept of genetic variation, which can occur at multiple levels from large chromosomal abnormalities to single-nucleotide changes.

Broadly, clinical genetic testing can be classified into two main categories: Cytogenetic testing and molecular genetic testing. Cytogenetics is a specialized branch of genetic analysis focused on examining the structure and number of chromosomes within cells to detect large-scale genetic abnormalities. Cytogenetic testing is used to identify chromosomal changes such as aneuploidy (abnormal number of chromosomes), translocations (exchange of segments between chromosomes), deletions (loss of chromosome segments), duplications (gain of additional segments), and inversions (reversal of a chromosome segment). Molecular genetic testing involves the analysis of DNA or RNA at the molecular level to identify small-scale genetic variations, such as single-nucleotide changes, insertions, deletions, or duplications that may be associated with disease. Unlike cytogenetic testing, which detects large chromosomal alterations, molecular

Table 6 Germline testing available for screening

No.	GI disorder/syndrome	Guideline source	Genes recommended for testing	Testing criteria
1	Lynch syndrome (hereditary nonpolyposis colorectal cancer)	ACG, NCCN, ESMO	<i>MLH1, MSH2, MSH6, PMS2, EPCAM</i>	Personal/family history of colorectal, endometrial, or other LS-associated cancers; tumor MSI or IHC abnormality
2	Familial adenomatous polyposis (FAP)	ACG, NCCN	<i>APC</i>	> 100 colorectal adenomas or family history of FAP
3	Attenuated FAP	ACG	<i>APC</i>	Patients with 10-99 adenomas
4	<i>MUTYH</i> -associated polyposis	ACG	<i>MUTYH</i> (biallelic)	Multiple adenomas and autosomal recessive inheritance
5	Peutz-Jeghers syndrome	NCCN, ESMO	<i>STK11</i>	Mucocutaneous pigmentation and hamartomatous polyps; family history
6	Juvenile polyposis syndrome	ACG, NCCN	<i>SMAD4, BMPR1A</i>	≥ 5 juvenile polyps or family history
7	Cowden syndrome/ <i>PTEN</i> hamartoma tumor syndrome	NCCN	<i>PTEN</i>	GI polyps with mucocutaneous lesions or macrocephaly
8	Hereditary pancreatic cancer	NCCN	<i>BRCA1/BRCA2, PALB2, ATM, CDKN2A, STK11</i>	Family history of pancreatic cancer or known mutation
9	Hereditary diffuse gastric cancer	NCCN	<i>CDH1</i>	Family history of diffuse gastric cancer or lobular breast cancer
10	Serrated polyposis syndrome	WHO, ACG	No known high-penetrance genes; <i>RNF43</i> under investigation	Multiple serrated polyps meeting WHO criteria

FAP: Familial adenomatous polyposis; ACG: American College of Gastroenterology; NCCN: National Comprehensive Cancer Network; ESMO: European Society for Medical Oncology; WHO: World Health Organization; LS: Lynch syndrome; MSI: Microsatellite instability; GI: Gastrointestinal; IHC: Immunohistochemistry.

genetic testing focuses on gene-level mutations that may not be visible under a microscope, like specific genes, exons, introns, or nucleotide sequences. In [Table 7](#), we have described various cytogenetic and molecular genetic testing with their clinical utility. Various molecular genetic tests are sanger sequencing, NGS, *etc.* Sanger sequencing, also known as the chain termination method, is a technique for DNA sequencing based upon the selective incorporation of chain-terminating dideoxynucleotides by DNA polymerase during *in vitro* DNA replication. NGS is a high-throughput technology that enables the simultaneous analysis of multiple DNA fragments within a single sample. NGS technologies include whole-genome sequencing, targeted panel sequencing, RNA sequencing, single-cell sequencing, duplex sequencing, reduced-representation sequencing, and long-read sequencing. Various platforms are used in NGS. The most common are 454/Roche, Illumina (MiSeq/HiSeq/NextSeq), SOLiD, and Ion Torrent. Panel-based testing eliminates the time and financial strain required to sequence several individual genes until the right gene is identified. Panel-based testing is also especially helpful when any of several genes may be known to cause a specific disorder[34]. [Table 7](#)[35-55] details the various genetic testing methods.

CLINICAL APPLICATION OF GENETIC MEDICINE

Apart from its role in screening and diagnosis of various disorders, genetic testing also assists clinicians in prognostication, prediction of therapeutic response, and decision-making regarding targeted therapy. In this section, we describe the role of genetic alterations in prognostication, prediction, pharmacogenetics and targeted therapy treatment of different GI disorders.

Prediction and prognostication

In the predictive setting, genetic testing helps categorize individuals based on their inherited risk of developing diseases like cancer, IBD, and other conditions. In the prognostic field, genetic profiling especially in oncology offers information on disease severity, likely progression, and response to treatment. For example, mutations in *BRCA1/BRCA2* not only indicate increased risk for breast and ovarian cancers but also influence treatment options and long-term outcomes. Similarly, tumor genomic profiling detects biomarkers linked to recurrence risk, treatment resistance, and overall survival. [Table 8](#)[56-89] describes the various genes that help in the prediction of phenotypes of disease and the prognostication of various disorders.

Pharmacogenetics

Pharmacogenetics is a field that examines how genetic variations influence an individual's response to pharmacologic

Table 7 Methods for genetic testing and its clinical implication[35-55]

Test	Detects	Clinical use	Benefit	Limitation	Ref.
Cytogenetic testing					
Karyotyping (conventional cytogenetics)	Detects large chromosomal abnormalities: Trisomies, translocations, deletions, G-banding of metaphase chromosomes	Down syndrome, Turner syndrome	Whole-genome overview, identifies balanced/unbalanced rearrangements	Low resolution, cannot detect small deletions/duplications, requires dividing cells	Genetic Alliance[35]
Fluorescence <i>in situ</i> hybridization (FISH)	Fluorescent probes bind specific DNA sequences on chromosomes	Detects gene amplifications, deletions, rearrangements (<i>e.g.</i> , <i>HER2</i> in gastric cancer, <i>ALK</i> in GI stromal tumors)	Rapid, targeted, works on interphase cells	Limited to known targets, one probe/test, cannot assess whole genome	Yilmaz and Demiray[36]
Comparative genomic hybridization (aCGH)	DNA from patient and control hybridized to a microarray	Detects copy number variations (<i>e.g.</i> , deletions in polyposis syndromes, microdeletion syndromes)	High-resolution, genome-wide, detects sub microscopic CNV	Cannot detect balanced rearrangements (<i>e.g.</i> , translocations), limited to CNVs only	Weiss <i>et al</i> [37]
Chromosomal microarray analysis	aCGH + SNP array	Used in syndromic GI diseases, unexplained developmental delay, congenital anomalies	Genome-wide, detects CNVs, uniparental disomy, mosaicism	Cannot detect balanced rearrangements, may report VUS	Myllykangas <i>et al</i> [38]
Spectral karyotyping	Whole chromosome painting with multicolor FISH	Identifies complex chromosomal rearrangements, often in cancers	Detects complex karyotypes, color-coded analysis	Expensive, not used for routine diagnostics, lower resolution than aCGH	Guo <i>et al</i> [39]
Molecular genetic testing					
Sanger sequencing	SNV, small insertions/deletions	Confirmatory testing (<i>e.g.</i> , known <i>APC</i> , <i>MLH1</i> mutations)	High accuracy for point mutation or small deletion/duplication/SNV, cost effective for single genetic testing	Only identify small subset of gene or single gene, not precisely quantifiable	Herpich <i>et al</i> [40]
NGS	Panel, exome, or genome-wide variants	Multigene panels for IBD, polyposis, CRC, gastric cancer, GIST	Multiple, individually produced readings of the target area mosaism, quantitative, whole exome or genome sequencing	Limited in their ability to detect copy number variations, incidental findings need to be verified by sanger sequencing	Satam <i>et al</i> [41]
Targeted gene panels	Focused sequencing of disease-specific genes	Panel specific to GIST, IBD, hereditary colorectal cancer panel, gist panel	Accurate diagnosis focus on specific genes cost-effective and efficient: Can be customized according to disorder	Limited coverage not detect structural rearrangements or copy number variants cannot identify novel or new gene related to disease	Málaga <i>et al</i> [42]
Whole exome sequencing	All coding regions	Early-onset or monogenic IBD, congenital diarrheal disorders (<i>e.g.</i> , <i>DGAT1</i> , <i>EPCAM</i> mutations). Hereditary pancreatitis (<i>e.g.</i> , <i>PRSS1</i> , <i>SPINK1</i>) colorectal cancer	Cost-effective WES allows deeper sequences WES captures approximately 85% of known disease-causing mutations	Misses non-coding variants incomplete exome coverage	Rabbani <i>et al</i> [43]; Uhlig <i>et al</i> [44]
WGS	Coding and non-coding genome variant	Identification of colorectal cancer genes. Undiagnosed complex disease	Cover both coding and non-coding region detection of structural variant both germline and somatic mutation	High cost difficult to pathogenic variant from benign variant	de Voer <i>et al</i> [45]
MLPA	Large deletions/duplications	Detects large deletions, especially <i>EPCAM</i> deletions causing <i>MSH2</i> inactivation	Efficient CNV detection cost-effective and high throughput applicable on degraded DNA	Cannot detect point mutations or small indels limited to pre-designed probes	Kuiper <i>et al</i> [46]; Schouten <i>et al</i> [47]
qPCR	Copy number variations or known mutations	Rapid screening for common mutations, detects bacterial, viral, and parasitic DNA/RNA rapidly and accurately, bacterial load determination in gastro intestinal disorder	High sensitivity and specificity, rapid turnaround, quantitative	Requires prior sequence knowledge	Shah <i>et al</i> [48]; Bamias <i>et al</i> [49]
Array	Sub microscopic	Genome-wide coverage,	High resolution can detect CNVs	Inability to detect balanced	McKay <i>et al</i>

comparative genomic hybridization (aCGH)	deletions/duplications, germline CNVs in genes like <i>APC</i> , <i>SMAD4</i> , and <i>BMPRI1A</i>	germline CNVs in genes like <i>APC</i> , <i>SMAD4</i> and <i>BMPRI1A</i>	as small as 50-100 kb	chromosomal rearrangements difficulties in interpreting CNVs of uncertain significance	[50]; Assämäki <i>et al</i> [51]
HLA typing (PCR-SSP, NGS-based)	HLA allele identification	Celiac disease, IBD pharmacogenetics IBD, primary sclerosing cholangitis drug-induced GI injury, idiosyncratic reactions to drugs causing hepatic/GI damage. Transplant compatibility	Cost-effective, simple requires minimal computational support	Limited resolution may not differentiate similar alleles. May yield ambiguous results	Megiorni and Pizzuti[52]
FISH	Large chromosomal rearrangements, gene fusions	In Barretts esophagus identifies chromosomal instability (<i>e.g.</i> , <i>20q</i> gain, <i>18q</i> loss), and <i>BRAF</i> rearrangements; detection of <i>HER2</i> gene amplification (<i>ERBB2</i> at 17q12) predicts response to trastuzumab therapy (gastric cancer)	High specificity and sensitivity for targeted chromosomal regions	Targeted approach only. Limited genomic coverage	Brankley <i>et al</i> [53]
PCR	Specific known mutations	Quick detection (<i>e.g.</i> , <i>PRSS1</i> in hereditary pancreatitis), <i>KRAS</i> in CRC	High sensitivity and specificity can detect minute amounts of target DNA/RNA. Rapid turnaround time. Typically, within a few hours. Quantitative provides absolute or relative quantification	Requires prior sequence knowledge. Primers must be designed for specific known targets. Cannot differentiate live from dead organisms, detects DNA from both	Tol <i>et al</i> [54]
RNA-seq	Gene expression, fusion transcripts	Detects tumor-specific expression changes, fusion transcripts (<i>e.g.</i> , NTRK fusions), and provides prognostic biomarkers in CRC reveals deregulated pathways (<i>e.g.</i> , WNT, PI3K), tumor microenvironment features, and therapeutic target molecular marker of pancreatic cancer	Unbiased and comprehensive: Captures all RNA species (mRNA, lncRNA, miRNA, circular RNA), high resolution. Detects single-nucleotide changes, splicing variants, and gene fusions	Expensive and resource-intensive, requires advanced sequencing and computational infrastructure, data analysis is complex, needs bioinformatics expertise and robust pipelines	Bailey <i>et al</i> [55]

GI: Gastrointestinal; FISH: Fluorescence *in situ* hybridization; CNV: Copy number variation; aCGH: Array comparative genomic hybridization; SNP: Single nucleotide polymorphism; VUS: Variant of uncertain significance; SNV: Single nucleotide variant; NGS: Next-generation sequencing; GIST: Gastrointestinal stromal tumor; IBD: Inflammatory bowel disease; CRC: Colorectal cancer; WES: Whole exome sequencing; WGS: Whole genome sequencing; MLPA: Multiplex ligation-dependent probe amplification; qPCR: Quantitative polymerase chain reaction; HLA: Human leukocyte antigen; PCR-SSP: Polymerase chain reaction sequence-specific primer; NTRK: Neurotrophic tyrosine receptor kinase; PCR: Polymerase chain reaction; PI3K: Phosphoinositide 3-kinase; RNA-seq: RNA sequencing; lncRNA: Long non-coding RNA; miRNA: MicroRNA; mRNA: Messenger RNA.

agents, with the aim of optimizing drug selection and dosing for improved therapeutic efficacy and minimized adverse effects. Variants in genes involved in drug metabolism, such as *DPYD*, can significantly impair the breakdown of 5-fluorouracil, predisposing patients to severe toxicity, especially in CRC. Genetic alterations can also impact drug targets; for instance, *KRAS* mutations are well-established predictors of resistance to anti-epidermal growth factor receptor therapies (*e.g.*, cetuximab, panitumumab) in metastatic CRC. Furthermore, polymorphisms in transporter genes like *ABCB1* can affect drug absorption, distribution, and resistance. Immune-related genetic factors, such as human leukocyte antigen-B alleles, are associated with drug-induced liver injury, while *HLA-DQ2/HLA-DQ8* are linked to hypersensitivity in celiac disease. Thus, pharmacogenetic testing provides valuable information for tailoring therapy and improving clinical outcomes. Genes that influence therapy to other drugs are described in Table 9[90-100]. Similarly, some genes determine the therapeutic response to targeted therapy (Table 10)[101-125].

Targeted therapies

Targeted therapy in gastroenterology refers to the use of drugs that specifically interact with molecular or genetic abnormalities in GI and HPB disorders. These therapies target specific genetic mutations, gene fusions, or overexpressed proteins, enabling precise treatment with minimal damage to normal cells unlike conventional chemotherapy. By blocking key oncogenic pathways or modulating the immune response, targeted therapies provide a personalized approach tailored to an individual's genetic profile. Although highly effective in selected patients, these treatments are often expensive and may not be accessible to all. Currently, most targeted therapies are used in the metastatic setting; however, emerging evidence supports their potential role in neoadjuvant and adjuvant settings. The NICHE-2 trial demonstrated the efficacy of neoadjuvant immunotherapy in locally advanced deficient mismatch repair colon cancer, with short-course nivolumab plus ipilimumab achieving a 98% pathological response rate, 68% complete pathological

Table 8 Genes that help in prediction and poor prognostications[56-89]

Disease	Prediction and prognostication	Genes	Ref.
FAP	Profuse polyposis	<i>APC</i> codon 1250-1464, 1250-1311, 1309-1324	Nagase <i>et al</i> [56]; Enomoto <i>et al</i> [57]; Ficari <i>et al</i> [58]; Walon <i>et al</i> [59]; Gebert <i>et al</i> [60]
	Desmoid tumors	<i>APC</i> codon 1924, 1962, 1444-1560, 1403-1987	Caspari <i>et al</i> [61]
	Upper gastrointestinal polyps	1445-1578	Davies <i>et al</i> [62]
	Gastric adenomas	1403-1987	Caspari <i>et al</i> [61]
	Multiple extracolonic manifestations	3'14451995, 3'1403	Caspari <i>et al</i> [61]
	CHRPE	311-1444, 413-1387, 542-1309	Caspari <i>et al</i> [61]
Crohn's disease	Stenotic/structuring behavior	<i>NOD2</i> , <i>TLR4</i> , <i>IL-12B</i> , <i>CX3CR1</i> , <i>IL-10</i> , <i>IL-6</i>	Tsianos <i>et al</i> [63]
	Penetrating/fistulizing behavior	<i>NOD2</i> , <i>IRGM</i> , <i>TNF</i> , <i>HLADRB1</i> , <i>CDKAL1</i>	Tsianos <i>et al</i> [63]
	Inflammatory behavior	<i>HLA</i>	Tsianos <i>et al</i> [63]
	Granulomatous disease	<i>TLR4</i> / <i>CARD15</i>	Tsianos <i>et al</i> [63]
	Upper gastrointestinal	<i>NOD2</i> , <i>MIF</i>	Tsianos <i>et al</i> [63]
	Ileal	<i>IL-10</i> , <i>CRP</i> , <i>NOD2</i> , <i>ZNF365</i> , <i>STAT3</i>	Tsianos <i>et al</i> [63]
	Ileocolonic	<i>ATG16 L1</i> , <i>TCF-4 (TCF7 L2)</i>	Tsianos <i>et al</i> [63]
	Colonic	<i>HLA</i> , <i>TLR4</i> , <i>TLR1</i> , <i>TLR2</i> , <i>TLR6</i>	
	Crohn's disease activity	<i>HSP70-2</i> , <i>NOD2</i> , <i>PAI-1</i> , <i>CNR1</i>	Tsianos <i>et al</i> [63]
	Surgery	<i>NOD2</i> , <i>HLA-G</i>	Tsianos <i>et al</i> [63]
	Dysplasia and cancer	<i>FHIT</i>	
	Ulcerative colitis	Extraintestinal manifestations	<i>CARD15</i> , <i>FcRL3</i> , <i>HLADRB103</i>
Extensive colitis and increased colectomy risk		<i>HLA-DRB1</i> alleles, <i>CASP9</i> gene on 1p36, <i>ATG16 L1 T300A</i>	Nam <i>et al</i> [64]
May influence severity and steroid dependence		<i>IL23R</i> , <i>STAT3</i> , <i>HSP70-2</i> , <i>MDR1</i>	Nam <i>et al</i> [64]
Early response to infliximab		<i>IL23R</i> higher gene expression <i>IL-17A</i> and <i>IFN-γ</i>	Jürgens <i>et al</i> [65]; Rismo <i>et al</i> [66]
Good response to therapy		<i>TNF ALPHA</i> expression	Olsen <i>et al</i> [67]
Non response to infliximab		<i>PR3-ANCA</i>	Yoshida <i>et al</i> [68]
Favorable response to treatment		<i>FCGR3A</i> , <i>TNFRSF1A</i> , <i>IL-6</i> , and <i>IL-1B</i>	
Failure of steroid therapy		<i>MDR1 (ABCB1)</i> , <i>TNFα (-308/-857 SNPs)</i> , <i>HLA-DQA1 05/DRB1</i> , <i>NOD2</i> , <i>ATG16 L1</i> , <i>IL13RA2</i> , <i>IL6</i> , <i>IL11</i> , <i>TNFAIP6</i>	
Unfavorable response to therapy (IBD)		<i>TLR2</i> and <i>TLR9</i> show a negative correlation	Sazonovs <i>et al</i> [69]
Development of ADA against infliximab and adalimumab		<i>HLA-DQA1 05</i>	Sazonovs <i>et al</i> [69]
Development of ADA against infliximab		<i>HLA-DRB1</i>	
Celiac disease		Increase severity of disease	<i>DQA1 05</i> and <i>DQB1 02</i> , homozygous for <i>DQ2.5</i> haplotype, second copy of the <i>DQB1 0201</i>
	Increased risk of disease	<i>PRSS1</i> pathogenic variants include p.Asn29Ile and p.Arg122His, p.Asn29Ile and p.Arg122His	Avanthi <i>et al</i> [72]; Whitcomb[73]
Hereditary pancreatitis	Increased severity and early onset of disease	<i>SPINK1</i> , c.101A>G p.Asn34Ser and <i>SPINK1</i> , c.56-37T>C	Abass <i>et al</i> [74]
GIST			

	Increase severity and relapse	Exon 11, 13, 17, <i>c-KIT</i> mutation; <i>SDH</i> deficient, <i>BRAF</i> mutation	Zhang and Liu[75]
Colorectal cancer	Increased severity and predict recurrence	<i>P53</i> , <i>KRAS</i> codon 12, loss of 18q	Andreyev <i>et al</i> [76]; Walther <i>et al</i> [77]
HCC	Increased severity	<i>EZH2</i> , <i>STAT3</i> , <i>YB-1</i> , <i>ANLN</i> , <i>NLRC5</i>	
	Poor prognosis	Overexpression of <i>CDCA5</i>	Wang and Lai[78]; Hashemi <i>et al</i> [79]; Svinka <i>et al</i> [80]; Chao <i>et al</i> [81]; Jia <i>et al</i> [82]; Peng <i>et al</i> [83]
Gall bladder cancer	Increased severity of disease	Overexpression of <i>CDCA5</i>	Tian <i>et al</i> [84]
		<i>SERPINB5</i> (maspin) <i>KRAS</i> , E-cadherin/beta-catenin, <i>PML</i> , <i>P53</i> , <i>CDKN21</i> loss	Kim <i>et al</i> [85]; Hirata <i>et al</i> [86]; Chang <i>et al</i> [87]
Intra hepatic cholangiocarcinoma	Increased severity and large tumor size	<i>BRAF</i>	Xin <i>et al</i> [88]
Pancreatic cancer	Poor prognosis	<i>KRAS</i> (<i>G12D/G12V/G12R</i>), <i>CDKN2A</i> (<i>p16</i>), <i>SMAD4</i> (<i>DPC4</i>)	Zhou <i>et al</i> [89]

FAP: Familial adenomatous polyposis; HCC: Hepatocellular carcinoma; GIST: Gastrointestinal stromal tumor; CHRPE: Congenital hypertrophy of the retinal pigment epithelium; ADA: Anti-drug antibodies; IBD: Inflammatory bowel disease; TNF- α : Tumor necrosis factor alpha.

Table 9 Pharmacogenetics in gastrointestinal disorders[90-100]

Disorder	Gene	Drug(s)	Clinical impact	Ref.
CRC, gastric, pancreatic cancers	<i>DPYD</i>	5-fluorouracil, capecitabine	Deficiency life-threatening toxicity (mucositis, myelosuppression)	De Moraes <i>et al</i> [90]; Ruzzo <i>et al</i> [91]
CRC, pancreatic cancer	<i>UGT1A1</i>	Irinotecan	<i>UGT1A1</i> 28/28 reduced glucuronidation increased toxicity (neutropenia, diarrhea)	Maitland <i>et al</i> [92]
IBD, autoimmune hepatitis	<i>TPMT/NUDT15</i>	Azathioprine, 6-MP	<i>TPMT</i> or <i>NUDT15</i> deficiency risk of myelosuppression	Moriyama <i>et al</i> [93]
IBD	<i>HLA-DQA102:01</i> , <i>HLA-DQB102:02</i>	Thiopurines	Increase risk of thiopurine-induced pancreatitis	Ås <i>et al</i> [94]
IBD	<i>HLA-DQ2</i>	Infliximab	Increased formation of antibody formation against infliximab	Brun <i>et al</i> [95]
GERD, <i>H. pylori</i> , ulcers	<i>CYP2C19</i>	PPIs (omeprazole, lansoprazole)	Poor metabolizers increase drug levels; rapid metabolizers treatment failure in <i>H. pylori</i>	El Rouby <i>et al</i> [96]
NAFLD, metabolic syndrome	<i>SLCO1B1</i>	Statins (<i>e.g.</i> , simvastatin)	Variants statin-induced myopathy risk	SEARCH Collaborative Group[97]
IBD	<i>ABCB1</i>	Various (<i>e.g.</i> , corticosteroids)	Associated with glucocorticoid resistance in some patients	Li <i>et al</i> [98]
Autoimmune hepatitis, liver transplant	<i>CYP3A5</i>	Tacrolimus	Expressors need higher doses; non-expressors risk overexposure	Kim <i>et al</i> [99]
IBD	<i>G6PD</i> deficiency	Sulfasalazine, dapsone	Increase risk of hemolysis	Dore <i>et al</i> [100]

CRC: Colorectal cancer; IBD: Inflammatory bowel disease; GERD: Gastroesophageal reflux disease; *H. pylori*: *Helicobacter pylori*; NAFLD: Non-alcoholic fatty liver disease; PPI: Proton pump inhibitor.

remission rate, and 100% 3-year disease-free survival. Similarly, the MATTERHORN trial showed improved outcomes with durvalumab plus perioperative FLOT compared to chemotherapy alone in resectable gastric and gastroesophageal junction cancer[126,127]. Together, these studies highlight the evolving role of immune checkpoint inhibitors in the neoadjuvant management of GI cancers. Table 11[128-148] details the present status of targeted therapy in disorders of GIT based on genetic testing.

GENE THERAPY IN GASTROENTEROLOGY

In this section, we describe various gene therapies, gene editing and their current status in GI disorders. We also highlight emerging treatments and discuss the limitations of gene therapy. We have also discussed various delivery systems tailored to GIT.

Table 10 Genes which regulates response to targeted therapy[101-125]

Disorder	Gene/mutation	Role	Treatment/clinical implication	Ref.
Colorectal cancer	<i>KRAS</i> (codon 12/13)	Predicts resistance to anti-EGFR therapy	Avoid cetuximab/panitumumab in mutant cases	Zhu <i>et al</i> [101]
Colorectal cancer	<i>NRAS</i> mutations	Similar to <i>KRAS</i>	Also predicts non-response to EGFR inhibitors	Hu <i>et al</i> [102]
CRC, cholangiocarcinoma	<i>BRAF V600E</i>	Poor prognosis, targetable	Consider <i>BRAF</i> + MEK inhibitors	Rizzo <i>et al</i> [103]
Gastric, colorectal cancer	<i>HER2 (ERBB2)</i> amplification	Targetable mutation	Responds to trastuzumab, pertuzumab	Bang <i>et al</i> [104]
CRC, gastric, biliary	MSI-H/dMMR	Biomarker for immunotherapy. Poor response to chemotherapy in stage 2 tumor	Eligible for checkpoint inhibitors (<i>e.g.</i> , pembrolizumab)	Le <i>et al</i> [105]
HCC	<i>CTNNB1</i> (β -catenin)	Resistance to immunotherapy	Poor response to immunotherapy	Shah <i>et al</i> [106]
	<i>EZH2</i>	Resistance to immunotherapy	Negatively express PD-L1	Xiao <i>et al</i> [107]
Crohn's disease (IBD)	SNP rs396991GG of gene <i>FCGR3A</i> , rs976881-AA + GA (<i>TNFRSF1B</i>), SNPs in loci <i>DENND1B</i> (rs2488397) and aryl hydrocarbon receptor (rs1077773) s1813443-CC and rs1568885-TT (<i>CNTN5</i>) from the immunoglobulin superfamily	Resistance to biologics	Poor response to immunotherapy	Curci <i>et al</i> [108]; Yoon <i>et al</i> [109]; Ye and McGovern [110]
	Polymorphisms in <i>ATG16 L1</i> (<i>C11orf30</i> ; rs7927894CC, <i>CCNY</i> ; rs1277960CC) (rs10210302)		Clinical response to adalimumab	Koder <i>et al</i> [111]
Crohn's disease (IBD)	Polymorphisms in <i>NOD2</i>		Loss of response to anti-TNF	Juanola <i>et al</i> [112]
UC	Polymorphisms in <i>IL-23R</i>		Early response to infliximab	Jürgens <i>et al</i> [65]; Golan <i>et al</i> [113]
Crohn's disease	<i>ATG16 L1</i> , <i>IRGM</i>	Autophagy pathway genes	Predict disease course and microbiome interaction	Rioux <i>et al</i> [114]
	Polymorphisms in <i>FcyRIIIa</i> , <i>HLA-DRB1</i> , <i>HLA-DQA1 05</i>		Development of ADA against infliximab and adalimumab	Salvador-Martín <i>et al</i> [115]; Billiet <i>et al</i> [116]
	Polymorphisms in <i>FAS</i> , <i>FASL</i> , and <i>CASP9</i> (apoptotic pharmacogenetic index)		Clinical response to infliximab and adalimumab	Hlavaty <i>et al</i> [117]
	Gene protein tyrosine phosphatase non-receptor type 2 (rs7234029AG + GG, <i>CASP9</i>)		Non-response to anti-TNF and ustekinumab	Hlavaty <i>et al</i> [117]
HCC	<i>EZH2</i>		Negatively regulate PD-L1 expression. Less response to PD-L1 agonist	Meng <i>et al</i> [118]
	<i>TOP2A</i> , <i>PRC1</i>		Resistance to chemotherapy	Meng <i>et al</i> [118]; Wang <i>et al</i> [119]
IBS	<i>TJP1</i> , <i>TPH1</i> , <i>SERT (SLC6A4)</i>	Serotonin signaling, barrier dysfunction	May guide use of 5-HT3 antagonists or SSRIs	Camilleri <i>et al</i> [120]; Kerckhoffs <i>et al</i> [121]
Hereditary pancreatitis	<i>SPINK1</i> , <i>PRSS1</i> , <i>CTRC</i>	Trypsin regulation defects	May influence early interventions and surveillance	Panchoo <i>et al</i> [122]
Autoimmune hepatitis	<i>HLA-DRB103</i> , <i>04</i>	Susceptibility and severity	May predict treatment response to steroids/immunosuppressants	
Gastric, pancreatic, cholangiocarcinoma	<i>ARID1A</i> mutations	Epigenetic dysregulation	May predict response to <i>EZH2</i> inhibitors or immunotherapy	
Pancreatic cancer	<i>KRAS</i>		Anti EGFR treatment in effective	Fotopoulos <i>et al</i> [123]
	<i>hENT1</i>		Good response to gemcitabine	

		therapy	
	<i>DCK</i>	Increase active form of gemcitabine and increase survival	
	<i>DPD</i>	Low <i>DPD</i> level associated with increase survival	
	<i>hMLH1/2</i>	Pancreatic cancer with MSI associated with less response to 5-FU	
	<i>TS</i>	Lower level of <i>TS</i> associated with better response to capecitabine and 5-FU	
	<i>WOXX</i>	Decreased expression interferes with gemcitabine sensitivity	
	<i>SMAD4 (DPC4)</i>	Poor response to chemotherapy	
GBC	<i>ARID1A</i>	Potential sensitivity to <i>EZH2</i> inhibitors or immunotherapy	Wardell <i>et al</i> [124]
	<i>CDKN2A</i> loss/mutation	Resistant to chemotherapy	Nakamura <i>et al</i> [125]

CRC: Colorectal cancer; HCC: Hepatocellular carcinoma; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; IBS: Irritable bowel syndrome; GBC: Gallbladder cancer; MSI-H: Microsatellite instability-high; dMMR: Deficient mismatch repair; SNP: Single nucleotide polymorphism; EGFR: Epidermal growth factor receptor; MEK: Mitogen-activated protein kinase; PD-L1: Programmed death-ligand 1; ADA: Anti-drug antibody; TNF: Tumor necrosis factor; SSRIs: Selective serotonin reuptake inhibitors; 5-HT₃: 5-hydroxytryptamine type 3 (serotonin receptor); DPD: Dihydro pyrimidine dehydrogenase; 5-FU: 5-fluorouracil.

Gene therapy: Concepts and approaches

Gene therapy involves modifying or manipulating gene expression to treat or prevent disease at its root cause. In the context of GIT disorders, this can include gene replacement (to restore a nonfunctional or missing gene), gene enhancement (to boost expression of beneficial genes), gene overexpression (to increase the production of protective proteins), gene function blocking (to suppress harmful gene activity), or transgenic somatic cell transplantation (inserting genetically modified cells into target tissues). The core principle of gene therapy is to deliver therapeutic genetic material directly into the body, usually in the form of DNA or RNA, to modify cellular function. This can be done by introducing DNA sequences that code for beneficial proteins or enzymes, using short hairpin RNA to silence disease-causing genes, or applying advanced tools such as clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) to precisely edit the genome at specific loci. The goal is to achieve long-lasting expression of therapeutic genes at levels sufficient to alleviate or cure disease symptoms, while simultaneously minimizing the risk of adverse effects[149]. Therapeutic gene materials for diseases can include plasmid DNA, messenger RNA (mRNA), small interfering RNA, microRNA, and short hairpin RNA. Current gene therapy strategies are of two types: *Ex vivo* and *in vivo*. *Ex vivo* gene therapy involves removing cells from a patient, genetically modifying them in a controlled laboratory environment, and then reintroducing the altered cells back into the body. This method is commonly applied to blood cells, stem cells, or immune cells due to their accessibility and ability to be expanded and manipulated outside the body. The typical process includes cell extraction (*e.g.*, from bone marrow or peripheral blood), introduction of therapeutic genes using viral or non-viral vectors, expansion and rigorous testing for safety and efficacy, followed by reinfusion into the patient. One of the main advantages of *ex vivo* gene therapy is the high level of control it offers genetic modifications that can be precisely assessed, and risks are minimized before the cells are returned to the patient. However, it requires complex laboratory infrastructure and may not be feasible for all tissue types, especially those that are difficult to isolate or culture. In contrast, *in vivo* gene therapy involves the direct delivery of therapeutic genetic material into a patient's body, targeting specific tissues or organs without the need to remove cells. This is typically achieved through viral vectors [such as adeno-associated viruses (AAV) or lentiviruses] or non-viral delivery systems like lipid nanoparticles or polymer-based carriers. The genetic payload may consist of DNA for gene replacement, RNA for gene silencing, or tools like CRISPR/Cas9 for precise genome editing.

The major advantage of the *in vivo* approach is that it is less invasive and technically simpler compared to *ex vivo* methods, making it suitable for tissues and organs that are difficult to access or manipulate outside the body. However, it offers less control over the site and extent of gene expression, and there is a higher risk of immune reactions or off-target effects. *In vivo* approach targets long-lived, non-dividing cells, allowing sustained gene expression as long as the introduced DNA remains stable[149]. Although various gene therapies are approved by the Food and Drug Administration for several diseases (hemgenix, zolgensma) but very few are approved and others are under trial for GIT disorders. Examples of some gene therapy for disorders of the GIT are described in Table 12[150-164].

Delivery systems for gene-based therapies

Gene-delivery systems currently include both viral and non-viral carriers. Viral vectors such as retroviruses, AAV, adenoviruses, and lentiviruses use their natural ability to infect cells[165,166]. Non-viral vectors include lipid-based

Table 11 Gastrointestinal and hepatopancreatic biliary disorders targeted therapy based on genetic testing[128-148]

Gene/pathway	Targeted drug(s)	Clinical status and trial setting	Ref.
<i>KRAS G12C</i>	Sotorasib, adagrasib (+ cetuximab)	Colorectal cancer, FDA approved	Ros <i>et al</i> [128]
<i>EGFR</i> (mAB)	Cetuximab, panitumumab, necitumumab	Colorectal cancer, gastric, FDA approved	Xie <i>et al</i> [129]
<i>EGFR</i> TKI	Erlotinib, gefitinib, afatinib, osimertinib, amivantamab	Colorectal cancer, gastric cancer, FDA approved	Corvaja <i>et al</i> [130]
<i>VEGF</i>	Bevacizumab, aflibercept	Colorectal cancer, gastric cancer	Mahaki <i>et al</i> [131]
<i>BRAF V600E</i>	Encorafenib, dabrafenib	Colorectal cancer, gastric cancer	Elez <i>et al</i> [132]
<i>CLDN18.2</i>	Zolbetuximab	Gastric/GEJ adenocarcinoma	Shitara <i>et al</i> [133]
<i>NTRK</i> fusion (<i>NTRK1/NTRK2/NTRK3</i>)	Larotrectinib, entrectinib	CRC, pancreatic, cholangiocarcinoma, gastric, others	Manea <i>et al</i> [134]
PD-1 (<i>CD274</i> gene, checkpoint pathway)	Dostarlimab, camrelizumab ¹ , nivolumab and pembrolizumab (keytruda)	Hepatocellular carcinoma, gastric and esophagogastric cancer	Abou-Alfa <i>et al</i> [135]
<i>RET</i> fusion	Selpercatinib, pralsetinib, avelumab	Rare GI/HPB tumors (cholangiocarcinoma, pancreatic)	Li <i>et al</i> [136]
<i>FGFR2</i> fusion/rearrangement	Pemigatinib, futibatinib, infigratinib ¹	Intrahepatic cholangiocarcinoma	Hyung <i>et al</i> [137]
<i>IDH1</i> mutation	Ivosidenib	Cholangiocarcinoma	Carosi <i>et al</i> [138]
<i>BRCA1/BRCA2, PALB2</i> (HRD pathway)	Olaparib (PARP inhibitor)	Pancreatic adenocarcinoma (germline <i>BRCA</i>)	Alhusaini <i>et al</i> [139]
<i>VEGFR, FGFR, PDGFR, RAF</i> (angiogenesis/multikinase)	Sorafenib, lenvatinib, regorafenib, cabozantinib, pazopanib	Hepatocellular carcinoma	Kim[140]
<i>APC</i> mutation/ <i>COX2</i> pathway	Celecoxib (<i>COX2</i> inhibitor)	FAP	Steinbach <i>et al</i> [141]
<i>NR1H4</i> (<i>FXR</i> nuclear receptor)	Obeticholic acid	Primary biliary cholangitis	Floreani <i>et al</i> [142]
<i>AGXT</i> mutation (glyoxylate metabolism)	Lumasiran (RNAi against glycolate oxidase)	Primary hyperoxaluria type 1	Garrelfs <i>et al</i> [143]
<i>SERPINA1</i> mutation (<i>A1AT</i> deficiency, liver disease)	Fazirsiran, ARO-AAT (RNAi)	Alpha-1 antitrypsin liver disease	Strnad <i>et al</i> [144]
<i>ATP7B</i> mutation	Chelators (penicillamine, trientine); zinc	Wilson disease	
Anti-TNF agents	Infliximab, adalimumab	IBD	Feng <i>et al</i> [145]
IL-12/23 pathway	Ustekinumab (anti-IL-12/23)	IBD	Feng <i>et al</i> [145]
$\alpha 4\beta 7$ integrin/cell trafficking	Vedolizumab (gut-specific anti-integrin)	IBD	Feng <i>et al</i> [145]
JAK-STAT pathway	Tofacitinib (pan-JAK), upadacitinib (JAK1)	IBD	Liu <i>et al</i> [146]
PD-L1 antibody	Durvalumab (imfinzi), atezolizumab, tislelizumab	GBC, HCC	Li <i>et al</i> [147]
<i>MET</i> amplification/overexpression	Foretinib ¹ , cabozantinib (multi-target TKIs), glumetinib ¹	GBC, HCC, gastric, cholangiocarcinoma	Zhang <i>et al</i> [148]

¹Not Food and Drug Administration approved.

TKI: Tyrosine kinase inhibitors; PD-L1: Programmed death-ligand 1; PD-1: Programmed death-1; HRD: Homologous recombination deficiency; TNF: Tumor necrosis factor; COX2: Cyclooxygenase-2; IL: Interleukin; JAK-STAT: Janus kinase-signal transducer and activator of transcription; PARP: Poly (adenosine diphosphate-ribose) polymerase; RNAi: RNA interference; GEJ: Gastroesophageal junction; FDA: Food and Drug Administration; CRC: Colorectal cancer; GI: Gastrointestinal; HPB: Hepatopancreatic biliary; FAP: Familial adenomatous polyposis; IBD: Inflammatory bowel disease; GBC: Gallbladder cancer; HCC: Hepatocellular carcinoma.

carriers like lipid nanoparticles, polymer-based systems, naked DNA or RNA, inorganic nanoparticles, and peptide-based vectors. Lipid nanoparticles are widely used for mRNA delivery. Polymer-based vectors, such as polyethyleneimine or poly (lactic-co-glycolic acid), provide controlled release and tissue-specific delivery. Although non-viral vectors generally have lower transfection efficiency compared to viral vectors, they offer significant advantages such as low immunogenicity, ease of large-scale production, and the ability to carry larger genetic payloads, including CRISPR components

Table 12 Different gene therapy under research/evaluation[150-164]

Therapy/product	Target	Ref.
Alicaforsen (antisense targeting ICAM-1) (phase III)	Pouchitis, left-sided UC	Greuter <i>et al</i> [150]
Glybera (AAV1-LPL) (withdrawn)	Lipoprotein lipase deficiency (severe pancreatitis)	Ferreira <i>et al</i> [151]
Oncolytic AAV-DC-CTL (phase 1)	Stage IV gastric cancer	Yan <i>et al</i> [152]
CRISPRedited TIL therapy (phase 1 completed)	Metastatic GI cancers (colorectal, pancreas, gallbladder, esophagus, stomach)	Lou <i>et al</i> [153]
CTX131 (allogeneic, CRISPR-engineered CD70-CAR-T) (phase 1/2 trial)	Pancreatic/oesophageal cancers	Pal <i>et al</i> [154]
CAN2409 (HSV thymidine kinase gene + pro-drug) (phase 2a)	Pancreatic cancer	Garrett Nichols <i>et al</i> [155]
Mutogene cevumeran (personalized mRNA vaccine) (phase 1b)	Pancreatic ductal adenocarcinoma	Lopez <i>et al</i> [156]
GENEGUT (preclinical settings)	Crohn's disease	Hoffmann <i>et al</i> [157]
AAVrh.10mAnti-Eos, a serotype rh.10 AAV vector coding for an anti-Siglec-F monoclonal antibody (preclinical)	Eosinophil esophagitis	Camilleri <i>et al</i> [158]
Local delivery of an adenoviral vector expressing the HSV-tk gene (aglatimagene besadenovec, AdV-tk) followed by anti-herpetic prodrug	Pancreatic cancer	Aguilar <i>et al</i> [159]
Thymidine kinase-based gene therapy	HCC	Sangro <i>et al</i> [160]
Adenovirus-mediated double-suicide gene therapy	PDAC	Lee <i>et al</i> [161]
Oncolytic virus pelareorep (reolysin) (phase 1/2 trial)	PDAC	Noonan <i>et al</i> [162]
GVAX pancreas prime and <i>Listeria Monocytogenes</i> expressing mesothelin (CRS-207) boost vaccines (preclinical)	PDAC	Le <i>et al</i> [163]
TNF-erade biologic (phase 1)	Esophageal cancer	Chang <i>et al</i> [164]
GNT-0003 (phase III trial)	Crigler-Najjar syndrome	
Pexa-Vec (JX-594) (phase 3 trial)	HCC	
DTX401 (AAV8-G6Pase gene therapy) (phase 3 trial)	Glycogen storage disorder 1a	
DTX301 (avalotcagene ontaparvovec) (phase 3 trial)	Ornithine transcarbamylase deficiency	
UX701 (rivunatpagene miziparvovec) (AAV9) (phase 1/2 trial)	Wilson disease	
VTX-802 (preclinical study)	PFIC type 2 (BSEP)	

ICAM-1: Intercellular adhesion molecule 1; AAV: Adeno-associated virus; LPL: Lipoprotein lipase; DC: Dendritic cell; CTL: Cytotoxic T lymphocyte; CRISPR: Clustered regularly interspaced short palindromic repeats; TIL: Tumor-infiltrating lymphocyte; CAR T: Chimeric antigen receptor T-cell; CD: Cluster of differentiation; HSV: Herpes simplex virus; mRNA: Messenger RNA; AAVrh.10: Adeno-associated virus serotype rh.10; Siglec-F: Sialic acid-binding immunoglobulin-like lectin F; HSV-tk: Herpes simplex virus thymidine kinase; AdV-tk: Adenoviral vector carrying herpes simplex virus thymidine kinase gene; GVAX: Granulocyte-macrophage colony-stimulating factor secreting tumor cell vaccine; TNF-erade: Tumor necrosis factor-alpha encoding adenoviral vector; UC: Ulcerative colitis; GI: Gastrointestinal; PDAC: Pancreatic ductal adenocarcinoma; HCC: Hepatocellular carcinoma; PFIC: Progressive familial intrahepatic cholestasis; BSEP: Bile salt export pump.

[167]. Nanoparticle-mediated DNA delivery is a cost-effective alternative to AAV systems and enables gene expression without the need for knockout strategies. However, DNA delivery *via* lipid nanoparticles is often inefficient due to nuclear membrane barriers in resting hepatocytes[168]. In contrast, rapidly dividing enterocytes experience nuclear membrane breakdown, allowing nanoparticle-mediated gene expression in rodent models[169]. The GI tract provides unique access for gene therapy through oral, endoscopic, and rectal routes, making it an attractive target for treating GI disorders.

Hydrodynamic delivery is a non-viral gene transfer technique that uses rapid, high-volume injection to introduce nucleic acids into specific organs, most notably the liver. The method temporarily increases vascular permeability and cell membrane porosity, allowing efficient uptake of genetic material. This approach holds promise for safe, efficient, and localized gene therapy without the risks associated with viral vectors[165,166].

Gene editing in gastroenterology

Gene editing refers to a set of molecular technologies that enable precise alterations in the DNA of living organisms. The most widely used tool is CRISPR-Cas9, a revolutionary system adapted from bacterial immune defense, which allows targeted cutting and modification of genes with unprecedented ease and accuracy. Recent advances include base editing and prime editing, which offer even more precise and less disruptive methods of correcting single-point mutations without causing double-strand breaks. mRNA can also express gene-editing enzymes like Cas9, which only need transient expression to modify the genome. In a recent example, base editing, achieved through modified CRISPR enzymes, has shown significant progress, knocking out *PCSK9* in primate liver to upregulate *LDLR* and significantly decrease cholesterol levels[167]. Gene editing techniques are of two types: *Ex vivo* and *in vivo* techniques (Table 13)[168]. In the subsequent section, we describe CRISPR as a gene-editing tool and also highlight some of the newer gene-editing technologies.

CRISPR and gene editing

CRISPR is a family of highly homologous DNA sequences found in genomes of prokaryotic organisms and archaea. Initially discovered in 1987 in *Escherichia coli*[150]. Later, *CAS* genes were found to be associated with CRISPR, shifting the focus to proteins encoded by *CAS* genes[169]. Cas9 protein was of particular significance in establishing the CRISPR/Cas gene editing system. This genome-editing tool is called CRISPR technology[170]. The CRISPR gene editing involves four phases: Designing the experiment, delivery of CRISPR components, induction and repair of double-strand breaks and analysis of genetic edits.

CRISPR technology has potential roles in screening, diagnosis, and treatment of various GI disorders. CRISPR/Cas9 is not only used to study known driver mutations but also to identify and functionally characterize novel driver genes. For example, Yau *et al*[171] performed a CRISPR/Cas9 knockout screen of 19050 human coding genes in *KRAS*-mutated *vs* wild-type HCT116 CRC cells and uncovered pathways such as *NADK* and fructose metabolism (*KHK*) as *KRAS*-specific vulnerabilities and potential therapeutic targets. Although most of the CRISPR-mediated gene therapy studies have been performed in organoid models, an increasing number are now being conducted directly in humans. Li *et al*[172] found that corrected, a mutation of the WNT pathway gene β -catenin in the human CRC cell line HCT116 with CRISPR/Cas9 resulted in increased protein phosphorylation and reduced proliferation of CRC. Zhang *et al*[173] found that knocking *PDEF* out *via* CRISPR/Cas9 in the AGS gastric cell line decreased proliferation, migration and invasion of the cell. Seino *et al*[174] found that CRISPR/Cas9-based knockdown of *GATA6* resulted in WNT self-activation through upregulation of *WNT7B* in the previously WNT-non-producing subtype. Similar studies of CRISPR-mediated therapy are summarized in Table 14[153,175-177].

Apart from CRISPR, several newer gene-editing tools are available, which are summarized in Table 15.

Limitations of gene therapy and gene editing

The majority of present gene therapy is *via* AAV, which has many limitations. Firstly, the safety of the vector. Although AAV predominantly remains episomal after entering hepatocyte nuclei, a small fraction can randomly integrate into the host genome. This integration has been linked to an increased risk of hepatocellular carcinoma (HCC) in mouse models [178,179]. Secondly, AAV can induce T-cell responses against capsid proteins, causing loss of transgene expression[180]. Third, sustained expression remains a challenge. AAV largely stays episomal and is gradually lost during cell division. This is especially problematic in the GI tract, where rapid mucosal turnover (every 2-6 days) limits gene persistence in enterocytes unless intestinal stem cells in the crypts are permanently modified[181]. Fourthly, the efficiency of delivery, as AAV delivers in a fraction of cells within an organ, and at levels often lower than the wild-type cells[182]. Regarding gene editing, safety is the prime concern, considering the possibility of off-target effects or unintended base edits, *i.e.*, edits in the wrong place and mosaicism. Additionally, many rare genetic liver disorders are caused by hundreds of distinct mutations, making them less suitable for precise correction of a single point mutation through current gene-editing techniques[183]. Since there is a potential for misuse, genome editing should be managed through policy and regulation[184].

EMERGING TOOLS AND NEWER CONCEPTS

As we advance further into the era of precision medicine, a wide range of innovative concepts and technologies are steadily emerging. Precision medicine (also called personalized medicine) uses genomics, biomarkers, and data analytics to tailor medical care to the individual characteristics of each patient. It has 4 core components: Genomics, pharmacogenomics, biomarkers, and data analysis. Personalized to each disease, whether hereditary or somatic, precision medicine helps in incorporating genes as the basis of all disorders. It will help in screening, early diagnosis and therapeutic potential, whether target therapy or gene editing. Many newer tools have already been discussed in earlier sections; others are still in the experimental or early translational phase. These include novel approaches such as multi-omics integration (combining genomics, transcriptomics, proteomics, and metabolomics for precision medicine), spatial genomics, RNA therapies, epigenome editing, synthetic biology-based therapeutics, and next-generation RNA therapies. Advances in delivery systems, including nanoparticle-based vectors and exosome-mediated gene transfer, are also expanding therapeutic possibilities. Additionally, AI and machine learning (ML) are being increasingly applied to analyze large genomic datasets, enabling better prediction of disease risk, treatment response, and drug development. Some of these emerging concepts are summarized in Table 16[185-189].

Table 13 Gene editing techniques and their application

Gene editing techniques	<i>In vivo</i> gene editing	<i>Ex vivo</i> gene editing
Technique	CRISPR-Cas system is delivered by various vectors to disease-associated cells or organs of the body to correct the mutations or treat the cause of diseases	Targeted cells of a patient are extracted, isolated, edited, expanded, and delivered back to the same patient
Application	Treatment of monogenic genetic disorders	Cancer immunotherapy. Treatment of hereditary diseases. Viral infection inhibition

CRISPR-Cas: Clustered regularly interspaced short palindromic repeats-associated protein 9.

Table 14 Representative studies using clustered regularly interspaced short palindromic repeats in gastrointestinal disorders and malignancies[153,175-177]

Serial No.	Model/sample size	Disease	CRISPR target	Key findings	Ref.
1	Phase 1 trial; 12 patients with metastatic colorectal cancer	Metastatic CRC (human trial)	CISH knockout in autologous T cells	CRISPR-edited T cells were safe, feasible, and showed preliminary anti-tumor activity	Lou <i>et al</i> [153]
2	Phase 1 trial; 3 patients with advanced cancers (incl 1 GI malignancy)	Advanced solid tumors	Knockout of <i>TRAC</i> , <i>TRBC</i> , <i>PD-1</i> ; insertion of NY-ESO-1 TCR	Demonstrated safety and persistence of CRISPR-edited T cells in humans; proof of feasibility	Stadtmauer <i>et al</i> [175]
3	Ongoing; sample size approximately 20 planned	Solid tumors (GI cancers included)	Endogenous TCR knockout + NY-ESO-1 TCR insertion	Designed to enhance adoptive T-cell therapy; early feasibility data available	Clinical trial (No. NCT03399448)
4	Human colon organoids	Colorectal cancer modeling	DNA repair genes (<i>MLH1</i> , <i>MSH2</i> , <i>APC</i> , <i>TP53</i>)	Sequential CRISPR editing in organoids recapitulated colorectal tumorigenesis	Drost <i>et al</i> [176]
5	Human intestinal organoids	Tumor suppressor modeling	<i>PTEN</i> , <i>APC</i>	High-efficiency CRISPR editing showed functional loss-of-gene effects; robust platform for GI cancer studies	Skoufou-Papoutsaki <i>et al</i> [177]

GI: Gastrointestinal; CRISPR: Clustered regularly interspaced short palindromic repeats; CRC: Colorectal cancer; CISH: Chromogenic *in situ* hybridization; NY-ESO-1: New York esophageal squamous cell carcinoma-1; TCR: T-cell receptor.

Table 15 Newer techniques of gene editing tools and their applications in gastrointestinal tract disorders

Technique	Mechanism	GIT applications
CRISPR-Cas9/12/13	DNA or RNA targeting <i>via</i> guide RNA and nuclease	Cancer mutations (<i>APC</i> , <i>KRAS</i>), viral hepatitis, IBD models
Base/prime editing	Precise base or sequence correction without DSBs	<i>CFTR</i> mutations, <i>APC</i> mutations
ZFNs	DNA-binding proteins fused to nucleases	HBV suppression (preclinical)
TALENs	TALE DNA-binding fused to nucleases	Cancer cell targeting, liver disease models
Epigenome editing	dCas9 fused to activators/repressors	Regulation of PD-L1, IBD immune genes
RNAi (siRNA, ASO)	Degrade/block specific mRNAs	Lumasiran (<i>PH1</i>), fazirsiran (<i>A1AT</i> deficiency)

GIT: Gastrointestinal tract; CRISPR: Clustered regularly interspaced short palindromic repeats; ZFNs: Zinc finger nucleases; TALENs: Transcription activator-like effector nucleases; RNAi: RNA interference; ASO: Antisense oligonucleotides; siRNA: Small interfering RNA; mRNA: Messenger RNA; DSBs: Double-strand breaks; TALE: Transcription activator-like effector; dCas9: Dead clustered regularly interspaced short palindromic repeats-associated protein 9; IBD: Inflammatory bowel disease; HBV: Hepatitis B virus; PD-L1: Programmed death-ligand 1.

RNA therapies

RNA therapies work by modulating gene expression at the RNA level either by blocking, replacing, or editing RNA messages inside cells. These therapies don't typically alter DNA directly but instead influence how proteins are made, which can help treat diseases caused by faulty gene expression, inflammation, or toxic proteins. RNA therapies can target previously "undruggable" genes. These are highly specific and customized, with no permanent DNA change, making them safer than some gene therapies. Table 17 describes the current RNA therapies in GIT disorders[190-193].

Table 16 Newer concepts in genetic medicine[185-189]

Area	Key advancements	Ref.
Multi-omics integration	Combined use of genomics, transcriptomics, proteomics, and metabolomics to understand complex GI diseases	Zhao <i>et al</i> [185]
Polygenic risk scores	Using multiple low-risk variants to predict risk of diseases like IBD, colorectal cancer	Cross <i>et al</i> [186]
Single-cell sequencing	Helps identify cell-specific pathways in diseases like IBD, gastric cancer	Misra <i>et al</i> [187]
Organoid models	Patient-derived GI organoids used for drug testing, personalized therapy, and gene editing studies	Yang <i>et al</i> [188]
Epigenomics	Studying methylation, histone modifications, especially in GI cancers (<i>e.g.</i> , <i>MLH1</i> methylation in CRC)	Struhl[189]
Artificial intelligence	AI-driven prediction models, imaging-genomics integration for early diagnosis and prognosis	

GI: Gastrointestinal; IBD: Inflammatory bowel disease; AI: Artificial intelligence; CRC: Colorectal cancer.

Table 17 RNA therapies[150,190-193]

Type	Mechanism of action	Example use	Ref.
Antisense oligonucleotides	Single-stranded RNA/DNA binds mRNA blocks translation or triggers degradation (<i>via</i> RNase H)	Alicaforsen in IBD (targets ICAM-1 mRNA) (phase 2/3 study)	Greuter <i>et al</i> [150]
Small interfering RNA	Double-stranded RNA binds to target mRNA guides RISC complex degrades mRNA	<i>STNM01</i> in Crohn's disease (fibrosis gene <i>CHST15</i>) (phase 1)	Suzuki <i>et al</i> [190]
mRNA replacement therapy	Synthetic mRNA encoding a therapeutic protein is delivered translated into protein	mRNA vaccines, IL-10 mRNA for colitis. Arcturus "lunar" mRNA, IL-10 mRNA LNPs (phase 1/2 study)	Qin <i>et al</i> [191]
CRISPR-Cas9 mRNA	mRNA encodes Cas9 protein + guide RNA edits DNA directly <i>via</i> targeted cleavage	Casgevy (CRISPR for β -thalassemia) (FDA approved)	Parums[192]
RNA aptamers	Structured RNA molecules bind and inhibit specific proteins or receptors	Macugen for eye disease; potential GI targets in research (preclinical)	Nagpal <i>et al</i> [193]

CRISPR-Cas: Clustered regularly interspaced short palindromic repeats-associated protein 9; mRNA: Messenger RNA; RISC: RNA-induced silencing complex; IBD: Inflammatory bowel disease; ICAM-1: Intercellular adhesion molecule 1; IL-10: Interleukin 10; LNPs: Lipid nanoparticles; GI: Gastrointestinal; FDA: Food and Drug Administration.

MRNA therapies

MRNA gene therapy is an innovative approach that involves delivering synthetic mRNA into the body to direct cells to produce specific therapeutic proteins. Unlike DNA-based therapies, mRNA functions in the cytoplasm and does not integrate into the genome, making it a safer alternative with reduced risk of permanent genetic alterations. Delivered typically *via* lipid nanoparticles, mRNA therapy enables transient and controlled expression of proteins, which is particularly useful for diseases requiring short-term or repeat interventions. Some examples of mRNA therapies are described in Table 18.

Epigenome editing

Epigenetic alterations such as DNA methylation and histone modifications play a key role in the pathogenesis of GI cancers. These tumors often display a dual epigenetic profile: Global DNA hypomethylation alongside hypermethylation at CpG islands. Such changes are increasingly recognized for their diagnostic, prognostic, and therapeutic value. Targeting epigenetic regulators, such as histone acetyltransferase inhibitors, histone deacetylase inhibitors (HDACis), and DNA methyltransferase inhibitors (DNMTis) offers a promising therapeutic strategy. Agents like azacitidine (DNMTi), vorinostat (HDACi), hydralazine (DNMTi), and tucidinostat (HDACi) are currently in early-phase clinical trials, underscoring the potential of epigenetic therapy in GI cancers[194].

Role of AI in genetic medicine

AI and ML can integrate and transform big data into clinically useful diagnostic and therapeutic tools. The term genetic AI refers to the application of AI methods to bioinformatics data, including amino acid, DNA, and RNA sequences. Several studies have demonstrated that by generating clinical, diagnostic, and therapeutic algorithms, often in the form of decision-support systems or flowcharts, genetic AI can assist clinicians in making faster and more informed decisions. AI also enables precision diagnostics by integrating genetic profiles with histopathology and imaging, thereby facilitating earlier and more accurate detection of GI disorders. In addition, AI applications aid in risk stratification, prediction of disease progression, and planning of surveillance strategies. Kang *et al*[195] analyzed single-nucleotide polymorphism genotype data from 337 patients with Crohn's disease and demonstrated that a combined clinical-genetic model using ML algorithms predicted the need for early intestinal resection more accurately than clinical features alone. Garza-

Table 18 Messenger RNA therapy in disorders of gastrointestinal tract

Agent/platform	Target/indication (GIT)	Study type/phase
RNA-4157/V940 (Moderna)	Individualized neoantigen vaccine colorectal cancer	Phase 2b/3 trial undergoing
BioNTech iNeST/BNT-pipeline	Personalized or fixed mRNA cancer vaccines for CRC, pancreatic, HCC	Phase 1/2 trials
Gritstone GRANITE	Personalized neoantigen immunotherapy MSS colorectal cancer	Phase 2 trial
MSK/investigator-initiated mRNA vaccine	Personalized mRNA neoantigen vaccine pancreatic adenocarcinoma	Early phase trial
OX40 L mRNA (LNP delivery)	Immune costimulatory agonist mRNA for HCC	Preclinical

GIT: Gastrointestinal tract; LNP: Lipid nanoparticle; mRNA: Messenger RNA; CRC: Colorectal cancer; HCC: Hepatocellular carcinoma; MSS: Microsatellite stable.

Hernandez *et al*[196], using Genome-Wide Association Studies (GWAS) datasets from the United Kingdom IBD Genetics Consortium, showed that multivariate prediction analysis can identify previously unrecognized IBD-associated loci. Schophaus *et al*[197], analyzing United Kingdom Biobank data, reported that ML-based analysis revealed a higher manganese intake to be associated with a lower risk of non-alcoholic fatty liver disease (NAFLD). Wang *et al*[198] developed a tumor-infiltrating immune cell signature score, which provided a novel prognostic tool and potential guidance for immunotherapy in esophageal squamous cell carcinoma.

Microbiome and host genetics

A complex interplay between human gut microbiome, brain and gut is known to play a significant role in the pathophysiology of various GI disorders including disorders of gut-brain interaction: Irritable bowel syndrome (IBS), functional dyspepsia, obesity and metabolic syndrome, malignancies: Esophageal cancer, gastric cancer, CRC, pancreatic, and liver cancers. Further developments in neurogastroenterology have suggested microbial dysbiosis *i.e.*, altered composition, is one of the important factors associated with various disorders of GIT[199]. The composition of the gut microbiome is influenced by various factors including host genetics and environmental influences. Host genetics is integral in shaping the composition[200]. Metagenomics is a study of genetics of the prokaryotic genome including bacteria, fungi, and viruses contained in a sample. Sequencing of a hypervariable region in 16S or 18S ribosomal RNA genes of bacteria, internal transcribed spacer (ITS) 1 and ITS2 regions on 5.8S rRNA of fungal using NGS helps in the profiling of the species, which further helps in precision medicine[201,202].

Polygenic risk scoring

Several polygenic risk scoring (PRS) systems have been developed for CRC screening[203,204]. These scores can help identify individuals who may benefit from a colonoscopy at a younger age. Beyond screening, PRS can also be applied to stratify disease severity in CRC. Similarly, PRS has been shown to predict disease severity in chronic liver disease[205]. In IBD, Gettler *et al*[206] designed a PRS using genomic data from 32595 individuals, demonstrating its potential clinical utility. De Vincentis *et al*[207] demonstrated that incorporating PRS provides prognostic insights beyond established clinical and biochemical parameters in NAFLD. Similarly, Thomas *et al*[208] reported that combining PRS with hepatic fat content enhances the prediction of HCC risk. PRS quantifies an individual's genetic predisposition to various diseases by analyzing multiple genetic variants, which in turn helps in risk assessment and genetic counselling[209]. There are various limitations of PRS. Firstly, most PRS are based on European ancestry GWAS datasets and accuracy drops significantly in non-European populations due to allele frequency differences and linkage disequilibrium patterns[210]. Secondly, PRS requires large sample sizes and complex computational methods to achieve reliable prediction. Thirdly, it does not account for environmental and lifestyle factors, limiting real-world applicability. Fourthly, its predictive accuracy often falls short of clinical utility. Transferability across ancestries is inconsistent, influenced by trait heritability and the diversity of training data, with admixed populations posing additional challenges. Moreover, the lack of standardization hampers implementation. Finally, PRS is dynamic and its stability is affected as new genetic discoveries continuously reshape risk estimates[211].

Multi-omics techniques and approaches

Multi-omics techniques refer to the integrated analysis of multiple layers of biological data such as genomics, transcriptomics, proteomics, metabolomics, epigenomics, and microbiomics to gain a comprehensive understanding of disease mechanisms (Figure 4)[212]. In GIT diseases, such as CRC, IBD, IBS, and celiac disease, multi-omics helps identify disease-associated genetic variants, altered gene expression patterns, epigenetic modifications, and dysregulated metabolic pathways. For instance, integrating genomic and transcriptomic data can reveal mutations (like in *KRAS* or *APC*) and corresponding changes in gene expression that drive colorectal carcinogenesis[213]. Multi-omics database is a structured repository that integrates multiple layers of biological information collected from patients, healthy controls, or model systems. Some of the databases are IBD multi-omics database (IBD), the Cancer Genome Atlas (CRC, gastric cancer, liver cancer), clinical proteomic tumor analysis consortium (CRC proteogenomics), international cancer genome consortium (liver/HCC) and Human Microbiome Project (HMP) 2/gutMGene/GMrepo (microbiome-host integration). These databases provide valuable insights into how different components of multi-omics contribute to understanding

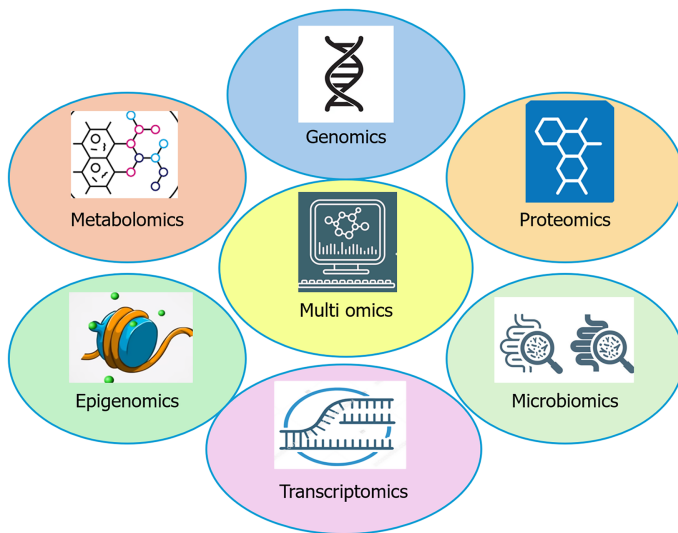


Figure 4 Various components of multi-omics.

disease mechanisms and guiding management. The HMP2 multi-omics study is a landmark effort that offered a comprehensive view of how the gut microbiome and its interactions with the host are altered in IBDs[214].

CHALLENGES AND ETHICAL CONSIDERATIONS

The emerging role of genetic medicine; poses ethical issues and several other issues of concern. Various issues and challenges are discussed below.

AAV toxicity

The liver acts as a major sink for systemically delivered AAV vectors, making hepatotoxicity the most frequent adverse event after intravenous administration. Recent reports of severe, immune-mediated liver injury, including fatalities at high doses, underscore vector-related immunotoxicity as a critical barrier to liver-directed gene therapies in GIT disorders [215].

Mutations and mosaicism

Since the technology is new and unpredictable, these errors are bound to occur and carry fatal consequences if germline mutations occur, affecting the individual and future generations. Off-target mutation *i.e.*, insertion of mutagenic gene. These off-target integrations can occur due to inaccurate gene delivery by the viral vector systems. Refinement of the vector systems may reduce this error[216,217]. Genetic mosaicism *i.e.*, different cells carry genetic information as a result of genetic mutations during the early development of an organism. This occurs when the vector can persist and transcribe, making it possible to further introduce the Cas protein into parts of already engineered cells and potentially initiate another cleavage, leading to mosaicism. This may impair embryo maturation[218].

Informed consent and privacy

All humans have the right to informed consent and privacy. Although it is feasible in the case of somatic gene therapy to have regulated informed consent. However, germline gene therapy raises complex regulatory challenges, particularly around who holds the authority to make informed decisions on behalf of future generations. Whether the consent of a future generation is required and, if so, who should express consent because embryos cannot consent to germline intervention[219,220]. Informed consent comes with the clause of privacy and data security. Stringent data protection policies and legislation should enforce absolute privacy and confidentiality.

Gene enhancement and misuse

Gene enhancement, *i.e.*, manipulating genes to improve the characteristics of an individual according to the interests of the person, remains a legitimate concern surrounding the application of gene therapy. Examples include the injection of recombinant human growth hormone, human recombinant erythropoietin. However, if the injection to children of normal height in an attempt to make them taller may create ethical issues[221]. The distinction between therapy and enhancement is often context-dependent and must be clearly defined.

Equity and fairness

Disparities exist in access to clinical genetic services and in the efficacy of those services. For instance, African-American women have poor access to *BRCA1* genetic testing than white women. As well, they are likely to receive ambiguous

genetic test results after exome sequencing, or be told that they have variants of unknown significance[222]. Although the global market for genetic testing is expanding rapidly, translating this progress into routine clinical practice remains limited and uneven across regions. Accessibility continues to be a significant barrier many healthcare systems, particularly in low- and middle-income countries, lack the infrastructure and trained personnel to offer advanced genetic services. Even in developed regions, disparities in availability between urban and rural healthcare centers persist.

For those who do gain access, affordability presents another major hurdle. Advanced genetic tests, multi-omics profiling, and personalized gene therapies are often prohibitively expensive, placing them out of reach for a large portion of the population and potentially widening health inequities.

Secondary findings in genetic analysis

Genomic sequencing frequently uncovers actionable secondary findings (*e.g.*, *BRCA*, Lynch genes) that have implications beyond the original indication. One should follow the guidelines from professional bodies to what to do with secondary findings.

High-profile events (Jesse Gelsinger's death, the He Jiankui's embryo edits) and recent AAV toxicities have driven stricter oversight and international governance recommendations[223]. For GIT applications where the liver is a common target, and tumor/germline testing often uncovers actionable hereditary findings, researchers must prioritize rigorous preclinical safety, robust consent and counselling, inclusive trial design, privacy protections, and long-term registries to ethically translate genomic advances.

CONCLUSION

With the development era of precision medicine, the genes and genetic medicine is going to take center stage in the management of many GI (GIT) disorders. The integration of genetic diagnostic testing, multi-omics approaches, targeted therapy, gene therapy, and gene editing has already transformed the landscape of gastroenterology. These advances enable a deeper understanding of disease mechanisms at the molecular level, allowing for more accurate diagnosis, individualized risk prediction, and tailored therapeutic strategies. In this evolving paradigm, it is imperative for gastroenterologists to keep pace with developments in genetic and genomic medicine, ensuring they remain at the forefront of patient care. Embracing precision medicine not only enhances clinical outcomes but also aligns with the future of personalized, predictive, and preventive gastroenterology.

FOOTNOTES

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