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Research Article

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Transforming the Landscape of Gastrointestinal Oncology: From Molecular Precision to Health Equity

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Abstract

Gastrointestinal (GI) malignancies remain a leading cause of global cancer morbidity and mortality. However, the past decade has witnessed a paradigm shift in their management driven by advances in molecular profiling, targeted therapies, immunotherapy, circulating tumor DNA (ctDNA), multidisciplinary care models, and supportive interventions. Concurrently, population-level research has revealed persistent disparities across socioeconomic, racial, and demographic strata that influence outcomes. This review synthesizes recent developments across major GI cancer subtypes — esophageal, gastric, hepatobiliary, pancreatic, colorectal, and neuroendocrine tumors — with emphasis on modern management strategies, emerging therapies, real-world evidence, and health equity considerations.

1. Introduction

GI cancers represent a heterogeneous group of diseases with distinct molecular drivers, clinical behaviors, and therapeutic vulnerabilities. Traditional cytotoxic chemotherapy has been supplemented or replaced by targeted agents, immune checkpoint inhibitors (ICIs), antibody-drug conjugates (ADCs), bispecific antibodies, adoptive cell therapies, and precision radiotherapy strategies.

Parallel to these therapeutic advances, large registry-based studies have highlighted substantial disparities in incidence, stage at diagnosis, access to care, and survival outcomes based on race, ethnicity, socioeconomic status, geography, nutritional status, and social determinants of health (SDOH). Recent studies by Dharia et al., Sivasubramanian et al., and others demonstrate persistent inequities particularly in biliary tract cancers, cholangiocarcinoma, and early-onset colorectal cancer (EOCRC) [1–3].

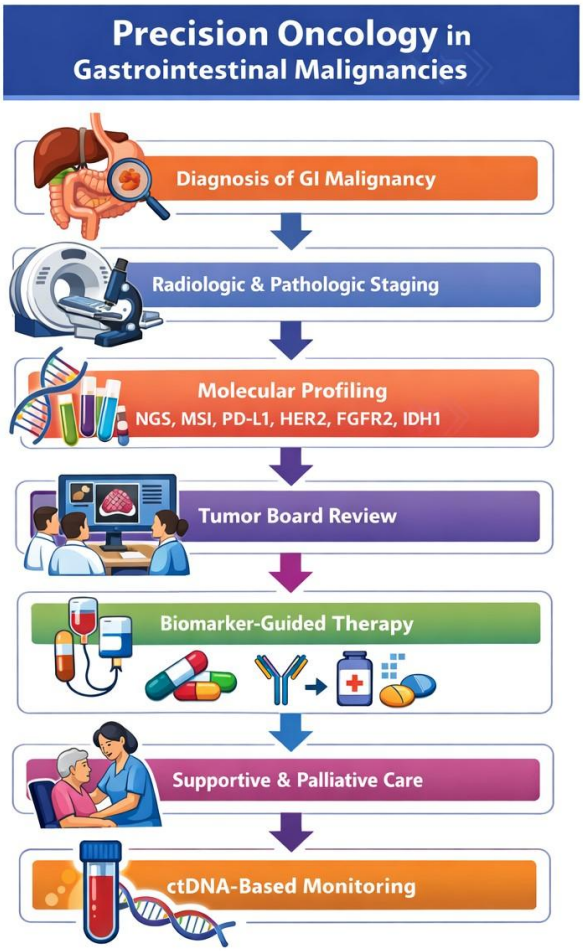

Figure 1. Stepwise integration of molecular diagnostics, multidisciplinary decision-making, and personalized treatment selection in gastrointestinal oncology.

1.1. Mechanism of action of immunotherapy in GI cancers

Immune checkpoint inhibitors (ICIs) and related immunotherapies work by **re-activating anti-tumor T-cell immunity** that is otherwise suppressed by tumor-intrinsic mechanisms and an immunosuppressive tumor microenvironment (TME). In GI malignancies, the magnitude and durability of benefit strongly depend on **tumor antigenicity** (e.g., MSI-H/dMMR, POLE/POLD1), **immune infiltration, PD-L1 expression**, and **TME context** (e.g., liver immune tolerance in HCC; desmoplasia in PDAC) [4-9].

1.2. Cancer–Immunity Cycle and Where ICIs Act

Anti-tumor immunity can be conceptualized as a cycle: tumor antigen release → antigen presentation → T-cell priming/activation → trafficking/infiltration → tumor recognition → tumor killing → further antigen release. Tumors interrupt this cycle via checkpoint pathways and immunosuppressive cytokines/cells. ICIs primarily act at the **T-cell activation and effector phases**, restoring cytotoxic function and clonal expansion of tumor-reactive lymphocytes [33,34].

1.3. PD-1/PD-L1 Axis: Restoring Exhausted T-Cell Function

PD-1 is an inhibitory receptor expressed on activated T cells; binding to **PD-L1/PD-L2** on tumor or immune cells transmits "stop" signals that reduce T-cell receptor signaling, cytokine production, proliferation, and cytotoxicity—features of **T-cell exhaustion**. Anti–PD-1 (e.g., pembrolizumab, nivolumab) and anti–PD-L1 (e.g., atezolizumab, durvalumab) antibodies prevent this interaction, enabling renewed killing of tumor cells [34,35].

1.4. Relevance in GI cancers:

- **Gastroesophageal cancers:** Many tumors exhibit inflamed/"hot" features with PD-L1 expression; adding PD-1 blockade to chemotherapy improves survival in biomarker-enriched populations, likely because chemotherapy increases antigen release and dendritic cell priming, providing more targets for reinvigorated T cells [20,21].

- **MSI-H/dMMR colorectal cancer:** High mutational burden creates abundant neoantigens, leading to pre-existing tumor-reactive T cells that are readily reactivated by PD-1 blockade—explaining the dramatic benefit observed clinically [27,29].

- **HCC:** The liver is an immune-tolerant organ; PD-1/PD-L1 blockade can reverse local T-cell dysfunction, and synergy occurs when combined with anti-angiogenic therapy that normalizes vasculature and reduces immunosuppressive signaling (see below) [24-36].

1.5. CTLA-4: Enhancing Priming and Broadening the T-Cell Repertoire

CTLA-4 is a checkpoint receptor that competes with CD28 for binding to B7 ligands (CD80/86) on antigen-presenting cells, restraining T-cell priming in lymph nodes. Anti–CTLA-4 therapy (e.g., ipilimumab, tremelimumab) enhances priming and can broaden the anti-tumor T-cell repertoire; it may also reduce suppressive regulatory T cells within the TME depending on context [35-37].

1.6. Relevance in GI Cancers:

- HCC (STRIDE/HIMALAYA concept): Brief CTLA-4 priming plus ongoing PD-L1 blockade aims to boost initial priming while sustaining effector function in the hepatic TME [30].

- MSI-H CRC and select settings: Dual checkpoint blockade can produce deep responses by combining enhanced priming (CTLA-4) with effector reinvigoration (PD-1) [27-29].

1.7. Why Combination Regimens Work: Chemo-, Anti-VEGF-, and Targeted-Immunotherapy Synergy

1.7.1. Chemo-immunotherapy (e.g., gastroesophageal cancers): Cytotoxic agents can increase tumor antigen release, induce immunogenic cell death, and reduce suppressive myeloid populations—creating a more permissive immune milieu for ICIs [20-33].

1.7.2. Anti-VEGF + ICI (e.g., HCC): VEGF signaling promotes abnormal vasculature, hypoxia, and immune suppression (Tregs, MDSCs). Anti-VEGF therapy can "normalize" vessels, improve T-cell trafficking, and reduce immunosuppressive cytokines, thereby potentiating PD-(L)1 blockade [24-36].

1.7.3. Targeted Therapy + ICI (selected scenarios): Some oncogenic drivers shape antigen presentation and immune infiltration; targeted therapy may modulate interferon signaling and antigen processing, potentially sensitizing to ICIs in specific biomarker-defined subsets [15-29].

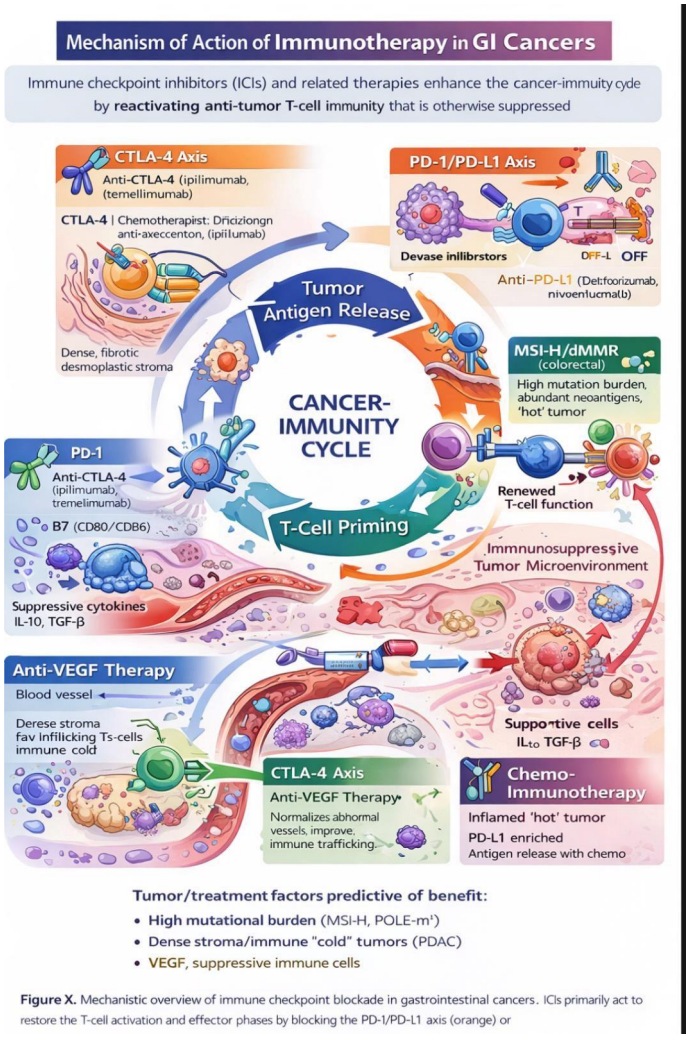

Figure X. Mechanistic overview of immune checkpoint blockade in gastrointestinal cancers. ICIs primarily act to restore the T-cell activation and effector phases by blocking the PD-1/PD-L1 axis (orange) or

1.8. Tumor Biology That Predicts Response in GI Cancers

High neoantigen load: MSI-H/dMMR and POLE-mutant tumors generate abundant neoantigens, fostering immune infiltration and sensitivity to PD-1 blockade [27-29]. ctDNA studies in hypermutated/POLE-mutated CRC demonstrate that immune-mediated tumor clearance can be tracked through rapid ctDNA decline, aligning biologic response with clinical benefit [16].

1.8.1. Immune-excluded or "cold" Tumors:

- PDAC commonly exhibits dense desmoplastic stroma, limited T-cell infiltration, suppressive macrophages, and low neoantigen visibility—making single-agent ICIs largely ineffective outside rare MSI-H cases, and driving exploration of vaccines, stromal modulation, and combinatorial strategies [19].

- Some MSS CRC similarly lacks sufficient antigenicity and effective infiltration, necessitating combination approaches and trial innovations [28-29].

1.9. Immune-Related Toxicity Mechanistically Mirrors Immune Activation

By lifting immune inhibition, ICIs can cause off-target immune activation against normal tissues (immune-related adverse events, irAEs). In GI oncology, clinically relevant toxicities include immune-mediated colitis, hepatitis, pancreatitis, and less commonly nephritis; prompt recognition and immunosuppression (e.g., corticosteroids) are essential to prevent complications [4,18]. Real-world reporting underscores the importance of standardized monitoring systems and early intervention pathways [4].

2. Esophageal and Gastric Cancers

2.1. Molecular Stratification

Key actionable biomarkers include:

- HER2 amplification
- PD-L1 combined positive score (CPS)
- MSI-H/dMMR
- Claudin 18.2 (CLDN18.2)
- FGFR2b overexpression
- EBV positivity

2.2. First-Line Management

Biomarker	Preferred Regimen
HER2+	Trastuzumab + chemotherapy ± pembrolizumab
PD-L1 CPS ≥ 5	Chemo-immunotherapy (nivolumab or pembrolizumab)
CLDN18.2	Zolbetuximab + CAPOX/FOLFOX
MSI-H	Single-agent immunotherapy

The CheckMate-649, KEYNOTE-590, KEYNOTE-811, and ESOPEC trials have reshaped frontline therapy [19–21].

2.3. Emerging Therapies

- ADCs: trastuzumab deruxtecan, zanidatamab zovodotin
- Bispecific antibodies (zanidatamab)
- Cellular therapies in EBV-positive gastric cancer
- Personalized perioperative strategies (ESOPEC trial)

3. Hepatocellular Carcinoma and Cholangiocarcinoma

3.1. Hepatocellular Carcinoma (HCC)

The IMbrave150 trial established atezolizumab + bevacizumab as first-line therapy. The HIMALAYA trial introduced durvalumab + tremelimumab.

3.2. Cholangiocarcinoma

Molecular testing is essential for:

- FGFR2 fusions
- IDH1 mutations
- BRAF V600E
- NTRK fusions
- HER2 amplification

Targeted therapies (pemigatinib, futibatinib, ivosidenib, dabrafenib/trametinib) and immunotherapy combinations are now standard for biomarker-selected patients [16-22].

Multidisciplinary models incorporating hepatology, interventional radiology, and oncology improve outcomes.

Cancer Type	Biomarker	Therapeutic	Implication
Esophagogastric	HER2	Trastuzumab ± pembrolizumab	[11,21]
Esophagogastric	CLDN18.2	Zolbetuximab	[26]
Colorectal	MSI-H/dMMR	Pembrolizumab, nivolumab	[27]
Colorectal	BRAF V600E	Encorafenib + cetuximab	[27]
Cholangiocarcinoma	FGFR2 fusion	Pemigatinib, futibatinib	[15]
Cholangiocarcinoma	IDH1 mutation	Ivosidenib	[23]

Pancreatic	BRCA1/2	PARP inhibitors	
Tumor-agnostic	NTRK fusion	Larotrectinib, entrectinib	[29]

Table 1: Key Actionable Biomarkers in Gastrointestinal Malignancies

cancer	First-Line Therapy	Ref
Esophagogastric	Chemotherapy + nivolumab/pembrolizumab	[20,21]
Hepatocellular carcinoma	Atezolizumab + bevacizumab	[24]
Cholangiocarcinoma	Gemcitabine + cisplatin ± durvalumab	[23]
Pancreatic adenocarcinoma	FOLFIRINOX or gemcitabine/nab-paclitaxel	[19]
MSI-H colorectal	Pembrolizumab	[27]
Neuroendocrine tumors	SSA → PRRT	[8]

Table 2: Standard First-Line Systemic Therapy by Gi Cancer Type

Determinant	Impact on Outcomes	Ref
Race/ethnicity	Worse survival in biliary and NETs	[1,3,8]
Income	Later stage at diagnosis	[1]
Rurality	Reduced access to trials	[10]
Marital status	Improved CRC survival when married	[10]
Nutrition	Higher mortality with malnutrition	

Table 3: Social Determinants Influencing GI Cancer Outcomes

4. Pancreatic Ductal Adenocarcinoma (PDAC)

4.1. Standard Management

Setting Preferred Strategy

Resectable Surgery + adjuvant modified FOLFIRINOX
Borderline resectable Neoadjuvant chemotherapy ± chemoradiation
Metastatic FOLFIRINOX or gemcitabine/nab-paclitaxel

4.2. Precision Oncology in PDAC

- Germline BRCA1/2 → PARP inhibitors
- KRAS G12C/D inhibitors (emerging)
- Claudin 18.2 targeting
- Tumor vaccines (GVAX, mRNA platforms)
- TME modulation

4.3. Complications and Supportive Care

Portal vein thrombosis significantly worsens outcomes [7]. Nutritional optimization is critical due to high prevalence of cachexia and malnutrition [6].

5. Colorectal Cancer (CRC)

5.1. Early-Onset CRC

Rising incidence in younger populations with higher metastatic burden and distinct biology (bone metastasis prognostic implications shown by Vadehra et al.) [2].

5.2. Biomarker-Driven Therapy

- MSI-H → pembrolizumab or nivolumab ± ipilimumab
- BRAF V600E → encorafenib + cetuximab
- HER2 → trastuzumab-based regimens
- POLE mutations → exceptional immunotherapy responses [17]

5.3. ctDNA

ctDNA is increasingly used for minimal residual disease (MRD) detection, recurrence prediction, and treatment escalation/de-escalation.

6. Neuroendocrine Tumors (NETs)

Small intestinal NETs exhibit survival disparities by race and socioeconomic status [8]. Management includes:

- Somatostatin analogs
- PRRT (177Lu-DOTATATE)
- Targeted agents (everolimus, sunitinib)
- Liver-directed therapies

7. Immunotherapy in GI Malignancies

7.1. Current Role

ICIs are standard in:

- MSI-H CRC
- PD-L1 high gastroesophageal cancers
- HCC (combination regimens)
- Select biliary cancers

7.2. Toxicity and Management

GI adverse events including colitis and hepatitis are common and require standardized monitoring and early intervention [4].

8. Supportive Care and Nutrition

Protein-energy malnutrition predicts poor survival and increased hospitalization [6]. Early nutritional intervention, pancreatic enzyme replacement, and palliative integration improve outcomes and quality of life.

9. Health Disparities and Social Determinants

Disparities in survival persist across GI cancers influenced by:

- Race/ethnicity
- Income and insurance
- Rurality
- Marital status and social support [10,11]

Addressing disparities requires policy reform, community outreach, decentralized trials, and inclusive research practices.

10. Future Directions

- Multi-omics-driven treatment
- AI-guided imaging and pathology
- Personalized vaccines
- Microbiome-modulated immunotherapy
- Decentralized and inclusive clinical trials

11. Conclusion

The management of GI cancers is undergoing rapid transformation through precision oncology, immunotherapy, advanced imaging, and supportive care integration. However, equitable implementation remains essential to ensure that advances translate into population-level survival benefits.

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