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GASTROENTEROLOGY AND HEPATOLOGY

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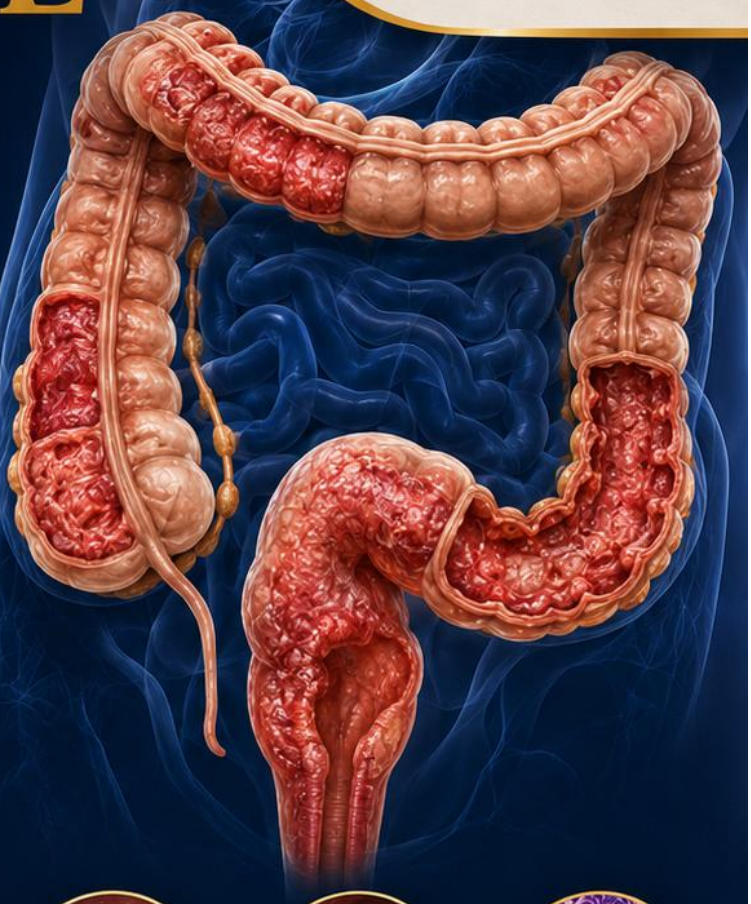
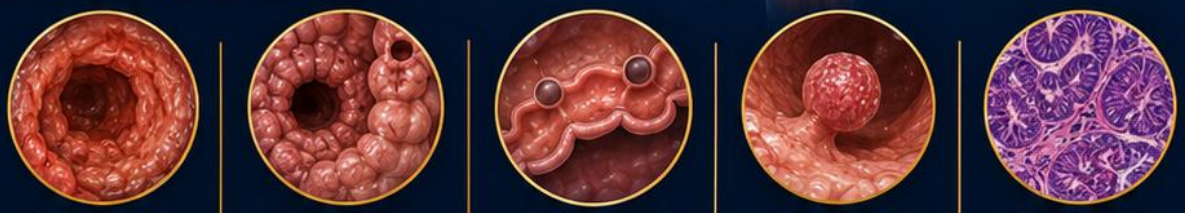
CHAPTERS 5-6

IBD AND LARGE BOWEL DISEASES





KNOWLEDGE TODAY
EXCELLENCE TOMORROW

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Dedication

In loving memory of my mother,

who recently returned to the mercy of Allah.

Her love, prayers, patience, and sacrifices were among the greatest blessings of my life. Whatever good I achieve carries something of her guidance and support.

May Allah forgive her, have mercy upon her, illuminate her grave, and grant her the highest place in **Jannat al-Firdaws**.

This work is dedicated to her memory.

أسأل الله أن يرحم أمي رحمة واسعه وأن يدخلها الفردوس الأعلى من الجنة، ورجاءً أسألكم لها خالص الدعاء..

Chapters 5-6: IBD and Large Bowel Diseases

150 Original Consultant-Level Mechanism-Based MCQs

Scope: Chapter 5 **IBD** (**ulcerative colitis**, **Crohn** disease, complications, surgical management, postoperative care) and Chapter 6 large bowel diseases (CRC, polyps, polyposis syndromes, **IBS**, **radiation** colitis, **ischemic colitis**, microscopic colitis, diverticular disorders, and related mimics).

Design: 100 direct/short case MCQs + 50 moderate-to-long case scenarios. All questions are original and source-derived from the uploaded reference pool; no existing questions are reproduced.

Emphasis: receptor pharmacology, intracellular signaling, immune pathways, comparative pharmacology, biomarker biology, molecular carcinogenesis, and pathophysiologic reasoning.

Format: each item contains five options with four plausible distractors; correct answers are randomized; high-yield mechanism keywords are bolded in color.

A. Direct and short case scenarios

Question 1. IBD innate immunity

A 23-year-old man with ileal **Crohn** disease has **Paneth**-cell abnormalities and a **NOD2** risk variant. His examiner asks why this genotype predisposes to chronic intestinal inflammation rather than simple immune deficiency. Which mechanism is most coherent?

A. Excess epithelial IgE signaling causes immediate mast-cell degranulation after gluten exposure

B. Loss of **APC** prevents **beta-catenin** degradation in colonic stem cells

C. Direct neutralization of IL-4 and IL-13 prevents Th2-driven epithelial remodeling

D. Defective intracellular sensing of muramyl dipeptide disturbs **NF-kB**/**MAPK** cytokine calibration against luminal bacteria

E. Constitutive **MLH1** promoter methylation accelerates crypt base adenoma formation

Answer: D

Mechanism pearl: NOD2 is an intracellular bacterial peptidoglycan sensor; risk variants disturb innate immune handling of luminal bacteria, amplifying maladaptive inflammation.

Question 2. IBD autophagy

A woman with stricturing ileal **Crohn** disease has an **ATG16L1** risk allele. The faculty asks which cellular process links this allele to small-bowel disease phenotype.

A. Loss of mismatch repair causes microsatellite slippage in every epithelial division

B. Hyperactivation of **guanylate cyclase-C** increases chloride secretion and watery diarrhea

C. Inhibition of **alpha-4 beta-7** prevents lymphocyte entry into the lamina propria

D. Impaired **autophagy** and **Paneth**-cell granule handling alter antimicrobial defense at the ileal crypt base

E. S1P receptor blockade traps lymphocytes in lymph nodes

Answer: D

Mechanism pearl: ATG16L1 links **Crohn** disease to **autophagy**, **Paneth**-cell biology, and defective epithelial-microbial homeostasis.

Question 3. IBD Th17 axis

A 29-year-old man with **Crohn** disease responds to an **IL-23** p19 antibody after anti-TNF failure. Which immunologic logic best explains why this can work despite prior biologic failure?

A. It blocks H2 receptors on parietal cells and decreases m**uc**osal acid exposure

B. The drug suppresses **IL-23**-dependent maintenance of pathogenic **Th17**/**ILC** inflammation rather than neutralizing **TNF-alpha**

C. It ind**uc**es global B-cell depletion and prevents IgM rheumatoid factor formation

D. It chelates luminal **bile acid**s and red**uc**es colonic secretion

E. It replaces defective mismatch repair protein **PMS2**

Answer: B

Mechanism pearl: Anti-p19 therapy targets **IL-23** selectively, downstream of innate cytokine activation and upstream of **Th17**-type m**uc**osal inflammation.

Question 4. Anti-TNF pharmacology

A **Crohn** patient with deep ulcers improves rapidly after **infliximab**. Which mechanism is most relevant to the anti-inflammatory effect?

A. Direct activation of epithelial CFTR through **cGMP**

B. Neutralization of soluble and membrane **TNF-alpha** red**uc**es macrophage/T-cell activation and cytokine amplification

C. Methylation of **MLH1** promoter CpG islands

D. Irreversible depletion of circulating neutrophils

E. Competitive inhibition of potassium binding at the gastric proton pump

Answer: B

Mechanism pearl: TNF-alpha is a central cytokine amplifier in **IBD**; anti-TNF agents red**uc**e cytokine signaling, leukocyte recruitment, and tissue injury.

Question 5. Therapeutic drug monitoring

A patient loses response to **infliximab**. Trough level is undetectable and anti-drug antibody titer is high. Which mechanism best explains relapse?

A. The disease is now driven by **bile acid** malabsorption only

B. Immunogenic drug clearance has red**uc**ed effective **TNF-alpha** blockade

C. The drug has switched its target from **TNF-alpha** to **IL-23**

D. The patient has developed **Lynch** syndrome with **MSI**-high colitis

E. The colon has become resistant because **APC** is mutated

Answer: B

Mechanism pearl: Low trough plus high antibodies = pharmacokinetic failure due to immunogenicity; the strategy differs from mechanistic failure with adequate trough.

Question 6. Mechanistic failure

A woman with active **Crohn** colitis has an adequate **infliximab** trough and no anti-drug antibodies. Colonoscopy confirms ulcers and fecal **calprotectin** is high. What is the most mechanism-based interpretation?

A. Inflammation is persisting despite sufficient TNF blockade, suggesting mechanistic failure and need to switch pathway

B. The patient has **toxic megacolon** due to opioid withdrawal

C. The correct response is always to add cholestyramine

D. The assay proves functional bowel disease because drug level is adequate

E. The finding proves **CMV** colitis without tissue biopsy

Answer: A
Mechanism pearl: Adequate trough with objective inflammation implies the dominant inflammatory pathway is not sufficiently TNF-dependent.

Question 7. Vedolizumab

A patient with **UC** and recurrent systemic infections is offered **vedolizumab**. Which pharmacologic property best explains the relative gut selectivity?

A. CCR5 antagonism prevents HIV entry into macrophages

B. IL-4 receptor alpha blockade suppresses type 2 airway inflammation

C. Pan-**JAK** inhibition suppresses cytokine signaling in all hematopoietic tissues

D. **Alpha-4 beta-7** integrin blockade prevents lymphocyte binding to **MAdCAM-1** in intestinal venules

E. **TNF-alpha** neutralization disrupts granuloma maintenance throughout the body

Answer: D
Mechanism pearl: **Vedolizumab** targets **alpha-4 beta-7**/**MAdCAM-1** gut-homing, not global cytokine signaling.

Question 8. Natalizumab comparison

A board examiner contrasts **natalizumab** with **vedolizumab** in **Crohn** disease. Which mechanism explains the higher concern for progressive multifocal leukoencephalopathy with **natalizumab**?

A. Blockade of **IL-23** p19 increases JC virus replication directly

B. **S1P** receptor modulation increases **bile acid** synthesis

C. **Calcineurin** inhibition causes epithelial **MSI**

D. Broader alpha-4 integrin blockade impairs leukocyte trafficking outside the gut, including CNS immune surveillance

E. Selective **alpha-4 beta-7** blockade is confined to intestinal **MAdCAM-1** interactions

Answer: D
Mechanism pearl: The broader anti-alpha-4 effect explains PML concern; gut-selective **alpha-4 beta-7** blockade has a different trafficking profile.

Question 9. Ustekinumab

A **Crohn** patient with psoriasis responds to **ustekinumab**. Which cytokine target explains dual intestinal and skin efficacy?

A. **Alpha-4 beta-7** integrin on neutrophils

B. p40 subunit shared by **IL-12** and **IL-23**, modifying Th1 and **Th17** pathways

C. **JAK**2 catalytic site used only by erythropoietin

D. **MLH1** promoter CpG islands

E. p19 subunit shared by IL-4 and IL-13

Answer: B
Mechanism pearl: **Ustekinumab** blocks **IL-12**/23 p40; newer **IL-23** antibodies target p19 and spare **IL-12**.

Question 10. JAK inhibitors

A woman with moderate-severe **UC** responds to an oral small molecule after biologic failure. Her physician says it acts inside immune cells, not by binding a circulating cytokine. Which mechanism is correct?

A. Restoration of **APC**-dependent **beta-catenin** degradation

B. Blockade of **MAdCAM-1** adhesion from the endothelial side only

C. Luminal binding of **bile acid**s to prevent secretory diarrhea

D. **JAK** inhibition interrupts intracellular cytokine receptor signaling through **STAT** transcriptional programs

E. Fc-mediated monoclonal antibody neutralization of **TNF-alpha**

Answer: D

Mechanism pearl: **JAK** inhibitors are intracellular signal transd**uc**tion drugs; they affect multiple cytokine pathways using **JAK-STAT** signaling.

Question 11. S1P modulation

A **UC** patient receiving ozanimod develops lymphopenia. Which mechanism best explains both laboratory effect and therapeutic action?

A. Selective IL-5 receptor depletion of eosinophils

B. Urease inhibition within gastric m**uc**us

C. Activation of **guanylate cyclase-C** in colonocytes

D. **TNF-alpha** neutralization at granulomas

E. **S1P** receptor modulation retains lymphocytes in lymphoid tissue and red**uc**es circulating gut-trafficking cells

Answer: E

Mechanism pearl: **S1P** modulators red**uc**e lymphocyte egress from lymph nodes; the fall in lymphocyte count is mechanism-linked.

Question 12. Corticosteroids

A patient with acute severe **UC** improves on IV methylprednisolone within 72 hours. Which molecular effect best explains the broad rapid anti-inflammatory action?

A. Mutation reversal in **APC** and T**P53**

B. Direct irreversible binding to epithelial chloride channels

C. Gl**uc**ocorticoid receptor-mediated transcriptional repression of **NF-kB** and AP-1 inflammatory programs

D. Specific p19 blockade of **IL-23** only

E. Selective bacterial beta-gl**uc**uronidase inhibition

Answer: C

Mechanism pearl: Steroids act at n**uc**lear receptor level to broadly suppress cytokine transcription; they ind**uc**e remission but are not maintenance therapy.

Question 13. 5-ASA

A man with mild left-sided **UC** asks why mesalamine is used topically in colitis but not as the main therapy for transmural **Crohn fistula**. Which mechanism fits best?

A. It prevents **MLH1** methylation in **serrated** lesions

B. Mesalamine acts mainly at the m**uc**osal surface through local anti-inflammatory pathways including prostaglandin/leukotriene modulation

C. It closes **fistula**s by neutralizing transmembrane **TNF-alpha**

D. It repairs **NOD2** mutations in **Paneth** cells

E. It blocks **alpha-4 beta-7** throughout the body

Answer: B
Mechanism pearl: 5-ASA is topical and m**uc**osal; it is mechanistically mismatched to deep transmural fistulizing **Crohn** disease.

Question 14. Thiopurines

A **Crohn** patient develops profound leukopenia shortly after azathioprine. Genetic testing shows absent **TPMT** activity. Which mechanism explains toxicity?

A. **S1P** receptor internalization in lymph nodes

B. **MLH1** promoter methylation in hematopoietic stem cells

C. Direct inhibition of **guanylate cyclase-C** in enterocytes

D. Excess accumulation of active thioguanine n**uc**leotides causes myelotoxicity due to impaired **thiopurine** methylation

E. Immediate IgE-mediated mast-cell degranulation to azathioprine

Answer: D
Mechanism pearl: **TPMT** and **NUDT15** influence **thiopurine** metabolite toxicity; mechanism-aware testing prevents severe myelosuppression.

Question 15. Methotrexate

A patient with steroid-dependent **Crohn** disease is started on weekly methotrexate. Which anti-inflammatory mechanism is most relevant at low weekly dosing?

A. Reversal of **APC** germline truncation

B. Direct killing of **C. difficile** spores

C. Selective blockade of **alpha-4 beta-7** integrin

D. Increased extracellular adenosine signaling and suppression of lymphocyte-driven inflammation

E. Immediate neutralization of **IL-23** p19

Answer: D
Mechanism pearl: Low-dose methotrexate has anti-inflammatory effects involving adenosine pathways, not simply cytotoxic folate antagonism.

Question 16. Calcineurin inhibitors

A patient with steroid-refractory acute severe **UC** receives **cyclosporine** as rescue therapy. Which mechanism explains its rapid effect?

A. **TNF-alpha** neutralization reverses fixed **fibrosis**

B. **BRAF** inhibition silences the **serrated** pathway

C. **Guanylate cyclase-C** activation increases stool water

D. **S1P** receptor agonism increases lymphocyte egress

E. **Calcineurin** inhibition prevents **NFAT**-dependent **IL-2** transcription and T-cell activation

Answer: E
Mechanism pearl: **Cyclosporine** and tacrolimus suppress T-cell activation through **calcineurin**/**NFAT**/**IL-2** signaling.

Question 17. Fecal calprotectin

A patient with treated **Crohn** disease reports pain but has normal **CRP** and very low fecal **calprotectin**. Which interpretation is most defensible?

A. Low neutrophil-derived luminal inflammatory signal argues against active m**uc**osal inflammation as the pain driver

B. Low **calprotectin** proves absence of any **stricture** or **fistula**

C. Low **calprotectin** confirms microscopic colitis

D. Low **calprotectin** proves **Lynch** syndrome is absent

E. Low **calprotectin** is a direct measure of **TNF-alpha** trough level

Answer: A

Mechanism pearl: Calprotectin reflects neutrophilic intestinal inflammation; it helps separate inflammatory relapse from **IBS**-like symptoms.

Question 18. CRP biology

A man with severe ileal **Crohn** ulcers has a low **CRP** despite active disease. Which principle explains why **CRP** should not be used alone?

A. **CRP** is suppressed by all active **Crohn** ulcers

B. **CRP** is an IL-6-driven hepatic acute-phase reactant with interindividual variability and imperfect sensitivity

C. **CRP** is specific for **colorectal cancer** rather than inflammation

D. **CRP** measures fecal neutrophil migration directly

E. **CRP** is prod**uc**ed only by colonic goblet cells

Answer: B

Mechanism pearl: CRP is useful but not definitive; objective m**uc**osal or imaging assessment may be needed when biology and symptoms disagree.

Question 19. Serology

A patient has pANCA positivity and ASCA negativity. The examiner asks why this should not override endoscopic and histologic findings. What is the best reason?

A. ASCA positivity is required for **Crohn** diagnosis

B. Serologies are the gold standard for **dysplasia** surveillance

C. pANCA directly measures **IL-23** p19 activity

D. ASCA negativity excludes small-bowel **Crohn** disease

E. **IBD** serologies are supportive patterns with limited diagnostic specificity and cannot define disease phenotype alone

Answer: E

Mechanism pearl: IBD serology may support a phenotype but does not replace integrated clinical, endoscopic, radiologic, and histologic diagnosis.

Question 20. Mucosal healing

A **UC** patient has no diarrhea on steroids but sigmoidoscopy shows friability and ulcers. Which concept best explains why treatment should not rely only on symptoms?

A. Fecal **calprotectin** is unrelated to m**uc**osal neutrophils

B. Endoscopic inflammation always proves functional bowel disease

C. Steroids permanently prevent **colorectal cancer** risk

D. Symptom control proves **p53** mutation reversal

E. Clinical remission can dissociate from persistent m**uc**osal inflammation that predicts relapse and complications

Answer: E
Mechanism pearl: Treat-to-target uses objective inflammation because symptoms can underestimate m**uc**osal disease.

Question 21. Anti-TNF and TB

A **Crohn** patient begins anti-TNF therapy without TB screening and later develops disseminated tuberculosis. Which immune mechanism explains the risk?

A. **TNF-alpha** blockade directly mutates **NOD2**

B. **TNF-alpha** neutralization increases gastric acid secretion

C. **TNF-alpha** is required for granuloma maintenance and macrophage containment of mycobacteria

D. **TNF-alpha** is required for **MLH1** promoter methylation

E. **TNF-alpha** blockade activates **alpha-4 beta-7** trafficking

Answer: C
Mechanism pearl: TNF blockade can destabilize latent granulomas; this is a classic mechanism-based safety issue.

Question 22. HBV reactivation

A patient with prior hepatitis B exposure is planned for biologic plus steroid therapy for **IBD**. Why is HBV screening mechanistically necessary?

A. **Vedolizumab** converts HBV into HCV

B. Immunosuppression may remove immune control of residual HBV templates, allowing viral replication rebound

C. Steroids irreversibly block HBsAg secretion

D. **TNF-alpha** antibodies chelate **bile acid**s in bile canaliculi

E. Biologics directly methylate **MLH1** in hepatocytes

Answer: B
Mechanism pearl: HBV risk is not only drug toxicity; it is loss of immune surveillance over persistent viral reservoirs.

Question 23. Opportunistic infection

A **UC** patient on a **JAK** inhibitor develops multidermatomal zoster. Which mechanism best explains increased susceptibility?

A. Interference with cytokine signaling used in antiviral immune surveillance, including interferon-related pathways

B. Loss of **APC** tumor suppressor function

C. Direct activation of VZV DNA polymerase

D. Blockade of gut **MAdCAM-1** only

E. Neutralization of luminal **bile acid**s

Answer: A
Mechanism pearl: **JAK** pathways participate in antiviral cytokine signaling; zoster risk is pharmacologically coherent.

Question 24. PSC-UC cancer risk

A 34-year-old man has PSC and apparently mild pancolitis. Which reasoning best explains why colonoscopic surveillance is intensified?

A. PSC prevents right-sided **dysplasia** from developing

B. PSC makes fecal **calprotectin** falsely low in all patients

C. PSC converts **UC** into microscopic colitis

D. PSC-**IBD** carries disproportionate colorectal neoplasia risk despite sometimes mild colitis symptoms

E. PSC eliminates the need for histologic assessment

Answer: D
Mechanism pearl: PSC-associated colitis can be clinically quiet but cancer-risk enriched, so symptom severity is misleading.

Question 25. Backwash ileitis

A patient with severe pancolitis has mild terminal ileal erythema. Biopsies lack granulomas and deep fissures. Which mechanism-based distinction favors backwash ileitis over **Crohn** ileitis?

A. Contiguous reflux/inflammatory extension from severe pancolitis without transmural granulomatous ileal disease

B. **Alpha-4 beta-7** blockade causing ileal apoptosis

C. **CMV** endothelial inclusions localized to the ileum

D. **MLH1**-deficient **serrated** pathway carcinoma

E. **NOD2**-related **Paneth**-cell dysfunction with skip ileitis

Answer: A
Mechanism pearl: Backwash ileitis is mild contiguous terminal ileal inflammation in pancolitis; **Crohn** ileitis is often patchy, transmural, and complicated.

Question 26. Toxic megacolon

A hospitalized **UC** patient with severe colitis develops colonic dilation, fever, tachycardia, and systemic toxicity. What mechanism best explains the dilation?

A. Functional **visceral hypersensitivity** dilates the colon

B. **Vedolizumab** causes immediate colonic denervation

C. **APC** mutation expands the crypt stem-cell compartment

D. **Bile acid** sequestration causes mechanical obstruction

E. Severe transmural inflammatory mediator release impairs neuromuscular function and smooth-muscle tone

Answer: E
Mechanism pearl: **Toxic megacolon** is inflammatory paralysis plus systemic toxicity; antidiarrheals and opioids can worsen it.

Question 27. CMV colitis in IBD

A steroid-refractory **UC** patient has large deep ulcers. Blood **CMV** PCR is low-positive. What is the most mechanism-based next diagnostic principle?

A. **CMV** is diagnosed by fecal **calprotectin** level

B. Tissue diagnosis is needed because clinically significant **CMV** colitis reflects viral cytopathic injury in colonic tissue

C. **CMV** colitis is defined by anti-drug antibodies

D. A negative stool culture excludes **CMV** colitis

E. Serum PCR alone proves **CMV** is driving all ulcers

Answer: B
Mechanism pearl: In steroid-refractory colitis, **CMV** must be assessed in tissue; viremia alone can mislead.

Question 28. C difficile and IBD flare

A patient with known **UC** presents with increased bloody diarrhea after antibiotics. The team plans steroid escalation. Which mechanism-based step prevents a dangerous error?

A. Measure **APC** mutation burden before giving steroids

B. Test for **C. difficile** because toxin-mediated epithelial injury can mimic or trigger an **IBD** flare

C. Assume symptoms prove anti-TNF failure

D. Give cholestyramine first because all post-antibiotic diarrhea is **bile acid**-mediated

E. Avoid stool testing because **UC** excludes infection

Answer: B
Mechanism pearl: IBD activity and infection can coexist; **C. difficile** toxins disrupt epithelial cytoskeleton and barrier integrity.

Question 29. Crohn fibrosis

A **Crohn** patient has a short ileal **stricture** with obstructive symptoms but minimal ulceration and low **calprotectin**. Why may biologic escalation be insufficient?

A. Fibrostenotic extracellular matrix remodeling may persist without active cytokine-driven inflammation

B. **JAK** inhibition dissolves mature collagen directly

C. **S1P** modulation reverses surgical adhesions

D. All **Crohn** **stricture**s are reversible with mesalamine

E. Low **calprotectin** proves there is no narrowing

Answer: A
Mechanism pearl: Inflammatory and fibrotic **stricture**s differ; anti-inflammatory therapy cannot reliably reverse fixed **fibrosis**.

Question 30. Fistulizing Crohn

A patient with perianal **Crohn** disease has a fluctuant abscess and complex **fistula**. What is the most mechanism-based sequence?

A. Proceed directly to **IPAA**

B. Start high-dose loperamide to reduce **fistula** output before drainage

C. Avoid imaging because **fistula**s are mucosal only

D. Drain sepsis first, then combine seton/control of inflammation with biologic therapy targeting transmural disease

E. Give mesalamine because **fistula**s are superficial ulcers

Answer: D
Mechanism pearl: Perianal **Crohn** **fistula**s are transmural and septic complications; source control and immune therapy are complementary.

Question 31. Postoperative Crohn recurrence

A man undergoes ileocolic resection for penetrating **Crohn** disease. Six months later ileocolonoscopy shows aphthous ulcers in the neoterminal ileum. Which concept explains surveillance?

A. Surgery removes the immune predisposition permanently

B. Postoperative **Crohn** recurrence begins only in the rectum

C. Endoscopic recurrence often precedes symptoms and guides early prevention of clinical recurrence

D. Fecal occult blood testing replaces ileocolonoscopy

E. Symptoms always precede m**uc**osal recurrence

Answer: C
Mechanism pearl: After ileocolic resection, recurrence commonly appears at the neoterminal ileum before symptoms.

Question 32. Postoperative prophylaxis

A smoker with prior penetrating ileal **Crohn** disease has ileocolic resection. Which mechanism-based rationale supports early prophylactic biologic therapy rather than waiting for severe symptoms?

A. Smoking protects **Crohn** patients from postoperative recurrence

B. All recurrence is **bile acid** diarrhea

C. High-risk phenotype predicts early cytokine-driven endoscopic recurrence that can be suppressed before str**uc**tural damage

D. Biologics prevent adhesions by dissolving fibrin directly

E. Endoscopic recurrence is unrelated to later clinical disease

Answer: C
Mechanism pearl: Risk-stratified postoperative therapy targets early immune recurrence, particularly in smokers and penetrating disease.

Question 33. Bile acid diarrhea after ileal disease

A **Crohn** patient with limited terminal ileal resection develops watery diarrhea that improves with cholestyramine. Which mechanism explains the response?

A. Excess **bile acid**s entering the colon stimulate secretion and motility; sequestration red**uc**es this effect

B. The diarrhea is caused by **MLH1** promoter methylation

C. The drug replaces pancreatic lipase

D. Cholestyramine activates **JAK-STAT** signaling

E. Cholestyramine neutralizes **TNF-alpha** in the lamina propria

Answer: A
Mechanism pearl: Limited ileal dysfunction causes **bile acid** diarrhea; extensive ileal loss may instead deplete the **bile acid** pool and cause steatorrhea.

Question 34. Anemia of inflammation

A patient with active **Crohn** colitis has low serum iron, low transferrin saturation, high ferritin, and high **CRP**. Which mechanism best explains this pattern?

A. IL-6-driven **hepcidin** ind**uc**tion traps iron in macrophages and red**uc**es intestinal iron export

B. **APC** mutation directly increases transferrin saturation

C. **S1P** receptor activation blocks ferritin synthesis

D. **Guanylate cyclase-C** activation chelates serum iron

E. **MUTYH** deficiency causes iron malabsorption

Answer: A
Mechanism pearl: Inflammatory anemia is **hepcidin**-mediated functional iron restriction; it can coexist with absolute iron deficiency.

Question 35. Thrombosis in IBD

A hospitalized patient with severe **UC** is not bleeding heavily but has active inflammation. Why is pharmacologic VTE prophylaxis usually emphasized?

A. **UC** patients are anticoagulated to suppress **TNF-alpha**

B. VTE prophylaxis reduces fecal **calprotectin** directly

C. Colectomy risk is determined by INR only

D. Thrombosis occurs only after biologic infusion

E. Systemic inflammation creates a hypercoagulable state with endothelial activation and increased thrombotic risk

Answer: E
Mechanism pearl: Active **IBD** is prothrombotic; bleeding fear should be balanced against high VTE risk.

Question 36. NSAIDs in IBD

A man with quiescent **Crohn** disease takes frequent NSAIDs for back pain and then develops ileocolitis. Which mechanism plausibly contributes?

A. NSAIDs restore **NOD2** signaling and trigger immune rebound

B. NSAIDs cause **MLH1** germline mutation

C. NSAIDs selectively activate **alpha-4 beta-7**

D. NSAIDs directly block **IL-23** p19

E. Cyclooxygenase inhibition weakens mucosal prostaglandin-dependent defense and may exacerbate intestinal injury

Answer: E
Mechanism pearl: NSAIDs can injure mucosa and may precipitate **IBD** activity in susceptible patients.

Question 37. Smoking

A 26-year-old smoker with ileal **Crohn** disease asks why stopping smoking is part of **IBD** management. Which mechanism-based statement is most defensible?

A. Smoking reliably induces **mucosal healing** in **Crohn** disease

B. Smoking prevents stricturing disease by inhibiting collagen

C. Smoking worsens **Crohn** outcomes and postoperative recurrence despite its complex epidemiologic relationship with **UC**

D. Smoking abolishes **TNF-alpha** production in macrophages

E. Smoking excludes the need for biologic therapy

Answer: C
Mechanism pearl: Smoking is harmful in **Crohn** disease and predicts recurrence; its apparently protective association in **UC** should not be generalized.

Question 38. EIMs

A patient with **UC** has peripheral arthritis that flares with colitis. Another has ankylosing spondylitis despite quiet bowel disease. Which concept explains the difference?

A. Axial disease is mediated by **bile acid** malabsorption

B. Peripheral arthritis is caused by colorectal adenomas

C. All EIMs prove **CMV** colitis

D. All EIMs disappear after mesalamine enemas

E. Some extraintestinal manifestations parallel gut inflammation whereas axial disease may run independently

Answer: E
Mechanism pearl: EIM behavior varies: peripheral arthritis and erythema nodosum often track colitis; PSC and axial disease may not.

Question 39. Monogenic VEO-IBD

An infant has severe colitis, perianal disease, recurrent infections, and consanguineous parents. Which mechanism should be considered before labeling typical **Crohn** disease?

A. Sporadic **MLH1** methylation causing **serrated** polyposis

B. Somatic **KRAS** mutation in a villous adenoma

C. Adult-onset **visceral hypersensitivity** from **IBS**

D. A monogenic defect such as IL-10 receptor signaling failure causing uncontrolled early mucosal inflammation

E. Age-related **ischemic colitis** at a watershed area

Answer: D
Mechanism pearl: Very-early-onset severe **IBD** can reflect monogenic immune defects; therapy may differ radically.

Question 40. Barrier function

A translational study in **UC** shows disrupted tight junctions before severe ulceration. Which mechanism links barrier injury to chronic inflammation?

A. Barrier dysfunction is diagnostic of **IBS** only

B. Barrier loss reverses **p53** mutations

C. Increased epithelial permeability permits luminal antigen exposure to lamina propria immune cells

D. Tight junction disruption prevents all leukocyte trafficking

E. Barrier loss suppresses dendritic-cell activation

Answer: C
Mechanism pearl: IBD emerges from failed homeostasis among epithelial barrier, **microbiome**, genetics, and immune response.

Question 41. Dysbiosis

A **Crohn** trial investigates microbial signatures rather than only host cytokines. Which rationale best supports this?

A. The **microbiome** is irrelevant once **TNF-alpha** is present

B. **Microbiome** testing replaces colonoscopy for **dysplasia**

C. **Dysbiosis** proves **Lynch** syndrome

D. **Dysbiosis** can alter antigenic stimulation, epithelial metabolites, and innate/adaptive immune tone

E. Bacteria produce **APC** germline mutations in every patient

Answer: D
Mechanism pearl: IBD pathogenesis involves **microbiome**-host immune interaction, not a single cytokine alone.

Question 42. IL-22

A study shows impaired epithelial repair during active colitis despite intense inflammation. Which cytokine is most plausibly linked to epithelial barrier repair and antimicrobial programs?

A. CEA from adenocarcinoma cells

B. **PMS2** from mismatch repair complexes

C. IgE from mast cells acting on parietal cells

D. **IL-22** from innate/adaptive lymphoid cells acting on epithelial cells

E. Gastrin from antral G cells

Answer: D

Mechanism pearl: **IL-22** is an epithelial-facing cytokine involved in barrier defense and repair; immune activation is not uniformly damaging.

Question 43. IL-10 tolerance

A child with severe colitis has a mutation impairing IL-10 receptor signaling. What is the central immunologic defect?

A. Failure of epithelial chloride secretion through CFTR

B. Failure of **serotonin** reuptake by SERT

C. Failure of **APC**-mediated **beta-catenin** degradation

D. Failure of **bile acid** conjugation in hepatocytes

E. Failure of anti-inflammatory regulatory signaling that restrains macrophage and T-cell responses to intestinal microbes

Answer: E

Mechanism pearl: IL-10 signaling is essential for m**uc**osal immune tolerance; loss can cause severe infantile enterocolitis.

Question 44. Biologic plus thiopurine

A young man with **Crohn** disease is placed on **infliximab** plus azathioprine. Which benefit and risk pair is mechanistically coherent?

A. Red**uc**ed **bile acid** secretion but increased adenoma formation

B. Red**uc**ed anti-drug antibody formation but increased immunosuppression-related lymphoma/infection concern

C. Direct collagen dissolution but increased **structure**s

D. Increased **alpha-4 beta-7** trafficking but red**uc**ed gut inflammation

E. Restored **NOD2** genotype but increased **CMV** DNA polymerase activity

Answer: B

Mechanism pearl: Combination therapy can improve anti-TNF pharmacokinetics by red**uc**ing immunogenicity, but safety tradeoffs matter.

Question 45. IL-23 p19 vs p40

A fellowship question asks why an **IL-23** p19 inhibitor is not identical to **ustekinumab**. Which explanation is correct?

A. p19 blockade treats only **IBS** by **serotonin** modulation

B. p19 blockade is a **JAK** inhibitor and p40 blockade is an **S1P** modulator

C. p19 blockade inhibits **TNF-alpha** and p40 blockade inhibits integrins

D. p19 blockade selectively inhibits **IL-23** while p40 blockade inhibits both **IL-12** and **IL-23**

E. p19 blockade targets **MLH1** and p40 targets **MSH2**

Answer: D
Mechanism pearl: Knowing cytokine subunits is exam-important: p40 = **IL-12**/23; p19 = **IL-23** selective.

Question 46. Integrin vs S1P

A resident confuses **vedolizumab** and ozanimod because both reduce lymphocyte entry into gut inflammation. Which comparison is most accurate?

A. Both neutralize soluble **TNF-alpha**

B. Both inhibit **calcineurin**/**NFAT**

C. Both activate chloride secretion through **cGMP**

D. **Vedolizumab** blocks intestinal adhesion; ozanimod reduces lymphocyte egress from lymphoid tissue

E. Both repair **ATG16L1** **autophagy**

Answer: D
Mechanism pearl: Both affect trafficking, but at different steps: adhesion/homing versus lymph-node egress.

Question 47. Acute severe UC rescue

A patient with acute severe **UC** fails IV steroids but has normal renal function and no uncontrolled infection. **Infliximab** and **cyclosporine** are discussed. Which comparison is mechanistically correct?

A. Both bind **bile acid**s in the colon

B. Both are **5-HT3** antagonists

C. **Cyclosporine** neutralizes **TNF-alpha** and **infliximab** blocks **NFAT**

D. **Infliximab** neutralizes **TNF-alpha**; **cyclosporine** inhibits **calcineurin**-dependent T-cell activation

E. **Infliximab** blocks **JAK1** while **cyclosporine** blocks **MLH1**

Answer: D
Mechanism pearl: Rescue drugs can both work rapidly but act through distinct immune mechanisms.

Question 48. Surgery and UC cure

A patient with refractory **UC** asks why colectomy can cure colitis but not necessarily all immune manifestations. Which reasoning is best?

A. Colectomy prevents ankylosing spondylitis by restoring **bile acid** uptake

B. Colectomy reverses HLA genotype

C. **UC** mucosal disease is colon-limited, but systemic immune-associated manifestations such as PSC may persist

D. PSC is caused by colonic stool burden only

E. **UC** is primarily small-bowel transmural disease

Answer: C
Mechanism pearl: Removing the colon removes the target organ for **UC**, but not every immune-associated disease process.

Question 49. Pouchitis

A post-**IPAA** patient develops increased stool frequency, urgency, and pouch ulcers that improve with antibiotics. Which mechanism is most likely?

A. **APC** mutation causing diffuse adenomas

B. Inevitable recurrent **UC** in native colon

C. Loss of gastric intrinsic factor

D. Acute appendicitis of the po**uc**h

E. Po**uc**h **dysbiosis** and m**uc**osal immune activation in a surgically created ileal reservoir

Answer: E
Mechanism pearl: Pouchitis is not simply **UC** in colon; it reflects po**uc**h **microbiome**-immune interaction.

Question 50. Crohn vs UC surgical planning

A patient labelled **UC** has skip ulcers, perianal **fistula**s, and small-bowel **stricture**s before planned **IPAA**. Why does this matter mechanistically?

A. Transmural **Crohn** biology increases risk of po**uc**h complications and makes **IPAA** selection hazardous

B. Small-bowel stricturing is caused by mesalamine response

C. Perianal **fistula** is typical uncomplicated **UC**

D. Skip lesions prove better po**uc**h outcomes

E. **IPAA** prevents all **Crohn** recurrence

Answer: A
Mechanism pearl: Correct phenotype matters: **Crohn** transmural disease can recur after colectomy and compromise po**uc**h outcomes.

Question 51. Colitis-associated cancer

A patient with long-standing extensive **UC** develops flat high-grade **dysplasia**. Which molecular pattern is more typical of colitis-associated carcinogenesis than sporadic adenoma sequence?

A. Direct **CMV** polymerase integration into colonocytes

B. **Bile acid** sequestration-ind**uc**ed **MSI**

C. Early **p53** alteration and field cancerization in chronically inflamed m**uc**osa

D. Pure **STK11**-driven hamartoma formation

E. Universal early **APC** mutation followed by decades of pedunculated growth

Answer: C
Mechanism pearl: Inflammation-associated CRC often has early **p53** changes and flat/multifocal **dysplasia**, unlike classic polypoid adenoma sequence.

Question 52. Chromoendoscopy rationale

A patient with long-standing colitis undergoes high-definition chromoendoscopy. Which mechanism-based rationale is strongest?

A. Chromoendoscopy treats **pouchitis** by changing the **microbiome**

B. Dye spray prevents future **TNF-alpha** release

C. Chromoendoscopy detects anti-drug antibodies directly

D. Dye spray differentiates **Lynch** from **FAP** genetically

E. **Dysplasia** can be subtle or flat within a field of chronically inflamed m**uc**osa, requiring enhanced m**uc**osal visualization

Answer: E

Mechanism pearl: IBD dysplasia surveillance is about detecting subtle neoplasia in a field-risk m**uc**osa.

Question 53. Granuloma

A biopsy from ileocolonic ulcers shows noncaseating granulomas away from ruptured crypts. What is the most useful interpretation?

A. It confirms microscopic colitis

B. It supports **Crohn** disease by reflecting organized macrophage/T-cell response to persistent antigenic stimulation

C. It proves **Lynch** syndrome with **MSI**-high cancer

D. It excludes **Crohn** disease because granulomas are never seen

E. It proves intestinal tuberculosis in all cases

Answer: B
Mechanism pearl: Granulomas are supportive but not required for **Crohn** disease; infection must be excluded when appropriate.

Question 54. UC histology

A patient with rectal bleeding has continuous distal colitis. Biopsies show crypt architectural distortion, basal plasmacytosis, and m**uc**osal inflammation without transmural **fistula**s. Which pathobiology fits?

A. Serrated neoplasia with **BRAF** mutation

B. IgE-mediated food allergy limited to subm**uc**osa

C. Nonocclusive watershed ischemia only

D. Chronic m**uc**osal immune injury beginning in the rectum and extending continuously proximally

E. Patchy transmural granulomatous inflammation with skip lesions

Answer: D
Mechanism pearl: UC is m**uc**osal and continuous; **Crohn** is discontinuous and transmural.

Question 55. Intestinal ultrasound/MRI biomarker

A **Crohn** trial uses bowel wall thickness and hyperemia as treatment targets. Which reason supports imaging biomarkers?

A. MRI directly measures **thiopurine** metabolites

B. Bowel wall thickness is a **serotonin** receptor assay

C. Hyperemia proves **Lynch** syndrome

D. Transmural inflammation may persist or progress beyond symptoms and m**uc**osal inspection alone

E. Imaging replaces pathology for **dysplasia** grading

Answer: D
Mechanism pearl: Crohn disease is transmural; imaging biomarkers complement endoscopy in small bowel and penetrating/stricturing disease.

Question 56. Leukocyte trafficking failure

A **UC** patient has primary nonresponse to **vedolizumab**. What mechanism-based explanation is plausible?

A. His dominant inflammatory circuit may not be sufficiently dependent on **alpha-4 beta-7** gut-homing lymphocyte trafficking

B. Vedolizumab cannot work because **UC** has no lymphocytes

C. **Vedolizumab** works only by killing **C. difficile**

D. Primary nonresponse proves all inflammation is **bile acid** diarrhea

E. The result proves anti-TNF antibodies are present

Answer: A
Mechanism pearl: Pathway selection matters: failure of one mechanism does not prove absence of inflammation.

Question 57. Biomarker discordance

A **Crohn** patient feels well on therapy but fecal **calprotectin** remains markedly elevated. What does this imply?

A. The correct response is to stop all therapy

B. The patient has functional remission and no risk of relapse

C. Ongoing m**uc**osal neutrophilic inflammation may persist despite symptomatic improvement

D. **Calprotectin** elevation proves **colorectal cancer**

E. **Calprotectin** is secreted by neurons during anxiety

Answer: C
Mechanism pearl: Calprotectin is an objective inflammation biomarker; symptom remission alone may miss active disease.

Question 58. Biosimilars

A patient worries that an **infliximab** biosimilar will have a completely different mechanism. Which explanation is most accurate?

A. It is a bacterial probiotic that replaces **dysbiosis**

B. It is a small-molecule **JAK** inhibitor

C. A biosimilar is designed to match the reference monoclonal antibody in **TNF-alpha** binding and clinical function within allowed comparability limits

D. It works by a different receptor pathway to avoid all infections

E. It is a **thiopurine** prodrug

Answer: C
Mechanism pearl: Biosimilar reasoning is comparative pharmacology: same target and highly similar biologic activity, not a new mechanism.

Question 59. Budesonide

A patient with mild ileocecal **Crohn** disease receives budesonide rather than systemic prednisolone. Which pharmacologic property explains the choice?

A. Irreversible **TNF-alpha** depletion

B. Direct **bile acid** sequestration

C. **Alpha-4 beta-7** antagonism

D. High first-pass metabolism allows topical ileocolonic gl**uc**ocorticoid effect with less systemic exposure

E. Selective **IL-23** p19 blockade

Answer: D
Mechanism pearl: Budesonide is still a steroid; its advantage is local delivery and first-pass metabolism, not maintenance efficacy.

Question 60. Topical therapy in UC

A woman has ulcerative proctitis with urgency and bleeding. Rectal mesalamine works better than oral-only therapy. Why?

A. Rectal mesalamine blocks **S1P** receptors in lymph nodes

B. Proctitis is transmural and requires local collagenase

C. Rectal therapy neutralizes systemic **TNF-alpha** better than IV **infliximab**

D. Mesalamine reverses T**P53** mutation

E. Maximal drug concentration is delivered directly to the inflamed distal m**uc**osa

Answer: E

Mechanism pearl: UC therapy is anatomy-aware; topical therapy is highly effective for distal m**uc**osal disease.

Question 61. Antibiotics in Crohn

A **Crohn** patient with a phlegmon and abscess is treated with antibiotics plus drainage. Why is this not equivalent to treating uncomplicated luminal inflammation?

A. Abscesses are functional pain syndromes

B. Drainage repairs **NOD2** mutations

C. Antibiotics replace all biologic therapy for **stricture**s

D. Antibiotics permanently suppress **IL-23** in **Th17** cells

E. Penetrating **Crohn** creates bacterial septic complications requiring source control in addition to immune modulation

Answer: E

Mechanism pearl: Abscess = infection plus **Crohn**; immunosuppression without source control is dangerous.

Question 62. Exclusive enteral nutrition

A pediatric **Crohn** patient achieves remission with exclusive enteral nutrition. Which mechanism is most plausible?

A. Calcineurin blockade of **IL-2** transcription

B. Gene editing of **ATG16L1** variants

C. MLH1 promoter demethylation

D. Alteration of luminal antigen exposure, **microbiome** function, and m**uc**osal inflammatory signaling

E. Direct irreversible neutralization of **TNF-alpha**

Answer: D

Mechanism pearl: Nutritional therapy can be immunologically active through luminal and **microbiome** effects, especially in pediatric **Crohn** disease.

Question 63. Histologic remission UC

A **UC** patient has endoscopic Mayo 0 m**uc**osa but biopsies show active neutrophilic cryptitis. Why might this matter?

A. Mayo 0 proves **p53** is normal

B. Histology is irrelevant once symptoms stop

C. Microscopic inflammation can predict relapse even when endoscopic appearance is healed

D. Cryptitis confirms **IBS** rather than colitis

E. Neutrophils indicate **Lynch** syndrome

Answer: C
Mechanism pearl: Histologic activity is an increasingly used deeper target, especially in **UC**.

Question 64. Colorectal cancer APC

A 51-year-old man has a conventional adenoma with early **APC** loss. Which molecular consequence initiates neoplastic growth?

A. Blockade of **TNF-alpha** transmembrane signaling

B. Retention of lymphocytes in lymph nodes by **S1P** modulation

C. Stabilization and n**uc**lear accumulation of **beta-catenin** with activation of **Wnt** target genes

D. Covalent activation of **guanylate cyclase-C**

E. Loss of IgA class switching in Peyer patches

Answer: C
Mechanism pearl: **APC** loss dysregulates **Wnt**/**beta-catenin** signaling, initiating conventional adenoma formation.

Question 65. KRAS and anti-EGFR

A meta**stat**ic left-sided **colorectal cancer** has a **KRAS** activating mutation. Why is anti-EGFR antibody therapy unlikely to work?

A. **KRAS** activation drives downstream **MAPK** signaling independent of EGFR blockade

B. **KRAS** mutation predicts response to cholestyramine

C. **KRAS** mutation prevents angiogenesis

D. **KRAS** mutation causes **MSI**-high neoantigen formation in all cases

E. **KRAS** mutation makes tumors dependent on **alpha-4 beta-7**

Answer: A
Mechanism pearl: RAS mutations bypass EGFR; anti-EGFR therapy needs RAS wild-type biology.

Question 66. TP53 late progression

A large villous adenoma contains foci of invasive cancer and T**P53** loss. What does this usually represent in the conventional sequence?

A. Earliest initiating event before **APC** loss

B. Late tumor-suppressor disruption facilitating transition from advanced adenoma to carcinoma

C. A biomarker of **IBS visceral hypersensitivity**

D. A germline proof of **Peutz-Jeghers** syndrome

E. A marker of ileal **Crohn** recurrence

Answer: B
Mechanism pearl: Conventional CRC progression accumulates changes: **APC** early, **KRAS** growth, T**P53**/18q late.

Question 67. Lynch syndrome

A 37-year-old woman with right-sided colon cancer has loss of **MSH2** and **MSH6** on immunohistochemistry. Which mechanism explains carcinogenesis?

A. **5-HT3** receptor blockade causing m**uc**osal ulceration

B. Defective mismatch repair causes microsatellite instability and frameshift mutations in growth-regulatory genes

C. **Bile acid** injury causing chronic ischemia

D. **STK11** loss causing hamartomatous small-bowel polyps

E. **APC** germline truncation causing thousands of adenomas

Answer: B
Mechanism pearl: Lynch syndrome is germline **MMR** deficiency; **MSI** is the molecular signature.

Question 68. Sporadic MSI

An 82-year-old woman has right-sided **MSI**-high colon cancer with **MLH1**/**PMS2** loss and **BRAF** V600E. What mechanism is most likely?

A. **MUTYH** biallelic base-excision repair failure

B. Sporadic **serrated**/**CIMP** pathway with **MLH1** promoter hypermethylation rather than **Lynch** syndrome

C. Germline **APC** mutation with second hit

D. **STK11** mutation causing **Peutz-Jeghers** syndrome

E. Chronic **ulcerative colitis** with early **p53** mutation

Answer: B
Mechanism pearl: BRAF mutation plus **MLH1** loss strongly suggests sporadic **MLH1** methylation in the **serrated** pathway.

Question 69. MSI immunotherapy

A patient with metastatic **MSI**-high colon cancer responds dramatically to immune checkpoint blockade. Which mechanism explains sensitivity?

A. Immunotherapy works by binding **bile acid**s

B. **MSI** tumors lack immune infiltration and are invisible to T cells

C. Checkpoint blockade restores **APC** protein in adenomas

D. PD-1 blockade inhibits **guanylate cyclase-C**

E. High frameshift mutation burden generates neoantigens that make the tumor more immune-responsive

Answer: E
Mechanism pearl: MMR-deficient cancers are neoantigen-rich; checkpoint blockade releases antitumor T-cell activity.

Question 70. Serrated pathway

A flat right-sided **serrated** lesion shows **BRAF** mutation and extensive CpG island methylation. Which pathway is implicated?

A. **Serrated** neoplasia/**CIMP** pathway that may silence **MLH1** and produce sporadic **MSI**-high cancer

B. **S1P** lymphocyte trafficking pathway

C. **NOD2**-**autophagy** **Crohn** pathway

D. **STK11** hamartoma pathway

E. Classic **APC**-**KRAS**-T**P53** sequence only

Answer: A
Mechanism pearl: Sessile **serrated** lesions are pathway lesions: **BRAF**, **CIMP**, possible **MLH1** methylation.

Question 71. FAP genetics

A teenager has hundreds of adenomas and a father who required colectomy. Which tumor biology explains adenoma multiplicity?

A. **Bile acid** malabsorption stimulating crypt proliferation

B. Germline **APC** loss with somatic second hits throughout colonic epithelium

C. **MLH1** methylation restricted to one sporadic right-sided lesion

D. Acquired RNF43 mutation in every polyp with no inheritance

E. Biallelic **STK11** mutation causing autosomal recessive hamartomas

Answer: B

Mechanism pearl: **FAP** is an autosomal dominant **APC** tumor suppressor syndrome with field-wide adenoma risk.

Question 72. MUTYH

A man has 40 adenomas but unaffected parents; his sister is also affected. Genetic testing shows biallelic **MUTYH** variants. Which mechanism fits?

A. **STK11** kinase activation causing m**uc**ocutaneous pigmentation

B. X-linked mismatch repair deficiency

C. Acquired **radiation** endarteritis

D. Autosomal dominant **APC** truncation with thousands of childhood polyps

E. Autosomal recessive base-excision repair defect causing oxidative DNA damage-associated mutations

Answer: E

Mechanism pearl: **MUTYH**-associated polyposis is recessive base-excision repair failure, often mimicking attenuated **FAP**.

Question 73. POLE/POLD1

A patient has oligopolyposis, early colon cancer, and a family history of endometrial cancer. Tumor sequencing shows an ultramutated profile but retained **MMR** proteins. Which germline syndrome is most plausible?

A. **Juvenile polyposis** from **SMAD4**/**BMPR1A**

B. **PTEN** hamartoma tumor syndrome only

C. Classic **FAP** due **APC** mutation cluster region

D. Polymerase proofreading-associated polyposis from **POLE** or **POLD1** exon**uc**lease-domain mutation

E. **Serrated** polyposis with no defined germline etiology

Answer: D

Mechanism pearl: **POLE**/**POLD1** mutations impair proofreading, causing an ultramutator phenotype distinct from **MSI**.

Question 74. Peutz-Jeghers

A young woman has m**uc**ocutaneous pigmentation and jejunal hamartomatous polyps causing intussusception. Which molecular pathway is most relevant?

A. **NOD2** loss causing defective muramyl dipeptide sensing

B. **MLH1** promoter methylation causing **MSI**

C. **Alpha-4 beta-7** blockade causing lymphocyte trapping

D. **STK11**/LKB1 tumor suppressor dysfunction affecting cellular polarity and AMPK/mTOR-related growth control

E. **APC** loss causing **Wnt** **beta-catenin** activation

Answer: D
Mechanism pearl: **Peutz-Jeghers** syndrome is **STK11**-associated hamartomatous polyposis with GI and extraintestinal cancer risk.

Question 75. Juvenile polyposis

A patient has multiple juvenile polyps, anemia, and a family history of hereditary hemorrhagic telangiectasia. Which gene best links these findings?

A. **MUTYH**, causing autosomal dominant thousands of adenomas

B. **APC**, connecting **FAP** with osteomas only

C. TNFSF15, defining **IBS**

D. **SMAD4**, connecting **juvenile polyposis** with TGF-beta/BMP signaling and HHT phenotype

E. **BRAF**, defining **Lynch** syndrome

Answer: D
Mechanism pearl: **SMAD4** **juvenile polyposis** can overlap with HHT; **BMPR1A** is another JPS gene.

Question 76. PTEN hamartoma syndrome

A woman has macrocephaly, thyroid disease, breast cancer history, and mixed GI hamartomas. Which pathway best explains the syndrome?

A. **PMS2** loss with microsatellite instability only

B. **APC** second hit with thousands of adenomas

C. **PTEN** loss with increased PI3K/AKT/mTOR growth signaling

D. **STK11** activation with red**uc**ed AMPK signaling

E. **JAK** inhibition with lymphopenia

Answer: C
Mechanism pearl: **PTEN** hamartoma tumor syndrome is a growth-signaling disorder with multisystem cancer risk.

Question 77. Serrated polyposis

A colonoscopy shows numerous **serrated** lesions throughout the colon, including multiple proximal lesions >10 mm. Genetic testing is unrevealing. What is the best mechanism-based **stat**ement?

A. It is excluded unless **APC** is mutated

B. **Serrated** polyposis is clinically defined; a single routine germline cause is often not identified

C. It is caused by universal **STK11** mutation

D. It proves **ulcerative colitis**-associated **dysplasia**

E. It is always biallelic **MUTYH** disease

Answer: B
Mechanism pearl: **Serrated** polyposis is diagnosis-by-phenotype; RNF43 variants are uncommon, and genetic testing is not universally diagnostic.

Question 78. Advanced adenoma biology

A 12-mm villous adenoma with high-grade **dysplasia** is removed. Why does this lesion carry higher risk than a 3-mm tubular adenoma?

A. Villous architecture proves **Peutz-Jeghers** syndrome

B. High-grade **dysplasia** indicates **IBS**

C. Size, villous architecture, and high-grade **dysplasia** reflect greater accumulated molecular progression toward carcinoma

D. Large adenomas are infectious lesions with bacterial invasion

E. Tubular adenomas cannot ever progress

Answer: C
Mechanism pearl: Advanced adenoma features are phenotypic markers of molecular progression.

Question 79. CEA biomarker

A patient asks whether CEA should be used to screen his asymptomatic relatives for colon cancer. Which biomarker principle is correct?

A. CEA replaces colonoscopy in **FAP**

B. CEA is a fecal neutrophil protein used for **IBD** monitoring

C. CEA is a direct readout of **KRAS** activity

D. CEA positivity defines **Lynch** syndrome

E. CEA lacks sufficient sensitivity and specificity for screening but can help monitor treated **colorectal cancer**

Answer: E
Mechanism pearl: CEA is a monitoring/prognostic adjunct, not a screening test for average-risk relatives.

Question 80. FIT biology

A patient with suspected proximal upper GI bleeding has a negative FIT. Why can FIT be more specific for lower GI bleeding?

A. FIT measures fecal **calprotectin** from neutrophils

B. FIT is positive only in **MSI**-high cancers

C. FIT detects heme porphyrin that resists digestion from all sources equally

D. FIT detects **APC** mutations in stool DNA

E. FIT detects human globin that is degraded during transit from upper GI sources

Answer: E
Mechanism pearl: FIT detects intact human globin, making it more lower-GI selective than guaiac-based heme testing.

Question 81. Stool DNA testing

A stool-based screening assay detects methylated DNA markers and mutant oncogenic signatures. Which principle explains its use?

A. Colorectal neoplasia sheds cells containing molecular alterations into stool

B. The assay detects **alpha-4 beta-7** expression

C. Stool DNA tests measure **bile acid** concentration

D. Only inflammatory neutrophils are detected

E. All adenomas release serum CEA before shedding cells

Answer: A

Mechanism pearl: Multitarget stool DNA is a cancer-detection strategy based on shed neoplastic molecular markers.

Question 82. Ischemic colitis

An elderly woman develops sudden crampy pain and hematochezia after hypotension. CT shows segmental left-sided colitis. Which mechanism is most likely?

A. Continuous rectal m**uc**osal autoimmunity from **UC**

B. **Serotonin** transporter mutation causing **IBS**

C. **STK11** hamartomatous polyposis

D. Toxin B-mediated Rho GTPase gl**uc**osylation

E. Transient low-flow m**uc**osal ischemia in watershed colonic circulation

Answer: E
Mechanism pearl: **Ischemic colitis** is often segmental and low-flow, especially at watershed regions.

Question 83. Right-sided ischemia

A dialysis patient develops severe right-sided **ischemic colitis** with pain out of proportion. Why is this more ominous than typical mild left-sided disease?

A. Right-sided ischemia is protective because the cecum has dual supply

B. Right-sided disease excludes vascular compromise

C. Right-sided ischemia is caused by **MLH1** methylation

D. Right-sided disease always means **UC**

E. Right colon ischemia may reflect more severe proximal mesenteric hypoperfusion and has higher risk of transmural injury

Answer: E
Mechanism pearl: Right-sided **ischemic colitis** is a red flag for severe vascular disease or low-flow **stat**e.

Question 84. Radiation proctopathy

A man treated with pelvic radiotherapy develops chronic rectal bleeding months later. Endoscopy shows **telangiectasias**. Which mechanism best explains chronic injury?

A. **Radiation**-ind**uc**ed obliterative endarteritis and m**uc**osal telangiectatic neovascular fragility

B. IgE-mediated food allergy

C. **NOD2**-related ileal **Paneth**-cell dysfunction

D. Germline **APC** second-hit adenoma formation

E. Acute toxin-mediated Rho GTPase injury

Answer: A
Mechanism pearl: Chronic **radiation** proctopathy is vascular-fibrotic injury, not simply active infectious colitis.

Question 85. Argon plasma coagulation

A patient with chronic **radiation** proctopathy has recurrent bleeding from diffuse **telangiectasias**. Why can argon plasma coagulation help?

A. It inhibits bacterial beta-gl**uc**uronidase

B. It repairs internal anal sphincter tone

C. Noncontact thermal coagulation ablates superficial fragile neovascular lesions

D. It demethylates **MLH1** promoter

E. It blocks **TNF-alpha** in the lamina propria

Answer: C
Mechanism pearl: APC treats bleeding **telangiectasias**; depth control is important to avoid ulceration/**stricture**.

Question 86. Diversion colitis

A diverted rectal stump develops friability and m**uc**us discharge months after colostomy. Which mechanism best explains inflammation?

A. Paneth-cell **autophagy** failure

B. Direct anti-TNF antibody reaction

C. Germline mismatch repair deficiency

D. Loss of luminal **short-chain fatty acids** deprives colonocytes of trophic metabolic substrate

E. Serrated pathway **BRAF** mutation

Answer: D
Mechanism pearl: Diversion colitis is driven by fecal stream deprivation, especially lack of SCFAs s**uc**h as **butyrate**.

Question 87. Microscopic colitis

A 67-year-old woman has chronic watery diarrhea, normal colonoscopy, and lymphocytic colitis on biopsy. Which diagnostic principle is correct?

A. The disease is defined by deep linear ulcers

B. It is a **colorectal cancer** syndrome

C. Biopsy is unnecessary if m**uc**osa is normal

D. Normal gross m**uc**osa does not exclude histologic colitis; random biopsies establish diagnosis

E. It is diagnosed by serum CEA

Answer: D
Mechanism pearl: Microscopic colitis is a histologic disease with often normal endoscopic appearance.

Question 88. C difficile toxin

A hospitalized patient develops pseudomembranous colitis after antibiotics. Which molecular injury is central?

A. STK11 loss activates mTOR

B. Toxin-mediated gl**uc**osylation of Rho-family GTPases disrupts cytoskeleton and epithelial barrier

C. APC truncation stabilizes **beta-catenin**

D. IL-23 p19 activates **Th17** cells

E. Bile acid sequestration causes osmotic diarrhea

Answer: B
Mechanism pearl: C. difficile toxins injure epithelium by targeting Rho GTPase cytoskeletal regulation.

Question 89. IBS visceral hypersensitivity

A patient has chronic abdominal pain related to defecation, normal colonoscopy, and low **calprotectin**. Baro**stat** testing would likely show which mechanism in many **IBS** patients?

A. **MLH1** promoter methylation with **MSI**-high m**uc**osa

B. Transmural granulomas with **fistula** formation

C. Lower threshold for pain with rectal distension due to peripheral and central sensitization

D. Pseudomembrane formation from toxin B

E. Obliterative endarteritis from **radiation**

Answer: C
Mechanism pearl: **IBS** pain is often linked to **visceral hypersensitivity** and altered brain-gut processing, not m**uc**osal ulceration.

Question 90. IBS serotonin pharmacology

A woman with severe **IBS**-D improves on a **5-HT3** antagonist but develops concern for constipation and **ischemic colitis**. Which mechanism explains benefit?

A. Red**uc**ed serotonergic excitatory signaling slows transit and dampens visceral afferent signaling

B. Peripheral mu-opioid antagonism accelerates transit

C. Activation of **guanylate cyclase-C** increases chloride secretion

D. **APC** restoration reverses adenomas

E. Anti-TNF neutralization heals m**uc**osal ulcers

Answer: A
Mechanism pearl: **5-HT3** antagonists red**uc**e diarrhea and pain signaling; safety concerns shape patient selection.

Question 91. IBS-C linaclotide

A patient with **IBS**-C receives **linaclotide**. Which intracellular messenger mediates increased secretion and analgesic effects?

A. **cGMP** downstream of **guanylate cyclase-C** activation

B. **NFAT** downstream of **calcineurin**

C. cAMP downstream of cholera toxin

D. **JAK-STAT** downstream of IL-6

E. **Beta-catenin** downstream of **APC** loss

Answer: A
Mechanism pearl: **Linaclotide** activates GC-C, increasing **cGMP** and chloride/bicarbonate secretion, with effects on pain signaling.

Question 92. Eluxadoline

A patient with **IBS**-D and prior cholecystectomy is considered for **eluxadoline**. Which mechanism explains both benefit and pancreatitis risk?

A. 5-HT4 agonism increases peristalsis

B. Mixed opioid receptor activity red**uc**es diarrhea but can increase sphincter of Oddi tone

C. GC-C activation increases secretion

D. **TNF-alpha** blockade increases gallbladder contraction

E. **MLH1** methylation blocks pancreatic secretion

Answer: B
Mechanism pearl: Eluxadoline is opioid-receptor pharmacology; sphincter effects explain risk in susceptible patients.

Question 93. Rifaximin IBS-D

A patient with bloating-predominant **IBS**-D improves after **rifaximin**. Which mechanism is most plausible?

A. **APC** tumor suppressor repair

B. Nonabsorbed antibiotic modulation of small-bowel/colonic microbial metabolism and gas-related signaling

C. Permanent restoration of SERT expression

D. Direct **IL-23** p19 neutralization

E. Inhibition of **5-HT3** receptors in the CNS

Answer: B
Mechanism pearl: Rifaximin targets luminal microbial factors; it is not a systemic immunosuppressant.

Question 94. Bile acid vs IBS-D

A patient labeled **IBS**-D has postprandial watery diarrhea after ileal **Crohn** resection. Why is a **bile acid** mechanism more likely than primary **IBS**?

A. **Bile acid** diarrhea requires intact terminal ileum

B. **IBS**-D is defined by high fecal **calprotectin**

C. Primary **IBS** causes low C4 complement

D. **Crohn** resection causes **MLH1** methylation

E. Ileal **bile acid** malabsorption delivers secretory **bile acid**s to the colon

Answer: E
Mechanism pearl: Mechanistic phenotyping prevents mislabeling treatable **bile acid** diarrhea as functional **IBS**-D.

Question 95. Postinfectious IBS

After Campylobacter gastroenteritis, a woman develops chronic **IBS**-D symptoms. Which mechanism best connects infection to persistent symptoms?

A. Persistent m**uc**osal immune activation, enterochromaffin-cell changes, and altered **serotonin** release can sensitize gut afferents

B. New germline **APC** mutation creates thousands of adenomas

C. Desmoid tumors obstr**uc**t the colon

D. **CMV** inclusions develop in rectal endothelial cells

E. **S1P** receptor blockade traps lymphocytes

Answer: A
Mechanism pearl: Postinfectious **IBS** links low-grade immune/mast-cell/5-HT changes to **visceral hypersensitivity**.

Question 96. Low FODMAP

A patient with **IBS** notes bloating after wheat, onions, and milk. Which mechanism best explains low-FODMAP benefit?

A. It chelates **bile acid**s in the colon

B. It prevents **MSI** by repairing **MMR** genes

C. It reverses **Crohn stricture**s by collagenolysis

D. Reducing poorly absorbed fermentable carbohydrates lowers osmotic water shifts and microbial gas production

E. It suppresses **TNF-alpha** transcription in macrophages

Answer: D
Mechanism pearl: Low-FODMAP therapy is luminal physiology: osmotic load and fermentation, not systemic immune suppression.

Question 97. IBS brain-gut

A woman with **IBS** has pain amplification during stress and hyperactivation of insula/anterior cingulate regions on research imaging. Which concept is being tested?

A. Sporadic **serrated** pathway carcinoma

B. Altered central processing of visceral afferent input within brain-gut networks

C. Deep transmural fistulizing **Crohn** disease

D. Mucosal **dysplasia** from chronic colitis

E. **Radiation**-induced telangiectasia

Answer: B
Mechanism pearl: **IBS** pathophysiology includes central sensitization, emotional arousal networks, and descending pain modulation.

Question 98. Alosetron adverse

A man asks why **5-HT3** antagonists are restricted in some **IBS**-D settings. Which serious adverse event is mechanistically linked to this class historically?

A. Hepatosplenic T-cell lymphoma from **thiopurine** use

B. Progressive multifocal leukoencephalopathy from alpha-4 blockade

C. TB reactivation from granuloma disruption

D. **CMV** esophagitis from steroid exposure

E. Severe constipation and **ischemic colitis** have been reported with potent transit-slowing **5-HT3** blockade

Answer: E
Mechanism pearl: **5-HT3** blockade can be effective but safety and patient selection are exam-relevant.

Question 99. Colonic inertia vs IBS-C

A patient with severe constipation has slow-transit markers throughout the colon but no pain relationship to defecation. Why is this not simply **IBS**-C?

A. All constipation responds to anti-TNF

B. **IBS**-C is diagnosed by **APC** mutation

C. Colonic inertia requires high **calprotectin**

D. Slow transit is always **UC** remission

E. **IBS** requires recurrent abdominal pain linked to defecation or stool change; isolated slow transit is a motility phenotype

Answer: E
Mechanism pearl: **IBS**-C overlaps with constipation but is defined by pain-stool relationship and brain-gut symptoms.

Question 100. Diverticular disease

An elderly man has recurrent sigmoid diverticulitis. Which mechanism best explains why disease clusters in the sigmoid colon?

A. **MLH1** methylation weakens the tenia coli

B. **IL-23** drives transmural granulomas in every diverticulum

C. High intraluminal pressure at vascular penetration points promotes pseudodiverticula in a segment with small caliber

D. **5-HT3** blockade causes congenital outpo**uc**hings

E. **Serrated BRAF** mutations create false diverticula

Answer: C
Mechanism pearl: Diverticula are pulsion pseudodiverticula at weak points where vasa recta penetrate.

B. Moderate-to-long case scenarios

Question 101. ASUC rescue

A 28-year-old woman is admitted with acute severe **UC**: 10 bloody stools/day, fever, tachycardia, **CRP** 92 mg/L, and deep ulcers on flexible sigmoidoscopy. Stool **C. difficile** testing is negative. After 3 days of IV hydrocortisone she still has 8 bloody stools/day and rising **CRP**. She has normal creatinine, no uncontrolled infection, and no perforation. The consultant asks which rescue option is mechanistically distinct from **infliximab** but rational in this setting.

A. **Cyclosporine**, because **calcineurin** inhibition suppresses **NFAT**-dependent **IL-2** transcription and T-cell activation

B. **Rifaximin**, because **microbiome** modulation closes acute severe m**uc**osal ulcers

C. **Linaclotide**, because **cGMP** secretion red**uc**es inflammatory diarrhea

D. Mesalamine, because topical prostaglandin modulation rapidly reverses systemic toxicity

E. Cholestyramine, because **bile acid** sequestration heals deep colonic ulcers

Answer: A
Mechanism pearl: Steroid-refractory AS**UC** rescue options include anti-TNF therapy or **calcineurin** inhibition; mechanism and contraindications guide selection.

Question 102. Infliximab pharmacokinetic failure

A 34-year-old man with penetrating ileocolonic **Crohn** disease had complete response to **infliximab** for 10 months. He now has recurrent ulcers and high fecal **calprotectin**. Drug monitoring shows **infliximab** trough <0.5 microgram/mL and high anti-**infliximab** antibodies. He has no abscess. Which therapeutic reasoning is best?

A. This is mechanistic failure with adequate TNF blockade, so dose escalation is mandatory

B. This proves **colorectal cancer** and requires colectomy

C. This is **bile acid** diarrhea and requires only cholestyramine

D. This proves symptoms are **IBS** because a drug level was measured

E. This is immunogenic pharmacokinetic failure; switch anti-TNF or change class and consider immunomodulator strategy rather than simply increasing the same dose

Answer: E
Mechanism pearl: TDM separates low-drug/high-antibody pharmacokinetic failure from adequate-level mechanistic failure.

Question 103. Infliximab mechanistic failure

A 41-year-old woman with **Crohn** colitis remains symptomatic on **infliximab** 10 mg/kg every 8 weeks. Colonoscopy shows large ulcers, fecal **calprotectin** is 1400 microgram/g, trough is therapeutic, and antibodies are absent. The team considers adding more **infliximab**. What is the most mechanism-based interpretation?

A. The correct step is always antibiotics because all colonic ulcers are infectious

B. The high trough means **infliximab** is causing **APC** mutation

C. The high trough excludes active inflammation and proves **visceral hypersensitivity**

D. The disease is cured and **calprotectin** is false by definition

E. Active inflammation despite adequate **TNF-alpha** neutralization suggests mechanistic failure and supports switching to a different pathway such as **IL-23** or integrin/**JAK** strategy

Answer: E
Mechanism pearl: Adequate drug exposure with objective inflammation means the inflammatory circuit is not sufficiently TNF dependent.

Question 104. Vedolizumab vs natalizumab

A 52-year-old woman with **Crohn** disease has a history of recurrent infections and JC-virus antibody positivity. A trainee suggests **natalizumab** because it blocks leukocyte adhesion. The consultant prefers **vedolizumab** if an anti-trafficking approach is selected. Which explanation is most accurate?

A. Both drugs activate **S1P** receptors and cause lymphopenia

B. **Vedolizumab** selectively blocks **alpha-4 beta-7**/**MAdCAM-1** gut homing, whereas **natalizumab** broadly blocks alpha-4 integrins and can impair CNS immune surveillance

C. **Vedolizumab** and **natalizumab** both selectively block **IL-23** p19

D. **Natalizumab** is safer because it blocks only intestinal **MAdCAM-1**

E. **Vedolizumab** is a **thiopurine** and prevents antibody formation

Answer: B
Mechanism pearl: Anti-trafficking therapies differ by selectivity; **alpha-4 beta-7** gut selectivity explains **vedolizumab**'s conceptual safety distinction.

Question 105. IL-23 selection

A 36-year-old man with **Crohn** disease and psoriasis failed anti-TNF due to mechanistic failure. He asks why an **IL-23** p19 inhibitor might work even though another biologic failed. His biopsies show active chronic colitis without infection. Which statement best explains the translational logic?

A. **IL-23** drugs are topical steroids with high first-pass metabolism

B. **IL-23** p19 blockade works by blocking **alpha-4 beta-7** adhesion to **MAdCAM-1**

C. **IL-23** blockade repairs the **APC** gene in colonic crypts

D. **IL-23** inhibition kills **CMV**-infected endothelial cells

E. **IL-23** maintains pathogenic **Th17**/**ILC** cytokine programs, so p19 blockade targets an upstream immune axis different from **TNF-alpha**

Answer: E
Mechanism pearl: Different biologics are not interchangeable labels; they target distinct immune nodes.

Question 106. JAK inhibitor adverse logic

A 58-year-old man with **UC**, prior zoster, obesity, and cardiovascular risk factors is considered for a **JAK** inhibitor after anti-TNF failure. Which mechanism-based counseling point is most appropriate?

A. **JAK** inhibitors act only by binding luminal **bile acids**

B. **JAK** blockade suppresses multiple cytokine signals, including antiviral pathways, so zoster and systemic safety risks must be weighed against oral efficacy

C. **JAK** inhibitors are gut-selective adhesion blockers and therefore have no systemic immune effects

D. **JAK** inhibition is equivalent to mesalamine topical therapy

E. **JAK** inhibitors cannot affect viral immunity because they are not biologics

Answer: B
Mechanism pearl: Small molecules are not necessarily safer because they are oral; intracellular multi-cytokine blockade has systemic implications.

Question 107. S1P and lymphopenia

A 47-year-old woman with **UC** begins ozanimod. Two weeks later, absolute lymphocyte count falls and she has mild transient bradycardia after first doses. Which integrated mechanism explains these effects?

A. **S1P** receptor modulation prevents lymphocyte egress from lymphoid tissue and can affect cardiac **S1P** receptor signaling early

B. TNF blockade directly inhibits sinoatrial beta receptors

C. **IL-23** p19 neutralization causes immediate sinus node suppression

D. **Alpha-4 beta-7** blockade prevents gut homing without lymphopenia or cardiac effects

E. **Thiopurine** methylation failure causes first-dose bradycardia

Answer: A
Mechanism pearl: S1P pharmacology links lymphocyte trafficking with first-dose cardiac considerations.

Question 108. Perianal Crohn abscess

A 30-year-old man with **Crohn** disease has fever, severe perianal pain, and MRI showing a horseshoe abscess with complex **fistula**. The junior wants immediate high-dose **infliximab**. What is the best mechanism-based plan?

A. Proceed to **IPAA** because **Crohn** is colon-limited

B. Start **infliximab** alone because TNF neutralization sterilizes abscess cavities immediately

C. Use loperamide to reduce **fistula** drainage before imaging

D. Give oral mesalamine because **fistula**s are superficial mucosal disease

E. Drain the abscess and control sepsis first, then use seton plus anti-inflammatory biologic therapy for transmural fistulizing **Crohn** disease

Answer: E
Mechanism pearl: Biologics treat inflammatory **fistula** biology; abscesses require source control before immunosuppression.

Question 109. Fibrostenotic Crohn

A 44-year-old man with ileal **Crohn** disease has recurrent postprandial obstruction. MRI enterography shows a 3-cm fibrotic **stricture** with prestenotic dilation, little mural edema, and no abscess. **CRP** and fecal **calprotectin** are low. He asks why escalating biologics may not relieve obstruction. Which mechanism is correct?

A. Low **calprotectin** proves there is no luminal narrowing

B. All **Crohn stricture**s are active inflammatory edema

C. Cholestyramine reverses prestenotic dilation

D. Biologics dissolve mature collagen within days

E. Fixed extracellular matrix remodeling and smooth-muscle hypertrophy may dominate after inflammation has subsided

Answer: E
Mechanism pearl: Crohn strictures contain variable inflammatory and fibrotic components; therapy must match biology.

Question 110. Postoperative recurrence prevention

A smoker with ileal **Crohn** disease undergoes ileocecal resection for perforating disease. The surgeon says margins are clear. Six months later he feels well. The gastroenterologist still schedules ileocolonoscopy. Why?

A. Colonoscopy is done only to detect **Lynch** syndrome

B. Endoscopic recurrence at the neoterminal ileum often precedes symptoms and predicts later clinical recurrence

C. Smoking protects against **Crohn** recurrence

D. Postoperative symptoms are the first reliable marker of recurrence

E. Clear surgical margins remove genetic susceptibility to **Crohn** disease

Answer: B

Mechanism pearl: Surgery treats complications but not the underlying immune-microbial predisposition; early endoscopic recurrence guides therapy.

Question 111. Pouchitis vs Crohn of pouch

A 38-year-old man underwent **IPAA** for presumed **UC**. He develops po**uc**h frequency and urgency. Po**uc**hoscopy shows diffuse po**uc**h inflammation that improves with ciprofloxacin. Later he develops prepo**uc**h ileitis and perianal **fistula**. What is the best mechanism-based interpretation?

A. Prepo**uc**h ileitis proves microscopic colitis

B. Antibiotic response proves **colorectal cancer**

C. Perianal **fistula** is expected after uncomplicated **UC pouchitis**

D. All po**uc**h inflammation is recurrent native-colon **UC**

E. Initial **pouchitis** may reflect **dysbiosis**-driven po**uc**h inflammation, but prepo**uc**h ileitis and **fistula** raise concern for **Crohn**-like transmural disease of the po**uc**h

Answer: E

Mechanism pearl: Po**uc**h disorders require phenotype revision; **fistula** and prepo**uc**h ileitis suggest **Crohn** biology.

Question 112. CMV steroid refractory colitis

A 63-year-old man with **UC** receives high-dose steroids for severe flare. After 7 days he worsens. Flexible sigmoidoscopy shows large punched-out ulcers. Blood **CMV** PCR is modestly positive. Biopsies are pending. Which mechanism-based reasoning is best?

A. Clinically relevant **CMV** colitis requires tissue evidence of viral cytopathic effect because viremia alone may not prove tissue-invasive disease

B. **CMV** cannot occur in **UC** patients receiving steroids

C. Any positive serum PCR mandates colectomy without biopsy

D. **CMV** is diagnosed by pANCA titer

E. **CMV** ulcers are treated by increasing mesalamine only

Answer: A

Mechanism pearl: Steroid-refractory colitis should trigger tissue evaluation for **CMV**; treatment decisions depend on invasive disease evidence.

Question 113. PSC-IBD neoplasia

A 32-year-old man with PSC has mild right-sided colitis and rectal sparing. He has few bowel symptoms and normal **CRP**. The fellow suggests average-risk CRC screening. What is the strongest reason this is wrong?

A. PSC makes colon cancer impossible until cirrhosis develops

B. PSC-associated **IBD** has high colorectal neoplasia risk that is not predicted by symptom severity

C. Normal **CRP** excludes **dysplasia**

D. Rectal sparing proves **IBS**

E. Right-sided colitis excludes **ulcerative colitis**-associated cancer risk

Answer: B
Mechanism pearl: PSC-**IBD** is a cancer-risk phenotype; surveillance is intensified despite mild intestinal symptoms.

Question 114. Colitis-associated dysplasia

A 49-year-old woman has 22 years of extensive **UC**. Chromoendoscopy shows a subtle flat lesion with high-grade **dysplasia** and random biopsies elsewhere show multifocal low-grade **dysplasia**. Which mechanism best explains why colectomy is strongly considered?

A. **Dysplasia** proves **CMV** colitis

B. Multifocal **dysplasia** is treated by cholestyramine

C. All **dysplasia** is caused by a single pedunculated adenoma with no field effect

D. Chronic inflammation creates field cancerization with multifocal molecular injury, often including early **p53** alteration

E. High-grade **dysplasia** in **UC** is biologically identical to a sporadic 3-mm tubular adenoma

Answer: D
Mechanism pearl: In long-standing colitis, invisible or multifocal **dysplasia** implies field risk, not just one removable polyp.

Question 115. VEO-IBD immune defect

A 9-month-old boy has severe colitis, folliculitis, perianal disease, and recurrent infections. His sister died in infancy after enterocolitis. Colonoscopy shows severe colitis but serologies are unhelpful. Which mechanism should the consultant prioritize?

A. Primary **IBS** with central sensitization

B. Adult-onset sporadic **MLH1** methylation

C. A monogenic immune-regulatory defect s**uc**h as IL-10/IL-10 receptor pathway failure

D. Age-related nonocclusive **ischemic colitis**

E. Classic **FAP** from **APC** mutation causing thousands of adenomas

Answer: C
Mechanism pearl: Infantile severe **IBD** suggests immune-defect evaluation; some forms require hematopoietic stem-cell approaches rather than standard escalation alone.

Question 116. Pregnancy and biologic transfer

A pregnant woman with **Crohn** disease is in deep remission on **infliximab**. She asks why the timing of late pregnancy doses and infant live vaccines are discussed. Which mechanism is relevant?

A. Mesalamine has the same Fc-mediated transfer profile

B. Anti-TNF drugs are not proteins and cannot reach the fetus

C. **Infliximab** crosses the placenta by **bile acid** transporters only in the first trimester

D. IgG1 monoclonal antibodies undergo Fc receptor-mediated placental transfer, especially later in pregnancy

E. Placental transfer occurs only with oral **JAK** inhibitors

Answer: D
Mechanism pearl: Monoclonal antibody structure and FcRn biology determine fetal exposure considerations.

Question 117. IBD anemia mixed

A woman with active **UC** has Hb 8.8 g/dL, ferritin 120 ng/mL, transferrin saturation 7%, **CRP** 80 mg/L, and ongoing rectal bleeding. The resident says ferritin excludes iron deficiency. Which mechanism-based explanation is best?

A. Low transferrin saturation proves hereditary hemochromatosis

B. Ferritin rises as an acute-phase reactant; inflammation-induced **hepcidin** can coexist with absolute blood-loss iron deficiency

C. Rectal bleeding cannot cause iron deficiency if **CRP** is high

D. Ferritin is secreted only by colonic neutrophils

E. Active **UC** prevents **hepcidin** production

Answer: B
Mechanism pearl: IBD anemia is often mixed: bleeding depletes iron while IL-6/**hepcidin** traps iron.

Question 118. IBD and thrombosis

A hospitalized man with acute severe **UC** has hematochezia but stable hemoglobin. The team hesitates to prescribe VTE prophylaxis. Which pathophysiologic argument supports prophylaxis?

A. Coagulation is unrelated to mucosal inflammation

B. VTE occurs only in **Crohn** disease after surgery

C. Hematochezia eliminates thrombotic risk

D. Heparin suppresses **calprotectin** and treats **UC** directly

E. Active colitis induces systemic inflammation, endothelial activation, platelet activation, and hypercoagulability

Answer: E
Mechanism pearl: IBD flares are prothrombotic; prophylaxis is usually considered unless bleeding risk is prohibitive.

Question 119. Lynch vs sporadic MSI

A 76-year-old woman has right-sided colon cancer. IHC shows loss of **MLH1**/**PMS2**. Tumor is **MSI**-high and **BRAF** V600E positive. Her son is anxious about **Lynch** syndrome. Which interpretation is best?

A. **BRAF** V600E with **MLH1**/**PMS2** loss supports sporadic **CIMP**/**MLH1** promoter methylation more than germline **Lynch** syndrome

B. **MSI**-high tumors cannot arise sporadically

C. This pattern is diagnostic of **MUTYH**-associated polyposis

D. **MLH1**/**PMS2** loss always means **FAP**

E. **BRAF** positivity confirms germline **MSH2** mutation

Answer: A
Mechanism pearl: Distinguish **Lynch** from sporadic **MSI**: **MLH1** methylation/**BRAF** mutation points to **serrated** sporadic origin.

Question 120. Checkpoint in MSI CRC

A 45-year-old man with metastatic colon cancer has **MSI**-high disease due to **MSH2** loss. He responds to PD-1 blockade. Which mechanism best explains this response?

A. PD-1 blockade repairs **MSH2** DNA sequence

B. The drug works by inhibiting EGFR in **KRAS**-mutant cells

C. Mismatch repair deficiency creates many frameshift neoantigens that can be recognized after checkpoint inhibition releases T-cell suppression

D. **MSI**-high tumors have no immune infiltrates and need no T cells

E. Response is due to reduced **bile acid** secretion

Answer: C
Mechanism pearl: **MSI**-high/**MMR**d tumors are immunogenic; checkpoint blockade leverages neoantigen-driven immune recognition.

Question 121. Anti-EGFR selection

A 59-year-old man has metastatic left-sided **colorectal cancer**. Molecular testing shows RAS wild-type and **BRAF** wild-type. Another patient has **KRAS** G12D mutation. Why does this distinction matter?

A. RAS mutation predicts response to **vedolizumab**

B. RAS mutation activates downstream signaling despite EGFR blockade, predicting resistance to anti-EGFR antibodies

C. **KRAS** mutation is required for cetuximab binding

D. RAS wild-type proves **Lynch** syndrome

E. **BRAF** wild-type makes immune checkpoint therapy mandatory

Answer: B
Mechanism pearl: Anti-EGFR efficacy depends on intact upstream dependence; RAS/**BRAF** testing is mechanism-based oncology.

Question 122. FAP desmoid

A 19-year-old woman has **FAP**, prior colectomy, osteomas, and a family history of aggressive intra-abdominal desmoid tumors. Genetic counseling discusses **APC** genotype-phenotype associations. Which concept best explains her cancer prevention strategy?

A. **FAP** is caused by germline **MLH1** promoter methylation

B. **FAP** polyps arise from **STK11**-driven hamartomas

C. Desmoids prove **Crohn** disease

D. **APC** is a tumor suppressor; widespread second hits create adenomas, while mutation location modifies extracolonic risks such as desmoid disease

E. Aspirin cures **FAP** by restoring **APC** protein

Answer: D
Mechanism pearl: **FAP** management is genotype-aware and organ-wide: colon, duodenum, thyroid/desmoid risks.

Question 123. MUTYH recessive counseling

A 42-year-old man has 65 adenomas and biallelic **MUTYH** pathogenic variants. His parents have normal colonoscopies, and his brother asks about risk. Which mechanism-based counseling is correct?

A. The disorder is X-linked and affects only men

B. The mechanism is **MMR** deficiency identical to **Lynch** syndrome

C. All children of the patient must have classic **FAP**

D. Autosomal recessive base-excision repair disease means siblings may be affected if both parents are carriers, even if parents are unaffected

E. Normal parental colonoscopy excludes carrier **stat**us

Answer: D
Mechanism pearl: MUTYH-associated polyposis is recessive; inheritance logic differs from **APC**-related **FAP**.

Question 124. POLE ultramutator

A 35-year-old woman has 25 adenomas, early colon cancer, and endometrial cancer in her mother. Tumor is MSS with intact **MMR** proteins but has extremely high tumor mutational burden. Germline testing finds a **POLE** exon**uc**lease-domain variant. Which mechanism explains cancer risk?

A. **MLH1** promoter methylation causes **MSI**-high phenotype

B. **APC** second hit causes thousands of childhood adenomas

C. **TNF-alpha** excess causes **dysplasia** directly

D. Defective DNA polymerase proofreading creates replication errors despite intact mismatch repair proteins

E. **STK11** loss causes arborizing smooth-muscle hamartomas

Answer: D
Mechanism pearl: Polymerase proofreading-associated polyposis is an ultramutator condition that can be MSS.

Question 125. Peutz-Jeghers and intussusception

A 17-year-old boy has recurrent small-bowel intussusception, m**uc**ocutaneous pigmentation, and arborizing hamartomatous polyps. His mother had pancreatic cancer. Which mechanism should be linked to his syndrome?

A. **MLH1**/**MSH2** mismatch repair deficiency

B. **APC** mutation cluster region truncation

C. **STK11**/LKB1 tumor suppressor loss affecting cell polarity and AMPK-mTOR growth regulation

D. Biallelic **MUTYH** oxidative base-repair failure

E. IL-10 receptor signaling failure

Answer: C
Mechanism pearl: Peutz-Jeghers syndrome is a hamartomatous polyposis syndrome with pancreatic and other cancer risks.

Question 126. Juvenile polyposis SMAD4-HHT

A 25-year-old man has recurrent epistaxis, m**uc**ocutaneous **telangiectasias**, anemia, and numerous juvenile polyps. Which gene/pathway best integrates the GI and vascular phenotype?

A. **PMS2** mutation causing isolated **MSI** colon cancer without polyps

B. **APC** mutation causing **beta-catenin** activation and osteomas only

C. **SMAD4** mutation disrupting TGF-beta/BMP signaling, causing **juvenile polyposis** with hereditary hemorrhagic telangiectasia overlap

D. **NOD2** mutation causing **Paneth**-cell dysfunction

E. **BRAF** V600E causing sporadic **serrated** lesions only

Answer: C
Mechanism pearl: SMAD4 links **juvenile polyposis** and HHT features; **BMPR1A** causes JPS without the same HHT association.

Question 127. PTEN hamartoma tumor syndrome

A 40-year-old woman has macrocephaly, trichilemmomas, thyroid nodules, breast cancer history, and multiple GI hamartomas/ganglioneuromas. Which mechanism-based diagnosis is best?

A. **Peutz-Jeghers** due **STK11** loss only

B. **Serrated** polyposis due RNF43 in all cases

C. **FAP** due **APC** truncation

D. **Lynch** syndrome due **MMR** deficiency

E. **PTEN** hamartoma tumor syndrome due loss of negative regulation of PI3K/AKT signaling

Answer: E

Mechanism pearl: PTEN is a tumor suppressor in PI3K/AKT signaling; the phenotype is multisystem, not just colorectal.

Question 128. Serrated polyposis surveillance

A 61-year-old woman has >20 **serrated** polyps distributed throughout the colon, including several proximal sessile **serrated** lesions. Germline testing is negative. Why does she still need intensive colonoscopic management?

A. The phenotype is treated by colectomy only in every case

B. **Serrated** polyposis is a clinical high-risk phenotype even when no defining germline mutation is found

C. Negative genetics excludes cancer risk

D. All **serrated** lesions are harmless hyperplastic rectal polyps

E. The mechanism is always biallelic **MUTYH**

Answer: B

Mechanism pearl: Serrated polyposis syndrome is not ruled out by negative genetic testing; phenotype drives surveillance.

Question 129. Right-sided serrated lesion missed

A patient develops interval right-sided colon cancer 3 years after colonoscopy. Review shows a subtle m**uc**us-capped flat proximal lesion likely missed. Tumor has **BRAF** mutation and **MLH1** methylation. Which pathway explains this interval cancer risk?

A. Classic pedunculated **APC** adenoma sequence only

B. **Peutz-Jeghers** hamartoma pathway

C. **Crohn** transmural **fistula** pathway

D. **Radiation** endarteritis pathway

E. Sessile **serrated** lesion pathway with **CIMP**-mediated **MLH1** silencing and rapid **MSI** progression after **dysplasia** develops

Answer: E

Mechanism pearl: Sessile **serrated** lesions are subtle, proximal, and biologically linked to **BRAF**/**CIMP**/**MLH1** methylation.

Question 130. Colitis-associated CRC vs sporadic adenoma

A man with 30-year pancolitis has a flat dysplastic lesion. Molecular testing reveals **p53** abnormality in nonpolypoid m**uc**osa adjacent to the lesion. Why does this differ from the classic adenoma-carcinoma model?

A. **IBD dysplasia** is never molecularly abnormal

B. Colitis-associated cancer always has **STK11** mutation

C. APC is never involved in sporadic CRC

D. Flat dysplasia is always benign

E. Inflammation-associated neoplasia may show early p53 abnormalities and field change rather than a single polypoid APC-first progression

Answer: E
Mechanism pearl: The examiner may test sequence differences: sporadic conventional CRC is often APC-first; colitis-associated CRC often has early p53/field effects.

Question 131. Malignant polyp decision

A 58-year-old man has a pedunculated sigmoid polyp removed en bloc. Pathology shows well-differentiated adenocarcinoma limited to the head, clear margin 3 mm, no lymphovascular invasion. Another patient has a sessile malignant polyp with deep submucosal invasion, poor differentiation, and lymphovascular invasion. Which mechanism explains different management?

A. All malignant polyps require colectomy regardless of histology

B. Access to lymphatics increases with adverse submucosal invasion biology, raising nodal metastasis risk and need for surgery

C. Villous histology alone mandates chemotherapy

D. No malignant polyp can metastasize if endoscopically removed

E. Only MSI status determines local surgery

Answer: B
Mechanism pearl: Malignant polyp decisions are risk biology: invasion depth, grade, lymphovascular invasion, budding, and margin.

Question 132. Ischemic colitis mimic

A 78-year-old woman with atrial fibrillation and recent dehydration presents with abrupt left lower quadrant pain and hematochezia. CT shows segmental thickening at the splenic flexure; colonoscopy shows sharply demarcated pale edematous mucosa with petechiae. Which mechanism best explains the pattern?

A. Low-flow injury in watershed circulation causing segmental mucosal ischemia with reperfusion bleeding

B. C. difficile toxin causing diffuse pseudomembranes after antibiotics

C. Lynch syndrome causing accelerated adenoma progression

D. Continuous rectal extension of UC from mucosal autoimmunity

E. IBS visceral hypersensitivity causing mucosal necrosis

Answer: A
Mechanism pearl: Ischemic colitis is segmental, abrupt, and vascular; distribution helps separate it from IBD and infection.

Question 133. Severe ischemia surgery

A dialysis patient develops right-sided colonic ischemia with peritonitis, metabolic acidosis, and pneumatosis. The intern suggests conservative care because most ischemic colitis is transient. What mechanism-based warning changes management?

A. Transmural infarction and necrosis imply irreversible vascular injury requiring urgent surgical assessment

B. Acidosis is expected with microscopic colitis

C. Peritonitis is treated with 5-HT3 antagonists

D. Pneumatosis proves IBS-C

E. Right-sided disease is always mild because of collateral flow

Answer: A
Mechanism pearl: Most **ischemic colitis** is m**uc**osal and self-limited, but peritonitis/acidosis/pneumatosis signal transmural necrosis.

Question 134. Radiation proctopathy

A 70-year-old man received pelvic **radiation** for pro**stat**e cancer. One year later he has painless rectal bleeding and iron deficiency. Endoscopy shows multiple distal rectal **telangiectasias** without deep ulcers. Biopsies are avoided. Which mechanism and treatment logic is best?

A. This is acute infectious colitis requiring stool ova testing only

B. It is **Crohn** fistulizing disease requiring **infliximab** before hemostasis

C. Chronic **radiation** endarteritis causes fragile **telangiectasias**; superficial endoscopic coagulation s**uc**h as **APC** can red**uc**e bleeding

D. It is **IBS**-D requiring **rifaximin**

E. The lesions are **FAP** adenomas needing colectomy

Answer: C
Mechanism pearl: Chronic **radiation** injury is vascular-fibrotic; biopsy can worsen bleeding/nonhealing in fragile irradiated m**uc**osa.

Question 135. Diversion colitis

A 45-year-old man has a Hartmann po**uc**h after trauma. Months later he has m**uc**us, bleeding, and friable rectal stump m**uc**osa. Cultures are negative. Symptoms improve after restoration of fecal stream. Which mechanism best explains the disease?

A. Absence of fecal stream deprives colonocytes of **short-chain fatty acids**, especially **butyrate**, causing m**uc**osal inflammation

B. Toxin B gl**uc**osylates Rho GTPases only in diverted bowel

C. Germline **APC** mutation develops after diversion

D. **TNF-alpha** neutralization causes rectal bleeding

E. **BRAF** mutation causes acute m**uc**osal friability

Answer: A
Mechanism pearl: Diversion colitis is a metabolic-luminal deprivation colitis; restoration of stream is mechanistically definitive.

Question 136. Microscopic colitis therapy reasoning

A 66-year-old woman on a PPI and NSAID has chronic watery diarrhea, nocturnal stools, normal colonoscopy, and biopsies showing a thick subepithelial collagen band. Fecal **calprotectin** is mildly elevated. Which mechanism-based management is most coherent?

A. Perform colectomy because collagenous colitis is premalignant

B. Give **vedolizumab** first because all watery diarrhea is **IBD**

C. Start anti-EGFR therapy because collagen band predicts **KRAS** wild-type cancer

D. Diagnose **IBS** because colonoscopy is normal and avoid biopsies

E. Stop potential triggers and treat collagenous microscopic colitis with locally active budesonide when symptomatic

Answer: E

Mechanism pearl: Microscopic colitis is histologic and inflammatory despite normal endoscopy; budesonide is effective due local steroid activity.

Question 137. C difficile recurrence

A 72-year-old man with **UC** develops recurrent **C. difficile** infection after antibiotics. He responds to vancomycin but relapses twice. Bezlotoxumab is considered. Which mechanism explains its role?

A. It blocks **TNF-alpha** and heals **UC** ulcers

B. It kills spores by inhibiting cell-wall synthesis

C. It binds **bile acid**s and prevents **IBS**-D

D. It neutralizes toxin B, red**uc**ing recurrence risk while antibacterial therapy treats vegetative organisms

E. It demethylates **MLH1** in colonocytes

Answer: D
Mechanism pearl: Bezlotoxumab is antitoxin therapy, not a replacement antibiotic; toxin B is central to epithelial injury and recurrence morbidity.

Question 138. IBS-D vs IBD relapse

A 31-year-old woman with prior **UC** in deep endoscopic remission develops abdominal pain and loose stools during stress. **CRP** is normal, fecal **calprotectin** is low twice, and sigmoidoscopy 3 months ago showed histologic remission. Which mechanism best explains symptoms?

A. Normal **CRP** confirms **toxic megacolon**

B. Histologic remission proves **bile acid** diarrhea in every case

C. Stress directly causes **p53** mutation in colonic m**uc**osa

D. Brain-gut axis dysregulation and **visceral hypersensitivity** can cause **IBS**-like symptoms without neutrophilic m**uc**osal inflammation

E. Low **calprotectin** proves **CMV** colitis

Answer: D
Mechanism pearl: IBD and **IBS** mechanisms can coexist; objective inflammatory biomarkers prevent unnecessary immunosuppression.

Question 139. Postinfectious IBS mechanism

A 24-year-old woman develops chronic urgency and abdominal pain after Salmonella gastroenteritis. Colonoscopy is normal, but research biopsies show increased mast cells near enteric nerves and altered enterochromaffin-cell signaling. Which mechanism best explains her pain?

A. APC mutation causing adenoma-carcinoma sequence

B. Low-grade immune activation and **serotonin**-mediated afferent sensitization after infection

C. STK11 hamartomatous polyposis

D. Alpha-4 beta-7 trafficking causing **UC**

E. Obliterative endarteritis after **radiation**

Answer: B
Mechanism pearl: Postinfectious **IBS** is a model of peripheral immune-neural sensitization without classic **IBD** ulceration.

Question 140. Alosetron safety

A woman with severe refractory **IBS**-D asks about alosetron. She has a history of chronic constipation and prior **ischemic colitis**. Which pharmacologic reasoning argues against use?

A. **5-HT3** antagonism can markedly slow transit and has been associated with severe constipation and **ischemic colitis**

B. Alosetron blocks alpha-4 integrin and causes PML

C. Alosetron activates GC-C and causes secretory diarrhea

D. Alosetron inhibits **MLH1** and causes **MSI**

E. Alosetron neutralizes **TNF-alpha** and reactivates TB

Answer: A

Mechanism pearl: Advanced exam questions may ask adverse events from receptor pharmacology, not just drug names.

Question 141. Linaclotide vs lubiprostone

A patient with **IBS**-C fails fiber. **Linaclotide** and **lubiprostone** are discussed. Which comparison is mechanistically accurate?

A. **Linaclotide** activates **guanylate cyclase-C**/**cGMP** signaling; **lubiprostone** increases intestinal chloride-rich secretion through chloride-channel pathways

B. Both are **5-HT3** antagonists used mainly for **IBS**-D

C. **Linaclotide** blocks **JAK-STAT** while **lubiprostone** blocks **IL-23**

D. Both are anti-TNF biologics

E. Both treat constipation by inhibiting opioid receptors in the sphincter of Oddi

Answer: A

Mechanism pearl: Constipation pharmacology is mechanistic: GC-C/**cGMP** vs chloride secretion vs 5-HT4 agonism vs PAMORAs.

Question 142. Eluxadoline risk

A 50-year-old woman with **IBS**-D had cholecystectomy and prior alcohol-related pancreatitis. **Eluxadoline** is proposed. Which mechanism-based concern is most important?

A. Opioid receptor effects may increase sphincter of Oddi tone and precipitate pancreatitis, especially without a gallbladder

B. **APC** mutation may cause pancreatitis

C. **Alpha-4 beta-7** blockade may cause appendicitis

D. GC-C activation may cause hypoglycemia

E. **5-HT3** antagonism may cause PML

Answer: A

Mechanism pearl: **Eluxadoline** benefits stool frequency via opioid effects but the same pathway explains pancreatobiliary risk.

Question 143. Rifaximin and microbiome

A 42-year-old man with **IBS**-D, bloating, and negative inflammatory evaluation improves after a 2-week course of **rifaximin** but relapses months later. Which explanation best fits its clinical behavior?

A. **Rifaximin** blocks **5-HT3** receptors irreversibly

B. A minimally absorbed antibiotic can transiently alter microbial metabolism/gas signaling without correcting central sensitization permanently

C. **Rifaximin** eradicates **Crohn** disease by reversing **NOD2** mutations

D. **Rifaximin** heals **radiation** **telangiectasias**

E. **Rifaximin** prevents **Lynch** syndrome cancers

Answer: B
Mechanism pearl: **Rifaximin** is a luminal **microbiome** therapy; relapse does not prove **IBD**.

Question 144. Bile acid diarrhea as IBS mimic

A 36-year-old woman has chronic watery diarrhea after cholecystectomy. Colonoscopy and biopsies are normal. Symptoms are postprandial and improve with a **bile acid** sequestrant. Which mechanism best explains this **IBS**-D mimic?

A. Mast-cell central sensitization is the only possible mechanism

B. **APC** second-hit adenomas secrete water

C. **PMS2** loss causes watery diarrhea

D. **S1P** receptors trap **bile acid**s in lymph nodes

E. Excess colonic **bile acid**s stimulate secretion and motility through epithelial and neural mechanisms

Answer: E
Mechanism pearl: **Bile acid** diarrhea is a treatable mechanistic mimic of **IBS**-D.

Question 145. Low FODMAP physiology

A 27-year-old woman with **IBS** has bloating worsened by onions, wheat, apples, and milk. Low-FODMAP diet improves distension but not all pain. Which mechanism best explains partial response?

A. The diet blocks **IL-23** and closes **fistula**s

B. FODMAP restriction reverses **UC** **dysplasia**

C. It demethylates **MLH1** in **serrated** lesions

D. Red**uc**ed poorly absorbed fermentable substrate lowers osmotic water and gas, while central/peripheral pain sensitization may persist

E. It cures microscopic colitis by collagen degradation

Answer: D
Mechanism pearl: **IBS** is multi-mechanistic; red**uc**ing luminal distension may not fully reverse sensitization.

Question 146. Colon cancer stool tests

An average-risk patient refuses colonoscopy. The physician compares FIT and multitarget stool DNA. Which mechanism-based distinction is correct?

A. FIT detects **APC** mutations and stool DNA detects fecal neutrophils

B. FIT detects human globin from bleeding lesions, whereas stool DNA testing detects shed neoplastic molecular alterations plus hemoglobin markers

C. Stool DNA is specific for **Crohn** ulcers only

D. Both tests directly visualize flat **serrated** lesions

E. FIT is positive only in **Lynch** syndrome

Answer: B
Mechanism pearl: Screening tests differ by biological signal: bleeding versus shed molecular neoplasia.

Question 147. Inflammatory pseudopolyps

A **UC** patient in remission has multiple filiform inflammatory pseudopolyps. Biopsies show post-inflammatory m**uc**osal islands without **dysplasia**. How should their cancer significance be framed?

A. They define **serrated** polyposis syndrome

B. They prove **Crohn** disease

C. They are **APC**-mutant adenomas and all require colectomy

D. They are hamartomas from **STK11** mutation

E. They are markers of prior severe inflammation and may make surveillance harder, but the pseudopolyps themselves are not adenomatous precursors

Answer: E

Mechanism pearl: Inflammatory pseudopolyps are not neoplastic adenomas, but they indicate cumulative inflammatory burden and can obscure **dysplasia**.

Question 148. SCAD vs UC

A 69-year-old man with sigmoid diverticulosis has rectal bleeding. Colonoscopy shows inflammation only in the sigmoid segment containing diverticula, with rectal and proximal colon sparing. Biopsies show chronic active colitis. Which diagnosis and mechanism are most likely?

A. Classic **UC** because any chronic active colitis begins in rectum

B. **Radiation** proctitis because sigmoid diverticula are **telangiectasias**

C. **Lynch** syndrome because diverticula cause **MSI**

D. **Crohn** disease because rectal sparing proves transmural **fistula**s

E. Segmental colitis associated with diverticulosis, a localized inflammatory process in the diverticular segment that can mimic **IBD**

Answer: E

Mechanism pearl: Distribution is mechanistic: SCAD is segmental around diverticulosis, unlike continuous rectal **UC**.

Question 149. Solitary rectal ulcer/dyssynergia

A 33-year-old woman has rectal bleeding, m**uc**us, digital evacuation, and excessive straining. Endoscopy shows an anterior rectal ulcer and polypoid erythematous m**uc**osa. Histology shows fibromuscular obliteration and displaced glands. Which treatment logic is most mechanistic?

A. Give PD-1 inhibitor because this is **MSI**-high cancer

B. Treat with antiviral therapy for **CMV**

C. Correct defecatory dysfunction with biofeedback because m**uc**osal prolapse/trauma drives the lesion

D. Start anti-TNF because this is transmural **Crohn** fistulizing disease

E. Use cholestyramine because **bile acid**s cause m**uc**osal prolapse

Answer: C

Mechanism pearl: Solitary rectal ulcer syndrome is a defecatory/m**uc**osal prolapse disorder; fixing mechanics is central.

Question 150. Angiodysplasia and aortic stenosis

An 82-year-old man with aortic stenosis and CKD has recurrent painless hematochezia. Colonoscopy shows right-colon angio**dysplasia**s. He also has acquired von Willebrand factor abnormality. Which integrated mechanism explains bleeding tendency?

A. **TNF-alpha** causes granulomatous venous rupture

B. **APC** mutation creates vascular polyps

C. **5-HT3** blockade causes telangiectasia

D. **S1P** modulation induces vWF cleavage

E. Fragile mucosal vascular ectasias plus shear-related loss of high-molecular-weight von Willebrand multimers increases bleeding

Answer: E

Mechanism pearl: Heyde physiology combines vascular lesions and acquired vWF dysfunction from high shear across stenotic valves.

Compact Answer Key

Q1: D Q2: D Q3: B Q4: B Q5: B Q6: A Q7: D Q8: D Q9: B Q10: D Q11: E Q12: C Q13: B Q14: D Q15: D Q16: E Q17: A Q18: B Q19: E Q20: E Q21: C Q22: B Q23: A Q24: D Q25: A

Q26: E Q27: B Q28: B Q29: A Q30: D Q31: C Q32: C Q33: A Q34: A Q35: E Q36: E Q37: C Q38: E Q39: D Q40: C Q41: D Q42: D Q43: E Q44: B Q45: D Q46: D Q47: D Q48: C Q49: E Q50: A

Q51: C Q52: E Q53: B Q54: D Q55: D Q56: A Q57: C Q58: C Q59: D Q60: E Q61: E Q62: D Q63: C Q64: C Q65: A Q66: B Q67: B Q68: B Q69: E Q70: A Q71: B Q72: E Q73: D Q74: D Q75: D

Q76: C Q77: B Q78: C Q79: E Q80: E Q81: A Q82: E Q83: E Q84: A Q85: C Q86: D Q87: D Q88: B Q89: C Q90: A Q91: A Q92: B Q93: B Q94: E Q95: A Q96: D Q97: B Q98: E Q99: E Q100: C

Q101: A Q102: E Q103: E Q104: B Q105: E Q106: B Q107: A Q108: E Q109: E Q110: B Q111: E Q112: A Q113: B Q114: D Q115: C Q116: D Q117: B Q118: E Q119: A Q120: C Q121: B Q122: D Q123: D Q124: D Q125: C

Q126: C Q127: E Q128: B Q129: E Q130: E Q131: B Q132: A Q133: A Q134: C Q135: A Q136: E Q137: D Q138: D Q139: B Q140: A Q141: A Q142: A Q143: B Q144: E Q145: D Q146: B Q147: E Q148: E Q149: C Q150: E

Topic Map

Q1: **IBD** innate immunity

Q2: **IBD autophagy**

Q3: **IBD Th17** axis

Q4: Anti-TNF pharmacology

Q5: Therapeutic drug monitoring

Q6: Mechanistic failure

Q7: **Vedolizumab**

Q8: **Natalizumab** comparison

Q9: **Ustekinumab**

Q10: **JAK** inhibitors

Q11: **S1P** modulation

Q12: Corticosteroids

Q13: 5-ASA

Q14: **Thiopurine**s

Q15: Methotrexate

Q16: **Calcineurin** inhibitors

Q17: Fecal **calprotectin**

Q18: **CRP** biology

Q19: Serology

Q20: **Mucosal healing**

Q21: Anti-TNF and TB

Q22: HBV reactivation

Q23: Opportunistic infection

Q24: PSC-**UC** cancer risk

Q25: Backwash ileitis

Q26: **Toxic megacolon**

Q27: **CMV** colitis in **IBD**

Q28: C difficile and **IBD** flare

Q29: **Crohn fibrosis**

Q30: Fistulizing **Crohn**

Q31: Postoperative **Crohn** recurrence

Q32: Postoperative prophylaxis

Q33: **Bile acid** diarrhea after ileal disease

Q34: Anemia of inflammation

Q35: Thrombosis in **IBD**

Q36: NSAIDs in **IBD**

Q37: Smoking

Q38: EIMs

Q39: Monogenic VEO-**IBD**

Q40: Barrier function

Q41: **Dysbiosis**

Q42: **IL-22**

Q43: IL-10 tolerance

Q44: Biologic plus **thiopurine**

Q45: **IL-23** p19 vs p40

Q46: Integrin vs **S1P**

Q47: Acute severe **UC** rescue

Q48: Surgery and **UC** cure

Q49: **Pouchitis**

Q50: **Crohn** vs **UC** surgical planning

Q51: Colitis-associated cancer

Q52: Chromoendoscopy rationale

Q53: Granuloma

Q54: **UC** histology

Q55: Intestinal ultrasound/MRI biomarker

Q56: Leukocyte trafficking failure

Q57: Biomarker discordance

Q58: Biosimilars

Q59: Budesonide

Q60: Topical therapy in **UC**

Q61: Antibiotics in **Crohn**

Q62: Exclusive enteral nutrition

Q63: Histologic remission **UC**

Q64: **Colorectal cancer APC**

Q65: **KRAS** and anti-EGFR

Q66: T**P53** late progression

Q67: **Lynch** syndrome

Q68: Sporadic **MSI**

Q69: **MSI** immunotherapy

Q70: **Serrated** pathway

Q71: **FAP** genetics

Q72: **MUTYH**

Q73: **POLE**/**POLD1**

Q74: **Peutz-Jeghers**

Q75: **Juvenile polyposis**

Q76: **PTEN** hamartoma syndrome

Q77: **Serrated** polyposis

Q78: Advanced adenoma biology

Q79: CEA biomarker

Q80: FIT biology

Q81: Stool DNA testing

Q82: **Ischemic colitis**

Q83: Right-sided ischemia

Q84: **Radiation** proctopathy

Q85: Argon plasma coagulation

Q86: Diversion colitis

Q87: Microscopic colitis

Q88: C difficile toxin

Q89: **IBS visceral hypersensitivity**

Q90: **IBS serotonin** pharmacology

Q91: **IBS**-C **linaclotide**

Q92: **Eluxadoline**

Q93: **Rifaximin IBS**-D

Q94: **Bile acid** vs **IBS**-D

Q95: Postinfectious **IBS**

Q96: Low FODMAP

Q97: **IBS** brain-gut

Q98: Alosetron adverse

Q99: Colonic inertia vs **IBS**-C

Q100: Diverticular disease

Q101: AS**UC** rescue

Q102: **Infliximab** pharmacokinetic failure

Q103: **Infliximab** mechanistic failure

Q104: **Vedolizumab** vs **natalizumab**

Q105: **IL-23** selection

Q106: **JAK** inhibitor adverse logic

Q107: **S1P** and lymphopenia

Q108: Perianal **Crohn** abscess

Q109: Fibrostenotic **Crohn**

Q110: Postoperative recurrence prevention

Q111: **Pouchitis** vs **Crohn** of po**uc**h

Q112: **CMV** steroid refractory colitis

Q113: PSC-**IBD** neoplasia

Q114: Colitis-associated **dysplasia**

Q115: VEO-**IBD** immune defect

Q116: Pregnancy and biologic transfer

Q117: **IBD** anemia mixed

Q118: **IBD** and thrombosis

Q119: **Lynch** vs sporadic **MSI**

Q120: Checkpoint in **MSI** CRC

Q121: Anti-EGFR selection

Q122: **FAP** desmoid

Q123: **MUTYH** recessive counseling

Q124: **POLE** ultramutator

Q125: **Peutz-Jeghers** and intussusception

Q126: **Juvenile polyposis SMAD4**-HHT

Q127: **PTEN** hamartoma tumor syndrome

Q128: **Serrated** polyposis surveillance

Q129: Right-sided **serrated** lesion missed

Q130: Colitis-associated CRC vs sporadic adenoma

Q131: Malignant polyp decision

Q132: **Ischemic colitis** mimic

Q133: Severe ischemia surgery

Q134: **Radiation** proctopathy

Q135: Diversion colitis

Q136: Microscopic colitis therapy reasoning

Q137: C difficile recurrence

Q138: **IBS**-D vs **IBD** relapse

Q139: Postinfectious **IBS** mechanism

Q140: Alosetron safety

Q141: **Linaclotide** vs **lubiprostone**

Q142: **Eluxadoline** risk

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Q145: Low FODMAP physiology

Q146: Colon cancer stool tests

Q147: Inflammatory pseudopolyps

Q148: SCAD vs **UC**

Q149: Solitary rectal ulcer/dyssynergia

Q150: Angio**dysplasia** and aortic stenosis