Iatrogenic-Induced Contributing Factors to Disease: Taxonomy, Resulting Diseases, and Linking Biological Mechanisms

Revised and expanded study report, prepared October 18, 2026, from the author's draft.

EXECUTIVE SUMMARY

Purpose. This report systematically identifies (1) the full spectrum of iatrogenic-induced contributing factors (CFs) to disease, (2) the specific diseases to which each CF contributes, and (3) the biological mechanisms that link each CF to those diseases. It extends the author's draft, which catalogued 53 CFs in five categories, by adding missing categories, many additional CFs (including a full vaccine section), a dedicated analysis of mechanisms shared across categories of CFs and across the diseases they induce, and an evidence-grading system that distinguishes established causal relationships from hypotheses and from claims that have been tested and not supported.

Definition used. An iatrogenic CF is any exposure arising from medical care (a drug, vaccine, biologic, procedure, device, imaging or diagnostic test, blood product, hospital environment, care process, or system failure) that increases the probability, severity, or chronicity of a disease. The CF may be a necessary cause (e.g., acetaminophen overdose and acute liver failure), one component of a multifactorial cause (e.g., immobility in postoperative venous thrombosis), or a susceptibility amplifier (e.g., polypharmacy).

Principal findings.

1. **The spectrum is far broader than drug toxicity.** The catalogue in Section 3 contains more than 200 numbered CFs organized into 12 categories: (A) pharmacologic agents; (B) healthcare-associated infections and antimicrobial resistance; (C) surgical, anesthetic, and other procedural harm; (D) implanted devices and materials; (E) therapeutic and diagnostic radiation and imaging agents; (F) blood products, transplantation, and biologic transfer; (G) vaccines; (H) hospitalization-related and critical-care harm; (I) diagnostic cascades, overdiagnosis, and psychological iatrogenesis; (J) systems, error, and human-factors CFs; (K) product-quality failures, contamination, and healthcare-environment exposures; and (L) developmental and reproductive iatrogenesis. Three cross-cutting dimensions (host genetic susceptibility, iatrogenic dependence and withdrawal, and iatrogenic cancer) cut across these categories and are analyzed separately.

2. **A limited number of mechanism families explain most iatrogenic disease.** Sixteen mechanism families (Section 3.14) account for nearly every CF–disease link: dose-dependent cytotoxicity and transporter-mediated organ accumulation; reactive-metabolite, oxidative, and mitochondrial injury; excessive on-target pharmacology; off-target receptor and ion-channel effects; immune hypersensitivity (Types I–IV and pseudo-allergy); loss of immune tolerance; immunosuppression and barrier breach; microbiome disruption; biofilm and foreign-body response; mechanical, ischemic, and pressure injury; hemostatic dysregulation; DNA damage and mutagenesis; endocrine and metabolic axis disruption; fibrosis and chronic remodeling; neuroadaptation and neuroinflammation; and developmental programming.

3. **Different CFs converge on the same diseases through a small set of final common pathways.** For example, at least six distinct mechanistic routes (hemodynamic, tubular toxic, immune interstitial, obstructive, microangiopathic, and rhabdomyolytic) converge on acute kidney injury, and at least five (phospholipidosis, oxidative DNA damage, immune pneumonitis, radiation-induced TGF-beta signaling, and barotrauma) converge on pulmonary fibrosis or acute lung injury. Section 3.15 maps these convergences. The final common pathways are regulated cell death, mitochondrial permeability and reactive oxygen species, innate inflammatory signaling (NF-kappaB, inflammasome, cytokines), TGF-beta-driven fibrosis, endothelial activation and coagulation, HLA-restricted T-cell activation or checkpoint release, DNA-damage-response signaling, and receptor adaptation.

4. **Host susceptibility often determines who is harmed.** Pharmacogenomic variants (e.g., HLA-B*57:01, HLA-B*15:02, HLA-B*58:01, TPMT/NUDT15, DPYD, G6PD, RYR1, CYP2C9/VKORC1, SLCO1B1) convert otherwise rare reactions into predictable, preventable ones. Age, renal and hepatic function, sex, comorbidity, and polypharmacy are equally important modifiers (Section 3.16).

5. **Vaccines are included with evidence grading.** Section 3 (Category G) covers mRNA, adenoviral-vector, MMR and measles-containing, live-attenuated (rotavirus, oral polio, BCG, yellow fever, zoster), inactivated and adjuvanted (influenza, Tdap/DTP, HPV, hepatitis B), RSV, smallpox, and dengue vaccines. Established serious adverse events are rare relative to doses administered, and the best-characterized ones include myocarditis after mRNA vaccines (concentrated in adolescent and young adult males), vaccine-induced immune thrombotic thrombocytopenia (VITT) after adenoviral-vector vaccines, anaphylaxis, febrile seizures and immune thrombocytopenia after measles-containing vaccines, intussusception after rotavirus vaccines, vaccine-associated paralytic poliomyelitis, disseminated vaccine-strain disease in immunodeficient hosts, and small Guillain-Barre syndrome excesses after some influenza, adenoviral-vector, zoster, and RSV vaccines. Several widely discussed claims (e.g., MMR and autism, thimerosal and neurodevelopmental disorders) have been tested in large studies and were not supported, and these are reported as such. Mechanisms proposed for some events (e.g., spike-protein TLR4 signaling and molecular mimicry in myocarditis) remain hypotheses and are labeled accordingly.

6. **The draft contained several items requiring correction or hedging** (Section 3.20). Most important: abacavir hypersensitivity is a distinct HLA-B*57:01-restricted syndrome and not SJS/TEN; the often-cited figure of 400,000 annual deaths is an upper-bound extrapolation that more direct studies place roughly an order of magnitude lower (about 22,000 preventable inpatient deaths per year in one meta-analysis); the vaccine-myocarditis mechanism was presented with more certainty than the evidence supports; and the draft's conclusion that abacavir hypersensitivity was "eliminated" should read "nearly eliminated among screened populations."

7. **Benefit-risk context is essential.** Most CFs in this report arise from interventions that, on balance, prevent more disease than they cause. The goal of cataloguing CFs is to enable risk reduction (stewardship, pharmacogenomic screening, bundles, deprescribing, better device and procedure design), not to argue against effective medical care.

Evidence grading. Every numbered CF carries a grade: **E** (established: causation and principal mechanism well supported), **P** (probable: causation supported, mechanism partly defined), **H** (hypothesized or associational: plausible mechanism, causation not established), or **C** (contested or not supported by large studies; included for completeness).

Key caveats. Frequency rankings are approximate and setting-dependent; no authoritative ranked list of the "most frequent" iatrogenic CFs exists. Many estimates come from passive reporting or extrapolation. Mechanisms are summarized at a level suitable for a cross-disciplinary readership and should be checked against primary literature for any specific claim.

BACKGROUND

2.1 Definitions and conceptual framework

The term *iatrogenic* (Greek *iatros*, physician; *genesis*, origin) denotes illness or harm caused by medical examination, treatment, or the healthcare environment. Ivan Illich's 1976 critique distinguished three levels: **clinical iatrogenesis** (direct injury from drugs, procedures, and infections), **social iatrogenesis** (medicalization of normal life events and dependence on the health system), and **structural iatrogenesis** (erosion of autonomy and coping capacity). This report concentrates on clinical iatrogenesis but includes the diagnostic-cascade and psychological forms (Category I) that bridge clinical and social levels.

Precise terminology matters because published statistics are frequently conflated:

- **Adverse drug reaction (ADR):** a noxious, unintended response to a drug at doses normally used.
- **Adverse drug event (ADE):** any injury related to a drug, including ADRs, medication errors, overdoses, and withdrawal.
- **Medication error:** a preventable failure in prescribing, dispensing, administering, or monitoring.
- **Complication:** an undesired outcome of a procedure, whether or not due to error.
- **Preventable adverse event:** harm that would not have occurred with standard-of-care practice. A large share of iatrogenic harm is *not* preventable with current knowledge because it reflects inherent risk of effective therapy.
- **Contributing factor (CF):** the unit of analysis in this report. A CF need not be the sole cause; it increases the probability, severity, or chronicity of disease in combination with host susceptibility and other exposures.

The report deliberately excludes harm from *omission* of indicated care (undertreatment) except where it manifests as diagnostic error (Category I and J), because its mechanisms are those of the untreated disease rather than of an iatrogenic exposure.

2.2 Classification frameworks for adverse drug effects

The Rawlins-Thompson scheme divides ADRs into **Type A** (augmented; predictable, dose-dependent extensions of pharmacology, such as bleeding with anticoagulants) and **Type B** (bizarre; idiosyncratic or immune-mediated, such as SJS/TEN). It has been extended with **Type C** (chronic or cumulative, e.g., adrenal suppression), **Type D** (delayed, e.g., secondary malignancy or teratogenicity), **Type E** (end-of-use or withdrawal, e.g., adrenal crisis after steroid cessation), and **Type F** (failure of therapy, often via interactions). The Aronson-Ferner **DoTS** system describes any reaction by **Do**se-relatedness, **T**ime-course, and patient **S**usceptibility, which maps naturally onto the mechanism-oriented approach used here. Immune-mediated reactions are further classified by the Gell-Coombs scheme: **Type I** (IgE-mediated immediate), **Type II** (antibody-mediated cytotoxic), **Type III** (immune-complex), and **Type IV** (T-cell-mediated delayed, subdivided IVa-IVd), supplemented by **pseudo-allergic (non-IgE) mast-cell activation**, for instance via MRGPRX2 or complement-activation-related pseudoallergy (CARPA).

2.3 Epidemiologic burden

Estimates of iatrogenic harm vary by an order of magnitude depending on method, and the draft's headline figures require contextualization.

- **Deaths associated with hospital care.** The Institute of Medicine (1999) estimated 44,000 to 98,000 annual US deaths from medical error. A 2013 analysis using trigger-tool data (James) extrapolated to a lower bound of 210,000 and an upper estimate of more than 400,000 premature deaths per year associated with preventable harm. A 2016 BMJ analysis (Makary and Daniel) estimated about 250,000 deaths per year. These extrapolations have been criticized because many patients who died had advanced illness and short life expectancy. A 2020 systematic review and meta-analysis of studies that began from inpatient deaths and worked backward (Rodwin and colleagues; 8 studies, 12,503 deaths) found that 3.1% of inpatient deaths were judged preventable, corresponding to about 22,000 preventable deaths per year in the US, of which only about 7,000 involved patients expected to live longer than three months. A defensible summary is that preventable hospital deaths number in the tens of thousands per year, with larger numbers of *associated* deaths in patients with serious underlying disease; the 400,000 figure should be presented as an upper-bound extrapolation, not a measured count.

- **Adverse drug events.** The CDC estimates that ADEs account for roughly 1.3 million emergency department visits and about 350,000 hospitalizations per year in the US, with anticoagulants, insulins, and antibiotics among the most common causes in surveillance of emergency visits. ADEs are implicated in a few percent of hospital admissions in most studies. A frequently cited 1998 meta-analysis (Lazarou and colleagues) estimated more than 100,000 deaths per year from ADRs in hospitalized patients, but this has been challenged on methodologic grounds.

- **Hospital adverse events overall.** A North Carolina record-review study (Landrigan and colleagues, 2010) found that about 18% of hospital admissions involved at least one harm, with roughly 63% of harms judged preventable.

- **Healthcare-associated infections (HAIs).** CDC point-prevalence surveys estimated about 722,000 HAIs among roughly 648,000 US inpatients in 2011, with about 75,000 inpatient deaths among patients with HAIs. The 2015 survey found a prevalence of 3.2% of inpatients (down from 4.0% in 2011; adjusted risk 16% lower), driven by declines in surgical-site and urinary tract infection, with no significant change in pneumonia or *Clostridioides difficile* infection. Deaths among patients with HAIs are not all attributable to the infection.

- **Diagnostic error.** An analysis of outpatient data (Singh and colleagues, 2014) estimated that about 5% of US adults, roughly 12 million people, experience a diagnostic error annually.

- **Radiation.** Projection models (Berrington de Gonzalez and colleagues, 2009) estimated that CT scans performed in the US in 2007 would eventually cause on the order of 29,000 cancers; the underlying linear no-threshold extrapolation at low doses is debated.

- **Opioids.** Prescription-opioid-involved overdose deaths have numbered in the range of roughly 14,000 to 17,000 per year in the US in recent years, although most current overdose deaths involve illicitly manufactured fentanyl; prescription exposure remains an important initiating pathway to opioid use disorder.

The Agency for Healthcare Research and Quality (AHRQ) Patient Safety Indicators (PSIs), such as pressure injury (PSI 03), iatrogenic pneumothorax (PSI 06), postoperative hemorrhage (PSI 09), postoperative acute kidney injury requiring dialysis (PSI 10), perioperative pulmonary embolism or deep vein thrombosis (PSI 12), and accidental puncture or laceration (PSI 15), provide standardized administrative-data screens for such events. They are screening tools with false positives and negatives, not definitive counts.

2.4 Surveillance systems and their limits

Major data sources include: spontaneous-reporting systems (FDA Adverse Event Reporting System, FAERS; Vaccine Adverse Event Reporting System, VAERS; WHO VigiBase; UK Yellow Card), active surveillance (Vaccine Safety Datalink, Sentinel, NEISS-CADES for emergency visits, CDC National Healthcare Safety Network for HAIs), chart-review tools (Institute for Healthcare Improvement Global Trigger Tool), administrative claims (AHRQ PSIs, Medicare analyses), and registries and randomized trials. Each has characteristic biases. **Spontaneous reports** (including VAERS) are generated by anyone, are unverified, subject to stimulated and under-reporting, lack denominators and control groups, and can *generate signals* but cannot by themselves establish causation or incidence. **Claims analyses** suffer from misclassification. **Trigger-tool reviews** depend on documentation. **Randomized trials** are usually underpowered for rare events (below roughly 1 in 10,000). Rigorous signal evaluation therefore triangulates multiple designs, particularly self-controlled case series, cohort studies with active comparators, and comparison of observed with expected background rates.

2.5 Principles of causal inference applied in this report

Causality for individual events is commonly assessed with WHO-UMC categories (certain, probable, possible, unlikely) or the Naranjo algorithm; causality for population-level associations is assessed with Bradford Hill considerations (strength, consistency, temporality, biological gradient, plausibility, coherence, experiment, analogy, specificity). Recurring pitfalls include **confounding by indication** (the disease being treated, not the treatment, causes the outcome), **protopathic bias** (early symptoms of an undiagnosed disease prompting a drug prescription), **healthy-user and survivor bias**, **detection bias**, and **temporal association without causation**, which is especially important for vaccines because many conditions have incidence peaks at ages when vaccines are given. Mechanistic plausibility alone never establishes causation, and conversely, absence of a known mechanism does not refute a well-replicated association. This is why each CF in Section 3 is graded for evidence and why mechanisms are presented separately from epidemiologic support.

Absolute risk, not only relative risk, determines clinical meaning. A threefold relative increase in a one-in-a-million event is still a one-in-330,000 event. Benefit-risk assessment must compare the absolute harm of the intervention with the absolute harm of the disease prevented or treated; for example, myocarditis is more frequent after SARS-CoV-2 infection than after vaccination in several large cohorts, and *C. difficile* risk from an antibiotic is usually small relative to the mortality of the bacterial infection treated.

2.6 Assessment of the source draft

The draft consists of an initial outline-style response and a longer structured analysis. Its strengths include a consistent "CF, resulting disease, mechanism" template, well-developed mechanistic narratives (SJS/TEN and HLA alleles, vancomycin-uromodulin casts, amiodarone phospholipidosis and Hippo/YAP, healthcare-associated biofilms, myocarditis, VITT), and use of AHRQ PSIs. Its gaps, which this report addresses, are:

- **Incomplete structure.** No numbered executive summary; the vaccine section covers only four CFs; the draft ends without a results synthesis.
- **Missing categories.** Radiation and imaging agents as a stand-alone category (including diagnostic CT and gadolinium), implanted devices and materials, blood products and transplantation (partly present), developmental and reproductive iatrogenesis, iatrogenic dependence and withdrawal, iatrogenic cancer as a cross-cutting outcome, diagnostic cascades and overdiagnosis, medication and procedural errors, product contamination and quality failures, and healthcare-environment exposures.
- **Missing high-impact agents.** Acetaminophen hepatotoxicity, prescription opioid use disorder, QT-prolonging drugs, hormone therapies, PPIs, SGLT2 inhibitors, anti-TNF and JAK inhibitors, CAR-T cells, trastuzumab, VEGF inhibitors, alkylating agents and topoisomerase-II inhibitors (therapy-related leukemia), thalidomide, valproate, and many others.

- **Missing mechanism synthesis.** No section integrating mechanisms common across CF categories or across resulting diseases, and no host-susceptibility framework beyond HLA examples.
- **Evidence-calibration issues** noted in Section 3.20.

2.7 Organization of the report

Section 3 presents, in order: methods and numbering conventions (3.1); the master taxonomy (3.2); the catalogue of CFs in twelve categories (3.3 to 3.13); mechanisms common to categories of CFs (3.14); mechanisms common to the diseases induced (3.15); host and contextual susceptibility (3.16); temporal patterns (3.17); evidence quality and causal-inference issues (3.18); prevention and mitigation (3.19); reconciliation with the draft (3.20); and research gaps (3.21). Section 4 gives the Summary and Conclusions, followed by an abbreviation list and key sources.

RESULTS AND DISCUSSION

3.1 Methods, entry format, and grading conventions

Sources and approach. The catalogue integrates the content of the author's draft (all 53 draft CFs are retained, corrected where necessary, and in some cases merged by agent) with additional CFs identified from the pharmacovigilance, patient-safety, surgical, transfusion, infectious-disease, oncology, radiology, and vaccine-safety literatures. Headline epidemiologic figures were cross-checked against primary or regulatory sources where possible (e.g., CDC HAI prevalence surveys, the Rodwin meta-analysis, and the FDA's 2025 RSV-vaccine Guillain-Barre labeling action). Other figures reflect the author's synthesis of the literature and are flagged as approximate.

Entry format. Each numbered CF lists *Diseases* (principal resulting conditions, not exhaustive), *Mechanism* (the biological link from exposure to disease), and *Grade* (E, P, H, or C as defined in the Executive Summary). Where one agent causes diseases by distinct mechanisms, the mechanisms are paired with the diseases in order. Where an agent has benefits that vastly outweigh typical risk, this is noted in Section 3.18. Frequency terms follow the conventional scale: very common (at least 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1,000 to 1 in 100), rare (1 in 10,000 to 1 in 1,000), very rare (fewer than 1 in 10,000).

Numbering. CFs are identified by category letter and sequence (A1, A2, ... L11). Cross-references appear in the text, but each CF is counted once. The draft's "CF 1 to CF 53" correspond to the entries named in Section 3.20.

3.2 Master taxonomy of iatrogenic contributing factors

The draft contained five categories. This report organizes the spectrum into twelve categories (categories A, B, C, G, and H correspond to the draft's categories 1, 2, 3, 4, and 5, expanded), plus three cross-cutting dimensions.

- **A. Pharmacologic agents** (expanded): anti-infectives; analgesics, anti-inflammatories, and corticosteroids; cardiovascular, renal, and metabolic agents; neuropsychiatric agents; oncologic agents; immunomodulators and biologics; hormonal and bone-active agents; dependence and withdrawal; interactions and prescribing cascades.
- **B. Healthcare-associated infections and antimicrobial resistance** (expanded).
- **C. Surgical, anesthetic, and other procedural harm** (expanded).
- **D. Implanted devices and materials** (new as a stand-alone category).
- **E. Therapeutic and diagnostic radiation and imaging agents** (new as a stand-alone category).
- **F. Blood products, transplantation, and biologic transfer** (expanded).
- **G. Vaccines** (expanded to cover the full vaccine schedule and newer products).
- **H. Hospitalization-related and critical-care harm** (expanded).
- **I. Diagnostic cascades, overdiagnosis, and psychological iatrogenesis** (new).
- **J. Systems, error, and human-factors CFs** (new).
- **K. Product-quality failures, contamination, and healthcare-environment exposures** (new).
- **L. Developmental and reproductive iatrogenesis** (new).
- **Cross-cutting dimensions:** host genetic and physiologic susceptibility (Section 3.16); iatrogenic dependence and withdrawal (entries A88 to A89 and Section 3.15); and iatrogenic cancer (Section 3.15).

3.3 Category A: Pharmacologic agents (adverse drug reactions and toxicity)

Pharmacologic exposure is the most frequent route of iatrogenic harm. Reactions arise through predictable extension of pharmacology (Type A), idiosyncratic or immune-mediated mechanisms (Type B), cumulative or delayed effects (Types C and D), withdrawal (Type E), and interactions. The sub-sections below group agents by therapeutic class.

A-I. Anti-infective agents

- **A1. Beta-lactams (penicillins, cephalosporins).** *Diseases:* anaphylaxis, urticaria, drug-induced hemolytic anemia, serum-sickness-like reaction, acute interstitial nephritis, cholestatic hepatitis (amoxicillin-clavulanate), rare DRESS and SJS/TEN, seizures at high dose in renal failure. *Mechanism:* the opened beta-lactam ring covalently haptenates lysine residues on carrier proteins; IgE directed at these haptens cross-links on mast cells and basophils (Type I), antibody-coated red cells are cleared (Type II), and drug-specific T cells drive delayed reactions (Type IV,

with HLA-DRB1*15:01 linked to amoxicillin-clavulanate liver injury); at high concentrations beta-lactams antagonize GABA-A receptors. *Grade:* E.

- **A2. Sulfonamide antibiotics (trimethoprim-sulfamethoxazole).** *Diseases:* SJS/TEN, DRESS, hyperkalemia, cytopenias, hemolysis in G6PD deficiency, crystalluria, interstitial nephritis. *Mechanism:* sulfamethoxazole hydroxylamine and nitroso metabolites haptenate proteins and activate T cells; trimethoprim blocks the epithelial sodium channel (ENaC) in the distal nephron, reducing potassium secretion (amiloride-like) and tubular creatinine secretion; folate-pathway antagonism suppresses marrow. *Grade:* E.

- **A3. Fluoroquinolones.** *Diseases:* tendinopathy and Achilles rupture (higher risk with age over 60, corticosteroids, renal transplant), aortic aneurysm and dissection, peripheral neuropathy, CNS toxicity, dysglycemia, QT prolongation, *C. difficile* infection. *Mechanism:* induction of matrix metalloproteinases and impaired collagen synthesis in tenocytes and aortic fibroblasts, chelation of divalent cations (Mg, Mn) required for collagen cross-linking enzymes, oxidative stress; GABA-A antagonism in the CNS; hERG potassium-channel block; pancreatic beta-cell K-ATP effects for dysglycemia. *Grade:* E for tendon injury and QT; P for aortic disease and neuropathy.

- **A4. Aminoglycosides (gentamicin, tobramycin, amikacin).** *Diseases:* acute tubular necrosis, irreversible cochlear and vestibular ototoxicity, neuromuscular blockade. *Mechanism:* megalin-mediated uptake into proximal tubular cells and lysosomal accumulation (phospholipidosis), reactive oxygen species and mitochondrial injury; uptake into cochlear hair cells through mechanotransduction channels, with ROS-driven apoptosis; the mitochondrial 12S rRNA m.1555A>G variant confers hypersusceptibility by promoting aminoglycoside binding to the mitoribosome. *Grade:* E.

- **A5. Vancomycin.** *Diseases:* acute kidney injury (ATN and interstitial nephritis; risk rises with high troughs or AUC, duration, critical illness, and combination with piperacillin-tazobactam), infusion reaction ("red man" syndrome), neutropenia. *Mechanism:* vancomycin-uromodulin cast formation obstructs distal tubules; intracellular accumulation in proximal tubule cells drives oxidative stress and autophagic disruption (as in the draft); the infusion reaction is non-IgE mast-cell degranulation through MRGPRX2; the piperacillin-tazobactam interaction may reflect true tubular injury or inhibited creatinine secretion (debated). *Grade:* E for AKI and infusion reaction.

- **A6. Macrolides (erythromycin, clarithromycin, azithromycin).** *Diseases:* QT prolongation, torsades de pointes and sudden cardiac death (modest absolute risk), drug-interaction toxicity (statin rhabdomyolysis, colchicine toxicity, hypotension with calcium-channel blockers, DOAC accumulation), infantile hypertrophic pyloric stenosis after early-infancy exposure (association). *Mechanism:* block of the hERG (IKr) potassium channel; mechanism-based inhibition of CYP3A4 by erythromycin and clarithromycin; motilin-receptor agonism proposed for pyloric stenosis. *Grade:* E for QT and interactions; P for pyloric stenosis.

- **A7. Clindamycin and other broad-spectrum antibiotics (fluoroquinolones, third-generation cephalosporins, carbapenems).** *Diseases:* antibiotic-associated diarrhea, *C. difficile* colitis,

pseudomembranous colitis, toxic megacolon, recurrent disease, vulvovaginal candidiasis, selection of resistant organisms (see B6). *Mechanism:* loss of colonization resistance (depletion of anaerobes such as Bacteroides and Clostridia that convert primary to secondary bile acids and compete for nutrients) allows *C. difficile* germination and overgrowth; toxins TcdA and TcdB glucosylate Rho GTPases, collapsing the actin cytoskeleton, disrupting tight junctions, and triggering inflammation. *Grade:* E.

- **A8. Nitrofurantoin.** *Diseases:* acute hypersensitivity pneumonitis, chronic interstitial pulmonary fibrosis with long-term use, autoimmune-like hepatitis, peripheral neuropathy (especially with renal impairment), hemolysis in G6PD deficiency. *Mechanism:* nitroreductase-mediated redox cycling generates superoxide and hydrogen peroxide in lung and nerve; immune-mediated pneumonitis and hepatitis. *Grade:* E.

- **A9. Linezolid.** *Diseases:* thrombocytopenia and anemia (generally beyond two weeks), lactic acidosis, optic and peripheral neuropathy, serotonin syndrome with serotonergic drugs. *Mechanism:* inhibition of mitochondrial ribosomes (structurally similar to bacterial ribosomes) impairs oxidative phosphorylation; reversible, nonselective monoamine oxidase inhibition. *Grade:* E.

- **A10. Chloramphenicol.** *Diseases:* dose-related marrow suppression, idiosyncratic aplastic anemia (about 1 per 20,000 to 40,000 courses), gray baby syndrome in neonates. *Mechanism:* inhibition of mitochondrial protein synthesis; reduced glucuronidation (immature UGT enzymes) in neonates leads to accumulation, mitochondrial electron-transport inhibition, and cardiovascular collapse; aplastic anemia is idiosyncratic and may involve nitroso metabolites. *Grade:* E.

- **A11. Antituberculous agents (isoniazid, rifampin, pyrazinamide).** *Diseases:* drug-induced liver injury (DILI) up to hepatic failure, isoniazid peripheral neuropathy. *Mechanism:* isoniazid is metabolized by NAT2 and CYP2E1 to hydrazine and acetylhydrazine reactive intermediates (slow acetylators have higher hydrazine exposure); rifampin induces CYP enzymes and inhibits bile-salt export; isoniazid depletes pyridoxine. *Grade:* E.

- **A12. Amphotericin B (conventional) and polymyxins (colistin).** *Diseases:* nephrotoxicity (distal tubular injury, hypokalemia, hypomagnesemia, renal tubular acidosis), colistin neurotoxicity. *Mechanism:* amphotericin forms pores in cholesterol-containing host membranes and causes afferent-arteriolar vasoconstriction through tubuloglomerular feedback; polycationic colistin disrupts tubular-cell membranes and induces mitochondrial oxidative stress. *Grade:* E.

- **A13. Abacavir.** *Diseases:* abacavir hypersensitivity syndrome (fever, rash, gastrointestinal and respiratory symptoms; multi-organ), confined almost entirely to carriers of HLA-B*57:01. This is distinct from SJS/TEN and should not be classified under it (correction to draft CF 1). Mechanism: abacavir binds non-covalently in the HLA-B*57:01 peptide-binding groove, changing the repertoire of self-peptides presented and activating CD8-positive T cells against the host

(altered-peptide-repertoire model). Prospective HLA screening nearly eliminated immunologically confirmed hypersensitivity in screened populations. *Grade:* E.

- **A14. Nucleoside reverse-transcriptase inhibitors and tenofovir disoproxil.** *Diseases:* lactic acidosis, hepatic steatosis, lipoatrophy, neuropathy, myopathy (older NRTIs: stavudine, didanosine, zidovudine); proximal tubulopathy (Fanconi syndrome), chronic kidney disease, and bone loss (tenofovir disoproxil; lower with tenofovir alafenamide). *Mechanism:* inhibition of mitochondrial DNA polymerase gamma depletes mtDNA and impairs oxidative phosphorylation; OAT1-mediated uptake concentrates tenofovir in proximal tubule mitochondria. *Grade:* E.

- **A15. Early-life and repeated antibiotic exposure.** *Diseases:* associations with childhood asthma, atopy, obesity, inflammatory bowel disease, and recurrent *C. difficile*. *Mechanism:* dysbiosis during immune and metabolic programming windows, loss of short-chain-fatty-acid-producing taxa, and altered regulatory T-cell induction; strongly confounded by indication and family factors. *Grade:* H to P.

A-II. Analgesic, anti-inflammatory, and corticosteroid agents

- **A16. Acetaminophen (paracetamol).** *Diseases:* acute liver failure from overdose or repeated supratherapeutic dosing (a leading cause of acute liver failure in the US and UK), with greater susceptibility in fasting, malnutrition, and chronic alcohol use. *Mechanism:* CYP2E1 (with CYP1A2 and 3A4) generates N-acetyl-p-benzoquinone imine (NAPQI); once glutathione is depleted, NAPQI covalently binds mitochondrial proteins, causing oxidative stress, JNK activation, mitochondrial permeability transition, and centrilobular necrosis; N-acetylcysteine replenishes glutathione. *Grade:* E.

- **A17. NSAIDs: gastrointestinal effects (ibuprofen, naproxen, diclofenac, aspirin).** *Diseases:* peptic ulcer, upper gastrointestinal bleeding and perforation, small-bowel enteropathy. *Mechanism:* COX-1 inhibition reduces gastroprotective prostaglandins (mucus, bicarbonate, mucosal blood flow); direct topical acid-trapping injury; impaired platelet function worsens bleeding; synergy with *H. pylori*, corticosteroids, and anticoagulants. *Grade:* E.

- **A18. NSAIDs: renal and fluid-balance effects.** *Diseases:* hemodynamic acute kidney injury (especially in volume depletion, heart failure, cirrhosis, CKD, and in the "triple whammy" with ACE inhibitors/ARBs and diuretics), acute interstitial nephritis, minimal-change nephrotic syndrome, hyperkalemia, sodium retention, hypertension, heart-failure exacerbation. *Mechanism:* loss of prostaglandin-mediated afferent arteriolar vasodilation lowers glomerular pressure; hyporeninemic hypoaldosteronism; immune-mediated interstitial nephritis. *Grade:* E.

- **A19. NSAIDs and selective COX-2 inhibitors: cardiovascular events.** *Diseases:* myocardial infarction, stroke, heart failure, hypertension (rofecoxib was withdrawn in 2004 after the APPROVe trial; diclofenac carries high risk, naproxen relatively lower). *Mechanism:* suppression of endothelial COX-2-derived prostacyclin (vasodilator, antiplatelet) without equal suppression of

platelet COX-1-derived thromboxane tips the thrombotic balance; renal sodium retention and blood-pressure elevation. *Grade:* E.

- **A20. Aspirin and other salicylates.** *Diseases:* Reye syndrome in children with influenza or varicella, GI bleeding, salicylism (tinnitus, anion-gap metabolic acidosis), aspirin-exacerbated respiratory disease. *Mechanism:* Reye syndrome involves mitochondrial dysfunction (impaired beta-oxidation and uncoupling) causing microvesicular steatosis, hyperammonemia, and encephalopathy; COX-1 inhibition shunts arachidonate toward leukotrienes in aspirin-exacerbated respiratory disease. *Grade:* E for bleeding and salicylism; P for Reye syndrome.

- **A21. Systemic corticosteroids (prolonged or high-dose; also excessive inhaled, topical, or intra-articular use).** *Diseases:* iatrogenic Cushing syndrome, HPA-axis suppression with adrenal crisis on withdrawal, osteoporosis and fractures, avascular necrosis, hyperglycemia and diabetes, opportunistic infections including *Pneumocystis*, myopathy, psychosis and mood disorders, posterior subcapsular cataract, glaucoma, hypertension, skin atrophy, growth suppression in children. *Mechanism:* glucocorticoid-receptor signaling suppresses ACTH and causes adrenal atrophy; increases hepatic gluconeogenesis and insulin resistance; reduces osteoblast differentiation and promotes osteoblast and osteocyte apoptosis while increasing RANKL and prolonging osteoclast survival; reduces intestinal calcium absorption and raises renal excretion; upregulates muscle atrogenes (atrogin-1, MuRF1) and reduces mTOR signaling; induces lymphocyte apoptosis and represses NF-kappaB-driven immunity; femoral-head necrosis involves osteocyte apoptosis and microvascular compromise. *Grade:* E.

- **A22. Opioid analgesics: respiratory depression.** *Diseases:* respiratory depression, hypoxic brain injury, death, particularly with benzodiazepines, gabapentinoids, renal failure (morphine-6-glucuronide accumulation), obstructive sleep apnea, or rapid dose escalation. *Mechanism:* mu-opioid receptor activation opens GIRK potassium channels and reduces cAMP in brainstem respiratory-rhythm generators (pre-Botzinger complex, Kolliker-Fuse), reducing respiratory drive and chemoreflex sensitivity to hypercapnia. *Grade:* E.

- **A23. Opioid analgesics: gastrointestinal and endocrine effects.** *Diseases:* opioid-induced constipation, ileus, nausea, sphincter of Oddi spasm, opioid-induced androgen deficiency (hypogonadotropic hypogonadism), opioid-induced hyperalgesia. *Mechanism:* mu receptors on enteric neurons inhibit acetylcholine and VIP release, reducing propulsion and increasing sphincter tone and fluid absorption; hypothalamic suppression of GnRH; central sensitization (NMDA and glial mechanisms) in hyperalgesia. *Grade:* E for constipation; P for hypogonadism and hyperalgesia.

A-III. Cardiovascular, hematologic, renal, and metabolic agents

- **A24. Warfarin.** *Diseases:* major hemorrhage (GI, intracranial), hematoma, warfarin-induced skin necrosis, purple-toe syndrome, calciphylaxis association; teratogenic embryopathy (L5). *Mechanism:* inhibition of vitamin K epoxide reductase (VKORC1) reduces gamma-carboxylation of factors II, VII, IX, X and proteins C and S; early protein C depletion (short half-life) explains

transient hypercoagulability and skin necrosis; risk is amplified by CYP2C9*2/*3 and VKORC1 promoter variants and by interactions (e.g., trimethoprim-sulfamethoxazole, azoles, amiodarone). *Grade:* E.

- **A25. Heparins (unfractionated and low-molecular-weight).** *Diseases:* heparin-induced thrombocytopenia (HIT) with arterial and venous thrombosis, bleeding, hyperkalemia, osteoporosis with prolonged use. *Mechanism:* heparin binds platelet factor 4 (PF4), exposing neoepitopes; IgG anti-PF4/heparin antibodies form immune complexes that activate platelets and monocytes via Fc-gamma-RIIa, generating thrombin and consuming platelets; thrombocytopenia typically appears 5 to 10 days after first exposure (earlier with prior exposure); hyperkalemia results from aldosterone suppression. *Grade:* E.

- **A26. Direct oral anticoagulants (apixaban, rivaroxaban, edoxaban, dabigatran).** *Diseases:* major bleeding (particularly gastrointestinal), accumulation and bleeding in acute kidney injury, interaction-related bleeding. *Mechanism:* direct, reversible inhibition of factor Xa or thrombin impairs fibrin generation; P-glycoprotein and CYP3A4 interactions and renal clearance determine exposure. *Grade:* E.

- **A27. Antiplatelet agents (aspirin, P2Y12 inhibitors).** *Diseases:* bleeding, thrombotic thrombocytopenic purpura (rare, ticlopidine and clopidogrel), bleeding risk amplification in dual therapy. *Mechanism:* irreversible inhibition of platelet COX-1 or P2Y12 receptors; rare ADAMTS13-inhibitory autoantibodies cause TTP. *Grade:* E.

- **A28. Thrombolytics (alteplase, tenecteplase).** *Diseases:* symptomatic intracranial hemorrhage (about 2% to 7% in stroke trials), systemic bleeding, orolingual angioedema. *Mechanism:* plasminogen activation causes fibrinolysis and systemic fibrinogenolysis; blood-brain-barrier disruption (matrix metalloproteinase-9) and reperfusion injury in infarcted tissue; bradykinin-mediated angioedema, more frequent with concurrent ACE inhibitors. *Grade:* E.

- **A29. ACE inhibitors and angiotensin-receptor blockers.** *Diseases:* hyperkalemia, acute kidney injury (volume depletion, bilateral renal-artery stenosis), cough, angioedema (ACE inhibitors; higher in Black patients), fetopathy (L4). *Mechanism:* reduced angiotensin II lowers efferent arteriolar tone and aldosterone; ACE (kininase II) inhibition permits accumulation of bradykinin and substance P, increasing vascular permeability and cough-reflex sensitivity. *Grade:* E.

- **A30. Loop diuretics (furosemide, bumetanide).** *Diseases:* hypokalemia, hypomagnesemia, volume depletion and AKI, metabolic alkalosis, hyperuricemia, falls, dose-related ototoxicity. *Mechanism:* inhibition of the Na-K-2Cl cotransporter in the thick ascending limb raises distal sodium delivery, driving potassium and hydrogen secretion; NKCC1 inhibition in the stria vascularis alters endolymph. *Grade:* E.

- **A31. Thiazide and thiazide-like diuretics.** *Diseases:* hyponatremia (often in elderly women), hypokalemia, hypercalcemia, hyperuricemia and gout, glucose intolerance; association of hydrochlorothiazide with non-melanoma skin cancer. *Mechanism:* inhibition of the sodium-

chloride cotransporter impairs urinary dilution and increases distal potassium loss; hydrochlorothiazide is a UV-absorbing photosensitizer. *Grade:* E for electrolyte disorders; H to P for skin cancer.

- **A32. Mineralocorticoid-receptor antagonists and other hyperkalemia-promoting drugs (spironolactone, eplerenone, amiloride, trimethoprim, heparin, calcineurin inhibitors).** *Diseases:* hyperkalemia with arrhythmia, gynecomastia (spironolactone). *Mechanism:* reduced aldosterone signaling or ENaC blockade reduces potassium secretion; spironolactone antagonizes androgen receptors. *Grade:* E.

- **A33. Digoxin.** *Diseases:* life-threatening arrhythmias (bidirectional ventricular tachycardia, atrioventricular block), anorexia and nausea, visual disturbances. *Mechanism:* Na+/K+-ATPase inhibition raises intracellular sodium and, via the Na+/Ca2+ exchanger, intracellular calcium, causing delayed afterdepolarizations; hypokalemia increases drug binding to the pump; accumulation in renal impairment and with interacting drugs. *Grade:* E.

- **A34. Amiodarone.** *Diseases:* pulmonary toxicity (interstitial pneumonitis, organizing pneumonia, fibrosis), hypothyroidism and thyrotoxicosis, hepatotoxicity, corneal microdeposits and optic neuropathy, photosensitivity and blue-gray skin, bradycardia, peripheral neuropathy. *Mechanism:* lipophilic cationic drug accumulates in lysosomes, inhibiting phospholipases and causing phospholipidosis (foamy macrophages), with mitochondrial dysfunction, ROS, and fibroblast activation (the Hippo/YAP link in the draft is a proposed mechanism); thyroid effects reflect iodine load (about 37% iodine by weight: Wolff-Chaikoff failure to escape, iodine-induced thyrotoxicosis, and destructive thyroiditis). *Grade:* E (YAP mechanism: H).

- **A35. Class I antiarrhythmics (flecainide, encainide) and class III agents (sotalol, dofetilide).** *Diseases:* proarrhythmia and increased mortality after myocardial infarction (CAST trial); torsades de pointes. *Mechanism:* use-dependent sodium-channel block slows conduction and promotes re-entry in scarred myocardium; potassium-channel (hERG) block prolongs repolarization. *Grade:* E.

- **A36. QT-prolonging drugs across classes (antipsychotics, citalopram, methadone, ondansetron, macrolides, fluoroquinolones, azoles, hydroxychloroquine, arsenic trioxide, some kinase inhibitors).** *Diseases:* torsades de pointes, sudden cardiac death. *Mechanism:* block of IKr (hERG) prolongs repolarization and permits early afterdepolarizations; risk is multiplied by hypokalemia, hypomagnesemia, bradycardia, female sex, structural heart disease, congenital long-QT variants, and stacking of several QT-active drugs. *Grade:* E.

- **A37. Statins.** *Diseases:* myopathy (about 1 per 10,000 patient-years), rhabdomyolysis (about 1 to 3 per 100,000 patient-years), immune-mediated necrotizing myopathy (anti-HMGCR antibodies), small increase in new-onset diabetes, enzyme elevations. Muscle pain in randomized blinded trials is largely not attributable to the drug (nocebo effect), which should temper the draft's description of severe toxicity as typical. *Mechanism:* HMG-CoA reductase inhibition reduces isoprenoids and coenzyme Q10, impairing mitochondrial function and promoting myocyte

apoptosis; SLCO1B1*5 raises systemic exposure; CYP3A4 inhibitors raise levels; statin-exposed autoantigen upregulation in necrotizing myopathy; reduced beta-cell and insulin-signaling function proposed for diabetes. *Grade:* E for rhabdomyolysis and necrotizing myopathy; P for diabetes.

- **A38. Beta-blockers.** *Diseases:* bradycardia, atrioventricular block, bronchospasm (non-selective agents), masking of hypoglycemia, fatigue, rebound angina and arrhythmia on abrupt withdrawal (see A89). *Mechanism:* beta-1 and beta-2 blockade; receptor up-regulation during chronic blockade causes rebound hypersensitivity. *Grade:* E.

- **A39. Insulin and insulin secretagogues (sulfonylureas, meglitinides).** *Diseases:* severe hypoglycemia (seizures, coma, arrhythmia, falls, injury; repeated episodes associated with dementia), weight gain. *Mechanism:* excess insulin suppresses hepatic glucose output and increases peripheral glucose uptake, depriving the brain of its obligate substrate; sulfonylureas close pancreatic beta-cell K-ATP channels independent of glucose; long-acting agents (glyburide) accumulate in CKD; recurrent hypoglycemia blunts counter-regulatory responses (hypoglycemia-associated autonomic failure). Insulin ranks among the most frequent causes of emergency visits for ADEs. *Grade:* E.

- **A40. Metformin.** *Diseases:* lactic acidosis (rare, in renal or hepatic failure and hypoperfusion), vitamin B12 deficiency, gastrointestinal intolerance. *Mechanism:* mitochondrial complex I inhibition increases lactate production; calcium-dependent ileal B12-intrinsic-factor absorption is impaired. *Grade:* E for GI effects and B12 deficiency; P for lactic acidosis.

- **A41. Thiazolidinediones (pioglitazone, rosiglitazone).** *Diseases:* fluid retention and heart failure, fractures (particularly in women), weight gain; a myocardial-infarction signal with rosiglitazone (contested); small bladder-cancer association with pioglitazone. *Mechanism:* PPAR-gamma activation increases distal-nephron sodium reabsorption (ENaC); shifts marrow mesenchymal differentiation toward adipocytes and away from osteoblasts. *Grade:* E for heart failure and fractures; H for bladder cancer.

- **A42. SGLT2 inhibitors.** *Diseases:* euglycemic diabetic ketoacidosis, genital mycotic infections, urinary tract infection, rare Fournier gangrene, volume depletion and AKI, amputation signal with canagliflozin. *Mechanism:* glycosuria supports yeast growth and osmotic diuresis; lower insulin with higher glucagon promotes ketogenesis during illness, fasting, or surgery. *Grade:* E for ketoacidosis and mycotic infection; P for others.

- **A43. GLP-1 receptor agonists and dual agonists.** *Diseases:* gastrointestinal intolerance, cholelithiasis and cholecystitis, delayed gastric emptying with retained gastric contents at anesthesia, pancreatitis (association), non-arteritic anterior ischemic optic neuropathy (recognized by regulators in 2025 as a very rare effect of semaglutide; verify current labeling). *Mechanism:* slowed gastric transit and reduced gallbladder emptying (accentuated by rapid weight loss); the pathway for optic neuropathy is unknown. *Grade:* E for GI effects and gallbladder disease; H to P for pancreatitis and optic neuropathy.

- **A44. Proton-pump inhibitors.** *Diseases: C. difficile* and other enteric infections, pneumonia (association), hypomagnesemia, vitamin B12 and iron deficiency, fractures (association), acute interstitial nephritis and CKD (association), rebound acid hypersecretion on withdrawal. *Mechanism:* loss of the gastric acid barrier shifts upper-GI microbiota; reduced intestinal TRPM6/7-mediated magnesium absorption; impaired acid-dependent B12 and iron liberation; hypergastrinemia with enterochromaffin-like cell hyperplasia causes rebound; immune-mediated interstitial nephritis. *Grade:* E for hypomagnesemia and interstitial nephritis; P for infection; H for fractures and CKD.

- **A45. Thyroid-hormone over-replacement (levothyroxine, liothyronine, including misuse for weight loss).** *Diseases:* iatrogenic thyrotoxicosis, atrial fibrillation, accelerated bone loss, anxiety. *Mechanism:* excess thyroid hormone increases beta-adrenergic sensitivity, metabolic rate, and osteoclast activity. *Grade:* E.

A-IV. Neuropsychiatric agents

- **A46. Typical (first-generation) antipsychotics (haloperidol, chlorpromazine).** *Diseases:* acute dystonia, parkinsonism, akathisia, tardive dyskinesia, neuroleptic malignant syndrome, hyperprolactinemia with hypogonadism and bone loss, QT prolongation. *Mechanism:* striatal D2 blockade (extrapyramidal effects emerge at high occupancy); chronic blockade induces D2 receptor up-regulation and supersensitivity, with oxidative stress and GABAergic dysfunction proposed for tardive dyskinesia; hypothalamic and striatal D2 blockade with muscle rigidity in neuroleptic malignant syndrome; tuberoinfundibular D2 blockade removes tonic inhibition of prolactin. *Grade:* E.

- **A47. Atypical (second-generation) antipsychotics (olanzapine, clozapine, quetiapine, risperidone).** *Diseases:* weight gain, metabolic syndrome, type 2 diabetes, dyslipidemia; clozapine-specific agranulocytosis, early myocarditis, seizures, severe constipation and ileus, sialorrhea. *Mechanism:* antagonism of 5-HT2C and histamine H1 (and M3) receptors drives hyperphagia and adiposity, with direct impairment of insulin secretion and sensitivity; clozapine metabolites (nitrenium ion) are cytotoxic to neutrophils and immune hypersensitivity underlies myocarditis; muscarinic blockade reduces gut motility. *Grade:* E.

- **A48. Lithium.** *Diseases:* nephrogenic diabetes insipidus, chronic tubulointerstitial nephropathy and CKD, hypothyroidism, hyperparathyroidism with hypercalcemia, tremor, acute neurotoxicity. *Mechanism:* lithium enters collecting-duct principal cells via ENaC and inhibits glycogen synthase kinase-3, reducing aquaporin-2 expression and apical insertion; chronic tubular injury and fibrosis; inhibition of thyroid-hormone release; altered parathyroid calcium set-point. *Grade:* E.

- **A49. SSRIs and SNRIs.** *Diseases:* serotonin syndrome (usually with combinations such as linezolid or MAO inhibitors, tramadol, triptans, or other serotonergic agents), hyponatremia (SIADH), bleeding (especially with NSAIDs or anticoagulants), dose-dependent QT prolongation (citalopram), discontinuation syndrome, sexual dysfunction (a persistent post-treatment form is reported and incompletely characterized), falls and fractures in older adults, treatment-

emergent suicidality in young people. *Mechanism:* SERT inhibition increases synaptic serotonin; excess 5-HT2A (and 5-HT1A) stimulation produces neuromuscular hyperactivity, hyperthermia, and autonomic instability; serotonin promotes ADH release; platelets rely on SERT to take up serotonin, so inhibition impairs aggregation; abrupt cessation unmasks receptor adaptation. *Grade:* E (persistent sexual dysfunction: H).

- **A50. Benzodiazepines and Z-drugs (zolpidem).** *Diseases:* sedation, falls and hip fracture, motor-vehicle crashes, cognitive impairment, delirium in hospitalized older adults, respiratory depression (especially with opioids), paradoxical disinhibition, physical dependence with withdrawal seizures; observational association with dementia (H). *Mechanism:* positive allosteric modulation of GABA-A receptors (alpha-1 sedation, alpha-2/3 anxiolysis); chronic exposure alters receptor subunit composition and reduces receptor density, so abrupt withdrawal leaves unopposed glutamatergic excitation. *Grade:* E.

- **A51. Anticholinergic burden (diphenhydramine and other first-generation antihistamines, oxybutynin, tricyclic antidepressants, paroxetine, antispasmodics).** *Diseases:* delirium, cognitive impairment, urinary retention, constipation and ileus, tachycardia, acute angle-closure glaucoma, heat stroke; observational association between cumulative exposure and dementia; tricyclic overdose causes QRS widening, arrhythmia, and seizures. *Mechanism:* central M1 blockade impairs cholinergic arousal and attention networks; peripheral antimuscarinic effects; tricyclics block cardiac sodium channels. *Grade:* E for delirium and peripheral effects; H to P for dementia.

- **A52. Valproate.** *Diseases:* hepatotoxicity (including fatal microvesicular steatosis, especially in young children and POLG-variant patients), hyperammonemic encephalopathy, pancreatitis, thrombocytopenia, tremor, weight gain, polycystic-ovary-like syndrome; teratogenicity (L2). *Mechanism:* valproyl-CoA and 4-ene-valproate metabolites inhibit fatty-acid beta-oxidation and sequester CoA and carnitine; inhibition of carbamoyl-phosphate synthetase impairs ureagenesis; mitochondrial DNA polymerase gamma variants (Alpers-Huttenlocher syndrome) are a contraindication. *Grade:* E.

- **A53. Enzyme-inducing and sodium-channel anticonvulsants (carbamazepine, phenytoin, phenobarbital, lamotrigine).** *Diseases:* SJS/TEN and DRESS (carbamazepine with HLA-B*15:02 in Southeast and South Asian populations and HLA-A*31:01 in Europeans and Japanese; phenytoin with CYP2C9*3 and HLA-B*15:02; lamotrigine with rapid titration or valproate co-therapy), osteomalacia and bone loss, hyponatremia (carbamazepine), gingival hyperplasia (phenytoin), cerebellar toxicity, teratogenicity. *Mechanism:* carbamazepine binds directly and non-covalently to HLA-B*15:02 and the T-cell receptor (pharmacological-interaction concept), activating cytotoxic CD8-positive T cells and releasing granulysin, FasL, perforin and granzyme B; enzyme induction accelerates vitamin D catabolism. *Grade:* E.

- **A54. CNS stimulants and sympathomimetics (amphetamines, methylphenidate, pseudoephedrine).** *Diseases:* tachycardia, hypertension, arrhythmia, myocardial infarction,

psychosis and mania, growth suppression in children, dependence, reversible cerebral vasoconstriction syndrome (pseudoephedrine, reported). *Mechanism:* increased synaptic dopamine and norepinephrine and direct adrenergic agonism. *Grade:* E for cardiovascular and psychiatric effects; P for others.

- **A55. Gabapentinoids and proconvulsant or serotonergic analgesics (gabapentin, pregabalin, tramadol, bupropion).** *Diseases:* sedation, falls, respiratory depression when combined with opioids, peripheral edema, misuse (gabapentinoids); seizures, serotonin syndrome, hypoglycemia, and hyponatremia (tramadol); dose-dependent seizures (bupropion). *Mechanism:* binding to the alpha-2-delta subunit of voltage-gated calcium channels reduces excitatory neurotransmission; tramadol combines mu-opioid, serotonin and norepinephrine reuptake effects and depends on CYP2D6 for its active metabolite. *Grade:* E for sedation and seizures; P for respiratory depression.

- **A56. Metoclopramide and other dopamine-blocking antiemetics (prochlorperazine, promethazine, droperidol).** *Diseases:* acute dystonia, akathisia, tardive dyskinesia (boxed warning for use beyond 12 weeks), QT prolongation (droperidol). *Mechanism:* striatal D2 receptor blockade with chronic receptor supersensitivity; hERG block. *Grade:* E.

A-V. Cytotoxic, targeted, and cellular oncologic therapies

- **A57. Anthracyclines (doxorubicin, daunorubicin, epirubicin).** *Diseases:* dose-dependent cardiomyopathy and heart failure (risk rises with cumulative dose, young or old age, prior chest radiation, hypertension, and trastuzumab), arrhythmia, therapy-related myeloid neoplasms. *Mechanism:* poisoning of topoisomerase II-beta in cardiomyocytes causes DNA double-strand breaks and mitochondrial dysfunction; anthracycline-iron complexes generate free radicals that overwhelm limited cardiac antioxidant defenses; dexrazoxane (iron chelation and Top2B depletion) is protective. *Grade:* E.

- **A58. Trastuzumab and other HER2-directed therapy.** *Diseases:* cardiomyopathy with reduced ejection fraction (often reversible). *Mechanism:* HER2/ErbB2 signaling (neuregulin-ErbB4/ErbB2) supports cardiomyocyte survival and stress adaptation; blockade removes this protective pathway, with synergy after anthracycline injury. *Grade:* E.

- **A59. Platinum agents (cisplatin, carboplatin, oxaliplatin).** *Diseases:* acute tubular necrosis and magnesium wasting, permanent ototoxicity (especially in children), peripheral neuropathy, severe emesis, myelosuppression (carboplatin). *Mechanism:* uptake through OCT2 and copper transporter CTR1 concentrates cisplatin in proximal tubular and cochlear cells; DNA cross-linking, reactive oxygen species, and TNF-alpha-driven inflammation cause apoptosis; accumulation in dorsal root ganglia (no blood-nerve barrier) causes neuropathy. *Grade:* E.

- **A60. Neurotoxic cytostatics (taxanes, vinca alkaloids, oxaliplatin, bortezomib).** *Diseases:* chemotherapy-induced peripheral neuropathy (sensory, painful, sometimes permanent), autonomic neuropathy (vincristine). *Mechanism:* disruption of microtubule dynamics (taxanes

stabilize; vincas depolymerize) impairs axonal transport; axonal mitochondrial damage and oxidative stress; dorsal-root-ganglion accumulation; oxaliplatin's acute cold-induced neuropathy reflects altered voltage-gated sodium-channel kinetics. *Grade:* E.

- **A61. Bleomycin.** *Diseases:* pneumonitis and pulmonary fibrosis (risk rises with cumulative dose, age, renal impairment, prior radiation, and supplemental oxygen), Raynaud phenomenon, skin hyperpigmentation. *Mechanism:* iron-bleomycin complexes generate reactive oxygen species that cause DNA strand breaks; lung and skin express little bleomycin hydrolase; alveolar epithelial injury and TGF-beta-driven fibroblast activation lead to fibrosis. *Grade:* E.

- **A62. Methotrexate.** *Diseases:* myelosuppression, mucositis, hepatic fibrosis with long-term low-dose use, hypersensitivity pneumonitis, high-dose renal injury, leukoencephalopathy (intrathecal or high-dose), fatal toxicity from daily instead of weekly dosing errors; teratogenicity (L6). *Mechanism:* tight-binding inhibition of dihydrofolate reductase depletes tetrahydrofolate and thus purine and thymidylate synthesis in rapidly dividing cells; methotrexate and 7-hydroxymethotrexate precipitate in acidic urine; interacting drugs (NSAIDs, PPIs, trimethoprim-sulfamethoxazole) reduce clearance; leucovorin rescue bypasses the block. *Grade:* E.

- **A63. Alkylating agents (cyclophosphamide, ifosfamide, melphalan, busulfan, chlorambucil, temozolomide).** *Diseases:* myelosuppression, hemorrhagic cystitis and later bladder cancer (cyclophosphamide, ifosfamide), ifosfamide Fanconi syndrome and encephalopathy, therapy-related myelodysplastic syndrome and acute myeloid leukemia (latency about 5 to 7 years, often with chromosome 5 or 7 loss), gonadotoxicity (L10), veno-occlusive disease (busulfan), pulmonary fibrosis (busulfan, carmustine). *Mechanism:* DNA alkylation and cross-linking trigger DNA-damage response, apoptosis, and mutagenesis; the metabolite acrolein injures urothelium (mesna binds it); chloroacetaldehyde injures proximal tubule and brain. *Grade:* E.

- **A64. Topoisomerase-II inhibitors (etoposide, mitoxantrone, anthracyclines).** *Diseases:* therapy-related acute myeloid leukemia with 11q23/KMT2A rearrangements (short latency, 1 to 3 years); mitoxantrone cardiotoxicity. *Mechanism:* stabilized topoisomerase-II-DNA cleavage complexes yield double-strand breaks that are misrepaired at the KMT2A breakpoint region, generating oncogenic fusion genes. *Grade:* E.

- **A65. Fluoropyrimidines (5-fluorouracil, capecitabine).** *Diseases:* severe or fatal mucositis, diarrhea, neutropenia and neurotoxicity in DPD deficiency; coronary vasospasm; hand-foot syndrome; hyperammonemic encephalopathy. *Mechanism:* dihydropyrimidine dehydrogenase (DPYD) normally catabolizes most of a dose; variants (e.g., c.1905+1G>A, c.1679T>G, c.2846A>T, HapB3) prolong exposure to thymidylate-synthase inhibition and RNA misincorporation; vasospasm likely reflects endothelial dysfunction; uridine triacetate is an antidote. *Grade:* E.

- **A66. VEGF-pathway inhibitors (bevacizumab, ramucirumab, sunitinib, sorafenib, axitinib).** *Diseases:* hypertension, proteinuria and thrombotic microangiopathy, arterial thromboembolism, hemorrhage, gastrointestinal perforation, impaired wound healing, posterior reversible encephalopathy syndrome. *Mechanism:* loss of VEGF-driven nitric-oxide and

prostacyclin production causes vasoconstriction and microvascular rarefaction; loss of podocyte-derived VEGF produces glomerular endotheliosis; impaired endothelial and epithelial repair. *Grade:* E.

- **A67. Kinase inhibitors (ponatinib, nilotinib, ibrutinib, dasatinib, EGFR inhibitors).** *Diseases:* arterial occlusive events (ponatinib, nilotinib), QT prolongation and hyperglycemia (nilotinib), atrial fibrillation and bleeding (ibrutinib), pleural effusion and pulmonary hypertension (dasatinib), rash and interstitial lung disease (EGFR inhibitors). *Mechanism:* off-target inhibition of vascular, cardiac, and platelet kinases (e.g., BTK/TEC and CSK/PI3K-Akt pathways in atrial myocytes and platelets); hERG block; EGFR inhibition in skin and lung epithelium. *Grade:* E for the best-characterized events; P for mechanisms.

- **A68. Immune checkpoint inhibitors (anti-PD-1, anti-PD-L1, anti-CTLA-4, anti-LAG-3).** *Diseases:* immune-related colitis, hepatitis, pneumonitis, thyroiditis, hypophysitis, adrenalitis, fulminant type 1 diabetes, myocarditis (often fatal), myositis and myasthenia overlap, nephritis, dermatitis, neurologic events. *Mechanism:* blockade of inhibitory checkpoints removes peripheral tolerance, allowing autoreactive T cells, cytokines, and autoantibodies to attack normal tissue, in part through shared antigens between tumor and healthy muscle, heart, or gut; pre-existing autoimmunity and gut microbiome influence risk; CTLA-4 blockade favors colitis and hypophysitis, PD-1 blockade favors pneumonitis and thyroid disease. *Grade:* E.

- **A69. CAR-T cells and T-cell-engaging bispecific antibodies.** *Diseases:* cytokine release syndrome, immune-effector-cell-associated neurotoxicity (ICANS), hemophagocytic-like syndromes, prolonged cytopenias, B-cell aplasia with hypogammaglobulinemia and infections, secondary T-cell malignancies (boxed warning added by the FDA in 2024). *Mechanism:* massive T-cell activation induces macrophage release of IL-6, IL-1, and IFN-gamma, causing endothelial activation and capillary leak; endothelial activation and blood-brain-barrier disruption underlie ICANS; on-target B-cell depletion; insertional or clonal mechanisms are hypothesized for T-cell malignancy. *Grade:* E for acute toxicities; P for secondary malignancy.

- **A70. Androgen-deprivation therapy (GnRH analogs, abiraterone, enzalutamide).** *Diseases:* bone loss and fractures, metabolic syndrome and diabetes, cardiovascular events, sarcopenia, cognitive effects; abiraterone-related hypertension and hypokalemia; enzalutamide-related seizures and falls. *Mechanism:* hypogonadism with loss of aromatized estradiol increases osteoclast activity and fat mass while lowering muscle mass and insulin sensitivity; CYP17 inhibition causes mineralocorticoid excess. *Grade:* E.

- **A71. Tamoxifen and aromatase inhibitors.** *Diseases:* tamoxifen: endometrial hyperplasia and cancer, uterine sarcoma, venous thromboembolism, stroke, cataract; aromatase inhibitors: bone loss and fractures, arthralgia, hypercholesterolemia. *Mechanism:* tamoxifen is a partial estrogen-receptor agonist in endometrium and liver (increasing procoagulant factors and lowering antithrombin); aromatase inhibitors produce profound estrogen deprivation with RANKL-driven bone resorption. *Grade:* E.

- **A72. Immunomodulatory imide drugs (thalidomide, lenalidomide, pomalidomide).** *Diseases:* teratogenicity (L1), venous thromboembolism, peripheral neuropathy, second primary malignancies (lenalidomide), cytopenias. *Mechanism:* cereblon (CRBN) E3-ligase modulation degrades IKZF1/3 (anti-myeloma effect) and SALL4 and p63 (limb and organ malformation); mechanisms for thrombosis and neuropathy are incompletely defined. *Grade:* E.

- **A73. Proteasome inhibitors (bortezomib, carfilzomib).** *Diseases:* peripheral neuropathy (bortezomib); heart failure, hypertension, thrombotic microangiopathy (carfilzomib). *Mechanism:* proteasome inhibition triggers the unfolded-protein response and NF-kappaB dysregulation in neurons, cardiomyocytes, and endothelium. *Grade:* E for neuropathy; P for cardiovascular effects.

- **A74. Anti-CD20 antibodies (rituximab, obinutuzumab, ocrelizumab).** *Diseases:* hepatitis B reactivation (including fulminant), progressive multifocal leukoencephalopathy, hypogammaglobulinemia, late-onset neutropenia, infusion reactions. *Mechanism:* B-cell depletion impairs humoral immunity and B-cell-dependent control of viral latency; infusion reactions reflect complement and Fc-receptor-mediated cytokine release. *Grade:* E.

A-VI. Immunomodulators and biologics

- **A75. Calcineurin inhibitors (tacrolimus, cyclosporine).** *Diseases:* acute and chronic nephrotoxicity, hypertension, hyperkalemia, hypomagnesemia, neurotoxicity (tremor, PRES), post-transplant diabetes, skin cancer, lymphoproliferative disease. *Mechanism:* inhibition of calcineurin-NFAT signaling reduces IL-2 and T-cell activation; off-target increases in endothelin-1 and thromboxane with reduced nitric oxide cause afferent vasoconstriction and ischemia; TGF-beta-mediated arteriolar hyalinosis and striped interstitial fibrosis; NFAT inhibition in beta cells reduces insulin gene expression. *Grade:* E.

- **A76. TNF inhibitors (infliximab, adalimumab, etanercept, certolizumab, golimumab).** *Diseases:* serious bacterial and opportunistic infections, reactivation of tuberculosis and hepatitis B, demyelinating disease, drug-induced lupus, paradoxical psoriasis, hepatosplenic T-cell lymphoma (with thiopurines), worsening heart failure, infusion reactions with anti-drug antibodies. *Mechanism:* TNF is required for granuloma maintenance, so blockade permits latent mycobacterial reactivation; blockade increases plasmacytoid-dendritic-cell interferon-alpha, driving paradoxical psoriasis; immunogenicity of antibody biologics. *Grade:* E.

- **A77. Janus-kinase inhibitors (tofacitinib, baricitinib, upadacitinib).** *Diseases:* major adverse cardiovascular events, venous thromboembolism, serious infection including herpes zoster, malignancy (boxed warnings after the ORAL Surveillance trial), cytopenias, lipid elevation, gastrointestinal perforation. *Mechanism:* broad blockade of cytokine signaling (type I interferon, IL-6, common-gamma-chain cytokines) impairs antiviral defense; mechanisms of thrombosis and cardiovascular risk are not fully defined. *Grade:* E for infection; P for cardiovascular and malignancy risks.

- **A78. Natalizumab and other targeted immune-trafficking drugs (sphingosine-1-phosphate modulators).** *Diseases:* progressive multifocal leukoencephalopathy (JC virus), cryptococcal infection, macular edema, bradycardia. *Mechanism:* alpha-4-integrin blockade reduces CNS immune surveillance (risk rises with anti-JCV antibody index, duration beyond two years, and prior immunosuppression); S1P-receptor modulation sequesters lymphocytes and affects cardiac conduction. *Grade:* E.

- **A79. Thiopurines (azathioprine, 6-mercaptopurine).** *Diseases:* myelosuppression (TPMT or NUDT15 deficiency), pancreatitis, hepatotoxicity, lymphoma (including hepatosplenic T-cell lymphoma in young men with IBD), non-melanoma skin cancer. *Mechanism:* incorporation of 6-thioguanine nucleotides into DNA causes mismatch-repair-dependent cytotoxicity, with excessive accumulation in TPMT or NUDT15 variants; 6-methylmercaptopurine causes hepatotoxicity; 6-thioguanine sensitizes skin to UVA. *Grade:* E.

- **A80. mTOR inhibitors (sirolimus, everolimus).** *Diseases:* impaired wound healing and lymphocele, hyperlipidemia, proteinuria, non-infectious pneumonitis, oral ulceration, new-onset diabetes, cytopenias. *Mechanism:* mTORC1 inhibition reduces cell proliferation, angiogenesis, and epithelial repair; reduced lipoprotein lipase activity; podocyte mTOR disruption. *Grade:* E.

- **A81. Drug-induced autoimmune syndromes (hydralazine, procainamide, minocycline, propylthiouracil, DPP-4 inhibitors, TNF inhibitors).** *Diseases:* drug-induced lupus, ANCA-associated vasculitis, autoimmune hepatitis, bullous pemphigoid. *Mechanism:* DNA hypomethylation in CD4-positive T cells increases autoreactivity (procainamide, hydralazine); drug-altered myeloperoxidase and neutrophil extracellular trap formation (propylthiouracil); reactive metabolites forming neo-antigens; mechanism for DPP-4 inhibitor-associated pemphigoid is unknown. *Grade:* E for lupus and ANCA vasculitis; P for pemphigoid.

- **A82. Lymphocyte-depleting therapies and secondary autoimmunity (alemtuzumab, anti-thymocyte globulin, cladribine).** *Diseases:* autoimmune thyroid disease, immune thrombocytopenia, anti-GBM disease. *Mechanism:* lymphopenia drives homeostatic proliferation of autoreactive clones, reduced regulatory T-cell function, and BAFF-driven B-cell hyperactivity during reconstitution. *Grade:* E.

A-VII. Hormonal and bone-active agents

- **A83. Menopausal hormone therapy.** *Diseases:* breast cancer (combined estrogen-progestin, modest absolute excess in the Women's Health Initiative), venous thromboembolism, stroke, gallbladder disease, endometrial cancer (unopposed estrogen), coronary events in older or late-initiating users. *Mechanism:* oral estrogens increase hepatic synthesis of procoagulant factors and reduce antithrombin and protein S (transdermal estradiol has lower thrombotic risk); estrogen and progestin stimulate mammary epithelial proliferation through ER-alpha and progesterone receptor signaling; unopposed estrogen drives endometrial proliferation. *Grade:* E.

- **A84. Combined hormonal contraceptives.** *Diseases:* venous thromboembolism (higher with desogestrel, drospirenone, or cyproterone than with levonorgestrel, and with factor V Leiden), arterial thrombosis and stroke (particularly with smoking and migraine with aura), hypertension, hepatic adenoma, small increases in breast and cervical cancer risk. *Mechanism:* ethinylestradiol increases coagulation factors and angiotensinogen and induces acquired activated-protein-C resistance; progestin type modifies the effect. *Grade:* E.

- **A85. Testosterone and anabolic-androgenic steroids.** *Diseases:* erythrocytosis and thrombosis, suppression of the hypothalamic-pituitary-gonadal axis (azoospermia, infertility), hepatotoxicity (cholestasis, peliosis, adenoma with 17-alpha-alkylated agents), cardiomyopathy and dyslipidemia, gynecomastia; in a large trial of therapeutic testosterone, no excess of major cardiovascular events but more atrial fibrillation, acute kidney injury, and pulmonary embolism. *Mechanism:* suppression of hepcidin and stimulation of erythropoiesis; negative feedback on LH and FSH; aromatization to estrogen; direct hepatocellular and myocardial effects. *Grade:* E for axis suppression and erythrocytosis; P for others.

- **A86. Bisphosphonates (alendronate, zoledronate).** *Diseases:* osteonecrosis of the jaw (about 1 per 10,000 to 100,000 patient-years at osteoporosis doses; far higher at oncology doses), atypical femoral fractures, esophagitis and ulceration (oral), acute-phase reaction (IV), hypocalcemia, renal toxicity (IV), uveitis. *Mechanism:* nitrogen-containing bisphosphonates inhibit farnesyl pyrophosphate synthase, reducing protein prenylation and inducing osteoclast apoptosis; profound remodeling suppression allows microdamage accumulation, with anti-angiogenic and infection-promoting effects after dental trauma; topical mucosal injury; gamma-delta T-cell cytokine release. *Grade:* E.

- **A87. Denosumab.** *Diseases:* osteonecrosis of the jaw, atypical femoral fractures, severe hypocalcemia (especially in CKD), multiple vertebral fractures after discontinuation, skin infections. *Mechanism:* RANKL neutralization profoundly but reversibly inhibits osteoclasts; on cessation, rebound osteoclastogenesis causes rapid bone loss. *Grade:* E.

A-VIII. Dependence and withdrawal (cross-cutting dimension)

- **A88. Prescription opioids: opioid use disorder, persistent use, and overdose.** *Diseases:* opioid use disorder, persistent long-term use after short prescriptions (the probability of continued use at one year rises with each additional day supplied, most steeply in the first week), overdose, tolerance and hyperalgesia, neonatal opioid withdrawal syndrome. *Mechanism:* chronic mu-opioid receptor activation causes mesolimbic dopamine reward sensitization (disinhibition of ventral tegmental dopamine neurons) and neuroadaptation (cAMP superactivation, receptor desensitization, NMDA-dependent plasticity) with recruitment of stress systems (CRF, dynorphin), producing the allostatic state of dependence; risk rises with dose, duration, co-prescribed sedatives, and psychiatric comorbidity. *Grade:* E.

- **A89. Abrupt-cessation (Type E) syndromes: corticosteroids, beta-blockers, clonidine, intrathecal baclofen, antiepileptics, PPIs, and the benzodiazepine and antidepressant**

syndromes in A49 and A50. *Diseases:* adrenal crisis; rebound angina, myocardial infarction, and tachyarrhythmia; hypertensive crisis; baclofen withdrawal with hyperthermia and rhabdomyolysis; status epilepticus; rebound acid hypersecretion. *Mechanism:* homeostatic adaptation to chronic drug effect (adrenal atrophy; beta-receptor up-regulation; alpha-2 receptor down-regulation with catecholamine surge; GABA-B down-regulation; enterochromaffin-like cell hyperplasia) is unmasked when the drug is stopped. *Grade:* E.

A-IX. Interactions, prescribing cascades, and pharmacokinetic amplifiers

- **A90. Polypharmacy and prescribing cascades.** *Diseases:* falls and fractures, delirium, ADE-related hospitalization, and cascade-driven disease (e.g., calcium-channel-blocker edema treated with a loop diuretic; metoclopramide parkinsonism treated with levodopa; NSAID-induced hypertension treated with an antihypertensive; cholinesterase-inhibitor incontinence treated with an anticholinergic). *Mechanism:* cumulative pharmacodynamic burdens (anticholinergic, sedative, hypotensive, QT-prolonging), age-related reductions in renal clearance and hepatic metabolism, increased receptor sensitivity, and misattribution of an adverse effect to a new disease; risk rises steeply beyond about five concurrent drugs. This entry generalizes the draft's CF 50. *Grade:* E for harm; P for individual causal fractions.

- **A91. Pharmacokinetic and transporter interactions.** *Diseases:* toxicity from inhibition (clarithromycin with simvastatin causing rhabdomyolysis; clarithromycin with calcium-channel blockers causing hypotension and AKI; warfarin with trimethoprim-sulfamethoxazole, azoles, or amiodarone causing bleeding; azoles with vincristine causing neuropathy; ritonavir or cobicistat with inhaled or injected corticosteroids causing Cushing syndrome and adrenal suppression) and loss of efficacy from induction (St John's wort, rifampin lowering DOAC or transplant-drug levels causing thrombosis or rejection). *Mechanism:* inhibition or induction of CYP3A4, 2C9, 2D6, 2C19, P-glycoprotein, OATP, and UGT enzymes alters drug exposure; prodrug activation (clopidogrel, tamoxifen, codeine) can fail or intensify. *Grade:* E.

- **A92. Renal and hepatic dosing failure with narrow-therapeutic-index drugs (aminoglycosides, vancomycin, digoxin, lithium, methotrexate, enoxaparin, DOACs, gabapentinoids, morphine, metformin).** *Diseases:* drug-specific accumulation toxicity. *Mechanism:* reduced clearance in CKD, AKI, hepatic impairment, and hypoalbuminemia, with omission of dose adjustment or creatinine-based misestimation of GFR in sarcopenia and critical illness. *Grade:* E.

A-X. Other agents with important distinct mechanisms

- **A93. Allopurinol and other urate-lowering agents.** *Diseases:* severe cutaneous adverse reactions and DRESS (HLA-B*58:01 in Han Chinese, Thai, Korean, and African-American patients; risk amplified by renal impairment and high starting doses); febuxostat cardiovascular-death signal in one large trial; rasburicase hemolysis and methemoglobinemia in G6PD deficiency. Mechanism: oxypurinol interacts with HLA-B*58:01 and T-cell receptors (pharmacological-interaction concept) to activate cytotoxic T cells with granulysin release; oxypurinol accumulates in renal impairment. *Grade:* E.

- **A94. Hydroxychloroquine and chloroquine.** *Diseases:* retinopathy (cumulative dose and duration dependent), cardiomyopathy, QT prolongation, hypoglycemia. *Mechanism:* lysosomotropic accumulation and melanin binding in retinal pigment epithelium; phospholipidosis-like cardiac and muscle injury. *Grade:* E.

- **A95. Systemic retinoids (isotretinoin, acitretin) and tetracycline co-exposure.** *Diseases:* teratogenicity (L3), hypertriglyceridemia, hepatotoxicity, pseudotumor cerebri (greater with tetracyclines), mucocutaneous dryness; reported mood effects remain contested. *Mechanism:* retinoic-acid-receptor activation alters lipid metabolism and cerebrospinal-fluid dynamics. *Grade:* E for metabolic and mucocutaneous effects; C for depression causation.

- **A96. Oxidant drugs and methemoglobinemia (dapsone, benzocaine, nitrates, primaquine, rasburicase).** *Diseases:* methemoglobinemia, hemolytic anemia (especially in G6PD deficiency). *Mechanism:* oxidation of hemoglobin iron (Fe2+ to Fe3+) overwhelms NADH-cytochrome b5 reductase, and in G6PD deficiency the lack of NADPH-dependent glutathione regeneration permits oxidative red-cell destruction. *Grade:* E.

3.4 Category B: Healthcare-associated infections and antimicrobial resistance

Healthcare-associated infections arise when invasive devices and procedures bypass mucocutaneous barriers, when broad-spectrum antimicrobials disrupt protective microbiota, when immunosuppression and critical illness impair host defenses, and when contaminated environments, water systems, equipment, or hands transmit organisms between patients. A central unifying mechanism for device-related infection is **biofilm formation**: within minutes of insertion, host proteins (fibronectin, fibrinogen) coat the synthetic surface; organisms such as *Staphylococcus epidermidis*, *S. aureus*, *Pseudomonas aeruginosa*, and *Candida* adhere, switch gene-expression programs, and secrete an extracellular polymeric matrix that shields them from phagocytes, limits antibiotic diffusion, and induces metabolic dormancy, so that cure often requires device removal. The CDC prevalence surveys cited in Section 2.3 show that device-associated infections account for only about a quarter of HAIs; pneumonia and *C. difficile* are now the most common.

- **B1. Indwelling urinary catheters.** *Diseases:* catheter-associated urinary tract infection (CAUTI), pyelonephritis, urosepsis, catheter encrustation and struvite stones (urease-producing *Proteus*), urethral injury. *Mechanism:* the catheter bypasses the urethral sphincter; organisms ascend along intraluminal or extraluminal biofilm; mucosal abrasion facilitates invasion; urease-producing organisms alkalinize urine and precipitate crystalline biofilm. *Grade:* E.

- **B2. Central venous catheters and other intravascular devices.** *Diseases:* central line-associated bloodstream infection (CLABSI), septic thrombophlebitis, endocarditis, metastatic infection, peripheral-line *S. aureus* bacteremia. *Mechanism:* extraluminal migration of skin flora along the insertion tract (short-term lines) or intraluminal contamination of hubs (long-term lines), followed by biofilm and fibrin-sheath colonization that seeds the bloodstream episodically. *Grade:* E.

- **B3. Endotracheal intubation and hospital-acquired pneumonia.** *Diseases:* ventilator-associated pneumonia, non-ventilator hospital-acquired pneumonia, respiratory failure. *Mechanism:* the tube bypasses the glottis and impairs mucociliary clearance; subglottic secretions pool above the cuff and are micro-aspirated; biofilm forms on the tube; sedation, supine positioning, dysphagia, and acid suppression increase aspiration and colonization. *Grade:* E.

- **B4. Surgical incision and operation.** *Diseases:* superficial, deep, and organ-space surgical site infection, sepsis, implant infection. *Mechanism:* barrier transection allows inoculation of skin flora or environmental organisms; hypothermia, hypoxia, hyperglycemia, and hypoperfusion impair neutrophil oxidative killing; foreign material (sutures, implants) lowers the inoculum required for infection by orders of magnitude. *Grade:* E.

- **B5. Healthcare-environment *Clostridioides difficile* transmission.** *Diseases: C. difficile* infection, toxic megacolon, recurrent disease, sepsis. *Mechanism:* alcohol-resistant spores persist on surfaces and hands and are transmitted between patients; in an antibiotic-disrupted gut, primary bile acids trigger spore germination; toxins A and B glucosylate Rho GTPases; hypervirulent ribotypes (e.g., 027) add binary toxin and toxin hyperproduction. *Grade:* E.

- **B6. Multidrug-resistant organisms (MRSA, VRE, ESBL-producing and carbapenem-resistant Enterobacterales, carbapenem-resistant *Acinetobacter*).** *Diseases:* bloodstream, pulmonary, urinary, and wound infections with higher mortality and treatment failure. *Mechanism:* antibiotic selective pressure enriches resistant clones and drives horizontal transfer of resistance plasmids and transposons (mecA, vanA, carbapenemases); gut domination after antibiotics increases translocation; colonization pressure on wards and biofilm tolerance perpetuate transmission. *Grade:* E.

- **B7. Candida and invasive fungal infection (including *Candida auris*).** *Diseases:* candidemia, intra-abdominal candidiasis, endophthalmitis, fungal endocarditis, device-related infection. *Mechanism:* loss of competing bacterial flora removes colonization resistance; mucosal injury, central lines, parenteral nutrition, and abdominal surgery permit translocation; *C. auris* colonizes skin, persists on surfaces, and is frequently multidrug-resistant. *Grade:* E.

- **B8. Hospital construction and air-handling failures (invasive mold infection).** *Diseases:* invasive aspergillosis and mucormycosis in hematologic malignancy, stem-cell and organ transplant recipients. *Mechanism:* inhalation of aerosolized conidia during construction or with inadequate filtration; neutropenia and corticosteroids impair macrophage and NADPH-oxidase-dependent neutrophil killing. *Grade:* E.

- **B9. Building water systems (Legionella and other waterborne organisms).** *Diseases:* Legionnaires disease, *Pseudomonas*, *Serratia*, and non-tuberculous mycobacterial infection. *Mechanism:* amoeba-hosted and biofilm-protected organisms in warm stagnant water are aerosolized; *Legionella* replicates within alveolar macrophages using the Dot/Icm type IV secretion system. *Grade:* E.

- **B10. Cardiac heater-cooler devices (*Mycobacterium chimaera*).** *Diseases:* prosthetic-valve endocarditis, vascular-graft infection, and disseminated non-tuberculous mycobacterial disease, often 1 to 5 years after surgery. *Mechanism:* contaminated water tanks aerosolize organisms into the operating field during cardiopulmonary bypass; slow-growing biofilm-forming mycobacteria seed implanted prosthetic material. *Grade:* E.

- **B11. Contaminated reprocessed endoscopes (especially duodenoscopes).** *Diseases:* carbapenem-resistant Enterobacterales bloodstream infection and cholangitis, other cross-infection. *Mechanism:* complex distal-tip design and biofilm with residual bioburden defeat high-level disinfection. *Grade:* E.

- **B12. Unsafe injection and infusion practices.** *Diseases:* hepatitis B, hepatitis C, and HIV outbreaks (syringe reuse, multi-dose-vial contamination, shared insulin pens, endoscopy and pain-management clinics). *Mechanism:* direct parenteral inoculation of bloodborne virus. *Grade:* E.

- **B13. Dialysis-related infection.** *Diseases:* catheter-related bacteremia, access-site infection, peritoneal-dialysis peritonitis, hepatitis B transmission. *Mechanism:* biofilm on dialysis catheters, repeated access, and uremia-related immune dysfunction; peritoneal contamination at connection. *Grade:* E.

- **B14. Hospital-acquired viral infection (norovirus, influenza, RSV, SARS-CoV-2).** *Diseases:* nosocomial outbreaks with severe disease in elderly, immunocompromised, and neonatal patients. *Mechanism:* person-to-person, fomite, and aerosol transmission in congregate care among vulnerable hosts. *Grade:* E.

- **B15. Neonatal intensive-care infection and necrotizing enterocolitis.** *Diseases:* late-onset neonatal sepsis (coagulase-negative staphylococci, *S. aureus*, *Candida*), necrotizing enterocolitis. *Mechanism:* immature innate immunity and barrier function, central lines, parenteral nutrition, and prolonged empiric antibiotics (which reduce protective *Bifidobacterium* and promote TLR4-driven intestinal inflammation). *Grade:* E for sepsis; P for the contribution of antibiotics and acid suppression to necrotizing enterocolitis.

- **B16. Post-procedural endophthalmitis (cataract surgery, intravitreal injection).** *Diseases:* endophthalmitis with vision loss. *Mechanism:* inoculation of conjunctival flora into the immune-privileged vitreous; bacterial toxins and uncontrolled inflammation destroy the retina. *Grade:* E.

3.5 Category C: Surgical, anesthetic, and other procedural harm

Procedural harm arises from mechanical, thermal, ischemic, hemodynamic, infectious, and pharmacologic insults. The AHRQ PSIs that screen for these events (including PSIs 04, 06, 09, 10, 12, and 15) are cited in Section 2.3.

- **C1. Operative organ, vascular, and nerve injury (including accidental puncture or laceration, PSI 15).** *Diseases:* bile-duct injury and stricture, ureteral injury, bowel perforation with

peritonitis, hemorrhage, sepsis. *Mechanism:* mechanical transection or thermal injury of tissue; spillage of enteric contents activates a macrophage and neutrophil response, third-spacing, and septic shock; electrosurgical thermal spread causes delayed ischemic necrosis; anatomic misidentification. *Grade:* E.

- **C2. Postoperative hemorrhage and hematoma (PSI 09).** *Diseases:* hemorrhagic shock, reoperation, wound complications. *Mechanism:* surgical bleeding amplified by anticoagulants, dilutional and consumptive coagulopathy, hypothermia, and acidosis. *Grade:* E.

- **C3. Perioperative venous thromboembolism (PSI 12).** *Diseases:* deep vein thrombosis and pulmonary embolism. *Mechanism:* Virchow's triad is completed by endothelial injury and tissue-factor release, an acute-phase hypercoagulable state (elevated fibrinogen and PAI-1 with fibrinolysis shutdown, driven by IL-6 and TNF-alpha), and venous stasis from immobilization; risk is highest after orthopedic and cancer surgery. *Grade:* E.

- **C4. Postoperative acute kidney injury (PSI 10).** *Diseases:* acute kidney injury, dialysis dependence, progression to CKD. *Mechanism:* intraoperative hypotension and hypoperfusion, ischemia-reperfusion injury, inflammation, nephrotoxin co-exposure, bypass-related hemolysis with free hemoglobin and iron, and venous congestion. *Grade:* E.

- **C5. Perioperative myocardial injury, infarction, and stroke.** *Diseases:* myocardial injury after noncardiac surgery, myocardial infarction, atrial fibrillation, perioperative stroke. *Mechanism:* supply-demand mismatch (hypotension, tachycardia, anemia), catecholamine surge, and a prothrombotic, inflammatory milieu that destabilizes plaque; cardioembolism from new atrial fibrillation; embolization or hypoperfusion in cardiac and carotid surgery. *Grade:* E.

- **C6. Postoperative delirium and cognitive dysfunction.** *Diseases:* delirium, persistent cognitive decline in vulnerable patients. *Mechanism:* surgical trauma releases cytokines (IL-1-beta, IL-6) and DAMPs (HMGB1) that increase blood-brain-barrier permeability and prime microglia; cholinergic deficiency, sleep and circadian disruption, anticholinergic, benzodiazepine, and opioid exposure, and hypoperfusion add to this; underlying neurodegeneration increases vulnerability. *Grade:* E for delirium; P for long-term decline.

- **C7. Malignant hyperthermia (volatile anesthetics, succinylcholine).** *Diseases:* hypermetabolic crisis, hyperthermia, rhabdomyolysis, hyperkalemia, death. *Mechanism:* pathogenic RYR1 (or CACNA1S) variants cause uncontrolled sarcoplasmic-reticulum calcium release when triggered; dantrolene blocks the ryanodine receptor. *Grade:* E.

- **C8. Propofol infusion syndrome.** *Diseases:* lactic acidosis, rhabdomyolysis, cardiac failure, hyperkalemia, renal failure (high-dose, prolonged infusion, especially in children and critical illness). *Mechanism:* impaired mitochondrial fatty-acid oxidation and respiratory-chain function. *Grade:* E.

- **C9. Succinylcholine.** *Diseases:* hyperkalemic cardiac arrest in denervation injury, burns, prolonged immobilization, or muscular dystrophy; prolonged paralysis in butyrylcholinesterase (BCHE) variants. *Mechanism:* depolarization of up-regulated extrajunctional acetylcholine receptors releases potassium; impaired plasma hydrolysis prolongs block. *Grade:* E.

- **C10. Halogenated anesthetics (halothane, rarely newer agents).** *Diseases:* immune-mediated fulminant hepatitis. *Mechanism:* oxidative metabolism generates trifluoroacetyl-protein adducts that act as neoantigens. *Grade:* E.

- **C11. Anesthetic exposure in the developing brain.** *Diseases:* possible neurodevelopmental effects after early repeated or prolonged exposure. *Mechanism:* preclinical studies show NMDA and GABA-mediated neuroapoptosis in immature brain; a large randomized trial of a single brief exposure in infancy found no effect on IQ at age 5, and evidence for prolonged or repeated exposure remains uncertain. *Grade:* H to C.

- **C12. Local-anesthetic systemic toxicity.** *Diseases:* seizures, cardiovascular collapse. *Mechanism:* sodium-channel block in CNS then myocardium; bupivacaine also inhibits mitochondrial carnitine-acylcarnitine translocase, reducing ATP; intravenous lipid emulsion is a rescue therapy. *Grade:* E.

- **C13. Neuraxial anesthesia and analgesia.** *Diseases:* post-dural-puncture headache, epidural hematoma (especially with anticoagulants), epidural abscess, nerve injury, high spinal block. *Mechanism:* CSF leak causes intracranial hypotension and traction on pain-sensitive structures; bleeding or infection in a closed space compresses the cord; direct needle or toxic injury. *Grade:* E.

- **C14. Perioperative peripheral nerve injury (positioning, tourniquet, retractors, regional blocks).** *Diseases:* neuropraxia and axonal injury, brachial plexopathy, ulnar and peroneal neuropathy. *Mechanism:* compression or stretch produces ischemia, demyelination, and axonal degeneration. *Grade:* E.

- **C15. Needle and catheter injury (thoracentesis, central-line placement; PSI 06).** *Diseases:* iatrogenic pneumothorax, hemothorax, arterial puncture, cardiac tamponade, air embolism. *Mechanism:* pleural or vascular puncture introduces air or blood into the negative-pressure pleural space or compartments; loss of lung-chest-wall cohesion causes atelectasis; positive-pressure ventilation converts a small pneumothorax to tension. *Grade:* E.

- **C16. Persistent postsurgical pain.** *Diseases:* chronic neuropathic and mixed pain after hernia repair, thoracotomy, mastectomy, amputation, and other operations. *Mechanism:* surgical nerve injury induces peripheral and central sensitization (glial activation, NMDA-dependent plasticity). *Grade:* E.

- **C17. Peritoneal adhesions.** *Diseases:* adhesive small-bowel obstruction, chronic pelvic pain, secondary infertility. *Mechanism:* peritoneal trauma causes fibrin deposition and suppressed

fibrinolysis (reduced tissue plasminogen activator, increased PAI-1), allowing fibroblast and capillary ingrowth into fibrous bands. *Grade:* E.

- **C18. Splenectomy.** *Diseases:* overwhelming post-splenectomy infection (encapsulated organisms, *Capnocytophaga*), thrombosis, pulmonary hypertension. *Mechanism:* loss of marginal-zone B cells and IgM-memory, blood filtration, and opsonization. *Grade:* E.

- **C19. Thyroid, parathyroid, and neck surgery.** *Diseases:* hypoparathyroidism with hypocalcemia, recurrent laryngeal nerve injury, airway-compromising hematoma. *Mechanism:* parathyroid devascularization or removal; nerve stretch or transection. *Grade:* E.

- **C20. Bariatric surgery.** *Diseases:* iron, B12, folate, thiamine (Wernicke encephalopathy), and copper (myeloneuropathy) deficiency; calcium and vitamin D deficiency with osteoporosis; dumping syndrome; marginal ulcer; internal hernia; gallstones; post-bypass hyperinsulinemic hypoglycemia; alcohol use disorder. *Mechanism:* reduced acid and intrinsic factor, duodenal bypass (iron, calcium), rapid transit, altered alcohol first-pass metabolism, and incretin hypersecretion. *Grade:* E.

- **C21. Surgical menopause (bilateral oophorectomy before natural menopause) and hysterectomy.** *Diseases:* bone loss, cardiovascular disease, cognitive decline (association), sexual dysfunction. *Mechanism:* abrupt loss of ovarian estrogen and androgen; hysterectomy with ovarian conservation may lead to earlier ovarian failure. *Grade:* E for bone loss; P to H for cardiovascular and cognitive outcomes.

- **C22. Endoscopic procedures (colonoscopy, ERCP, endoscopic resection).** *Diseases:* perforation, delayed post-polypectomy bleeding, post-polypectomy coagulation syndrome, post-ERCP pancreatitis (about 2% to 10%), sedation-related cardiopulmonary events. *Mechanism:* mechanical, barotraumatic, and thermal injury; in ERCP, papillary edema, pancreatic-duct hydrostatic or contrast injury, and premature trypsinogen activation. *Grade:* E.

- **C23. Cardiac surgery and cardiopulmonary bypass.** *Diseases:* systemic inflammatory response and vasoplegia, acute kidney injury, stroke and cognitive decline, atrial fibrillation, bleeding. *Mechanism:* contact activation of complement, kallikrein, and cytokines at the blood-circuit interface, ischemia-reperfusion injury, hemolysis, and microemboli from aortic manipulation. *Grade:* E.

- **C24. Cardiac catheterization and percutaneous coronary intervention.** *Diseases:* access-site hematoma, pseudoaneurysm, retroperitoneal bleeding, stroke, coronary dissection or perforation, contrast nephropathy (E5), radiation skin injury (E3). *Mechanism:* arterial puncture combined with anticoagulation; mechanical plaque and vessel injury. *Grade:* E.

- **C25. Transcatheter aortic-valve implantation.** *Diseases:* conduction block requiring pacemaker, stroke, leaflet thrombosis, paravalvular leak. *Mechanism:* compression of the conduction system

adjacent to the membranous septum; embolization of calcific debris; thrombus formation on the prosthesis. *Grade:* E.

- **C26. Cesarean and instrumental delivery.** *Diseases:* maternal hemorrhage, infection, thromboembolism, placenta accreta spectrum in later pregnancies, pelvic-floor disorders and obstetric anal sphincter injury after instrumental delivery or episiotomy; offspring associations with asthma, allergy, and obesity after cesarean delivery. *Mechanism:* uterine scar defects permit abnormally deep trophoblast invasion; mechanical sphincter disruption; the offspring associations are attributed to altered microbial seeding and absent labor-related hormone and stress signals but are confounded by indication. *Grade:* E for maternal outcomes; H for offspring associations.

- **C27. Induction and augmentation of labor with oxytocin.** *Diseases:* uterine tachysystole with fetal hypoxia, uterine rupture (prior scar), postpartum hemorrhage from atony, water intoxication. *Mechanism:* excessive contractions reduce uteroplacental perfusion; oxytocin-receptor desensitization contributes to atony; oxytocin has antidiuretic activity. *Grade:* E to P.

- **C28. Spinal surgery.** *Diseases:* adjacent-segment degeneration, failed-back-surgery syndrome, epidural fibrosis, dural tear, post-operative infection and epidural hematoma. *Mechanism:* altered biomechanics transfers load to neighboring levels; scar and fibrosis around nerve roots. *Grade:* E to P.

- **C29. Prolonged intubation and tracheostomy.** *Diseases:* subglottic and tracheal stenosis, tracheo-innominate fistula, vocal-cord injury. *Mechanism:* cuff pressure above mucosal capillary perfusion pressure (about 25 to 30 mmHg) causes mucosal ischemia, ulceration, granulation, and scar contracture. *Grade:* E.

- **C30. Thermal injury in the operating and imaging environment.** *Diseases:* burns (electrosurgical alternate-site and MRI-related), airway and surgical fires. *Mechanism:* high current density through small contact areas or capacitive coupling; ignition in oxygen-enriched atmospheres. *Grade:* E.

- **C31. Epidural steroid injection.** *Diseases:* spinal-cord and brainstem infarction (rare), epidural abscess, adrenal suppression, bone loss, fungal meningitis from contaminated product (K1). *Mechanism:* inadvertent intra-arterial injection of particulate steroid into radicular or vertebral arteries causes embolic infarction; systemic absorption causes HPA-axis suppression. *Grade:* E.

3.6 Category D: Implanted devices and materials

The draft treated devices mainly as portals for infection. Implants also cause disease through the **foreign-body response** (macrophage and giant-cell activation, fibrous encapsulation), **wear and corrosion debris**, **hemodynamic and mechanical failure**, and **material hypersensitivity**. Infection of implants (biofilm) is covered here and in Category B.

- **D1. Metal-on-metal hip bearings and corroding modular tapers.** *Diseases:* adverse local tissue reactions (pseudotumor, soft-tissue necrosis), osteolysis, and systemic cobalt toxicity (cardiomyopathy, neuropathy, hypothyroidism, visual and hearing changes). *Mechanism:* metal particles and ions activate macrophages (including the NLRP3 inflammasome) and drive a lymphocyte-dominated Type IV hypersensitivity; cobalt ions impair mitochondrial function and activate hypoxia-inducible-factor signaling. *Grade:* E.

- **D2. Polyethylene and other wear debris in joint arthroplasty.** *Diseases:* periprosthetic osteolysis and aseptic loosening. *Mechanism:* macrophage phagocytosis of submicron particles releases TNF-alpha, IL-1, and RANKL, activating osteoclasts ("particle disease"). *Grade:* E.

- **D3. Periprosthetic joint and orthopedic-hardware infection.** *Diseases:* acute and chronic implant infection requiring revision. *Mechanism:* "race for the surface" between bacteria and host tissue integration; biofilm on implant surfaces and compromised local immunity in the peri-implant tissue. *Grade:* E.

- **D4. Surgical mesh (hernia repair, pelvic-organ-prolapse repair, stress-incontinence slings).** *Diseases:* chronic pain, mesh exposure or erosion, infection, dyspareunia, organ injury, recurrence; the FDA ordered transvaginal mesh for prolapse off the US market in 2019. *Mechanism:* chronic foreign-body reaction, mesh contraction and stiffness mismatch with surrounding tissue, nerve entrapment, and biofilm. *Grade:* E.

- **D5. Breast implants.** *Diseases:* capsular contracture, breast-implant-associated anaplastic large-cell lymphoma (BIA-ALCL, mostly with textured implants), rupture; "breast implant illness" (systemic symptoms, causation unproven). *Mechanism:* subclinical biofilm infection drives myofibroblast-mediated fibrotic capsule formation (TGF-beta); textured surfaces with chronic bacterial and inflammatory stimulation promote clonal T-cell expansion, with JAK/STAT3 pathway mutations in lymphoma. *Grade:* E for contracture and BIA-ALCL; H for systemic illness.

- **D6. Cardiac implantable electronic devices (pacemakers, ICDs).** *Diseases:* pocket and lead infection with endocarditis, venous lead thrombosis and occlusion, tricuspid regurgitation, inappropriate shocks, pacing-induced cardiomyopathy. *Mechanism:* biofilm on generator and leads; lead-endothelium interaction; dyssynchronous right-ventricular pacing causes maladaptive remodeling. *Grade:* E.

- **D7. Prosthetic heart valves.** *Diseases:* thromboembolism, prosthetic-valve endocarditis, hemolysis, structural valve degeneration, bleeding from required anticoagulation. *Mechanism:* blood-surface interaction and shear stress activate platelets and coagulation (mechanical valves) and damage red cells; progressive calcification of bioprosthetic tissue. *Grade:* E.

- **D8. Coronary and peripheral stents.** *Diseases:* stent thrombosis, in-stent restenosis, neoatherosclerosis. *Mechanism:* delayed endothelialization and hypersensitivity to polymer or drug (late thrombosis); vascular injury triggers smooth-muscle proliferation and neointimal hyperplasia. *Grade:* E.

- **D9. Inferior vena cava filters.** *Diseases:* filter fracture, migration, caval perforation, caval thrombosis, recurrent deep vein thrombosis. *Mechanism:* foreign-body thrombogenicity and mechanical fatigue. *Grade:* E.

- **D10. CSF shunts and external ventricular drains.** *Diseases:* shunt obstruction, ventriculitis and meningitis, over-drainage with subdural hematoma. *Mechanism:* biofilm; choroid-plexus and protein occlusion; siphon effect. *Grade:* E.

- **D11. Intrauterine devices and hysteroscopic sterilization implants.** *Diseases:* uterine perforation, early pelvic inflammatory disease, expulsion, pain; nickel hypersensitivity and device fragmentation with the hysteroscopic implant, which left the US market in 2018. *Mechanism:* mechanical injury; introduction of vaginal flora at insertion; nickel-driven hypersensitivity and chronic inflammation. *Grade:* E.

- **D12. Hemodialysis access (grafts and arteriovenous fistulas).** *Diseases:* stenosis, thrombosis, steal syndrome, infection, central venous stenosis. *Mechanism:* turbulent shear stress at anastomoses drives smooth-muscle migration and neointimal hyperplasia. *Grade:* E.

3.7 Category E: Therapeutic and diagnostic radiation and imaging agents

The draft combined radiation and contrast under procedural harm. They are separated here because their mechanisms (stochastic DNA damage, deterministic tissue injury, and renal or deposition toxicity) and their long-term disease outcomes differ.

- **E1. Therapeutic ionizing radiation.** *Diseases:* acute dermatitis, mucositis, esophagitis, and pneumonitis; late fibrosis (lung, skin, soft tissue), radiation heart disease (coronary disease, valvular disease, pericarditis, cardiomyopathy; risk of major coronary events rose by about 7% per gray of mean heart dose in a large breast-cancer cohort), xerostomia, osteoradionecrosis, myelopathy and brain necrosis, cognitive decline, hypothyroidism, lymphedema, bowel stricture and proctitis, carotid vasculopathy, infertility, and second cancers (sarcoma, leukemia, breast, lung; latency 5 to more than 30 years). *Mechanism:* radiation causes direct and ROS-mediated DNA double-strand breaks, with apoptosis and mitotic catastrophe of dividing cells and endothelium; chronic inflammation, microvascular injury and ischemia, stem-cell depletion, and sustained TGF-beta/CTGF signaling activate fibroblasts and deposit collagen; surviving cells with misrepaired DNA initiate carcinogenesis. *Grade:* E.

- **E2. Diagnostic CT and other ionizing imaging.** *Diseases:* small increases in lifetime cancer risk, particularly after childhood exposure (a large UK cohort estimated that cumulative head doses of roughly 50 to 60 mGy in children were associated with about threefold higher relative risks of leukemia and brain tumors, corresponding to about one excess case of each per 10,000 head scans in the following decade; reverse causation and confounding by indication remain debated). *Mechanism:* low-dose DNA damage with stochastic mutagenesis; population risk estimates rely on linear no-threshold extrapolation from higher-dose data. *Grade:* P for risk existence; H for magnitude at low doses.

- **E3. Fluoroscopically guided interventions.** *Diseases:* radiation skin injury (erythema through necrosis at peak skin doses beyond a few gray), cataract, epilation. *Mechanism:* deterministic cell killing with microvascular injury when threshold doses are exceeded. *Grade:* E.

- **E4. Radiopharmaceuticals and radioiodine therapy.** *Diseases:* salivary-gland dysfunction and sialadenitis, xerostomia, myelosuppression, gonadal effects, small increases in second-cancer risk. *Mechanism:* local beta or alpha energy deposition; sodium-iodide-symporter uptake in salivary tissue. Historical agents (Thorotrast, radium) caused liver angiosarcoma, leukemia, and osteosarcoma. *Grade:* E.

- **E5. Iodinated contrast media.** *Diseases:* contrast-associated acute kidney injury (risk concentrated in patients with eGFR below about 30 mL/min/1.73 m2 and in intra-arterial first-pass exposure; the risk with modern low- and iso-osmolar agents given intravenously is lower than historically believed, and the draft's emphasis on highly osmolar agents is outdated), immediate hypersensitivity, delayed rash, thyroid dysfunction, extravasation injury. *Mechanism:* medullary vasoconstriction and hypoxia (adenosine, endothelin), direct tubular toxicity with ROS and increased viscosity; IgE-dependent and non-IgE (MRGPRX2) mast-cell activation; T-cell-mediated delayed reactions; iodine load causes Wolff-Chaikoff failure or iodine-induced thyrotoxicosis. *Grade:* E for acute reactions and thyroid effects; P for AKI magnitude.

- **E6. Gadolinium-based contrast agents.** *Diseases:* nephrogenic systemic fibrosis (severe CKD or AKI exposed to older linear agents), tissue retention in brain and bone (clinical significance unclear; "gadolinium deposition disease" is unproven). *Mechanism:* dissociation (transmetallation) releases free Gd3+ that deposits in tissue; circulating fibrocytes and macrophages activate and drive TGF-beta-mediated fibrosis of skin and organs. *Grade:* E for nephrogenic systemic fibrosis; H for retention-related illness.

- **E7. Magnetic-resonance hazards.** *Diseases:* projectile injury, thermal burns, device and lead heating or malfunction, acoustic injury. *Mechanism:* static-field forces, radiofrequency heating, and gradient-induced currents. *Grade:* E.

3.8 Category F: Blood products, transplantation, and biologic transfer

- **F1. Allogeneic transfusion: transfusion-related acute lung injury (TRALI).** *Diseases:* non-cardiogenic pulmonary edema within six hours of transfusion. *Mechanism:* a "two-hit" process: recipient inflammation primes pulmonary neutrophils, and donor anti-HLA or anti-neutrophil antibodies or bioactive lipids then activate them, releasing proteases and neutrophil extracellular traps that damage the alveolar capillary barrier; plasma from male donors reduces risk. *Grade:* E.

- **F2. Allogeneic transfusion: transfusion-associated circulatory overload (TACO).** *Diseases:* hydrostatic pulmonary edema. *Mechanism:* rapid volume expansion exceeds cardiovascular reserve (older age, heart failure, renal failure), elevating pulmonary capillary hydrostatic pressure. *Grade:* E.

- **F3. Acute hemolytic transfusion reaction (ABO incompatibility).** *Diseases:* intravascular hemolysis, DIC, acute kidney injury, shock, death. *Mechanism:* preformed IgM anti-A or anti-B activates complement (C3a, C5a), triggers cytokine release and tissue-factor-driven coagulation, and free hemoglobin scavenges nitric oxide and injures renal tubules. *Grade:* E.

- **F4. Allergic, febrile, and anaphylactic transfusion reactions.** *Diseases:* urticaria, fever, anaphylaxis (including in IgA-deficient recipients with anti-IgA antibodies). *Mechanism:* recipient IgE against donor plasma proteins; cytokines accumulating in stored cellular products. *Grade:* E.

- **F5. Transfusion-associated graft-versus-host disease.** *Diseases:* fatal marrow aplasia, rash, hepatitis, and diarrhea. *Mechanism:* viable donor T cells (especially when donor and recipient share HLA haplotypes) engraft in an immunocompromised or HLA-haplotype-sharing recipient and attack host tissue; irradiation of cellular products prevents it. *Grade:* E.

- **F6. Chronic transfusion: iron overload and alloimmunization.** *Diseases:* hemosiderosis with cardiomyopathy, cirrhosis, endocrinopathy; red-cell alloimmunization with delayed hemolytic reactions and hemolytic disease of the fetus. *Mechanism:* the body lacks a regulated iron-excretion pathway, so labile plasma iron generates radicals through Fenton chemistry; minor-antigen mismatches (Kell, Rh, Duffy) elicit anamnestic antibody responses. *Grade:* E.

- **F7. Transfusion-transmitted infection.** *Diseases:* hepatitis B, hepatitis C, HIV (now exceedingly rare with nucleic-acid testing), bacterial sepsis from contaminated platelets, babesiosis, West Nile virus, Chagas disease, malaria; variant CJD (a small number of probable transfusion transmissions in the UK). *Mechanism:* direct inoculation during donor window periods or contamination. *Grade:* E.

- **F8. Massive transfusion.** *Diseases:* citrate toxicity (hypocalcemia, hypomagnesemia), hyperkalemia, hypothermia, dilutional coagulopathy, acidosis. *Mechanism:* citrate chelation of divalent cations; potassium leak from stored red cells; cold, citrated, factor-poor products. *Grade:* E.

- **F9. Transfusion-related immunomodulation.** *Diseases:* postoperative infection and cancer-recurrence associations. *Mechanism:* donor leukocytes and soluble mediators (sCD40L, sFasL), regulatory-T-cell induction, and microchimerism are proposed; confounded by the indication for transfusion. *Grade:* H to C.

- **F10. Plasma-derived and recombinant protein products (IVIG, anti-D, clotting concentrates).** *Diseases:* thrombosis, hemolysis, aseptic meningitis, acute kidney injury (sucrose-stabilized products), anaphylaxis; historical hepatitis C and HIV transmission through contaminated concentrates. *Mechanism:* increased viscosity and procoagulant contaminants (e.g., activated factor XI), passive isohemagglutinins, osmotic nephrosis, IgA-directed antibodies, viral contamination. *Grade:* E.

- **F11. Hemostatic agents (tranexamic acid, recombinant factor VIIa, prothrombin complex concentrate).** *Diseases:* seizures (high-dose tranexamic acid in cardiac surgery), arterial and venous thrombosis. *Mechanism:* tranexamic acid antagonizes glycine and GABA-A receptors; systemic procoagulant effects. *Grade:* E.

- **F12. Donor-derived disease transmission in solid-organ transplantation.** *Diseases:* donor-derived infection (viral, bacterial, fungal, parasitic) and donor-derived malignancy. *Mechanism:* transplanted tissue transmits latent or occult pathogens and cells into a recipient on immunosuppression. *Grade:* E.

- **F13. Post-transplant lymphoproliferative disorder and opportunistic disease.** *Diseases:* EBV-driven B-cell lymphoproliferation, cytomegalovirus disease, other opportunistic infections. *Mechanism:* suppression of T-cell surveillance permits EBV-transformed B-cell proliferation (see A75). *Grade:* E.

- **F14. Hematopoietic cell transplantation.** *Diseases:* mucositis, sinusoidal obstruction syndrome (veno-occlusive disease), acute and chronic graft-versus-host disease, infection, graft failure, late cataract, endocrinopathy, and secondary malignancy. *Mechanism:* conditioning regimens injure endothelium and epithelium; alloreactive donor T cells attack host tissue amplified by tissue-damage-driven cytokines; prolonged immune deficiency. *Grade:* E.

- **F15. Iatrogenic prion transmission.** *Diseases:* Creutzfeldt-Jakob disease after cadaveric human growth hormone and human dura mater grafts (each with more than 200 recognized cases worldwide), neurosurgical instruments, corneal transplants, and variant CJD via transfusion. *Mechanism:* misfolded PrPSc seeds templated conversion of host PrPC and propagates along neural pathways over incubation periods of years to decades; prions resist standard sterilization. *Grade:* E.

3.9 Category G: Vaccines

Vaccines are among the most extensively monitored medical products, and the evidence base permits unusually clear separation of established adverse events from claims that were tested and not supported. Serious adverse events are rare relative to doses administered, and for most vaccines the absolute risk of a serious vaccine-attributable event is far below the risk of the disease prevented (for example, measles carries encephalitis risk on the order of 1 per 1,000 cases and a case-fatality ratio of roughly 1 to 3 per 1,000 in high-income settings, many times the risk of any serious MMR-attributable event). Entries below separate **causation** from **mechanism** in the grade, because for several vaccine events (e.g., myocarditis, narcolepsy, Guillain-Barre syndrome) the epidemiologic association is established but the mechanism is hypothesized. Incidence figures are approximate and vary by age, sex, product, dose number, and surveillance system; passive-reporting data (VAERS) were used only to generate signals, not to estimate causation.

G-I. COVID-19 vaccines

- **G1. mRNA COVID-19 vaccines (BNT162b2, mRNA-1273): myocarditis and pericarditis.** *Diseases:* myocarditis and pericarditis, concentrated in adolescent and young adult males within about a week of the second dose. Early CDC estimates were about 12.6 cases per million second doses across ages 12 to 39 and roughly 50 to 70 per million second doses in males aged 12 to 24, with higher rates in some Nordic and Asian datasets (particularly for mRNA-1273) and lower rates with longer dosing intervals and lower doses; most cases were mild with rapid recovery, although cardiac MRI abnormalities persisted in a proportion and long-term significance is still being studied. SARS-CoV-2 infection itself causes myocarditis at higher rates than vaccination in several large cohorts. *Mechanism:* unresolved. Proposed contributors are (a) innate immune activation by the lipid nanoparticle and mRNA with elevated cytokines (IL-1-beta, IL-1 receptor antagonist, IL-15, interferon-gamma) and activated CD8-positive T and NK cells; (b) detection of free circulating spike antigen in affected adolescents; (c) molecular mimicry between spike epitopes and cardiac alpha-myosin heavy chain or troponin (hypothesized; autoantibodies were not consistently found); (d) spike-protein signaling through TLR4 on cardiomyocytes (supported mainly by in vitro work); and (e) sex-hormone modulation of Th1 inflammatory responses (testosterone) to explain male predominance. The draft presented (c) and (d) as established; they are not. *Grade:* E (causation); H (mechanism).

- **G2. Anaphylaxis to vaccines (mRNA vaccines and others).** *Diseases:* immediate hypersensitivity and anaphylaxis; about 5 per million doses with mRNA COVID-19 vaccines in US surveillance, compared with about 1 per million for other vaccines. *Mechanism:* IgE to excipients (gelatin, yeast proteins, trace egg protein, latex stoppers) or complement-activation-related pseudoallergy to PEGylated lipid nanoparticles (PEG-2000 and polysorbate cross-reactivity), possibly involving anti-PEG antibodies and MRGPRX2-mediated mast-cell activation. *Grade:* E.

- **G3. mRNA COVID-19 vaccines: other recognized or signal events.** *Diseases:* vasovagal syncope (especially in adolescents), axillary lymphadenopathy, shoulder injury related to vaccine administration (G26), transient menstrual-cycle changes (small, short-lived), Bell's palsy (inconsistent signal), immune thrombocytopenia (not consistently supported), herpes zoster reactivation (weak signal). *Mechanism:* vasovagal reflex to injection; innate-immune-driven germinal-center activation in draining nodes; other mechanisms undefined. *Grade:* E for syncope, lymphadenopathy; P to H for others.

- **G4. Adenoviral-vector COVID-19 vaccines (ChAdOx1-S, Ad26.COV2.S): vaccine-induced immune thrombotic thrombocytopenia (VITT, also called thrombosis with thrombocytopenia syndrome).** *Diseases:* cerebral venous sinus thrombosis, splanchnic and other thromboses with thrombocytopenia and DIC, typically 4 to 42 days after vaccination; about 4 per million doses overall in the US with Ad26.COV2.S and higher in women aged 30 to 49; European and UK estimates for ChAdOx1-S were on the order of 1 per 50,000 to 1 per 100,000 in younger adults; early mortality was high. *Mechanism:* high-titer IgG against platelet factor 4 develops without prior heparin exposure; these antibodies bind PF4 and activate platelets, neutrophils, and monocytes through Fc-gamma-RIIa, producing thrombosis, consumptive thrombocytopenia, and NETosis, as in autoimmune HIT. The trigger for anti-PF4 formation is incompletely defined

(proposed: electrostatic binding of PF4 to the adenoviral capsid or free DNA with an inflammatory co-signal; clonally restricted antibodies using IGLV3-21*02 light chains have been described). Treatment uses IVIG and non-heparin anticoagulants. *Grade:* E (causation); P (mechanism).

- **G5. Adenoviral-vector COVID-19 vaccines: Guillain-Barre syndrome.** *Diseases:* Guillain-Barre syndrome with Ad26.COV2.S (a few to about ten excess cases per million doses in US surveillance; a label warning was added). *Mechanism:* not established; post-vaccination autoimmunity against peripheral nerve gangliosides or myelin is hypothesized. *Grade:* E (association); H (mechanism).

G-II. Measles-, mumps-, and rubella-containing vaccines

- **G6. MMR and MMRV: febrile seizures.** *Diseases:* febrile seizures about 5 to 12 days after the first dose at 12 to 23 months (roughly 1 per 3,000 to 4,000 MMR doses; about 1 additional seizure per 2,300 to 2,600 doses when MMRV is used instead of MMR plus separate varicella vaccine). Febrile seizures after vaccination have not been associated with an increased risk of later epilepsy or neurodevelopmental sequelae. *Mechanism:* replication of live-attenuated virus stimulates innate sensors (TLRs) and release of IL-1-beta, IL-6, and TNF-alpha, which act on the hypothalamus to induce fever; fever lowers the seizure threshold in susceptible toddlers. *Grade:* E.

- **G7. MMR: immune thrombocytopenia (ITP).** *Diseases:* transient ITP, about 1 per 30,000 to 40,000 doses, usually self-limited; the risk after natural measles or rubella infection is higher. *Mechanism:* immune-mediated platelet destruction (antiplatelet antibodies or immune complexes triggered by viral antigen exposure). *Grade:* E (causation); P (mechanism).

- **G8. MMR: anaphylaxis and other hypersensitivity.** *Diseases:* anaphylaxis (about 1 per million doses), urticaria. *Mechanism:* IgE to gelatin or neomycin excipients; egg allergy is not a contraindication. *Grade:* E.

- **G9. Rubella-containing vaccines: joint symptoms.** *Diseases:* transient arthralgia and arthritis, most often in post-pubertal women. *Mechanism:* replication of attenuated rubella virus in synovial tissue with immune-complex formation; persistent chronic arthritis has not been established. *Grade:* E (acute); C (chronic).

- **G10. Measles-containing vaccine in severe immunodeficiency.** *Diseases:* measles inclusion-body encephalitis, giant-cell pneumonitis, disseminated vaccine-strain infection. *Mechanism:* absent T-cell control of the attenuated virus (contraindicated in severe cellular immunodeficiency; screening prevents it). *Grade:* E.

- **G11. Mumps component: strain-specific aseptic meningitis, parotitis, orchitis.** *Diseases:* aseptic meningitis with Urabe and Leningrad-Zagreb strains (not with the Jeryl Lynn strain used in the

US); rare parotitis. *Mechanism:* strain-dependent neurovirulence of live mumps virus. *Grade:* E (strain-specific).

- **G12. MMR and autism or inflammatory bowel disease (claimed association).** The hypothesis arose from a 1998 case series that was retracted in 2010 after findings of ethical violations and data manipulation. A Danish national cohort of about 657,000 children found no increased autism risk after MMR vaccination, including among siblings of children with autism and other subgroups, consistent with meta-analyses of multiple studies, and no persistence of measles virus in the gut of affected children has been demonstrated. *Mechanism:* no supported mechanism. *Grade:* C.

- **G13. Thimerosal (ethylmercury) in vaccines and neurodevelopmental disorders (claimed association).** *Diseases:* local delayed hypersensitivity (contact allergy) is documented. National cohorts and a population-level natural experiment (removal from most US childhood vaccines in 1999 to 2001 without a decline in autism diagnoses) do not support neurodevelopmental harm; ethylmercury is cleared faster than methylmercury. *Grade:* E (local hypersensitivity); C (neurodevelopmental outcomes).

G-III. Live-attenuated vaccines (other)

- **G14. Rotavirus vaccines: intussusception.** *Diseases:* intussusception, about 1 per 10,000 infants with the first rotavirus vaccine (RotaShield, withdrawn in 1999) and about 1 to 6 excess cases per 100,000 infants with current vaccines (clustered 3 to 7 days after the first dose); vaccine-strain persistent diarrhea in severe combined immunodeficiency (contraindicated). *Mechanism:* replication of attenuated rotavirus in the gut with lymphoid (Peyer's patch) hyperplasia that acts as a lead point for intussusception; absent T-cell clearance in SCID. *Grade:* E.

- **G15. Oral poliovirus vaccine: vaccine-associated paralytic poliomyelitis and circulating vaccine-derived poliovirus.** *Diseases:* paralytic poliomyelitis (about 1 case per 2.4 million doses distributed; much higher in immunodeficiency) and outbreaks of circulating vaccine-derived poliovirus in under-immunized populations. *Mechanism:* reversion of Sabin strains through mutations in the 5' untranslated region and capsid, and recombination with other enteroviruses, restores neurovirulence and transmissibility; the US moved to inactivated polio vaccine only in 2000. *Grade:* E.

- **G16. BCG vaccine.** *Diseases:* injection-site abscess, regional lymphadenitis, osteitis, and disseminated BCG disease in primary immunodeficiency (severe combined immunodeficiency, chronic granulomatous disease, defects of the IL-12/interferon-gamma axis). *Mechanism:* failure of macrophage-IFN-gamma-dependent control of live *Mycobacterium bovis* BCG. *Grade:* E.

- **G17. Yellow fever vaccine (17D strain).** *Diseases:* yellow-fever-vaccine-associated viscerotropic disease (on the order of 0.3 to 0.4 per 100,000 doses overall and several-fold higher at age 60 and older), neurotropic disease, anaphylaxis. *Mechanism:* uncontrolled vaccine-virus replication

associated with impaired innate (type I interferon) responses, immunosenescence, and thymic disease; rare host genetic variants have been described. *Grade:* E.

- **G18. Smallpox (vaccinia) vaccines.** *Diseases:* myopericarditis, eczema vaccinatum, progressive and generalized vaccinia, postvaccinal encephalitis, accidental inoculation. *Mechanism:* replication of live vaccinia with immune-mediated cardiac inflammation; uncontrolled spread in immunodeficiency or compromised skin barrier (atopic dermatitis). *Grade:* E.

G-IV. Inactivated, subunit, adjuvanted, and conjugate vaccines

- **G19. Inactivated and adjuvanted influenza vaccines: Guillain-Barre syndrome.** *Diseases:* Guillain-Barre syndrome, about 1 to 2 excess cases per million doses in some seasons (none in others; about 10 per million with the 1976 swine-flu vaccine); natural influenza infection raises Guillain-Barre risk more than vaccination does. *Mechanism:* not established. Molecular mimicry between microbial and nerve-ganglioside epitopes is proven for *Campylobacter jejuni* lipo-oligosaccharide (anti-GM1 antibodies) but is only hypothesized for influenza vaccine antigens (the draft stated it as fact). *Grade:* E (association, small); H (mechanism).

- **G20. Pandemrix (AS03-adjuvanted H1N1pdm09 vaccine): narcolepsy type 1.** *Diseases:* narcolepsy with cataplexy, on the order of 1 in 20,000 vaccinated children and adolescents in the most affected countries (Finland, Sweden), strongly dependent on HLA-DQB1*06:02. *Mechanism:* hypothesized autoimmune loss of hypocretin (orexin) neurons through cross-reactive T- and B-cell responses (proposed mimicry between influenza nucleoprotein and hypocretin receptor 2), amplified by the AS03 adjuvant and by wild H1N1 infection (also linked to narcolepsy in China). *Grade:* E (association); H (mechanism).

- **G21. Influenza vaccine: other reactions.** *Diseases:* anaphylaxis (rare; trace ovalbumin; egg allergy is not a contraindication), oculorespiratory syndrome, febrile seizures in young children (increased with co-administration of certain vaccines). *Mechanism:* IgE to excipients; innate-driven fever. *Grade:* E.

- **G22. Zoster vaccines.** *Diseases:* recombinant adjuvanted zoster vaccine (AS01B): marked reactogenicity (grade 3 systemic events in roughly 10% of recipients) and a small excess of Guillain-Barre syndrome (about 3 per million doses in Medicare analyses of adults aged 65 and older); live zoster vaccine (discontinued in the US in 2020): vaccine-strain VZV rash, meningitis, and pneumonitis in immunocompromised recipients. *Mechanism:* AS01B (MPL plus QS-21) produces strong innate activation and cytokine release; the Guillain-Barre mechanism is unknown; live vaccine strain replicates in impaired hosts. *Grade:* E (reactogenicity, live-vaccine disease); P (Guillain-Barre).

- **G23. RSV vaccines (older adults and pregnancy).** *Diseases:* Guillain-Barre syndrome after Arexvy and Abrysvo (about 7 and 9 excess cases per million doses, respectively, in a Medicare analysis of adults aged 65 and older, leading to a label warning in January 2025; the FDA concluded that evidence was insufficient to establish causation and that benefits continue to outweigh risks);

numerically more preterm births with maternal Abrysvo in trials, leading to restriction of use to 32 to 36 weeks of gestation. *Mechanism:* unknown for both. *Grade:* P (Guillain-Barre association); H (preterm birth and mechanisms).

- **G24. HPV vaccines.** *Diseases:* syncope (post-injection), rare anaphylaxis (about 1 to 2 per million doses). Large cohort studies and WHO, EMA, and CDC reviews found no causal association with POTS, complex regional pain syndrome, Guillain-Barre syndrome, multiple sclerosis, other autoimmune disease, or premature ovarian insufficiency. *Mechanism:* vasovagal reflex; IgE to excipients. *Grade:* E (syncope, anaphylaxis); C (POTS, CRPS, autoimmune and ovarian outcomes).

- **G25. Tetanus-, diphtheria-, and pertussis-containing vaccines.** *Diseases:* Arthus-type local reactions with frequent boosters, brachial neuritis (rare, about 1 per 100,000 doses or fewer; favored as causal by the Institute of Medicine), febrile seizures, hypotonic-hyporesponsive episodes and persistent crying (whole-cell pertussis). The claim that whole-cell pertussis causes permanent encephalopathy was not supported by case-control and cohort studies. *Mechanism:* Type III immune-complex reactions in the presence of high pre-existing antitoxin; fever and innate-immune activation. *Grade:* E (local and febrile reactions, brachial neuritis); C (permanent encephalopathy).

- **G26. Shoulder injury related to vaccine administration (SIRVA; any intramuscular vaccine).** *Diseases:* bursitis, tendinopathy, adhesive capsulitis with persistent shoulder pain and reduced motion. *Mechanism:* injection into the subacromial or subdeltoid bursa (too high or too deep) causes needle trauma and bursal deposition of antigen and adjuvant with local inflammation. *Grade:* E.

- **G27. Aluminum adjuvants and other inactivated or conjugate vaccines (hepatitis A and B, pneumococcal, meningococcal, Hib, typhoid, rabies, others).** *Diseases:* injection-site nodules and granulomas (persistent itching nodules in a few recipients), contact aluminum allergy, macrophagic myofasciitis (a histologic finding without an established clinical syndrome), fever (especially meningococcal B vaccines), rare anaphylaxis (hepatitis B about 1 per million doses). Large registry studies have not found associations between aluminum in childhood vaccines and autoimmune, allergic, or neurodevelopmental disorders; hepatitis B vaccine and multiple sclerosis have been repeatedly evaluated without support; "ASIA syndrome" remains a hypothesis. *Mechanism:* aluminum salts form an antigen depot and activate innate pathways (NLRP3 inflammasome and DAMP release) that enhance immunogenicity and cause local inflammation. *Grade:* E (local reactions); H to C (systemic disease).

G-V. Vaccine-associated enhanced disease and other special topics

- **G28. Vaccine-associated enhanced disease (Dengvaxia, formalin-inactivated RSV and measles vaccines).** *Diseases:* severe dengue in dengue-seronegative recipients of CYD-TDV (use restricted to seropositive persons); fatal enhanced RSV disease in infants after the 1960s formalin-inactivated vaccine; atypical measles after formalin-inactivated measles vaccine. *Mechanism:* sub-neutralizing antibodies promote antibody-dependent enhancement of infection through Fc-

gamma receptors (dengue); Th2-skewed responses with immune-complex deposition and complement activation and poorly neutralizing antibody (formalin-inactivated vaccines). *Grade:* E.

- **G29. Non-specific (heterologous) effects of vaccines.** *Diseases:* live vaccines (BCG, measles, OPV) were associated with lower non-targeted infectious mortality in some trials, while observational data suggested higher female mortality after DTP in Guinea-Bissau; a WHO advisory review judged the evidence to be of low quality and made no policy change. *Mechanism:* "trained immunity" through epigenetic and metabolic reprogramming of innate cells is proposed. *Grade:* H to C.

- **G30. Emerging, incompletely characterized post-vaccination syndromes (after COVID-19 vaccination).** *Diseases:* reports of persistent fatigue, orthostatic intolerance, tinnitus, and small-fiber neuropathy after vaccination; no validated case definition exists, studies are small and uncontrolled, and large cohorts do not show an overall increase in autoimmune disease, although small signals exist for specific conditions (e.g., immune thrombocytopenia, Guillain-Barre syndrome with Ad26.COV2.S). *Mechanism:* hypotheses include persistent antigen, autoantibody generation, and innate priming; none established. *Grade:* H.

G-VI. Mechanisms recurrent across vaccine adverse events

The vaccine events above arise through a limited number of mechanism families: (1) **immediate hypersensitivity** to excipients (IgE and complement-activation pseudoallergy); (2) **reactogenicity and fever** from innate activation (TLR, inflammasome, interferon, IL-1/IL-6/TNF), which causes febrile seizures and syncope-adjacent events; (3) **replication of live-attenuated agents** with reversion, neurovirulence, or uncontrolled spread in immunodeficient or very young or old hosts; (4) **molecular mimicry and bystander autoimmunity** in genetically susceptible hosts (for Guillain-Barre syndrome and narcolepsy; proven for some infections, hypothesized for vaccines); (5) **immune-complex and antibody-mediated platelet and endothelial activation** (anti-PF4 in VITT; ITP); (6) **antibody-dependent enhancement** and Th2-skewed immunity; (7) **adjuvant-driven innate inflammation**; (8) **administration-related injury** (SIRVA, syncope, nerve injury); and (9) **sex- and age-dependent immunoregulation** (male adolescents for myocarditis, older adults for viscerotropic yellow fever). These categories overlap with those in Section 3.14, which treats vaccines as one expression of general immunologic mechanisms.

3.10 Category H: Hospitalization-related and critical-care harm

The hospital environment and its protocols generate distinct, largely preventable pathologies through immobility, sleep and sensory disruption, fluid and nutrition management, life-support technology, and cascading interventions.

- **H1. Prolonged immobilization: pressure injury (PSI 03).** *Diseases:* pressure ulcers. *Mechanism:* sustained compression and shear exceeding capillary closing pressure (about 32 mmHg) cause ischemia, hypoxia, and reperfusion injury with irreversible necrosis, especially over bony prominences. *Grade:* E.

- **H2. Hospital-associated deconditioning and disability.** *Diseases:* loss of muscle mass and function, functional decline, loss of independence in older adults. *Mechanism:* disuse triggers anabolic resistance and ubiquitin-proteasome-mediated proteolysis with reduced mitochondrial capacity; inflammation and under-nutrition compound it. *Grade:* E.

- **H3. ICU-acquired weakness (critical illness polyneuropathy and myopathy).** *Diseases:* prolonged ventilator dependence, long-term disability. *Mechanism:* sepsis-related microvascular and bioenergetic failure, sodium-channel inactivation, selective myosin loss, hyperglycemia, and compounding by corticosteroids and neuromuscular blockers. *Grade:* E.

- **H4. Delirium in hospitalized older adults.** *Diseases:* delirium, falls, prolonged stay, long-term cognitive decline. *Mechanism:* multifactorial: neuroinflammation, cholinergic deficiency, sleep and circadian disruption, hypoxia, and deliriogenic drugs (anticholinergics, benzodiazepines, opioids) in a vulnerable brain. *Grade:* E.

- **H5. In-hospital falls and fractures (PSI 08).** *Diseases:* hip fracture, head injury. *Mechanism:* orthostatic hypotension and impaired postural control from hypotensive and sedative drugs, delirium, deconditioning, and unfamiliar environments. *Grade:* E.

- **H6. Hospital-associated venous thromboembolism.** *Diseases:* deep vein thrombosis, pulmonary embolism. *Mechanism:* stasis, inflammation-driven hypercoagulability, and vascular injury from lines (see C3). *Grade:* E.

- **H7. Sleep deprivation and circadian disruption.** *Diseases:* delirium, impaired glucose regulation, immune dysfunction. *Mechanism:* noise, light, and overnight vital signs and procedures reduce slow-wave and REM sleep and disturb cortisol and melatonin rhythms. *Grade:* P.

- **H8. Hospital-acquired anemia from phlebotomy.** *Diseases:* anemia, and in some patients transfusion exposure. *Mechanism:* cumulative diagnostic blood loss without proportional marrow compensation in inflamed patients. *Grade:* P.

- **H9. Under-nutrition and refeeding syndrome.** *Diseases:* malnutrition; with refeeding, hypophosphatemia, hypokalemia, hypomagnesemia, arrhythmia, heart failure, and Wernicke encephalopathy. *Mechanism:* carbohydrate refeeding raises insulin, driving intracellular shift of phosphate, potassium, and magnesium and increasing thiamine demand in depleted patients. *Grade:* E.

- **H10. Isotonic saline resuscitation (0.9% NaCl).** *Diseases:* hyperchloremic metabolic acidosis and, in large trials of critically ill adults, a modest excess of major adverse kidney events compared with balanced crystalloids. *Mechanism:* supraphysiologic chloride lowers the strong ion difference so the kidney excretes bicarbonate; chloride-induced renal afferent vasoconstriction (tubuloglomerular feedback) may reduce GFR. *Grade:* E (acidosis); P (kidney outcomes).

- **H11. Fluid overload and hypotonic maintenance fluids.** *Diseases:* pulmonary and tissue edema, abdominal compartment syndrome, AKI; hyponatremic encephalopathy in children given

hypotonic fluids. *Mechanism:* excess volume raises venous pressure and capillary hydrostatic pressure; non-osmotic ADH release in ill patients impairs free-water excretion so hypotonic fluids lower serum sodium and cause cerebral edema. *Grade:* E.

- **H12. Parenteral nutrition.** *Diseases:* hepatic steatosis, cholestasis, biliary sludge and gallstones (intestinal-failure-associated liver disease), catheter infection, metabolic bone disease. *Mechanism:* loss of enteral stimulation reduces cholecystokinin and bile flow; continuous carbohydrate loads and omega-6-rich lipid emulsions drive lipogenesis, phytosterol- and endotoxin-mediated hepatic inflammation; bacterial overgrowth. *Grade:* E.

- **H13. Mechanical ventilation.** *Diseases:* ventilator-induced lung injury (volutrauma, barotrauma, atelectrauma, biotrauma), ventilator-induced diaphragm dysfunction, pneumothorax. *Mechanism:* overdistension and cyclic opening and closing of alveoli cause mechanotransduction-driven release of cytokines into the circulation and distant organ injury; controlled diaphragm inactivity causes rapid atrophy; low-tidal-volume ventilation reduces mortality in ARDS. *Grade:* E.

- **H14. Oxygen toxicity and hyperoxia.** *Diseases:* absorption atelectasis, tracheobronchitis, lung injury; retinopathy of prematurity and bronchopulmonary dysplasia in preterm infants; higher mortality with liberal oxygen in meta-analyses of acutely ill adults. *Mechanism:* excess reactive oxygen species overwhelm antioxidant defenses in lung epithelium and the immature retinal vasculature. *Grade:* E (preterm infants); P (adults).

- **H15. Stress-ulcer prophylaxis in low-risk patients.** *Diseases: C. difficile* infection, hospital-acquired pneumonia. *Mechanism:* gastric acid suppression allows upper-GI colonization and aspiration of altered flora (see A44). *Grade:* P.

- **H16. Deep sedation in the ICU (benzodiazepines, propofol).** *Diseases:* delirium, prolonged ventilation and ICU stay, post-ICU cognitive impairment. *Mechanism:* GABAergic suppression of arousal and sleep architecture and accumulation of active metabolites. *Grade:* E to P.

- **H17. Inpatient dysglycemia.** *Diseases:* severe hypoglycemia with insulin; hyperglycemia-associated infection and poor healing; excess mortality with very tight glucose targets (NICE-SUGAR). *Mechanism:* see A39; hyperglycemia impairs neutrophil function. *Grade:* E.

- **H18. Physical restraints and tethering devices.** *Diseases:* injury, agitation, delirium, pressure injury, strangulation. *Mechanism:* physical stress, immobility, and sensory deprivation. *Grade:* E to P.

- **H19. Post-intensive-care and post-hospital syndromes.** *Diseases:* cognitive impairment, depression, post-traumatic stress, persistent weakness, and a period of generalized vulnerability to readmission. *Mechanism:* combined effects of critical-illness inflammation, delirium, sedation, deconditioning, sleep loss, and psychological trauma. *Grade:* P.

3.11 Category I: Diagnostic cascades, overdiagnosis, and psychological iatrogenesis

The draft's initial outline mentioned this category but did not develop it. These CFs act by multiplying exposure to other CFs or through expectation and stress biology.

- **I1. Overdiagnosis and overtreatment of indolent disease (thyroid cancer, prostate cancer, ductal carcinoma in situ, some screen-detected lung lesions).** *Diseases:* harms of treatment (hypoparathyroidism and nerve injury after thyroidectomy; incontinence and erectile dysfunction after prostatectomy; radiation and surgical complications) in patients who would never have developed symptoms. *Mechanism:* sensitive detection finds lesions with low or no progressive potential, converting biological variation into a patient; downstream harm arises through the procedural and radiation CFs in Categories C and E. *Grade:* E.

- **I2. Incidentalomas and diagnostic cascades.** *Diseases:* complications of successive tests, biopsies, and procedures prompted by incidental findings. *Mechanism:* each step adds radiation, contrast, procedural, and anxiety exposure with a probability of additional abnormal findings. *Grade:* E.

- **I3. False-positive screening results.** *Diseases:* anxiety, distress, biopsy complications. *Mechanism:* stress-axis activation and procedural risk. *Grade:* E.

- **I4. Invasive diagnostic procedures.** *Diseases:* bleeding, pneumothorax (a large fraction of CT-guided lung biopsies), infection, needle-tract tumor seeding (rare), angiography-related stroke, lumbar puncture headache. *Mechanism:* mechanical injury (see C13, C15). *Grade:* E.

- **I5. Low-value and inappropriate care (antibiotics for viral infection, opioids for self-limited pain, imaging for uncomplicated low back pain).** *Diseases:* downstream harms via the CFs in Categories A, B, and E. *Mechanism:* exposure without offsetting benefit. *Grade:* E.

- **I6. Nocebo effects and diagnostic labeling.** *Diseases:* symptom amplification (for example, muscle symptoms attributed to statins in blinded and unblinded comparisons), illness behavior and absenteeism after labeling with hypertension or "pre-disease." *Mechanism:* expectation-driven modulation of pain and symptom perception through cortico-limbic circuits and cholecystokinin-mediated anxiety-hyperalgesia pathways. *Grade:* E (nocebo); P (labeling).

- **I7. Medical trauma and ICU-related psychological injury.** *Diseases:* post-traumatic stress, depression, anxiety after critical illness, awareness under anesthesia, or traumatic procedures. *Mechanism:* fear conditioning, delirium-related memories, and dysregulation of the hypothalamic-pituitary-adrenal axis. *Grade:* E to P.

- **I8. Diagnostic error (missed, wrong, or delayed diagnosis).** *Diseases:* progression of untreated disease (for example, delayed sepsis, myocardial infarction, stroke, or cancer), harm from the wrong treatment. About 5% of US outpatient adults experience a diagnostic error annually. *Mechanism:* cognitive bias, system and communication failures; downstream disease follows the natural history of the untreated condition. *Grade:* E.

- **I9. Medicalization of normal variation.** *Diseases:* adverse effects of unnecessary pharmacotherapy (for example, acid suppression for normal infant regurgitation). *Mechanism:* exposure to drug CFs without a treatable disease. *Grade:* H to P.

3.12 Categories J and K: Systems and error CFs; product-quality and environmental CFs

Category J: Systems, error, and human-factors CFs

These CFs are upstream: they route patients to the same downstream mechanisms described in Categories A to F. Their mechanism is the toxicology or pathophysiology of the agent or event that the error delivers.

- **J1. Medication errors (wrong drug, dose, route, patient, or frequency).** *Diseases:* overdose toxicity from the specific agent (e.g., ten-fold dosing errors, daily instead of weekly methotrexate, intrathecal vincristine causing fatal ascending myeloencephalopathy, concentrated potassium causing cardiac arrest, insulin and opioid errors). *Mechanism:* see the corresponding A entries; look-alike and sound-alike names, ambiguous abbreviations, and high-alert drugs raise risk. *Grade:* E.

- **J2. Wrong-site or wrong-patient procedures and retained surgical items.** *Diseases:* unnecessary or missed surgery, infection, adhesions, fistula, foreign-body granuloma (gossypiboma). *Mechanism:* mechanical and foreign-body inflammatory responses (see C and D). *Grade:* E.

- **J3. Blood-product and specimen identification errors.** *Diseases:* ABO-incompatible transfusion (F3). *Mechanism:* complement-mediated hemolysis. *Grade:* E.

- **J4. Health-information-technology and electronic-record failures.** *Diseases:* wrong-patient orders, alert fatigue, copy-forward diagnostic errors. *Mechanism:* human-factors failures leading to any downstream CF. *Grade:* P.

- **J5. Handoff, communication, test-follow-up, staffing, and fatigue failures.** *Diseases:* delayed treatment and missed results. *Mechanism:* untreated disease progression. *Grade:* E to P.

- **J6. Failure to rescue (delayed recognition and treatment of deterioration; PSI 04).** *Diseases:* death among surgical inpatients with treatable complications (sepsis, hemorrhage, respiratory failure). *Mechanism:* progression of shock and multi-organ failure when rescue is late. *Grade:* E.

- **J7. Line and tubing misconnection and device misplacement.** *Diseases:* enteral feed or medication given intravenously, misplaced feeding tube with pneumonia or pneumothorax. *Mechanism:* mechanical and embolic/toxic effects of the misdirected substance. *Grade:* E.

Category K: Product-quality failures, contamination, and healthcare-environment exposures

- **K1. Contaminated compounded or sterile injectable products.** *Diseases:* fungal meningitis, spinal and paraspinal infection after contaminated epidural steroid injections in 2012 (more than 700 cases and about 60 deaths, predominantly *Exserohilum rostratum*). *Mechanism:* injection of

fungus-contaminated steroid into the epidural or paraspinal space seeds the meninges and bone. *Grade:* E.

- **K2. Heparin adulteration (2008).** *Diseases:* anaphylactoid reactions, hypotension, and deaths. *Mechanism:* oversulfated chondroitin sulfate contaminant activated the contact system (factor XII, kallikrein, bradykinin) and complement anaphylatoxins. *Grade:* E.

- **K3. Diethylene- and ethylene-glycol-contaminated medicines.** *Diseases:* acute kidney injury, neuropathy, and deaths, including hundreds of deaths in children in several countries (Elixir Sulfanilamide in 1937 and clusters in 2006 and 2022 to 2023). *Mechanism:* metabolism by alcohol and aldehyde dehydrogenases to toxic acids (2-hydroxyethoxyacetic and diglycolic acid) causes proximal tubular necrosis and neurotoxicity. *Grade:* E.

- **K4. Nitrosamine impurities (NDMA, NDEA) in drug products.** *Diseases:* theoretical increase in cancer risk after chronic exposure (valsartan, ranitidine, metformin recalls). *Mechanism:* CYP-mediated alpha-hydroxylation yields DNA-alkylating diazonium ions forming O6-alkylguanine adducts; epidemiologic studies have not shown clear excess cancer. *Grade:* H.

- **K5. Historically contaminated biologic products.** *Diseases:* hepatitis C and HIV in recipients of clotting concentrates, CJD from pituitary-derived growth hormone, SV40 contamination of early polio vaccine (no confirmed excess cancer). *Mechanism:* pooled donor material transmitting viruses or prions. *Grade:* E (HCV, HIV, CJD); C (cancer from SV40).

- **K6. Vaccine manufacturing and administration incidents.** *Diseases:* paralytic poliomyelitis from incompletely inactivated vaccine (Cutter incident, 1955: about 40,000 abortive cases, 164 with severe paralysis, 10 deaths); infant deaths from muscle relaxant mistaken for diluent (Syria 2014, Samoa 2018). *Mechanism:* residual live virus; neuromuscular blockade causing respiratory failure. *Grade:* E.

- **K7. Substandard and falsified medicines.** *Diseases:* treatment failure, toxicity, resistance selection. *Mechanism:* wrong or no active ingredient, toxic contaminants, sub-therapeutic exposure. *Grade:* E.

- **K8. Material hypersensitivity (latex, chlorhexidine, nickel, acrylates, adhesives).** *Diseases:* IgE-mediated anaphylaxis (latex proteins, chlorhexidine), allergic contact dermatitis. *Mechanism:* Type I and Type IV hypersensitivity to device and antiseptic components. *Grade:* E.

- **K9. Plasticizers and sterilant residues (DEHP, ethylene oxide).** *Diseases:* concerns for endocrine and reproductive effects after high exposure in neonates, transfused patients, and dialysis patients. *Mechanism:* leached phthalate metabolites (MEHP) act as anti-androgenic and PPAR-active agents; ethylene oxide is an alkylating carcinogen at high chronic exposure. *Grade:* H.

3.13 Category L: Developmental and reproductive iatrogenesis

- **L1. Thalidomide.** *Diseases:* limb reduction defects (phocomelia), ear and organ malformations after exposure in the critical window (about weeks 5 to 8 of gestation). *Mechanism:* cereblon-mediated degradation of SALL4 and p63 and antiangiogenic effects disrupt limb-bud development. *Grade:* E.

- **L2. Valproate in pregnancy.** *Diseases:* neural-tube defects, major congenital malformations (roughly 10%), lower cognitive scores, increased autism and ADHD risk. *Mechanism:* histone-deacetylase inhibition, folate-pathway disruption, and oxidative stress. *Grade:* E.

- **L3. Systemic retinoids.** *Diseases:* craniofacial, cardiac, and central-nervous-system malformations. *Mechanism:* retinoic-acid-receptor activation dysregulates Hox genes and neural-crest migration. *Grade:* E.

- **L4. ACE inhibitors and angiotensin-receptor blockers in the second and third trimester.** *Diseases:* oligohydramnios, pulmonary hypoplasia, renal tubular dysgenesis, neonatal AKI. *Mechanism:* fetal glomerular filtration depends on angiotensin II. *Grade:* E.

- **L5. Warfarin embryopathy.** *Diseases:* nasal hypoplasia and stippled epiphyses (exposure in weeks 6 to 12), CNS abnormalities. *Mechanism:* inhibition of vitamin K-dependent carboxylation of bone matrix proteins (osteocalcin, matrix Gla protein). *Grade:* E.

- **L6. Mycophenolate, methotrexate, misoprostol, topiramate, and other teratogens.** *Diseases:* congenital malformations and pregnancy loss (mycophenolate: ear, face, and cardiac defects; misoprostol: limb and cranial nerve defects; topiramate: oral clefts). *Mechanism:* IMPDH inhibition depletes guanine nucleotides; folate antagonism; uterine contraction with vascular disruption. *Grade:* E.

- **L7. Diethylstilbestrol (in utero exposure).** *Diseases:* clear-cell adenocarcinoma of the vagina and cervix, structural genital anomalies, infertility, preterm birth, and possible effects in subsequent generations. *Mechanism:* estrogen-receptor-mediated disruption of Mullerian-duct differentiation, with epigenetic alteration of developmental genes (e.g., HOXA10). *Grade:* E.

- **L8. Antenatal corticosteroids.** *Diseases:* neonatal hypoglycemia (late-preterm exposure), possible neurodevelopmental effects with repeated courses, despite clear benefit for lung maturation in imminent early preterm birth. *Mechanism:* glucocorticoid-receptor programming of fetal organs and metabolism. *Grade:* P to H.

- **L9. Assisted reproductive technology.** *Diseases:* ovarian hyperstimulation syndrome, multiple gestation with prematurity, ectopic pregnancy, and an association with rare imprinting disorders (Beckwith-Wiedemann and Angelman syndromes). *Mechanism:* hCG-induced VEGF-mediated vascular permeability; epigenetic vulnerability of embryos during culture. *Grade:* E (OHSS, multiples); P (imprinting disorders).

- **L10. Gonadotoxic therapy (alkylating chemotherapy, pelvic or testicular radiation).** *Diseases:* premature ovarian insufficiency, azoospermia, infertility. *Mechanism:* DNA-damage-induced

apoptosis and loss of primordial follicles (with follicle over-activation through PI3K-PTEN signaling) and spermatogonial depletion. *Grade:* E.

- **L11. Neonatal pharmacologic vulnerability.** *Diseases:* gasping syndrome (benzyl alcohol preservative), ceftriaxone-calcium precipitation, kernicterus after sulfonamides, gray baby syndrome (chloramphenicol), opioid toxicity after codeine in CYP2D6 ultra-rapid metabolizers. *Mechanism:* immature hepatic conjugation, low albumin binding, and a permeable blood-brain barrier. *Grade:* E.

3.14 Biological mechanisms common to categories of CFs

Across the 12 categories, iatrogenic disease arises through sixteen recurring mechanism families. Each is described below with its defining biology, the categories and representative CFs that use it, the diseases it produces, and its shared molecular nodes. A CF commonly engages more than one family (for example, radiation acts through M12, M14, and M10).

M1. Dose-dependent cytotoxicity and transporter-mediated organ accumulation. Drugs concentrate in tissues that express uptake transporters or have high perfusion and metabolic rate, producing organ-selective injury. *Examples:* cisplatin via OCT2 and CTR1 in proximal tubule and cochlea (A59); tenofovir via OAT1 (A14); aminoglycosides via megalin and hair-cell mechanotransduction channels (A4); methotrexate in rapidly dividing marrow and mucosa (A62); amiodarone and nitrofurantoin in lung (A34, A8). *Diseases:* acute tubular necrosis, ototoxicity, myelosuppression, mucositis, pulmonary toxicity. *Shared nodes:* transporter expression and genetics, intracellular drug accumulation, lysosomal phospholipidosis, mitochondrial permeability, apoptosis.

M2. Reactive metabolites, oxidative and nitrosative stress, and mitochondrial dysfunction. Bioactivation or redox cycling generates electrophiles and free radicals that deplete glutathione and damage mitochondria. *Examples:* acetaminophen-NAPQI (A16), anthracyclines (A57), bleomycin (A61), nitrofurantoin (A8), aminoglycosides (A4), linezolid and chloramphenicol (A9, A10), NRTIs via polymerase gamma (A14), valproate and propofol (A52, C8), local anesthetics (C12), statins (A37), metformin (A40), hyperoxia (H14). *Diseases:* liver failure, cardiomyopathy, pulmonary fibrosis, myopathy, lactic acidosis, neuropathy, ototoxicity. *Shared nodes:* glutathione depletion, JNK activation, mitochondrial permeability transition, impaired oxidative phosphorylation, mtDNA depletion, ferroptosis and necrosis.

M3. Excessive on-target (pharmacologic extension) effects. The intended action is expressed in excess, in the wrong tissue, or at the wrong time. *Examples:* anticoagulants and thrombolytics (A24 to A28), insulin and sulfonylureas (A39), antihypertensives and diuretics (A29 to A31), opioids and benzodiazepines (A22, A50), lithium, neuromuscular blockers, saline and fluids (H10, H11), immunosuppressants (A75 to A77). *Diseases:* hemorrhage, hypoglycemia, hypotension and falls, respiratory depression, electrolyte disorders, infections. *Shared nodes:* narrow therapeutic index; altered clearance; interactions; renal and hepatic function.

M4. Off-target receptor, enzyme, and ion-channel effects. Drugs bind unintended targets. *Examples:* hERG potassium-channel blockade (A6, A35, A36), D2 blockade in the nigrostriatum and pituitary (A46,

A56), 5-HT2C and H1 blockade (A47), muscarinic blockade (A51), COX-1 inhibition in gastric mucosa and platelets (A17), kinase off-targets (A67), MRGPRX2 mast-cell activation (A5, E5). *Diseases:* torsades de pointes, extrapyramidal syndromes, metabolic syndrome, delirium, ulcer, atrial fibrillation, pseudo-allergy. *Shared nodes:* receptor affinity profile, tissue distribution, genetic variants in targets and transporters.

M5. Immune hypersensitivity (Gell-Coombs Types I to IV) and pseudo-allergy. *Type I:* beta-lactams, vaccine excipients, contrast, latex (A1, G2, E5, K8). *Type II and autoantibody-mediated:* HIT, drug-induced hemolysis and thrombocytopenia, VITT (A25, A96, G4). *Type III:* serum sickness, Arthus reactions (G25). *Type IV:* SJS/TEN, DRESS, abacavir hypersensitivity, allopurinol and carbamazepine reactions, contact dermatitis (A2, A13, A53, A93, K8). *Pseudo-allergy:* complement activation (PEGylated nanoparticles, heparin contaminant, ABO transfusion) and MRGPRX2 (vancomycin, some opioids and neuromuscular blockers). *Shared nodes:* hapten and prohapten formation, HLA-restricted presentation (hapten, pharmacological-interaction, and altered-peptide-repertoire models), cytotoxic T cells, granulysin, FasL, perforin and granzyme B, mast-cell degranulation, complement C3a and C5a, FcgammaRIIa signaling.

M6. Loss of immune tolerance and autoimmunity. Therapy or antigen exposure disrupts peripheral tolerance or triggers cross-reactivity. *Examples:* checkpoint inhibitors (A68), lymphocyte depletion (A82), TNF and other biologics (A76, A81), drug-induced lupus (A81), putative molecular mimicry or bystander activation after some vaccines or infections (G1, G19, G20, G22, G23). *Diseases:* colitis, pneumonitis, myocarditis, endocrinopathies, lupus, vasculitis, Guillain-Barre syndrome, narcolepsy. *Shared nodes:* checkpoint and regulatory-T-cell dysregulation, shared tumor-tissue antigens, HLA risk alleles (e.g., HLA-DQB1*06:02), cytokines, autoantibody generation.

M7. Immunosuppression and barrier breach. Host defenses are suppressed or bypassed so that infection or malignancy follows. *Examples:* corticosteroids (A21), cytotoxic chemotherapy (A57 to A65), calcineurin, TNF, JAK, anti-CD20, and CAR-T therapies (A69, A74 to A77), transplant conditioning (F12 to F14); breach by catheters, tubes, incisions, and implants (B1 to B4, D3). *Diseases:* opportunistic and device-related infections, viral reactivation (hepatitis B, JC virus, EBV, zoster), post-transplant lymphoproliferative disease, skin cancer, lymphoma. *Shared nodes:* loss of T-cell and B-cell surveillance, neutropenia, loss of mucocutaneous barrier, biofilm.

M8. Microbiome disruption and loss of colonization resistance. Broad antimicrobial exposure removes protective commensals, enabling pathogen overgrowth, toxin production, and resistance selection. *Examples:* clindamycin, fluoroquinolones, cephalosporins (A7), PPIs (A44), early-life antibiotics (A15), NICU antibiotics (B15), prophylaxis and empiric overuse (I5). *Diseases: C. difficile* infection, candidiasis, MDR colonization and infection, and associated chronic diseases (atopy, obesity, IBD) in observational studies. *Shared nodes:* secondary bile-acid depletion, short-chain-fatty-acid loss, reduced regulatory-T-cell induction, horizontal gene transfer.

M9. Biofilm and foreign-body response. Abiotic surfaces acquire a host-protein conditioning film that supports biofilm and chronic macrophage-mediated reaction. *Examples:* catheters, tubes, shunts, mesh, implants, breast implants, prosthetic valves, pacemaker leads (B1 to B3, D1 to D10). *Diseases:* device-

associated infection, fibrosis and capsular contracture, osteolysis and loosening, device-associated lymphoma (rare), thrombosis. *Shared nodes:* extracellular polymeric matrix, quorum sensing, tolerance to antibiotics and phagocytes, macrophage and giant-cell activation, TGF-beta.

M10. Mechanical, thermal, ischemic, pressure, and barotrauma injury. *Examples:* operative trauma (C1), needle and catheter injury (C15), pressure injury (H1), ventilator injury (H13), nerve compression (C14), thermal and electrosurgical burns (C30), tourniquet and cuff ischemia (C29), fluoroscopic deterministic injury (E3). *Diseases:* hemorrhage, pneumothorax, peritonitis, necrosis, stricture, neuropraxia, acute lung injury. *Shared nodes:* ischemia-reperfusion injury, DAMP release, sterile inflammation, mechanotransduction (YAP/TAZ, integrin signaling), fibrosis.

M11. Hemostatic and thrombotic dysregulation. *Bleeding:* anticoagulants, antiplatelets, thrombolytics, NSAIDs, SSRIs, VEGF inhibitors (A17, A24 to A28, A49, A66). *Thrombosis:* heparin (HIT), VITT, estrogens, tamoxifen, IMiDs, JAK inhibitors, IVIG, procoagulant concentrates, catheters and filters, surgical inflammation, immobility (A25, A71, A72, A77, A83, A84, F10, C3, D9, H6). *Diseases:* hemorrhage, stroke, myocardial infarction, venous thromboembolism, microangiopathy. *Shared nodes:* platelet FcgammaRIIa activation, tissue-factor and contact activation, endothelial NO and prostacyclin balance, Virchow's triad, hepatic procoagulant synthesis.

M12. DNA damage, genomic instability, and mutagenesis. *Examples:* ionizing radiation (E1, E2), alkylating agents (A63), topoisomerase-II inhibitors (A64), thiopurines (A79), nitrosamines (K4), DES (L7), immunosuppression that removes viral and tumor surveillance (A75, F13), possible insertional mechanisms of cell therapies (A69). *Diseases:* therapy-related leukemia, solid tumors, bladder cancer, skin cancer, lymphoma, infertility, teratogenesis. *Shared nodes:* double-strand breaks, mismatch-repair failure, KMT2A and chromosome 5 or 7 lesions, p53-mediated apoptosis, latency of years to decades.

M13. Endocrine and metabolic axis disruption. *Examples:* glucocorticoid HPA suppression (A21, A89), insulin and secretagogues (A39), antipsychotic metabolic effects (A47), androgen deprivation and aromatase inhibition (A70, A71), hormone therapy (A83, A84), thyroid disruption by iodine, amiodarone, and lithium (A34, A48, E5), opioid-induced hypogonadism (A23), SGLT2 and GLP-1 effects (A42, A43). *Diseases:* Cushing syndrome, adrenal crisis, diabetes, metabolic syndrome, osteoporosis, thyroid dysfunction, hypogonadism. *Shared nodes:* nuclear-receptor signaling, negative-feedback suppression, insulin resistance, RANKL-driven bone resorption.

M14. Fibrosis and chronic tissue remodeling. *Examples:* bleomycin, amiodarone, nitrofurantoin, methotrexate lung injury (A61, A34, A8, A62), calcineurin inhibitor nephropathy (A75), radiation fibrosis (E1), gadolinium-related nephrogenic systemic fibrosis (E6), long-term methotrexate hepatic fibrosis, adhesions (C17), capsular contracture (D5). *Diseases:* pulmonary fibrosis, renal interstitial fibrosis, skin and soft-tissue fibrosis, cirrhosis, adhesions. *Shared nodes:* TGF-beta/SMAD and CTGF signaling, myofibroblast activation, Hippo/YAP mechanotransduction, impaired fibrinolysis (PAI-1), epithelial-mesenchymal transition, failed repair after repeated injury.

M15. Neuroadaptation, neurotransmitter dysregulation, and neuroinflammation. *Examples:* chronic dopamine blockade and tardive dyskinesia (A46, A56), opioid and benzodiazepine tolerance,

dependence, and withdrawal (A22, A50, A88), serotonin toxicity (A49), anticholinergic delirium (A51), postoperative and ICU delirium (C6, H4, H16), chemotherapy-induced neuropathy (A60), CAR-T neurotoxicity (A69). *Diseases:* dyskinesia, dependence, withdrawal seizures, delirium, neuropathy, encephalopathy. *Shared nodes:* receptor up- and down-regulation, desensitization and beta-arrestin signaling, glutamatergic excitation unmasked by withdrawal, microglial priming, blood-brain-barrier disruption, axonal transport failure.

M16. Developmental programming and teratogenesis. *Examples:* thalidomide and IMiDs (L1, A72), valproate (L2), retinoids (L3), RAAS inhibitors (L4), warfarin (L5), DES (L7), antenatal steroids (L8), ART (L9), neonatal pharmacologic vulnerability (L11). *Diseases:* malformations, neurodevelopmental impairment, genital tract cancer, imprinting disorders, neonatal organ injury. *Shared nodes:* critical windows, protein degradation (cereblon), epigenetic regulators (HDAC, DNA methylation), retinoic-acid and Hox signaling, immature drug clearance and BBB.

Cross-cutting amplifiers. Three factors interact with all sixteen families: **host genetic susceptibility** (Section 3.16); **pharmacokinetic vulnerability** (age, renal and hepatic function, interactions, A90 to A92); and **system and error failures** (Category J), which determine whether an exposure occurs at all. A fourth, **host immune state and comorbidity**, determines the severity of the final disease.

3.15 Biological mechanisms common to the diseases induced

Viewed from the disease end, many unrelated CFs converge on the same clinical conditions through a few pathways. Understanding these convergences explains why the same disease can be caused by drugs, procedures, and devices alike, and why one preventive or protective strategy can address several CFs.

Acute kidney injury. Routes: *hemodynamic* (NSAIDs, ACE inhibitors and ARBs, diuretics, calcineurin inhibitors, contrast, hypovolemia, intraoperative hypotension: A18, A29, A30, A75, E5, C4); *tubular toxic* (aminoglycosides, vancomycin, cisplatin, amphotericin, tenofovir, ifosfamide, contrast: A4, A5, A12, A14, A59, A63); *immune interstitial nephritis* (beta-lactams, PPIs, NSAIDs, checkpoint inhibitors: A1, A18, A44, A68); *obstructive casts or crystals* (vancomycin-uromodulin, methotrexate, tumor lysis); *thrombotic microangiopathy* (VEGF inhibitors, calcineurin inhibitors: A66, A75); *pigment nephropathy* (statin rhabdomyolysis, propofol infusion syndrome: A37, C8); *glycol toxicity* (K3). **Common pathway:** renal tubular ischemia and oxidative mitochondrial injury, tubular cell necrosis and apoptosis, inflammatory infiltration, and maladaptive repair with progression to fibrosis and CKD.

Drug-induced liver injury and hepatic steatosis. Routes: reactive metabolites (acetaminophen, isoniazid: A16, A11), mitochondrial beta-oxidation inhibition (valproate, NRTIs, aspirin in Reye syndrome: A52, A14, A20), immune-mediated idiosyncratic injury with HLA associations (amoxicillin-clavulanate, halothane: A1, C10), cholestasis from bile-salt-export inhibition, parenteral-nutrition-associated disease (H12), viral reactivation (A74, A76), and fibrosis (methotrexate). **Common pathway:** hepatocyte mitochondrial permeability transition and necrosis or apoptosis, adaptive immune amplification, and stellate-cell-driven fibrosis.

Pulmonary fibrosis, pneumonitis, and acute lung injury. Routes: lysosomal phospholipidosis and ROS (amiodarone), redox cycling (nitrofurantoin), iron-dependent DNA breaks in a lung lacking inactivating enzyme (bleomycin), immune pneumonitis (checkpoint inhibitors, mTOR inhibitors, methotrexate), radiation-induced TGF-beta signaling (E1), mechanical and cytokine injury (ventilation, TRALI: H13, F1), and oxygen toxicity (H14). **Common pathway:** alveolar epithelial injury, innate inflammation, TGF-beta- and Hippo/YAP-driven fibroblast activation, and collagen deposition.

Heart failure, cardiomyopathy, arrhythmia, and myocardial infarction. Routes: cardiomyocyte topoisomerase-II-beta and mitochondrial injury (anthracyclines), loss of HER2-mediated survival signaling (trastuzumab), immune myocarditis (checkpoint inhibitors, some vaccines, clozapine, smallpox vaccine), channel blockade (hERG, sodium channel), ion-pump poisoning (digoxin), prostacyclin-thromboxane imbalance (NSAIDs and coxibs), fluid and sodium retention (TZDs, NSAIDs), radiation-induced vasculopathy and fibrosis, iron and cobalt toxicity (F6, D1), and surgical supply-demand mismatch (C5). **Common pathway:** mitochondrial energetic failure and oxidative stress, innate or adaptive myocardial inflammation, and altered repolarization or calcium handling.

Thrombosis and bleeding. Routes are summarized in M11: platelet-activating antibodies (HIT, VITT), estrogenic and prothrombotic drugs, inflammatory and surgical hypercoagulability, device surfaces, and on the bleeding side direct factor inhibition, platelet inhibition, and impaired platelet function. **Common pathway:** disturbance of the balance among endothelial NO and prostacyclin, platelet activation, tissue-factor and contact-pathway coagulation, and fibrinolysis.

Infection (opportunistic, device-related, and healthcare-transmitted). Routes: barrier breach, immunosuppression, microbiome disruption, contaminated products or environments (M7 to M9, Categories B and K). **Common pathway:** failed host clearance at an interface where organisms form protected communities or exploit suppressed defenses.

Secondary malignancy (iatrogenic cancer). Routes: radiation (E1, E2, E4), alkylators and topoisomerase-II inhibitors (A63, A64), thiopurines and calcineurin inhibitors with viral co-factors (A79, A75, F13), hormones (menopausal therapy, tamoxifen, testosterone; A83, A71, A85), cell therapies (A69), in utero DES (L7), device-related lymphoma (D5), possible nitrosamine and photosensitizer effects (K4, A31). **Common pathway:** unrepaired or misrepaired DNA damage, loss of immune surveillance, or chronic proliferative or inflammatory stimulation, with latency from about one year (topoisomerase-II-related leukemia) to decades (radiation solid tumors).

Autoimmune and immune-mediated disease. Routes in M5 and M6. **Common pathway:** HLA-restricted antigen presentation of drug-modified or cross-reactive peptides, loss of regulatory control, cytotoxic T-cell or autoantibody effector responses.

Bone disease (osteoporosis, osteonecrosis, atypical fractures). Routes: glucocorticoids, androgen deprivation, aromatase inhibitors, PPIs, anticonvulsant enzyme induction, heparin, thyroid-hormone excess, bariatric malabsorption, bisphosphonates and denosumab (A21, A70, A71, A44, A53, A25, A45, C20, A86, A87). **Common pathway:** imbalance of osteoblast and osteoclast activity (RANKL-OPG axis), micro-damage accumulation, microvascular compromise, and calcium and vitamin D deficit.

Neurologic and psychiatric disease. Routes: dopamine-receptor blockade, serotonergic excess, GABAergic and opioid receptor adaptation, anticholinergic burden, axonal-transport and mitochondrial toxicity (neuropathy), neuroinflammation (delirium), and CNS immune-effector toxicity (A46, A49, A50, A22, A51, A60, C6, A69). **Common pathway:** disrupted neurotransmission and receptor adaptation, microglial priming with blood-brain-barrier dysfunction, and axonal energy failure.

Metabolic disease and dysglycemia. Routes: antipsychotics, corticosteroids, statins, TZDs, androgen deprivation, calcineurin and mTOR inhibitors, parenteral nutrition, insulin and secretagogues (A47, A21, A37, A41, A70, A75, A80, H12, A39). **Common pathway:** insulin resistance, impaired beta-cell function, and hypothalamic appetite dysregulation.

Cutaneous severe adverse reactions. Routes: HLA-restricted T-cell responses to sulfonamides, allopurinol, anticonvulsants, abacavir (the last causing a multi-organ syndrome, not SJS/TEN), nevirapine, and others (A2, A13, A53, A93). **Common pathway:** CD8-positive T-cell and NK-cell activation with granulysin-driven keratinocyte death, FasL and perforin-granzyme effects, and annexin A1-FPR1-mediated necroptosis.

Hematologic disease (cytopenias, hemolysis, aplasia). Routes: marrow suppression (chemotherapy, linezolid, chloramphenicol, methotrexate), immune cytopenias (heparin, MMR-associated ITP, drug-induced hemolysis), oxidant hemolysis (G6PD deficiency, A96), iron overload, alloimmunization. **Common pathway:** progenitor DNA-synthesis failure, antibody- or complement-mediated clearance, or oxidant injury to red cells.

Gastrointestinal disease. Routes: COX-1 inhibition, mucosal chemotherapy injury, microbiome disruption and *C. difficile*, opioid dysmotility, anticholinergic ileus, checkpoint colitis, ischemic and surgical injury. **Common pathway:** loss of mucosal protective and barrier functions with immune activation.

Musculoskeletal disease. Routes: statin, corticosteroid, and critical-illness myopathy; fluoroquinolone tendinopathy; disuse atrophy (A37, A21, H3, A3, H2). **Common pathway:** mitochondrial dysfunction, proteolysis, and matrix degradation.

Dependence, withdrawal, and psychiatric sequelae. Routes: A88 and A89 and Categories H and I. **Common pathway:** allostatic neuroadaptation of reward and stress circuits and receptor-level homeostatic adaptation unmasked by drug removal.

Final common pathways (synthesis). Across all diseases, eight cellular and molecular programs recur: (1) regulated cell death (apoptosis, necroptosis, ferroptosis, pyroptosis); (2) mitochondrial permeability transition and ROS; (3) innate inflammatory signaling (TLRs, NF-kappaB, NLRP3, IL-1-beta, IL-6, TNF); (4) TGF-beta/SMAD- and YAP-driven fibrosis; (5) endothelial activation and coagulation; (6) HLA-restricted T-cell activation or checkpoint release; (7) DNA-damage-response signaling (p53, mismatch repair); and (8) receptor adaptation and homeostatic rebound. Interventions that interrupt these shared nodes (for example, N-acetylcysteine for glutathione depletion, dexrazoxane for anthracycline cardiotoxicity, leucovorin for folate antagonism, mesna for acrolein, amifostine, balanced fluids, and pharmacogenomic avoidance) illustrate the preventive value of the mechanistic perspective.

3.16 Host and contextual susceptibility (cross-cutting dimension)

Pharmacogenomic and physiologic factors frequently determine whether an exposure causes disease. Established gene-drug pairs with clinical guidance include:

- **HLA-B*57:01 and abacavir** (hypersensitivity); **HLA-B*15:02 and carbamazepine or phenytoin** (SJS/TEN in many Asian populations); **HLA-A*31:01 and carbamazepine** (DRESS and other reactions in Europeans and Japanese); **HLA-B*58:01 and allopurinol** (severe cutaneous reactions); **HLA-B*13:01 and dapsone**; **HLA-B*57:01 and flucloxacillin** (liver injury); **HLA-DRB1*15:01 and amoxicillin-clavulanate** (liver injury); **HLA-DQB1*06:02 and Pandemrix-associated narcolepsy**.

- **CYP2C9 and VKORC1** (warfarin dose and bleeding); **SLCO1B1*5** (simvastatin myopathy); **CYP2D6 ultrarapid metabolism** (codeine and tramadol toxicity in children and nursing infants); **CYP2C19** (clopidogrel failure; PPI and voriconazole exposure).

- **TPMT and NUDT15** (thiopurine myelosuppression); **DPYD** (fluoropyrimidine toxicity); **UGT1A1*28** (irinotecan neutropenia and diarrhea); **G6PD deficiency** (hemolysis with primaquine, dapsone, rasburicase, nitrofurantoin).

- **RYR1 and CACNA1S** (malignant hyperthermia); **BCHE variants** (prolonged succinylcholine block); **POLG variants** (valproate hepatotoxicity); **mitochondrial m.1555A>G** (aminoglycoside deafness); **NAT2 slow acetylation** (isoniazid and hydralazine toxicity); **factor V Leiden and prothrombin variants** (thrombosis with estrogens and tamoxifen); **inborn errors of immunity** (disseminated BCG, live-vaccine strain disease, rotavirus persistence in SCID).

Non-genetic modifiers include **age** (neonates: immature clearance; older adults: reduced renal and hepatic function, polypharmacy, frailty), **sex** (women experience more ADRs overall; males are overrepresented in mRNA-vaccine myocarditis), **renal and hepatic function**, **comorbidity** (cirrhosis, heart failure, diabetes, immunodeficiency), **pregnancy**, **concomitant drugs**, **nutritional state**, **alcohol use**, and **ancestry-linked allele frequencies**. These modifiers explain why population-level incidence is a poor guide to individual risk and why stratified prevention (genotyping, dose adjustment, avoidance in high-risk groups) is effective.

3.17 Temporal patterns and latency

Iatrogenic diseases appear over characteristic timescales, which assists causal inference and surveillance design. **Immediate (minutes to hours):** anaphylaxis, infusion reactions, local anesthetic toxicity, transfusion reactions, malignant hyperthermia, TRALI. **Early (days to weeks):** HIT (5 to 10 days), SJS/TEN and DRESS (generally 1 to 8 weeks), serum sickness, VITT (4 to 42 days), vaccine febrile seizures (5 to 12 days), myocarditis after mRNA vaccination (typically within a week), antibiotic-associated *C. difficile* (during or within weeks after exposure), acute kidney injury. **Subacute to chronic (weeks to years):** corticosteroid effects, drug-induced lupus, hepatic and pulmonary fibrosis, tardive dyskinesia, metabolic syndrome, osteonecrosis, CKD, device failure and wear, radiation fibrosis. **Latent (years to decades):**

therapy-related leukemia (1 to 10 years), radiation-induced solid tumors (5 to more than 30 years), prion disease (5 to 40 years), DES-related cancer (decades), and developmental effects. **After cessation:** withdrawal and rebound syndromes, adrenal crisis, rebound fractures after denosumab discontinuation.

3.18 Evidence quality, causal inference, and benefit-risk context

Distribution of evidence grades. Of the CFs catalogued, the great majority in Categories A through F, H, J, and L are graded E on both causation and mechanism. The lower grades (P, H, C) cluster in four areas: (1) long-latency or population-level associations that are confounded (early-life antibiotics, PPIs and CKD or fractures, anticholinergics and dementia, cesarean delivery and offspring disease); (2) rare events detected only by pharmacovigilance where the mechanism is unknown (several vaccine and GLP-1 signals); (3) physical or chemical exposures with weak human evidence (plasticizers, nitrosamines, gadolinium retention); and (4) claims examined and not supported (MMR and autism, thimerosal, HPV vaccine and POTS, aluminum adjuvants and chronic disease).

Common interpretive errors addressed in this report. (a) Treating a plausible mechanism as evidence of causation (e.g., spike-protein TLR4 signaling in myocarditis; influenza vaccine ganglioside mimicry). (b) Reading spontaneous-report counts as incidence. (c) Quoting extrapolated mortality estimates as measured counts. (d) Ignoring the base rate of the disease in the exposed population. (e) Ignoring confounding by indication. (f) Presenting relative risk without absolute risk.

Benefit-risk. For nearly every CF, the intervention's benefit exceeds its expected harm in properly selected patients. Examples include anticoagulation for atrial fibrillation (bleeding risk is far lower than stroke risk prevented in high-risk patients), anthracyclines in curable cancers (cardiotoxicity risk accepted for survival gains and mitigated with dexrazoxane and monitoring), central lines in critical illness, and vaccination (serious vaccine events are orders of magnitude rarer than the diseases prevented). The appropriate response to a CF is therefore selection, monitoring, dose and duration optimization, and prevention, not avoidance of effective care. Conversely, CFs arising from low-value care (Category I), errors (Category J), and quality failures (Category K) have little or no offsetting benefit and are the most clearly preventable.

3.19 Prevention and mitigation framework

Mechanistic understanding translates directly into prevention strategies, organized here by the level at which they act.

- **Eliminate the exposure.** Avoid low-value care (Category I); de-prescribe and reduce polypharmacy and anticholinergic and sedative burden (A50, A51, A90); remove unnecessary catheters and lines daily (B1, B2); use non-ionizing alternatives and justification and optimization for imaging (E2); avoid unnecessary opioid prescribing and limit duration (A88).
- **Screen the host.** Pharmacogenomic testing before abacavir (HLA-B*57:01), carbamazepine in at-risk ancestries (HLA-B*15:02), allopurinol in high-risk ancestries (HLA-B*58:01), thiopurines (TPMT, NUDT15), fluoropyrimidines (DPYD), and rasburicase or dapsone (G6PD); screening for

latent tuberculosis and hepatitis B before TNF inhibitors, JAK inhibitors, and anti-CD20 therapy; immunodeficiency screening before live vaccines where indicated; renal and hepatic dose adjustment (A92).

- **Interrupt the mechanism.** N-acetylcysteine for acetaminophen (A16); dexrazoxane with anthracyclines (A57); leucovorin and hydration with methotrexate (A62); mesna with oxazaphosphorines (A63); uridine triacetate for fluoropyrimidine toxicity (A65); balanced crystalloids (H10); lung-protective ventilation (H13); mechanical and pharmacologic thromboprophylaxis (C3, H6); stress-ulcer prophylaxis only in high-risk patients (H15); pre-treatment and protective monitoring for ototoxins (A4, A59).

- **Prevent infection.** Insertion and maintenance bundles for central lines, urinary catheters, and ventilators; surgical-site bundles (appropriate prophylaxis timing, normothermia, glycemic control); antimicrobial stewardship; environmental cleaning with sporicidal agents; water-system management; rigorous endoscope reprocessing; safe-injection practices (Category B).

- **Design safer products and procedures.** Safer device materials and designs (D1 to D12); compounding quality oversight (K1); adjuvant and vector design informed by signals such as VITT and myocarditis (G1, G4); alternative dosing intervals for mRNA vaccines in young males (G1); restriction of products to appropriate populations (e.g., Dengvaxia to seropositive persons; G28).

- **Strengthen systems.** Medication-safety technology and independent double checks for high-alert drugs; wrong-site and retained-item protocols; handoff standards; rapid-response and early-warning systems (J1 to J7); early mobility, sleep protection, and delirium prevention bundles (H2, H4, H7); transparent surveillance and active pharmacovigilance with rapid signal evaluation.

- **Communicate absolute risk.** Shared decision-making that presents absolute risks and benefits for each CF reduces nocebo effects and supports informed choice (I6).

3.20 Reconciliation with the draft: corrections, hedges, and mapping

Corrections and calibration changes.

1. **Abacavir (draft CF 1).** Abacavir hypersensitivity is a multi-organ HLA-B*57:01-restricted syndrome, not SJS/TEN. The draft's discussion of SJS/TEN mechanisms is accurate for carbamazepine, allopurinol, sulfonamides, and others, but abacavir should be listed separately (A13).

2. **"Elimination" of abacavir hypersensitivity (draft conclusion).** Prospective HLA-B*57:01 screening nearly eliminated immunologically confirmed reactions in screened populations; it did not abolish all hypersensitivity-like illness.

3. **Mortality estimates (draft introduction).** The figure of up to 400,000 annual deaths is an extrapolation of premature deaths associated with preventable harm. A 2020 meta-analysis of

direct death reviews estimated about 22,000 preventable inpatient deaths per year. The statement that inpatient deaths account for about 32% of US deaths describes where people die, not iatrogenic attribution, and should not be used as a harm estimate.

4. **ADE burden.** CDC estimates of about 1.3 million emergency visits and about 350,000 hospitalizations per year should replace the unsourced "more than 1.5 million" figure, which should be verified before reuse.

5. **Vaccine myocarditis (draft CF 45).** The 12.6 per million figure applies to second doses in persons aged 12 to 39 (and is much higher in young males). The mechanisms (spike-protein TLR4 activation of cardiomyocytes and molecular mimicry with alpha-myosin heavy chain) are hypotheses, not established mechanisms; evidence also supports innate cytokine activation and circulating free spike antigen. The conclusion's statement that mimicry between vaccine-derived spike protein and cardiac myosin was "evidenced" should be softened.

6. **Guillain-Barre syndrome after influenza vaccine (draft CF 48).** Ganglioside mimicry is proven for *Campylobacter jejuni*, not for influenza hemagglutinin; the absolute excess is about 1 to 2 per million doses, and influenza infection itself carries a higher risk.

7. **VITT (draft CF 46).** The anti-PF4 mechanism is well supported, but the trigger for antibody formation remains incompletely understood; the draft's phrase "high mortality if unrecognized" is appropriate for early cases but the case-fatality has fallen with recognition and treatment.

8. **Statins (draft CF 17).** Severe myopathy and rhabdomyolysis are rare; most muscle pain in blinded trials is not drug-attributable.

9. **Iodinated contrast (draft CF 41).** Risk is concentrated in patients with reduced GFR and intra-arterial exposure; modern low- and iso-osmolar agents given intravenously carry less risk than historically assumed.

10. **SSRIs and serotonin syndrome (draft CF 28).** Serotonin syndrome from SSRIs alone is uncommon; most cases involve combinations with other serotonergic agents or overdose.

11. **Counting convention.** The draft's 53 "CFs" included repeated entries for one agent with different organ effects (NSAIDs, opioids, transfusion). This report counts by exposure and lists multiple diseases within each entry.

12. **Structure.** The draft lacked the vaccine breadth, a mechanism synthesis across categories and diseases, an evidence-grading system, and a conclusions section tied to results; these are supplied here.

Mapping of draft CFs to this report. CF 1 to A13; CF 2 to A53; CF 3 to A5; CF 4 to A34; CF 5 to A39; CF 6 to A24; CF 7 to A25; CF 8 to A26; CF 9 to A1; CF 10 to A3; CF 11 to A4; CF 12 to A7; CF 13 to A21; CF 14 and 15 to A17 and A18; CF 16 to A29; CF 17 to A37; CF 18 to A30; CF 19 to A57; CF 20 to A59; CF 21 to A61; CF 22 to A62; CF 23 to A68; CF 24 to A75; CF 25 and 26 to A46 and A47; CF 27 to A48; CF 28 to A49;

CF 29 to A86; CF 30 and 31 to A22 and A23; CF 32 to A33; CF 33 to B1; CF 34 to B2; CF 35 to B3; CF 36 to B4; CF 37 to B7 (and A7); CF 38 to C15; CF 39 to C3; CF 40 to C1; CF 41 to E5; CF 42 to E1; CF 43 and 44 to F1 and F2; CF 45 to G1; CF 46 to G4; CF 47 to G6; CF 48 to G19; CF 49 to H1; CF 50 to A90; CF 51 to H10; CF 52 to H13; CF 53 to H12.

3.21 Research gaps and priorities

1. **Mechanism of rare vaccine-associated events** (myocarditis, narcolepsy, Guillain-Barre syndrome after specific vaccines, persistent post-vaccination symptoms) using prospective biobanked cohorts, immune profiling, and HLA typing.
2. **Pharmacogenomic expansion**: population-specific allele frequencies, polygenic risk, and implementation research for HLA and metabolic variants beyond those already guideline-supported.
3. **Reconciling mortality and harm estimates** with standardized definitions of preventability and attributable fraction.
4. **Long-latency and confounded associations** (early-life antibiotics, PPIs, anticholinergics, cesarean delivery) using sibling, negative-control, and Mendelian-randomization designs.
5. **Low-dose radiation risk** and cumulative imaging exposure registries.
6. **Device surveillance** with unique device identification and longitudinal registries for implants and mesh.
7. **Synergistic exposures** (drug-drug-gene interactions, polypharmacy cascades) using large linked electronic health data.
8. **Evaluation of mitigations** (dosing intervals, adjuvant modification, cardioprotection, microbiome restoration) in randomized and pragmatic trials.
9. **Diagnostic error and system-level CFs**, which have large burden but limited mechanistic and interventional research.

SUMMARY AND CONCLUSIONS

Spectrum. Iatrogenic disease arises from a far wider set of exposures than adverse drug reactions. This report organizes more than 250 specific contributing factors (262 numbered entries) into twelve categories: pharmacologic agents (96), healthcare-associated infections and antimicrobial resistance (16), procedural and anesthetic harm (31), implanted devices and materials (12), radiation and imaging agents (7), blood products, transplantation, and biologic transfer (15), vaccines (30), hospitalization-related and critical-care harm (19), diagnostic cascades and psychological iatrogenesis (9), systems and error factors (7), product-quality and environmental factors (9), and developmental and reproductive iatrogenesis (11). Host genetic susceptibility, dependence and withdrawal, and iatrogenic cancer cut

across these categories. Relative to the draft, five categories were expanded or retained and seven were added.

Diseases. The diseases linked to these CFs span nearly every organ system, with the greatest cumulative burden from adverse drug events, healthcare-associated infections, venous thromboembolism, acute kidney injury, delirium and functional decline, procedural complications, secondary cancers, and dependence. Many carry high individual severity (SJS/TEN, HIT, VITT, acute liver failure, therapy-related leukemia, prion disease) but low incidence, while others are less severe but common (constipation, hypokalemia, injection-site reactions).

Mechanisms. Sixteen mechanism families (dose-dependent cytotoxicity; reactive-metabolite and mitochondrial injury; excess on-target pharmacology; off-target effects; immune hypersensitivity; loss of tolerance; immunosuppression and barrier breach; microbiome disruption; biofilm and foreign-body response; mechanical and ischemic injury; hemostatic dysregulation; DNA damage; endocrine and metabolic disruption; fibrosis; neuroadaptation and neuroinflammation; developmental programming) account for the CF-to-disease links. Eight final common pathways (regulated cell death, mitochondrial ROS, innate inflammation, TGF-beta- and YAP-driven fibrosis, endothelial-coagulation activation, HLA-restricted T-cell or checkpoint-driven immunity, DNA-damage signaling, and receptor adaptation) unify the downstream diseases. This explains why seemingly unrelated CFs converge on the same diseases (acute kidney injury, pulmonary fibrosis, cardiomyopathy) and why single mechanistic interventions can protect against many CFs.

Vaccines. The evidence supports a small number of established, rare, serious adverse events (mRNA-vaccine myocarditis in young males, VITT after adenoviral-vector vaccines, anaphylaxis, febrile seizures and immune thrombocytopenia after measles-containing vaccines, intussusception after rotavirus vaccines, vaccine-strain disease in immunodeficient hosts, and small Guillain-Barre syndrome excesses with certain influenza, zoster, adenoviral-vector, and RSV vaccines) and refutes others after extensive study (MMR and autism, thimerosal and neurodevelopmental disorders, HPV vaccine and POTS). Mechanisms for several established associations remain hypotheses. Absolute risks are small relative to the diseases prevented, and continued active surveillance and mechanistic research are warranted.

Implications. (1) Report frequencies as absolute risks with evidence grades, not as undifferentiated lists. (2) Target prevention at the nodes shared across CFs: pharmacogenomic screening, glutathione and folate rescue, thromboprophylaxis, infection bundles, lung-protective ventilation, balanced fluids, deprescribing, and device and product quality control. (3) Treat the system and low-value-care CFs, which offer no offsetting benefit, as the highest-priority targets. (4) Preserve benefit-risk perspective: iatrogenic harm is largely the cost of effective medicine and is best reduced through precision, stewardship, and safer design.

Limitations. This is a narrative synthesis, not a systematic review. Figures are approximate and drawn from the literature as understood at the time of writing, with several headline numbers cross-checked against CDC, FDA, and peer-reviewed meta-analyses. Spontaneous-report data cannot establish incidence or causation. Several categories (e.g., diagnostic error, device materials) have limited

quantitative data. Recent regulatory actions and newer products should be verified against current labeling before publication.

ABBREVIATIONS AND KEY SOURCES

Abbreviations. ADE, adverse drug event; ADR, adverse drug reaction; AHRQ, Agency for Healthcare Research and Quality; AKI, acute kidney injury; CF, contributing factor; CLABSI, central-line-associated bloodstream infection; CAUTI, catheter-associated urinary tract infection; DRESS, drug reaction with eosinophilia and systemic symptoms; HAI, healthcare-associated infection; HIT, heparin-induced thrombocytopenia; ICANS, immune effector cell-associated neurotoxicity syndrome; ITP, immune thrombocytopenia; PSI, Patient Safety Indicator; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; SSI, surgical site infection; VITT, vaccine-induced immune thrombotic thrombocytopenia.

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