7

Metagenomics from bench to bedside and from bedside to bench

7.1 Metagenomics for decision-making in diagnosis and treatment

7.1.1 Metagenomics for disease screening

As we can reasonably believe based on the previous chapters, the human microbiome at various body sites could contribute to and respond to the shifting trends of human diseases in the last few decades (Fig. 7.1). When trying to improve living conditions, nutrition, and hygiene practices in an underdeveloped region, it would also probably be better to beware of the changes to expect in the human microbiome and disease prevalence.

While scientists are always excited about new technologies, in order for metagenomic sequencing to be routinely used in hospitals, it will be important to have a clear view of what is really needed for the disease in question (Table 7.1). For a patient with liver disease that is about to enter a coma? For a child with leukemia that is about to receive a bone marrow transplant? Adult data show that a very low-diversity fecal microbiome before and during the transplant could cost one's life [1–3]; Similar evidence is also emerging for pediatric patients, including fecal, oral, and nasal microbiome before and after the bone marrow transplant [4,5].

With vaccination against Hepatitis B Virus (HBV), reduced exposure to aflatoxin, and medication to treat Hepatitis C Virus (HCV), the trend for liver diseases has shifted. Nonalcoholic fatty liver disease (NAFLD), following the global increase in obesity, is by far the most prevalent liver disease on the way to acute hospitalizations or hepatocellular carcinoma (HCC) [6]. NAFLD includes a spectrum of conditions from hepatic steatosis (fatty liver), nonalcoholic steatohepatitis (NASH), and cirrhosis. Fatty liver is quite common from ultrasound examinations, and levels of liver enzymes such as ALT (alanine aminotransferase) and GGT (γ-glutamyl transpeptidase) can also be high

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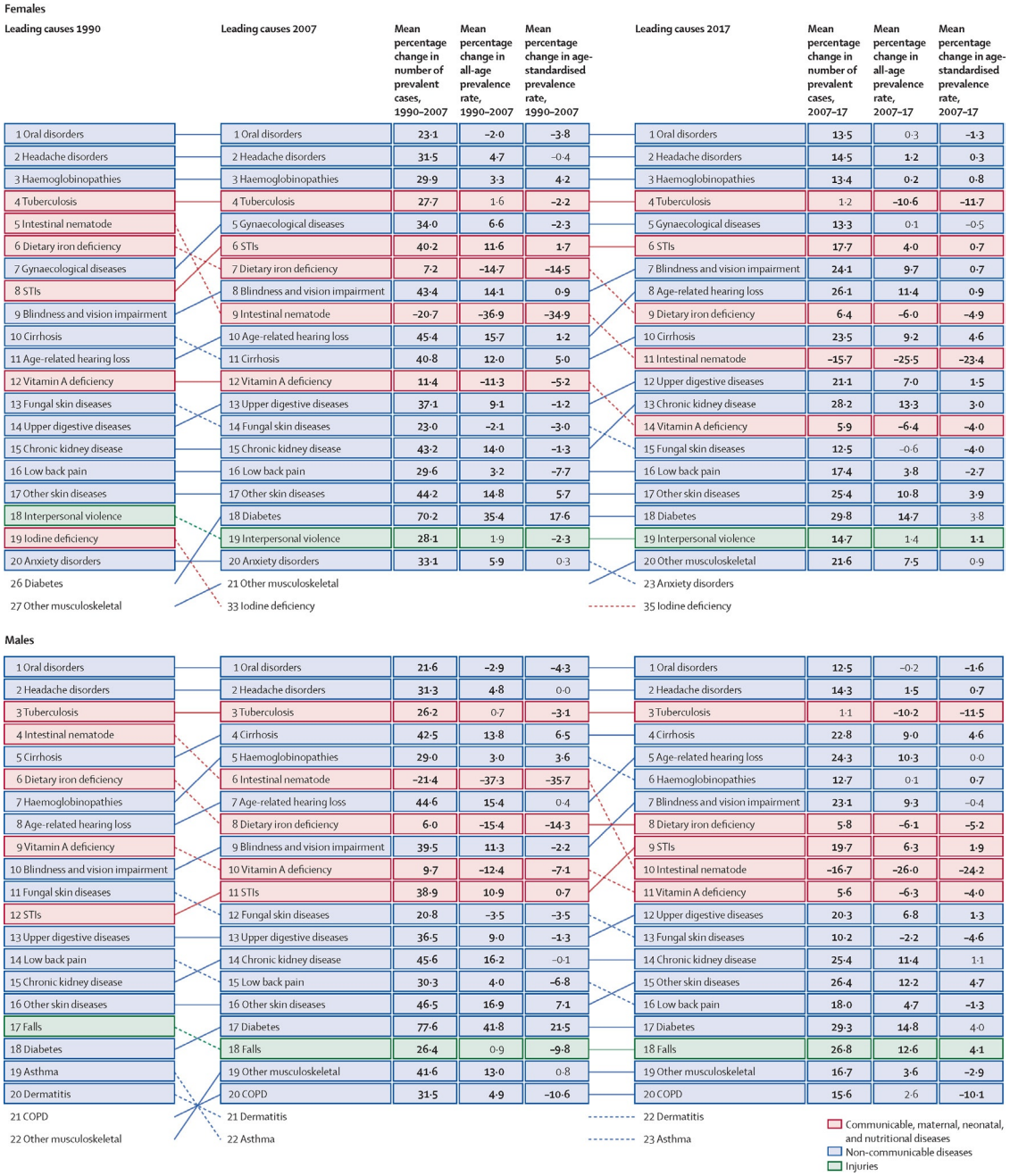


Fig. 7.1 Leading 20 Level 3 causes of global prevalence for 1990, 2007, and 2017, with the percentage change in number of cases and all-age and age-standardized rates for each sex. Level 1 contains three broad cause groups: communicable, maternal, neonatal, and nutritional diseases; noncommunicable diseases; and injuries. For nonfatal health estimates, there are 22 Level 2 causes, 167 Level 3 causes, and 288 Level 4 causes. Causes are connected by lines between time periods; solid lines are increases and dashed lines are decreases. For the time periods 1990–2007 and 2007–17, three measures of change are shown: percentage change in the number of cases, the percentage change in the all-age prevalence rate, and percentage change in the age-standardized prevalence rate. Communicable, maternal, neonatal, and nutritional diseases are shown in *red*; noncommunicable causes in *blue*; and injuries in *green*. Statistically significant changes are shown in bold. *COPD*, chronic obstructive pulmonary disease; *STIs*, sexually transmitted infections. Credit: Fig. 7 of GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789–858. https://doi.org/10.1016/S0140-6736(18)32279-7.

Table 7.1 Considering microbiome tests for clinical practice.

Considerations	Available technology
How soon would the results be needed?	
How sensitive and how accurate do the results need to be?	
Do we need another technology to work in combination?	
What is the current gold-standard practice that could still follow the microbiome test (to further decrease false negatives, and to confirm the positive diagnosis)?	Or a panel of experts
How much would the test cost, and who is paying?	

Please go through above questions and answers for the particular situation you would like to help improve.
Credit: Huijue Jia.

from routine health examinations [7]. The fecal and oral microbiome might help predict who is more likely to progress into liver cirrhosis, and from cirrhosis to carcinoma. Sex differences in the levels of secondary bile acids processed from the gut microbiome offer an explanation for the higher incidence of liver carcinoma in men [8]. Ethanol production by some *Klebsiella pneumoniae* strains in NAFLD is one of the possible mechanisms for NAFLD [9]. The microbiome may be no less important in acute events. Acetaminophen, commonly used for pains and colds, is a leading cause of acute liver failure and causes a more severe liver injury at night. Gut microbial metabolites such as 1-phenyl-1,2-propanedione have been found in a mice study to explain such diurnal difference in acetaminophen toxicity, through depletion of liver glutathione [10].

Colonoscopy is now common practice in many developed countries. Metagenomic shotgun sequencing, or qPCR for just a few bacteria, could be a more convenient and robust technology than FOBT (fecal occult blood test) and qPCR for methylation of host genes. The incentive for governments would be to save costs on unnecessary colonoscopy. The incentive for individuals would be no fear of microbiome disturbance due to bowel cleansing, and in the case of metagenomic sequencing, to potentially know ones' risks for other diseases and options for treatment (more in Chapter 8). For lung cancer, sending in sputum samples for metagenomics [11] may help reduce the waiting line for high-resolution computed tomography (CT) scans and might work in combination with cell-free DNA (cfDNA) (Box 7.1) to improve the utility of both technologies in screening for new patients and in watching out for relapses. Oral microbiome biomarkers have also been reported for diseases such as pancreatic cancer

[12–14], awaiting further validation. Fecal *Achromobacter* appeared to promote biliary tract cancer, according to results from Mendelian Randomization (MR, Chapter 6, Box 6.2) [15]. More generally, the microbiome is probably a key factor in the different disease incidences in different populations around the world (Chapter 8, Fig. 8.1).

For cardiovascular diseases (Chapter 4) and mental disorders, oral or fecal metagenomic samples could be sent from patients' home on a regular basis, to capture early signs of a relapse. This may also be a valid approach for detecting early signs of relapse in cancer patients. For body fluid samples with a high proportion of human sequences, cell-free DNA or RNA would also be an option to detect pathogens (Box. 7.1) [16,17], although losing intracellular and adherent microbes.

For diagnostic purposes, one has to be aware of the false positives and false negatives of the method as well as the model (Table 7.1). Life-threatening diseases require diagnosis as early as possible, so the cutoff is typically not at the largest area under the curve (AUC), but tends to minimize false negatives (e.g., can 1 miss in 10,000 people be tolerated?). Insurance can be combined with the test to prepare for rare incidences. False positives could be checked with another existing method, yet one also needs to estimate the number of such further tests for the cutoff value used. Trying a multicancer blood

Box 7.1 Cell-free DNA or RNA in human body fluids

Prenatal diagnosis of diseases using cell-free DNA (cfDNA) from pregnant mothers has safeguarded childbirth in many countries. Screening for tumors and predicting recurrence, using cfDNA or cell-free RNA (cfRNA) from plasma samples, is also proceeding into clinics [18–20]. Although the coverage is typically low, and the data may be intrinsically fragmental [21], nonhuman reads in such plasma cfDNA or cfRNA could map to viruses, bacteria, and fungi. For all these microbes, rapid sequencing and bioinformatic analyses could allow the doctor to know the taxa that are enriched in the patient, along with drug resistance genes, virulence, and lineage according to the metagenomically derived microbial genomes (Chapter 5), before trying for a few days to culture all the possible microbes. The pathogen database and the population baseline for such efforts are by no means perfect at this early stage of application.

cfDNA in umbilical cord blood identified bacteria that enriched in cases of suspected chorioamnionitis (infection of the membranes that surround the fetus and the amniotic fluid) compared to healthy controls [22]. For invasive fungi infections, e.g., during chronic immune suppression after organ transplant, fungi identified by plasma cfDNA have shown good agreement with plate culture experiments or targeted sequencing results in 7 out of 9 patients and could relieve the need for tissue biopsy [23]. The strength of metagenomics lies more in unbiased detection of microbes, even in culture-negative or (targeted) PCR-negative samples (Chapter 1, Fig. 1.2) [16,17], and would be the first test to see a shifting trend in pathogens for the same apparent symptoms.

test (human cfDNA and protein markers) in 10,006 women between 65 and 75 years old in the United States led to the detection of 26 cancer cases, followed by PET-CT (positron emission tomography-computed tomography) imaging, while conventional methods detected another 24 cases [18]. Actually, individuals who tested positive but do not yet have clinical symptoms should still be followed in subsequent years. So the tests are not necessarily false but reflect individual differences in the time course and severity of clinical manifestation. Ethically and economically, each population-wide screen should be carefully designed to minimize unnecessary anxiety and costs. Most screens are performed on older people, because the disease incidence is too low in young people and the tests would result in too many false positives (a small fraction of a big number of healthy individuals is still a big number). Young people, however, could be interested in participating in longitudinal studies without a simple answer (Chapter 8).

7.1.2 Metagenomics for personalized treatment

Microbiome composition could predict response to cancer immunotherapy and chemotherapy (Table 7.2), response to medication for rheumatoid arthritis, type 2 diabetes, etc. [32,33]. For example, it remains to be validated with more patients that *Veillonella* sp. in the saliva of rheumatoid arthritis patients was better reduced after treatment with methotrexate plus *Tripterygium wilfordi* (thunder god vine) glycosides or *T. wilfordi* glycosides alone, compared to methotrexate alone [32]. Methotrexate treatment has been found to negatively associate with pulmonary fibrosis in early rheumatoid arthritis patients [34], without studying the respiratory or the oral microbiome. For malignant glioma, clinical trials are being performed for immune checkpoint inhibitors, peptide vaccines, dendritic cell vaccines, etc. [35], and the gut, oral, and potentially cerebrospinal fluid (CSF) microbiome might all influence the outcome. Gut microbial tryptophan metabolism has been implicated in metabolic, autoimmune, neuropsychiatric diseases and cancer [36–41], and clinical trials targeting the tryptophan pathways should probably take into account the microbiome (Tables 7.3 and 7.4), which would potentially impact the dose, toxicity and efficacy of the drug (Fig. 7.2).

Mechanistically, metabolism of a drug by the microbiome could activate, deactivate or toxify the drug (Fig. 7.2, Table 7.5), and could work together with human genetic variations (Table 7.6). Note that mice experiments are typically performed on male mice, to decrease variability due to the female mice's estrus cycle, so the difference between animal results and human cohorts could have

Table 7.2 Microbiome and response to cancer therapies.

Cancer	Treatment	Microbes	Reference
Mice with subcutaneous injection of fibrosarcoma, melanoma, or mastocytoma cell lines	CpG-oligonucleotide (CpG-ODN) immunotherapy; platinum chemotherapy (oxaliplatin)	For CpG-ODN, *Alistipes shahii*, *Ruminococcus* sp. positively correlated with intratumoral TNF (tumor necrosis factor) expression; *Lactobacillus* spp. negatively correlated with TNF. Effects of *Alistipes shahii* and *L. fermentum* were verified experimentally	[24]
Mice with subcutaneous injection of lymphoma, melanoma or colon carcinoma cell lines	Cyclophosphamide (CTX)	CTX induced translocation of *Lactobacillus* spp. (e.g., *L. johnsonii*) and *Enterococcus hirae* into secondary lymphoid organs. Such Gram-positive bacteria were necessary for the induction of Th17 cells that mediate the effects of CTX	[25]
Mice with subcutaneous injection of fibrosarcoma or colon carcinoma cell lines; patients with advanced lung cancer or ovarian cancer	CTX	*Enterococcus hirae* translocated from the small intestine to secondary lymphoid organs and increased the intratumoral CD8/Treg ratio; *Barnesiella intestinihominis* accumulated in the colon and promoted the infiltration of IFN-γ-producing γδT cells in cancer lesions. Both were restrained by Nod2. *E. hirae* and *B. intestinihominis* specific-memory Th1 cell immune responses predicted longer progression-free survival in advanced lung and ovarian cancer patients treated with chemo-immunotherapy	[26]
Mice model of melanoma	Anticytotoxic T lymphocyte antigen (CTLA-4)	T-cell responses for *Bacteroides thetaiotaomicron* or *Bacteroides fragilis* associated with the efficacy of CTLA-4 blockade; Experimentally verified effects of *B. thetaiotaomicron*, *B. fragilis* alone, *B. fragilis* together with *Burkholderia cepacia*, *B. fragilis* polysacharides, and *B. fragilis*-specific T-cells	[27]
Mice model of melanoma	Antiprogrammed cell death ligand 1 (PD-L1)	*Bifidobacterium* spp. (*B. breve*, *B. longum*) enhanced the efficacy of anti-PD-L1 therapy	[28]

Table 7.2 Microbiome and response to cancer therapies—cont'd

Cancer	Treatment	Microbes	Reference
Nonsmall cell lung cancer (NSCLC) patients, renal cell carcinoma (RCC) patients	Antiprogrammed cell death 1 (PD-1)	Higher relative abundance of *Akkermansia muciniphila* in patients who responded to PD-1 treatment; Verified by supplementing *Akkermansia muciniphila* into nonresponder feces to show response in mice model	[29]
Melanoma patients	PD-1	Higher α-diversity, higher relative abundance of the Ruminococcaceae family in patients who responded to PD-1 treatment	[30]

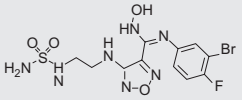
Existing research has focused on the fecal microbiome. A number of clinical trials are being performed [31].
Credit: Huijue Jia.

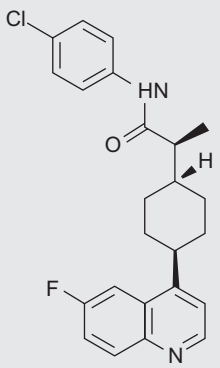
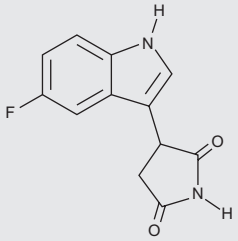
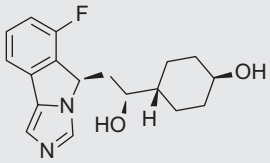
been increased partly due to the microbiome and immunological differences between sexes, in addition to the "enterotype" difference (Chapter 2).

Testing for the microbes before treatment saves critical time and helps recommend the effective medication and other therapies to prescribe (Figs. 7.2–7.4). The optimal dose for each patient depends on both the human genome and the microbiome, which could activate, inactivate or convert a diverse range of molecules, including medication (Figs. 7.2 and 7.3; Tables 7.5 and 7.6) [91,92]. Some of the disease-associated microbes remain unaffected by standard medication [32,93], calling for combinatorial treatment, or further development of new drugs. Microbiome information could also be leveraged to predict or manage side effects, e.g., during cancer immunotherapy [94]. If patients tend to spontaneously discontinue the use of a medication, regular tests of the microbiome showing the trend of improvement toward a healthy state might also help them stay on. Microbiome tests after treatment may also inform decisions to continue, stop, or switch to other treatments.

High-intensity interval training has been tried in prediabetic patients, and patients with Alzheimer's disease [95–98]. Given the associations between fecal, oral, vaginal microbiomes and physical activity, measures of muscle strength, lung capacity, etc. [99–101], microbiome tests could also help guide more personalized physical exercises. In addition, exercises may be a proxy for sweating, which secretes nonessential or toxic trace metals in addition to sodium chloride, urea, lactate, creatinine, etc. [102], and might also reduce the disease risks.

Table 7.3 List of currently investigated IDO1 (indoleamine 2,3-dioxygenase 1) inhibitors.

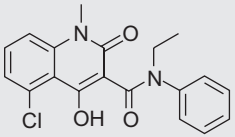
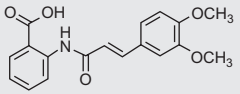
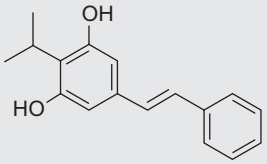
Molecule	Structure and properties	Investigations	Published studies	Active or recruiting studies
1-MT-L-Trp (1-methyl-L-tryptophan)	Analog of L-Trp; Nonspecific competitive inhibitor of IDO1; Increases the effectiveness of anticancer drugs and increases KYNA in vivo and ex vivo regardless of IDO	Fundamental research [42]	Advanced malignancies: well tolerated (monotherapy) [43]	Phase I/II: breast (NCT01042535, NCT01792050), pancreatic (NCT02077881), prostate (NCT01560923), nonsmall cell lung cancer (NCT02460367), solid (NCT00567931, NCT01191216), brain tumors (NCT04049669, NCT02052648, NCT02502708), leukemia (NCT02835729), and melanoma (NCT03301636, NCT02073123)
1-MT-D-Trp (1-methyl-D-tryptophan, indoximod)	Low in vitro activity but effective in vivo, preferentially inhibit IDO2; May promote tumor growth by off-target effect; Prodrug: NLG802	Cancers (alone or in combination) [44,45]		
Epacadostat INCB024360 	Selective reversible competitive inhibitor of IDO1; Antitumoral (decreases Tregs, increases the synthesis of IFNγ by T cells) but lack of activity as a monotherapy; Metabolized by the intestinal microbiota and the enzyme UGT1A9 (AhR target)	Cancers (only in combination) [46,47]	Ovarian cancer: no benefit [48] Tumors: well tolerated and had encouraging antitumor activity [49] Metastatic melanoma: no benefit [50]	Phase I/II: thymic carcinoma (NCT02364076), naso-pharyngeal (NCT04231864), gastric (NCT03196232), gastrointestinal (NCT03291054), pancreatic (NCT03006302), urothelial bladder (NCT03832673), nonsmall cell lung (NCT03322566, NCT03322540), and rectal (NCT03516708) cancers, melanoma (NCT01961115), sarcoma (NCT03414229), metastatic solid tumors (NCT03347123) Phase III: urothelial (NCT03361865, NCT03374488) and renal carcinoma (NCT03260894), head and neck carcinoma (NCT03358472)

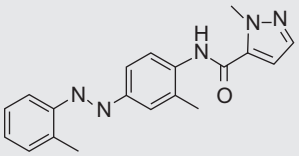
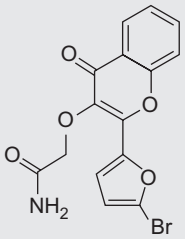
Linrodostat BMS-986205 	Potent, selective, and irreversible IDO1 inhibitor, restores T-cell proliferation and reduces intratumoral L-kyn up to 90%	Cancers [51–53]	Tumors: well tolerated (± nivolumab), need further investigations for efficacy [52]	Phase I/II: pharmacokinetics (NCT03378310, NCT03312426) and safety (NCT03192943), endometrial (NCT04106414), liver (NCT03695250), gastric (NCT02935634) head and neck (NCT03854032) and bladder (NCT03519256) cancers, solid tumors (NCT03792750, NCT03459222, NCT02658890) glioblastoma (NCT04047706) Phase III: bladder cancer (NCT03661320, NCT03661320), melanoma (NCT03329846)
EOS200271 	IDO1 specific noncompetitive inhibitor; Oral use Brain permeable	Glioma Association with PD-L1 inhibitors [54,55]	Malignant glioma: well tolerated [55]	
Navoximod, GDC-0919, or NLG-919 	Moderately selective noncompetitive reversible inhibitor; Dose-dependent activation and proliferation of effector T cells; Regression of large established tumors; Synergy with indoximod; Increases survival (± chemotherapy) currently optimized by prodrug formulation	Cancers [56]	Recurrent advances solid tumors: well tolerated and reduced plasmatic L-kyn [57]	Phase I/II: solid tumors (NCT02471846, NCT02048709)

IFN, interferon; *KYNA*, kynurenic acid; *L-kyn*, L-kynurenine; *Treg*, regulatory T cell. Clinical trials can be accessed at https://www.clinicaltrials.gov.

Credit: Table 1 of Modoux M, Rolhion N, Mani S, Sokol H. Tryptophan metabolism as a pharmacological target. Trends Pharmacol Sci 2021;42:60–73. https://doi.org/10.1016/j.tips.2020.11.006.

Table 7.4 List of currently investigated AhR (aryl hydrocarbon receptor) agonists and antagonists.

Molecule	Structure and properties	Investigations	Published studies	Active or recruiting studies
AhR agonists				
Laquinimod 	Quinoline 3-carboxamide structural similar to KYNA; AhR-dependent effects on encephalomyelitis; Mixed results (Phase II and III clinical trials—multiple sclerosis); Allows remyelination	Huntington's Multiple sclerosis Crohn's disease [58,59]	Multiple sclerosis: well tolerated, significant reduction in brain atrophy [60,61] Crohn's disease: well tolerated, promising effects [62]	Phase I/II: efficacity and safety in relapsing multiple sclerosis (NCT01047319), Huntington's disease (NCT02215616), lupus arthritis (NCT01085084), lupus nephritis (NCT01085097), Crohn's disease (NCT00737932), relapsing multiple sclerosis (NCT01975298)
Tranilast 	Synthetic analog of ANA	Asthma (marketed) Rheumatoid arthritis Multiple sclerosis Hyperuricemia Cancer [63]	Prostate cancer: benefit on prognosis [63]	Phase I/II: mucinoses (NCT03490708), scleredema diabeticorum (NCT03512873), sarcoidosis (NCT03528070), cryopyrin-associated periodic syndrome (NCT03923140), pterygium (NCT01003613), hyperuricemia (NCT00995618, NCT01052987), gout (NCT01109121), rheumatoid arthritis (NCT00882024)
Tapinarof (benvitimod) 	Bacterial stilbene; Free radical scavenger; Dermal application	Psoriasis atopic dermatitis [64]	Psoriasis and atopic dermatitis: well tolerated [65,66]	Phase I/II: safety, tolerability, and pharmacokinetics of tapinarof cream, 1% (extensive plaque psoriasis) (NCT04042103) Phase III: efficacy and safety of topical tapinarof cream, 1% (plaque psoriasis) (NCT03956355)

AhR antagonists				
CH223191 	Competitive selective antagonist; No antagonistic activity with non-HAH ligands	Fundamental research but may be a promising effect in pancreatic cancer [67]	No active clinical trials	
CB7993113 	Good oral bioavailability; Blocks tumor cell migration and reduces the invasive phenotype of ER-/PR-/HER2- breast cancer cells in vitro	[68,69]		
StemRegenin-1	Ex vivo application; Expand CD34 + cells	Stem cell transplantation Neutropenia Thrombocytopenia	CD34 + cell expansion [68,70]	Malignant hemopathies (NCT01474681 and NCT01930162) Neutropenia and thrombocytopenia (NCT03406962)

Non-HAH ligands (halogenated aromatic hydrocarbons) include polycyclic aromatic hydrocarbons (PAHs) as well as endogenous L-Trp ligands. HAHs are distinguished from PAHS and endogenous ligands by very slow metabolism and a prolonged effect on the AhR receptor. *ANA*, Anthranilic acid; *ER*, estrogen receptor; *HER*, human epidermal growth factor receptor 2; *KYNA*, kynurenic acid; *PR*, progesterone receptor. Clinical trials can be accessed at https://www.clinicaltrials.gov/.

Credit: Table 3 of Modoux M, Rolhion N, Mani S, Sokol H. Tryptophan metabolism as a pharmacological target. Trends Pharmacol Sci 2021;42:60–73. https://doi.org/10.1016/j.tips.2020.11.006.

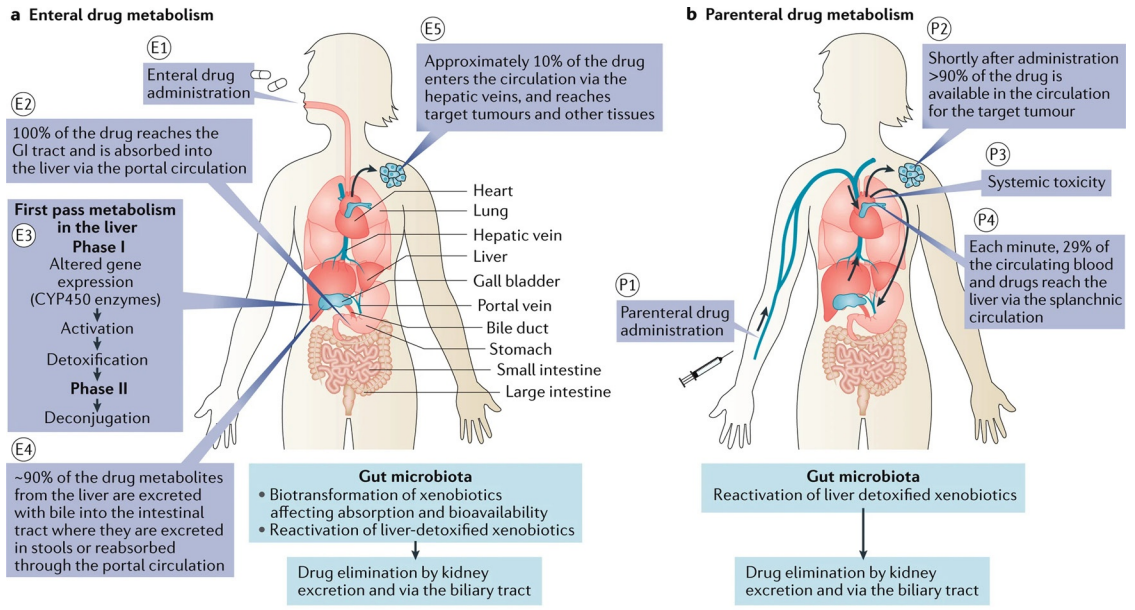


Fig. 7.2 Major pathways of drug metabolism and the role of microbiota following enteral (e.g., oral) or parenteral (e.g., intravenous) administration. (A) Enteral drug metabolism. Orally administered drugs (E1) sit in the stomach for 30–45 min before reaching the intestine and being absorbed into the liver by the portal circulation (E2). In the intestine, host and microbial enzymes induce metabolic alterations to the drug that together with direct binding to bacterial products and segregation control intestinal absorption. In the liver, following phase I and phase II processing (first pass metabolism; E3), approximately 90% of the oral drug is metabolized and destroyed or eliminated through biliary secretion (E4). The drugs secreted into the intestine via the biliary duct can be reabsorbed via portal circulation or excreted in stools. As a consequence, only 10% of the oral drug enters the circulation through the hepatic veins and is available to reach the target tumors and other tissues (E5). Phase I and phase II processing are also affected by the gut microbiota through the regulation of the level of host enzymes involved in drug processing. (B) Parenteral drug metabolism. Following intravenous administration (P1) close to 100% of the drug enters the circulation and is available to reach the target tumors (P2); however, the drug is also distributed systemically, inducing adverse toxic reactions (P3). Any remaining drug not retained in tissues can be rapidly excreted by the kidney. Each minute 29% of the circulating drug is transported via the splanchnic circulation (hepatic, mesenteric, and splenic arteries) to the liver (P4), where the drug is processed similarly to enterally administered drugs. The detoxified drugs that are secreted from the liver to the intestine through the biliary excretion route can be reactivated by bacterial enzymes, inducing intestinal toxicity. *CYP450*, cytochrome P450; *GI*, gastrointestinal. Credit: Fig. 2 of Roy S, Trinchieri G. Microbiota: a key orchestrator of cancer therapy. Nat Rev Cancer 2017. https://doi.org/10.1038/nrc.2017.13.

Table 7.5 Selected drug modifications made by human gut microbiome.

Phenotypic effect	Microbial modification	Subclass: drugs	Outcome	Host effect	Reference
Activation and reactivation	Reduction	Azoreduction: sulfasalazine (SSZ), balsalazide, ipsalazide, olsalazine	Prodrug activation: local 5-ASA release	Antiinflammatory treatment	[71]
		Azoreduction: prontosil, neoprontosil	Antibiotic activation	Bacterial killing	[72]
	Dealkylation	*N*-dealkylation: amiodarone	Increased bioavailability of active metabolite	Increased half-life, possible drug interactions	[71]
	Deconjugation	Deglucuronidation: morphine, codeine	Reformation of active metabolite	Increased AUC, enterohepatic circulation	[71]
	Other	Desulfation: sodium picosulfate	Solubility increase	Activation of laxative effect	[72]
Inactivation	Reduction	Nitroreduction: benzodiazepines: nitrazepam, clonazepam, bromazepam	Change to inactive metabolite	Inactivation of drug, a possible overdose intervention	[71,72]
		Lactone ring reduction: digoxin	Change to inactive metabolite	Narrow therapeutic window	[71]
	Dealkylation	*N*-demethylation: methamphetamine	Change to inactive metabolite	Decreases therapeutic effect	[71]
	Dehydroxylation	*P*-dehydroxylation: L-dopa	Decrease in L-dopa absorption, caused by *Helicobacter pylori*	Decreases therapeutic effect	[71,72]
	Proteolysis	Insulin, calcitonin	Breakdown of therapeutic protein	Decreases therapeutic effect	[72]
	Acetylation	*N*-acetylation: 5-ASA	Change to inactive metabolite	Less efficacy, possible pancreatic toxicity	[71]

Continued

Table 7.5 Selected drug modifications made by human gut microbiome—cont'd

Phenotypic effect	Microbial modification	Subclass: drugs	Outcome	Host effect	Reference
Toxification	Reduction	Nitroreduction: chloramphenicol	*p*-Aminophenyl-2-morphine-glucuronide amino-1,3-propanediol generation (speculated)	Bone marrow toxicity	[72]
		Nitroreduction: benzodiazepines: nitrazepam, clonazepam, bromazepam	Amino-metabolite generation, Inactivation	Teratogenicity	[71,72]
	Dealkylation	*N*-dealkylation: brivudine, sorivudine	Generation of additional bromovinyluracil, drug AUC decrease, interaction with 5-fluorouracil (5-FU)	*Bacteroides*-mediated hepatotoxicity, potentially fatal 5-FU accumulation	[73]
	Deconjugation	Deglucuronidation: irinotecan, diclofenac, ketoprofen, indomethacin	Reformation of cytotoxic drug	Diarrhea, bowel distress, GI lesions	[71,72]

5-ASA, 5-aminosalicylate. AUC, area under the curve, which shows plasma concentration of a drug over time, so a higher AUC means more drug in the body.
Credit: Table 1 of Hitchings R, Kelly L. Predicting and understanding the human Microbiome's impact on pharmacology. Trends Pharmacol Sci 2019;40:495–505. https://doi.org/10.1016/j.tips.2019.04.014.

Table 7.6 Drugs with potential human and bacterial sources of variance.

Drug	Human pharmacogene	Effect of polymorphism	Microbiome-associated metabolism	Effect of microbiome metabolism	References
Warfarin	*CYP2C9*	Altered activity of drug	Vitamin K production	Microbiomes produce variable concentrations of vitamin K. Alterations in vitamin K production by microbiome may alter warfarin metabolism	[74–76]
Irinotecan	*UGT1A1*28* "Gilbert's syndrome"	Defect in glucuronidation, increased toxicity	Deglucuronidation of excreted SN-38G metabolite	Reformation of cytotoxic Irinotecan	[77,78]
Codeine	*CYP2D6*	Variant alleles may cause absent, decreased, or increased rate of biotransformation to morphine	Deglucuronidation of excreted morphine-glucuronide metabolite	Reformation of morphine, higher morphine AUC due to enterohepatic circulation	[79,80]
Morphine	*SLC22A1, OCT1*	Decreased clearance of morphine	Deglucuronidation of excreted morphine-glucuronide metabolite	Reformation of morphine, higher morphine AUC due to enterohepatic circulation Induces virulence in some strains of *Pseudomonas aeruginosa*	[79,81,82]
Acetaminophen	*UGT1A, SULT1A3*	Increased rate of glucuronidation and decreased risk of liver failure due to unintentional overdose, decreased sulfation	Sulfonation	Increase in sulfonated metabolite, may be competitively inhibited by p-cresol sulfonation	[81,83,84]
Simvastatin	*SLCO1B1*	221% increase in simvastatin AUC for homozygotes	Unknown	Increased efficacy hypothesized to be due to microbial alteration of primary bile acids	[75,85–87]
Digoxin	*ABCB1*	Increased AUC may increase toxicity	Lactone ring reduction	Decreased AUC, narrow therapeutic window	[88,89]
Brivudine and sorivudine	*DYPD*	Increased drug-drug interactions with pyrimidine analogs	Generation of additional bromovinyluracil	Hepatotoxicity, bromovinyluracil prevents clearance of 5-FU	[73,90]

Vitamin K is also known as menaquinone, which often shows up in KEGG (Kyoto Encyclopedia of Genes and Genomes) analyses of the microbiome (e.g., Ref. [32]). AUC, area under the curve, which shows plasma concentration of a drug over time, so a higher AUC means more drug in the body; 5-FU, 5-fluorouracil.

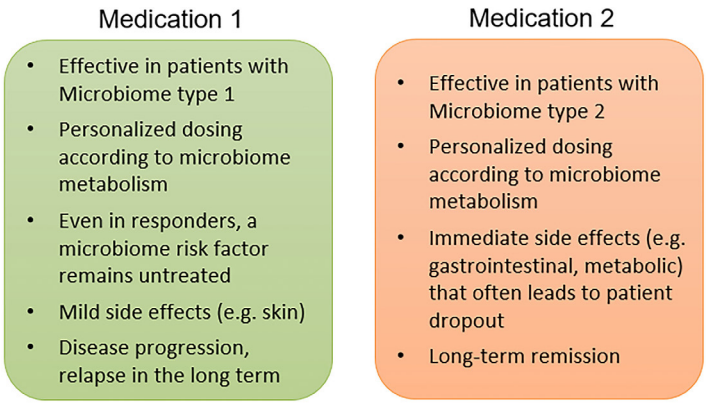


Fig. 7.3 A hypothetical example of how microbiome information could facilitate more personalized choice of the types and dose of medication, better compliance despite side effects, and more effective long-term management of diseases. Credit: Huijue Jia.

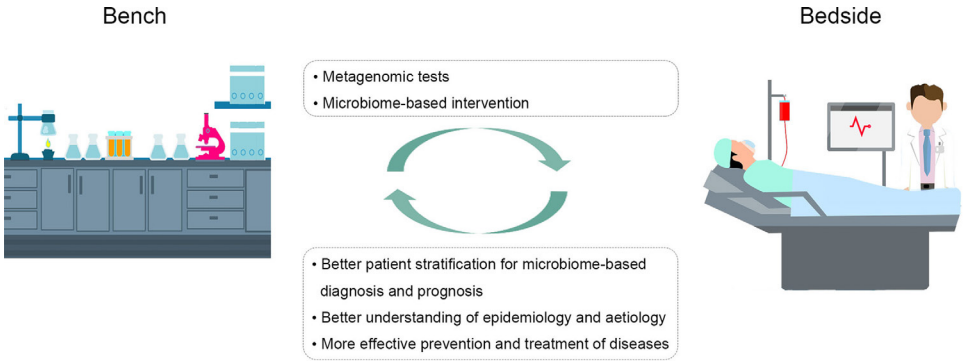


Fig. 7.4 From bench to bedside and from bedside to bench. Credit: Huijue Jia, Yanmei Ju, BGI-Shenzhen.

7.2 Further research to be inspired by clinical practice

New medication, new vaccines, new foods or additives, new materials and devices to be inserted into the body. The human microbiome might again play important roles. As discussed in Chapter 4, doctors are uniquely positioned to find out the full loop of events that takes place in the human body. Noninvasive tests of the oral and fecal microbiome can be performed on individuals at-risk for pancreatic cancer (Fig. 7.5, the very deadly pancreatic ductal adenocarcinoma, PDAC), while tissue samples may be available before treatment, followed by more noninvasive tests during long-term management. Metastasis may also carry microbes from the original site, which may be sequenced to trace their evolution, and treated locally if necessary. A lot of the drug and food metabolites end up in the urine, and it is currently unknown how these may influence the microbiome there.

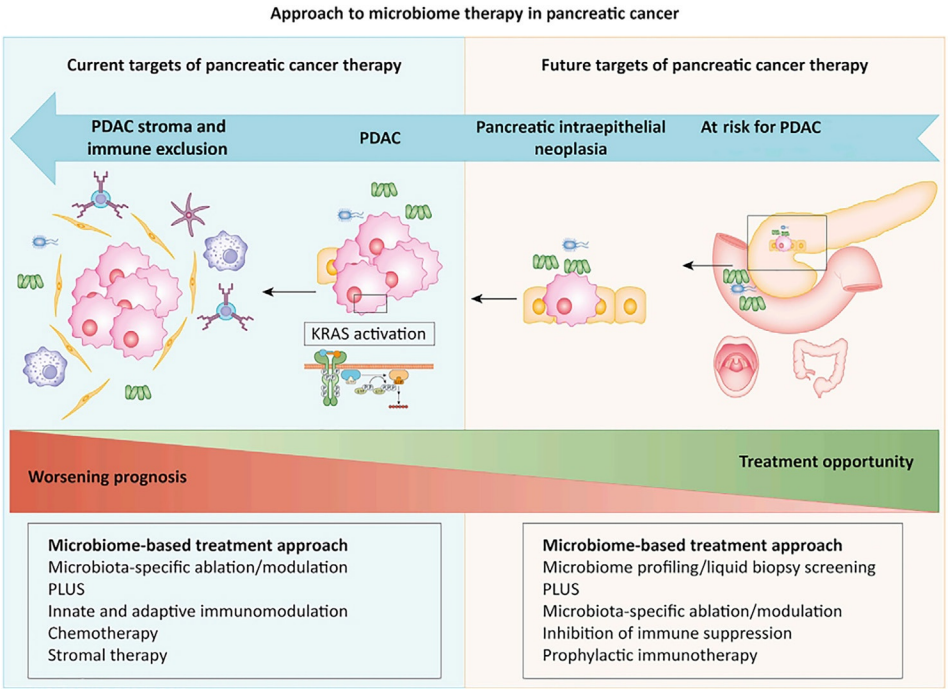


Fig. 7.5 Graphic illustration of the stages of pancreatic cancer development. Current therapy for pancreatic cancer is focused on early and advanced PDAC *(light blue box)*, which generally harbors a poor prognosis. At this stage, microbiota-specific ablation and immunomodulation have the potential to improve pancreatic cancer outcomes, but the therapeutic effect may be limited due to additional oncogenic factors including KRAS activation and immune cell exclusion in the tumor microenvironment. Instead, microbiome modulation may prove more impactful at the earliest stages of pancreatic cancer development *(light orange box)*, when microbiota directly contributes to tumor oncogenesis in the absence of an unfavorable tumor microenvironment. Microbiome profiling, screening, and augmentation may also lead to earlier PDAC diagnosis and open more therapeutic opportunities. Abbreviation: *PDAC*, pancreatic ductal adenocarcinoma. Credit: Fig. 1 of Vitiello GA, Cohen DJ, Miller G. Harnessing the microbiome for pancreatic cancer immunotherapy. Trends Cancer 2019;5:670–76. https://doi.org/10.1016/j.trecan.2019.10.005.

If metagenomic tests for semen, endometrium/cervical, urine, and fecal samples can enter fertility clinics, there will be more work to do regarding the various types of male and female fertility [103–107]. Other than getting a baby, long-term effects on health should also be an important consideration (Chapter 8).

Lung infections can evolve over time (Fig. 7.6). Metagenomically assembled genomes could complement traditional methodology, and improve the database for faster analyses and action in the future. The metagenomic associations among different members of the microbiome would be informative for the accurate prediction of outcomes in each patient. It has been shown in mice that the lung microbiome is

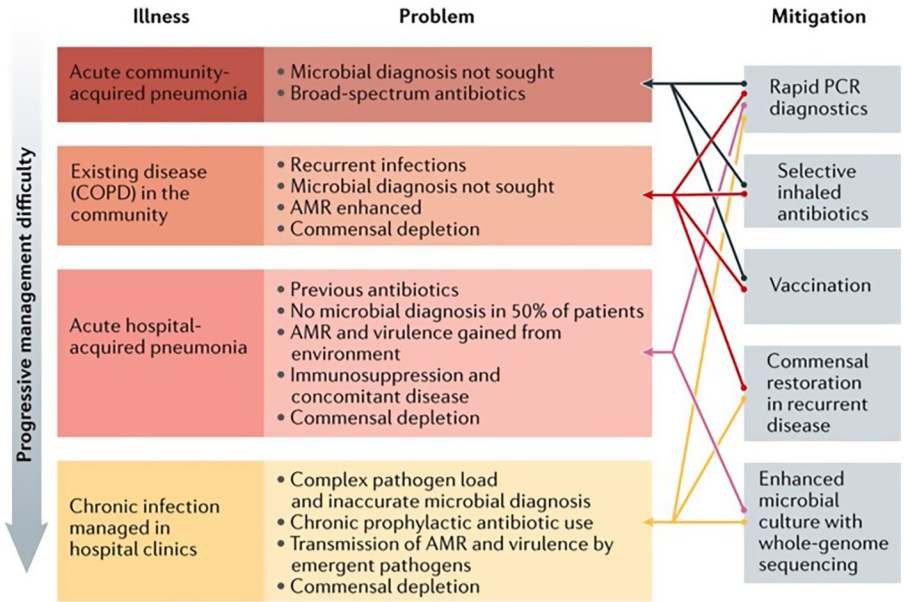


Fig. 7.6 Management of acute and chronic lung infections. PCR, if designed for the correct pathogen, is still more real-time than metagenomic shotgun sequencing. Detailed analyses of the microbiome and the evolution of members of the microbiome could lead to better long-term care. *AMR*, antimicrobial resistance; *COPD*, chronic obstructive pulmonary disease. Credit: Fig. 2 of Cookson WOCM, Cox MJ, Moffatt MF. New opportunities for managing acute and chronic lung infections. Nat Rev Microbiol 2017. https://doi.org/10.1038/nrmicro.2017.122.

required for the progression of lung adenocarcinoma through γδT cells and neutrophils [108]. Lung adenocarcinoma would also reorganize the circadian metabolic clock in the liver [109]. Epidemiologically, dietary fiber, cruciferous vegetables, and probiotics are associated with a reduced risk of lung cancer, while a high intake of coffee in men interacted with smoking and showed a higher risk [110–112].

Skin infections also tend to be refractory. How the different fungi *Malassezia* species, the lack of *Dermacoccus*, and strain-level evolution (Chapter 5) in the skin microbiome predicts atopic dermatitis flares warrant further investigation [113]. The different presentations of autoimmune disorders might be matched with different skin, mucosal, and circulating microbiome.

A cocktail of three bacteriophages against antibiotic-resistant *Mycobacterium abscessus* was used to treat multiple skin lesions on a 15-year-old cystic fibrous patient following a lung transplant. After the intravenous phage treatment which was generally effective and only elicited weak immune reactions, *M. abscessus* could still be cultured

from slowly resolving skin nodules [114]. Antibodies against the *M. abscessus* phages were also detected in an 81-year-old patient with bronchiectasis, in which case the phages became ineffective after two months [115].

For the major types of inflammatory bowel diseases (IBD), feces of Crohn's diseases (CD) patients might have more *Ruminococcus gnavus*, while feces of Ulcerative colitis (UC) patients might have more *R. torques* [116], and the decrease in *Bacteroides* spp. is usually accompanied with overgrown *Enterobactericeae* [117,118]. The subtypes and sequence of events need to be better worked out in patients. Some *R. gnavus* strains encode superantigens that stimulate a potent IgA response [119], which is expected to impact the gut microbiome (Chapter 2). For some people, the more *R. torques*, blood group B, and loose stool at 30 years old [99] may never manifest as UC at an older age. Epidemic strains of *Peptoclostridium difficile* (formerly *Clostridium difficile*) that emerged in North America in the early 2000s grow fast in the presence of trehalose [120], but people with a functional gut microbiome do not need to be too worried about trehalose consumption. Fecal Microbiome Transplant (FMT) for IBD is not nearly as effective as FMT for *P. difficile* infections [121–124], and replacement of patients' strains with donors' strains using FMT was more difficult for CD than for UC [125]. The fecal microbiome may help predict immune markers [125,126], the oral microbiome is also a reservoir for immune derangement [127,128], and more effective treatment can potentially be selected for each patient.

For dentists, will we one day have enough data to be able to predict which teeth are more likely to fall off, and keep the other ones for longer? Orthodontal practices may also change the aeration in the mouth, and the protective layer of saliva on teeth. Given the association between the oral microbiome and all kinds of diseases, how can hospitals foster more collaborations between different departments?

7.3 Potential to modify existing categorization of diseases with knowledge of the microbiome

Naming of diseases is perhaps no less historical as the naming of microbes. With the key layer of information provided by the microbiome, some grouping, regrouping, and dividing of disease categories might be warranted.

Colorectal cancer without a strong genetic cause (e.g., Lynch syndrome) is referred to as sporadic. But we now know that on top of the dietary and obesity risk factors, a few bacteria could be the culprits, and a patient does not have to have all of them. If more evidence becomes available regarding the prognosis, and the optimal treatment,

for the different fecal or mucosal bacteria enriched singly or in combination, they may well be named as subtypes of colorectal cancer and adenomas [129–136]. Presumably, the mutation and immune subtypes [137,138] result from the long-term interaction between gene, microbiome, and environment. *Fusobacterium* spp., especially *F. nucleatum*, is most studied for colorectal cancer in recent years [139,140]. In addition to being a biomarker for adenomas and carcinomas, a higher amount of tissue *F. nucleatum* DNA was associated with tumor location in the proximal colon, higher pT stage (deeper invasion), poor tumor differentiation, Microsatellite Instability (MSI)-high, *MLH1* hypermethylation, CpG island methylator phenotype (CIMP)-high, and *BRAF* mutation [141]. *F. nucleatum* has also been implicated with recurrence after chemotherapy [142].

Such updates for the nomenclature of complex diseases may also be needed for autoimmune diseases, in combination with the underlying genetics (Fig. 7.7) [143]. For example, none of the bacteria implicated in rheumatoid arthritis (Chapter 4) is 100% prevalent, just like none of the autoimmune antibodies is 100% prevalent. Which of the patients are more likely to have faster bone erosion and may require more aggressive/expensive treatments to begin with, instead of beginning with methotrexate alone and waiting for an unsatisfactory response [144]?

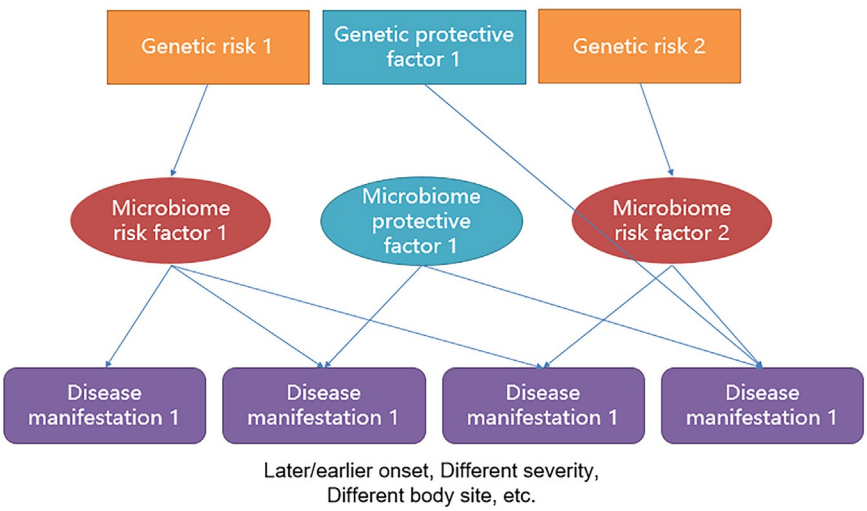


Fig. 7.7 An oversimplified illustration of genetic and microbiome factors that could lead to disease subtypes. Other clinically available data, e.g., autoantibodies, affected lymph nodes, should also be incorporated into the classification. Credit: Huijue Jia.

Worked sample 7.1

For patients with colorectal cancer, how would you look for clinical differences between those with high *Parvimonas micra*, *Peptostreptococcus stomatis* (or *Peptostreptococcus anaerobius* [130,145]), *Porphyromonas asaccharolytica*, or *Escherichia coli* in the fecal microbiome? Or, starting with existing subtypes, do you see certain subtypes to be more frequent in a particular group of people?

What kind of samples and other information could you collect before, during, and after treatment?

Besides surgical removal of the tumor, how do you think the treatment could be more targeted?

7.4 Summary

With all the knowledge about members of the microbiome that contribute to or prevent diseases, it is high time that we apply this knowledge to clinical practices wherever necessary. Healthcare professionals would have to decide whether to collect surgical samples for investigation, and whether to prescribe metagenomic tests before or after a treatment to see whether the medication works for a particular patient. The microbiome heterogeneity among patients is also an important consideration, after the human genomes, for the rational design of clinical trials in the development of effective new drugs. While the biomarkers for various diseases, in combination with current best practice, would enable population-scale screening. It would also be important to keep the clinical investigations going, and continue to refine the microbiome models for diagnosis and treatment, and reach a better understanding of many complex diseases (Figs. 7.4 and 7.7).

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