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Future Perspectives on Infections Associated with Gastrointestinal Tract Diseases

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KEYWORDS

• Gastrointestinal • Infection • Molecular techniques • Future • Technology

CHANGING BURDEN OF GASTROINTESTINAL DISEASE

In 2004, in the United States, there were 72 million presentations with a primary diagnosis of a digestive disease and 104 million presentations with combined gastrointestinal (GI) tract diseases and other diseases (**Table 1**).[1] It was also found that those who are older tend to have more GI problems, there was no difference in the rates of digestive disease between the African Americans and the whites, and women were 20% more likely to present than men with digestive diseases. Thus, more than one-third (35%) of all presentations are for digestive diseases. In 2009, in the United States, the cancer statistics revealed 275,720 new cases of GI cancer, with colorectal and pancreatic cancer in the top 10 for both men and women.[2] There were 135,830 deaths due to GI cancer, with colorectal, pancreatic, hepatic, and esophageal cancers in the top 10 for both men and women, except for esophageal cancer, which was only listed for men (**Fig. 1**).[2] Furthermore, 2 of these 3 cancers that have an increasing mortality were GI tract cancers for both genders, with esophageal and hepatic cancers among men and pancreatic and hepatic cancers among women. Worldwide the rates of digestive diseases are staggering.

From 1979 to 1989, in the United States, a decrease was observed in the ambulatory care visits and hospital discharges for digestive diseases. These rates remained constant between 1990 and 1999, until 2000 when the rates climbed dramatically and was still increasing in 2004 (**Fig. 2**).[1] During this period, substantial increases in the

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Table 1
Burden of selected digestive diseases in the United States, 2004

Digestive Disease	Deaths, Underlying Cause[a]	Years of Potential Life Lost to Age 75 Years[a]	Ambulatory Care Visits, All-Listed Diagnoses[b]	Hospital Discharges, All-Listed Diagnoses[c]
All Digestive Diseases	236,164	2,007,500	104,790,000	13,533,000
All Digestive Cancers	135,107	945,200	4,198,000	726,000
Colorectal Cancer	53,226	333,000	2,589,000	255,000
Pancreatic Cancer	31,800	206,800	415,000	68,000
Esophageal Cancer	13,667	113,800	372,000	44,000
Gastric Cancer	11,253	84,200	141,000	31,000
Primary Liver Cancer	6323	72,400	63,000	33,000
Bile Duct Cancer	4954	32,900	—	17,000
Gall Bladder Cancer	1939	10,900	—	6000
Cancer of the Small Intestine	1115	9300	—	9000
Liver Disease	36,090	559,100	2,398,000	759,000
All Viral Hepatitis	5393	101,800	3,510,000	475,000
Hepatitis C	4595	87,500	2,747,000	419,000
Hepatitis B	645	11,800	729,000	69,000
Hepatitis A	58	800	—	10,000
GI Infections	4396	12,800	2,365,000	450,000
Peptic Ulcer Disease	3692	19,700	1,473,000	489,000
Pancreatitis	3480	42,800	881,000	454,000

Diverticular Disease	3372	8600	3,269,000	815,000
Abdominal Wall Hernia	1172	6900	4,787,000	372,000
Gastroesophageal Reflux Disease	1150	6000	18,342,000	3,189,000
Gallstones	1092	4400	1,836,000	622,000
All Inflammatory Bowel Disease	933	9100	1,892,000	221,000
Crohn Disease	622	7000	1,176,000	141,000
Ulcerative Colitis	311	2000	716,000	82,000
Appendicitis	453	5000	782,000	325,000
All Functional Intestinal Disorders	423	2500	11,648,000	1,241,000
Chronic Constipation	137	900	6,306,000	700,000
Irritable Bowel Syndrome	20	0	3,054,000	212,000
Hemorrhoids	14	200	3,275,000	306,000

[a] Vital statistics of the United States.
[b] The National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey.
[c] The Healthcare Cost and Use Project Nationwide Inpatient Sample.

Data from Everhart JE, editor. The burden of digestive diseases in the United States. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Washington, DC: US Government Printing Office, 2008; NIH Publication No. 09–6443; p. 6–7.

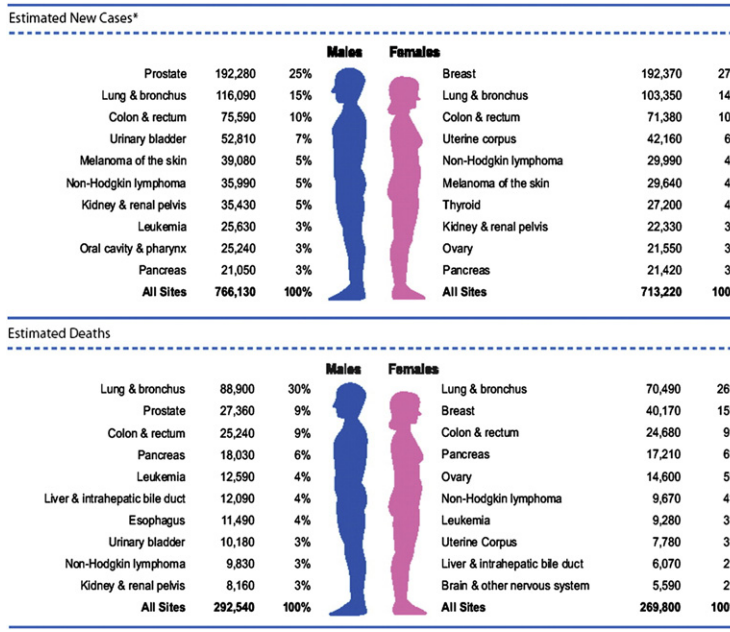

Fig. 1. The 10 leading cancer types among the estimated new cancer cases and deaths, by sex, in the United States in 2009. (*From* Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225–49; with permission.)

prevalence were observed for certain GI tract diseases, including gastroesophageal reflux disease (GERD) with an increase of 376 per 100,000 population, hepatitis C with 79 per 100,000 population, chronic constipation with 62 per 100,000 population, intestinal infections with 41 per 100,000 population, and pancreatitis with 23 per 100,000 population.[1]

The prevalence of digestive diseases around the world is enormous and varies from country to country (**Table 2**). Worldwide there has been a dynamic shift in the epidemiology of GI tract diseases, with some diseases such as peptic ulcer decreasing dramatically since the discovery of *Helicobacter pylori* infection and a larger number of conditions increasing, such as GERD, nonalcoholic fatty liver disease, diverticular disease, Barrett esophagus, cholelithiasis, alcoholic liver disease, hepatitis C, chronic pancreatitis, esophageal cancer and colorectal cancer.[3–8] In conjunction with this increasing incidence of digestive diseases are the re-emergence of certain infectious agents (**Box 1**) (eg, cholera) and the identification of new agents (eg, *H pylori*, *Laribacter*, *Campylobacter concisus*), which are associated with GI tract diseases.[9] Since the discovery of *H pylori* there has been an enormous interest in the relationship between microorganisms and GI tract diseases, including cancers.

CAUSE-AND-EFFECT ISSUES

One of the main issues associated with infections and disease is determining the relationship of the cause and effect. The landmark article by Sir Austin Bradford Hill in 1965 titled The environment and disease: association or causation? became widely known as the Bradford Hill's criteria.[10] There were 8 criteria that were required to

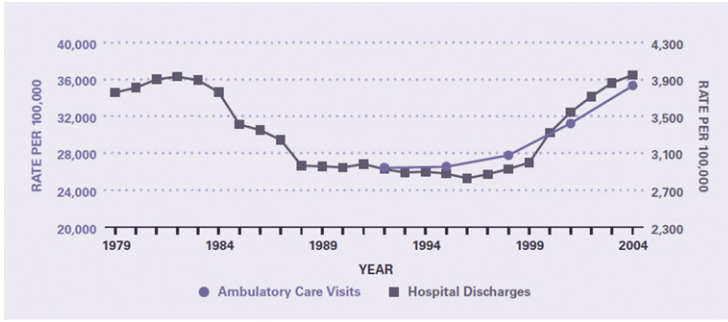

Fig. 2. For all digestive diseases, age-adjusted rates of ambulatory care visits and hospital discharges with all-listed diagnoses in the United States from 1979 to 2004. (*From* Everhart JE, editor. The burden of digestive diseases in the United States. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Washington, DC: US Government Printing Office, 2008; NIH Publication No. 09–6443 p. 6–7.

be met to determine a cause-and-effect relationship (**Box 2**). It is usually difficult to meet all these criteria, particularly when trying to find the cause-and-effect relationships between organisms in the small intestine or colon because of the large number of organisms living in these environments. Even for *H pylori* infection and the relationship with gastric cancer, although it is currently the only bacterium classified as a class I carcinogen, the evidence supporting this relationship is not complete in terms of Bradford Hill's criteria.

ORGANISMS ASSOCIATED WITH GI TRACT DISEASES

There are a large number of organisms believed to be responsible for diseases of the digestive system. Some of these organisms are true pathogens, whereas others are merely commensal in nature and are unlikely to ever produce any pathologic condition. **Table 3** shows the various types of microbes that are associated with diseases of the GI tract covered in this issue; it is by no means all-inclusive but provides the current magnitude of an ever-increasing field of research. At present, some of these diseases are only associated with a single group of organisms (eg, irritable bowel syndrome), whereas other diseases are affected by all groups of organisms (eg, appendicitis).

FUTURE CHALLENGES

There are a variety of methodological and technical issues related to infectious agents and their role in digestive diseases. For diseases of the colon, the major limitation remains the inability to completely identify these organisms. Identification of bacteria was mainly conducted using culture-based methods. Now, the focus in identification of bacteria is increasingly based on using molecular techniques. Many of these techniques allow the detection and identification of viable but nonculturable cells that are metabolically active but not reproducing. Gene sequencing using single-stranded RNA has been a key method in being able to elucidate multitudes of organisms that remain unknown. At present, there are approximately 9000 bacterial species, and this number is estimated as just the tip of the iceberg. The development of molecular

Table 2
Estimates of digestive disease burden around the world

Country/Region	Extrapolated Prevalence	Population Estimated Used
Digestive Diseases in North America (Extrapolated Statistics)		
United States of America	64,776,924	293,655,405[a]
Canada	7,170,854	32,507,874[b]
Digestive Diseases in Europe (Extrapolated Statistics)		
Austria	1,803,256	8,174,7622
Belgium	2,282,707	10,348,276[b]
Britain (United Kingdom)	13,295,008	60,270,708 for UK[b]
Czech Republic	274,892	10,246,178[b]
Denmark	1,194,130	5,413,392[b]
Finland	1,150,259	5,214,512[b]
France	13,328,869	60,424,213[b]
Greece	2,348,719	10,647,529[b]
Germany	18,181,898	82,424,609[b]
Iceland	64,845	293,966[b]
Hungary	2,213,023	10,032,375[b]
Liechtenstein	7375	33,436[b]
Ireland	875,637	3,969,558[b]
Italy	12,806,795	58,057,477[b]
Luxembourg	102,063	462,690[b]
Monaco	7118	32,270[b]
Netherlands (Holland)	3,599,602	16,318,199[b]
Poland	8,520,517	38,626,349[b]
Portugal	2,321,502	10,524,145[b]
Spain	8,885,465	40,280,780[b]

Sweden	1,982,294	8,986,400[b]
Switzerland	1,643,573	7,450,867[b]
United Kingdom	13,295,008	60,270,708[b]
Wales	643,676	2,918,000[b]
Digestive Diseases in the Balkans (Extrapolated Statistics)		
Albania	781,942	3,544,808[b]
Bosnia and Herzegovina	89,913	407,608[b]
Croatia	991,956	4,496,869[b]
Macedonia	450,018	2,040,085[b]
Serbia and Montenegro	2,388,066	10,825,900[b]
Digestive Diseases in Asia (Extrapolated Statistics)		
Bangladesh	31,178,044	141,340,476[b]
Bhutan	482,110	2,185,569[b]
China	286,510,493	1,298,847,624[b]
East Timor	224,834	1,019,252[b]
Hong Kong SAR	1,512,159	6,855,125[b]
India	234,942,036	1,065,070,607[b]
Indonesia	52,599,913	238,452,952[b]
Japan	28,088,161	127,333,002[b]
Laos	1,338,555	6,068,117[b]
Macau SAR	98,224	445,286[b]
Malaysia	5,188,782	23,522,482[b]
Mongolia	606,907	2,751,314[b]
Philippines	19,023,902	86,241,697[b]
Papua New Guinea	1,195,649	5,420,280[b]
Vietnam	18,234,440	82,662,800[b]
Singapore	960,417	4,353,893[b]

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Table 2
(*continued*)

Country/Region	Extrapolated Prevalence	Population Estimated Used
Pakistan	35,116,837	159,196,336[b]
North Korea	5,006,812	22,697,553[b]
South Korea	10,639,799	48,233,760[b]
Sri Lanka	4,390,845	19,905,165[b]
Taiwan	5,018,346	22,749,838[b]
Thailand	14,308,570	64,865,523[b]
Digestive Diseases in Eastern Europe (Extrapolated Statistics)		
Azerbaijan	1,735,673	7,868,385[b]
Belarus	2,274,379	10,310,520[b]
Bulgaria	1,658,376	7,517,973[b]
Estonia	295,955	1,341,664[b]
Georgia	1,035,417	4,693,892[b]
Kazakhstan	3,340,522	15,143,704[b]
Latvia	508,743	2,306,306[b]
Lithuania	795,860	3,607,899[b]
Romania	4,931,371	22,355,551[b]
Russia	31,758,982	143,974,059[b]
Slovakia	1,196,375	5,423,567[b]
Slovenia	443,707	2,011,473[b]
Tajikistan	1,546,666	7,011,556[b]
Ukraine	10,529,134	47,732,079[b]
Uzbekistan	5,825,826	26,410,416[b]
Digestive Diseases in Australasia and Southern Pacific (Extrapolated Statistics)		
Australia	4,392,605	19,913,144[b]
New Zealand	880,989	3,993,817[b]

Digestive Diseases in the Middle East (Extrapolated Statistics)		
Afghanistan	6,289,781	28,513,677[b]
Egypt	16,790,606	76,117,421[b]
Gaza Strip	292,277	1,324,991[b]
Iran	14,890,412	67,503,205[b]
Iraq	5,597,358	25,374,691[b]
Israel	1,367,428	6,199,008[b]
Jordan	1,237,765	5,611,202[b]
Kuwait	497,988	2,257,549[b]
Lebanon	833,209	3,777,218[b]
Libya	1,242,261	5,631,585[b]
Saudi Arabia	5,690,280	25,795,938[b]
Syria	3,974,310	18,016,874[b]
Turkey	15,197,187	68,893,918[b]
United Arab Emirates	556,745	2,523,915[b]
West Bank	509,824	2,311,204[b]
Yemen	4,417,249	20,024,867[b]
Digestive Diseases in South America (Extrapolated Statistics)		
Belize	60,208	272,945[b]
Brazil	40,610,537	184,101,109[b]
Chile	3,490,578	15,823,957[b]
Colombia	9,333,258	42,310,775[b]
Guatemala	3,150,131	14,280,596[b]
Mexico	23,152,850	104,959,594[b]
Nicaragua	1,182,299	5,359,759[b]
Paraguay	1,365,742	6,191,368[b]
Peru	6,075,949	27,544,305[b]
Puerto Rico	859,844	3,897,960[b]
Venezuela	5,518,541	25,017,387[b]

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Table 2
(*continued*)

Country/Region	Extrapolated Prevalence	Population Estimated Used
Digestive Diseases in Africa (Extrapolated Statistics)		
Angola	2,421,739	10,978,552[b]
Botswana	361,595	1,639,231[b]
Central African Republic	825,547	3,742,482[b]
Chad	2,104,090	9,538,544[b]
Congo Brazzaville	661,332	2,998,040[b]
Congo Kinshasa	12,864,050	58,317,030[b]
Ethiopia	15,736,007	71,336,571[b]
Ghana	4,578,756	20,757,032[b]
Kenya	7,275,464	32,982,109[b]
Liberia	747,934	3,390,635[b]
Niger	2,506,000	11,360,538[b]
Nigeria	3,915,519	125,750,356[b]
Rwanda	1,817,354	8,238,673[b]
Senegal	2,393,855	10,852,147[b]
Sierra Leone	1,297,916	5,883,889[b]
Somalia	1,831,897	8,304,601[b]
Sudan	8,635,623	39,148,162[b]
South Africa	9,804,809	44,448,470[b]
Swaziland	257,920	1,169,241[b]
Tanzania	7,956,793	36,070,799[b]
Uganda	5,821,380	26,390,258[b]
Zambia	2,432,137	11,025,690[b]
Zimbabwe	809,969	12,671,860[b]

Abbreviation: SAR, special administrative region.
[a] US Census Bureau, population estimates, 2004.
[b] US Census Bureau, international database, 2004.

Box 1
List of the National Institute of Allergy and Infectious Diseases on emerging and re-emerging diseases

Group I: pathogens newly recognized in the past 2 decades

Acanthamebiasis

Australian bat Lyssavirus

Babesia, atypical

Bartonella henselae

Ehrlichiosis

Encephalitozoon cuniculi

Encephalitozoon hellem

Enterocytozoon bieneusi

H pylori

Hendra or equine *morbillivirus*

Hepatitis C

Hepatitis E

Human herpesvirus 8

Human herpesvirus 6

Lyme borreliosis

Parvovirus B19

Group II: re-emerging pathogens

Enterovirus 71

Clostridium difficile

Mumps virus

Streptococcus, group A

Staphylococcus aureus

Group III: Agents with bioterrorism potential

National Institute of Allergy and Infectious Diseases (NIAID): category A

- *Bacillus anthracis* (anthrax)
- *Clostridium botulinum* toxin (botulism)
- *Yersinia pestis* (plague)
- Variola major (smallpox) and other related poxviruses
- *Francisella tularensis* (tularemia)
- Viral hemorrhagic fevers
- Arenaviruses: lymphocytic choriomeningitis virus, Junin virus, Machupo virus, Guanarito virus, Lassa fever
- Bunyaviruses: Hantaviruses, Rift Valley fever, Flaviviruses, dengue virus
- Filoviruses: Ebola, Marburg

NIAID: category B

- *Burkholderia pseudomallei*

- *Coxiella burnetii* (Q fever)
- *Brucella* species (brucellosis)
- *Burkholderia mallei* (glanders)
- *Chlamydia psittaci* (psittacosis)
- Ricin toxin (from *Ricinus communis*)
- Epsilon toxin of *Clostridium perfringens*
- *Staphylococcus* enterotoxin B
- Typhus fever (*Rickettsia prowazekii*)
- Food- and waterborne pathogens
- Diarrheagenic *Escherichia coli*
- Pathogenic vibrios
- *Shigella* species
- *Salmonella*
- *Listeria monocytogenes*
- *Campylobacter jejuni*
- *Yersinia enterocolitica*
- Viruses (Caliciviruses, Hepatitis A)
- Protozoa: *Cryptosporidium parvum*, *Cyclospora cayetanensis*, *Giardia lamblia*, *Entamoeba histolytica*, *Toxoplasma*
- Fungi
- Microsporidia
- Additional viral encephalitides: West Nile virus, La Crosse virus, California encephalitis virus, Venezuelan equine encephalitis virus, Eastern equine encephalitis virus, Western equine encephalitis, Japanese encephalitis virus, Kyasanur forest virus

NIAID: category C

- Emerging infectious disease threats such as Nipah virus and additional hantaviruses
- NIAID priority areas
- Tick-borne hemorrhagic fever viruses: Crimean-Congo hemorrhagic fever virus
- Tick-borne encephalitis viruses
- Yellow fever
- Multidrug-resistant tuberculosis
- Influenza
- Other rickettsias
- Rabies
- Prions
- Chikungunya virus
- Severe acute respiratory syndrome–associated coronavirus
- Antimicrobial resistance, excluding research on sexually transmitted organisms
  - Research on mechanisms of antimicrobial resistance
  - Studies of the emergence and/or spread of antimicrobial resistance genes within pathogen populations

Studies of the emergence and/or spread of antimicrobial-resistant pathogens in human populations

Research on therapeutic approaches that target resistance mechanisms

Modification of existing antimicrobials to overcome emergent resistance

Antimicrobial research, as related to engineered threats and naturally occurring drug-resistant pathogens, focused on the development of broad-spectrum antimicrobials

Innate immunity, defined as the study of nonadaptive immune mechanisms that recognize, and respond to, microorganisms, microbial products, and antigens

Coccidioides immitis

Coccidioides posadasii

methods offers great promise not only in research and development but also in the diagnostic setting (eg, stool samples) (**Table 4**).[11,12] Clearly, metagenomics, in which genetic material is directly retrieved from environmental sources, will play a critical role in the future development of determining infectious agents of the GI tract. The use of high-throughput technology has already produced important findings in relation to the GI tract microflora, including the differences between adults and children, with numerous uncultured organisms being the crux of the normal human adult gut flora which remain stable but other organisms change depending on environmental and genetic factors, whereas in infants there appear to be a constant transformation of organisms over time (**Figs. 3** and **4**).[11] There have been several new detection methods developed, with some of these using nanoscale electrochemical detectors and others using DNA sensors (extrachromosomal DNA).[13] The use of stable-isotope probing is also being investigated, but even this technique has limitations.[14] Although these technologies are increasing the understanding of the gut microflora, there remains large gaps of knowledge regarding the metabolic functions of these organisms and the relationship they have with human GI disease. These will be extremely fruitful areas of research and development in the coming years.

Box 2
Bradford Hill's criteria for causality

Consistency: The association is consistent when results are replicated in studies in different settings using different methods.

Strength: This is defined by the size of the risk as measured by appropriate statistical tests.

Specificity: This is established when a single putative cause produces a specific effect.

Dose-response relationship: An increasing level of exposure (in amount and/or time) increases the risk.

Temporal relationship: Exposure always precedes the outcome.

Biologic plausibility: The association agrees with currently accepted understanding of pathobiologic processes. This criterion should be applied with caution.

Coherence: The association should be compatible with existing theory and knowledge.

Experiment: The condition can be altered by an appropriate experimental regimen. Experiment is possibly the most important support for a causal relationship.

Table 3
Organisms associated with GI tract disease in humans

GI Tract Disease	Bacteria	Virus	Parasite	Fungi
Esophageal Cancer	α-hemolytic streptococcus, β-hemolytic streptococcus, *Bacteroides fragilis*, *Bacteroides melaninogenicus*, *Bacteroides* sp, *Clostridium* sp, coagulase-negative *Staphylococcus*, *Corynebacterium* sp, *Escherichia coli*, *Fusobacteria* sp, *Haemophilus influenzae*, *Lactobacillus* sp, *Neisseria catarrhalis*, nonhemolytic streptococcus, *Peptococcus*, *Pneumococcus*, *Proteus mirabilis*, *Staphylococcus albus*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus viridans*, *Candida albicans* *Mycobacterium avium*, *Mycobacterium tuberculosis*	Cytomegalovirus, Epstein-Barr virus, Herpes simplex virus, Varicella-zoster virus	Cryptosporidium	Histoplasma capsulatum,
Gastric Cancer	*H pylori*	Epstein-Barr virus	—	—
Cholangiocarcinoma	—	Hepatitis C virus, Hepatitis B virus	*Clonorchis sinensis*, *Opistochus vivarini*	—
Gall Bladder Disease	*E coli*, *H pylori*, *Helicobacter* sp, Enterobacteriaceae, Leptospira, *Salmonella enteritidis*, *Salmonella typhi*, *Staphylococcus aureus*, *Micrococcus* sp	Cytomegalovirus, Epstein-Barr virus, Dengue virus	*C sinensis*, *O vivarini, Ascaris lumbricoides*, *Dolosigranulum pigrum*	*Actinomyces* sp, *Candida* sp,
Hepatocellular Carcinoma	—	Hepatitis B virus, Hepatitis C virus	—	—

Acute Pancreatitis	*Mycoplasma pneumoniae*, *S typhi*, *Leptospira*, *Yersinia enterocolitica*, *Yersinia pseudotuberculosis*, *Campylobacter jejuni*, *M tuberculosis*, *M avium*, *Legionella* sp, *Brucellosis*, *Actinomyces*, *Nocardia*	Measles virus, Coxsackie B virus, hepatitis B virus, Cytomegalovirus, herpes simplex virus, varicella virus, human immunodeficiency virus, Epstein-Barr virus, vaccinia, rubella, adenovirus	*A lumbricoides, Echinococcus granulosus*	*Aspergillus* sp, *Cryptococcus neoformans*, *Coccidioides immitis*, *Paracoccidioides brasiliensis*, *Histoplasma capsulatum*, *Pneumocystis carinii*
Small Intestinal Bacterial Overgrowth	*Streptococcus* sp, *E coli*, *Staphylococcus* sp, *Micrococcus* sp, *Klebsiella* sp, *Methanobrevibacter smithii*, *Bacteroides* sp, *Firmicutes* sp	—	—	—
Irritable Bowel Syndrome	*Salmonella* sp, *Campylobacter* sp, *Shigella* sp, Enterobacteriaceae, Clostridia	—	—	—
Inflammatory Bowel Disease	*E coli*, *M avium*, *Streptococcus* sp, Clostridia, Actinobacteria, Proteobacteria, *Clostridium leptum*, *Faecalibacterium prausnitzii*, *Bacteroides*, Fusobacteria	—	—	—
Appendicitis	*Y enterocolitica, Y pseudotuberculosis, Actinomyces israelii*, *Mycobacterium*, *C jejuni*, *Clostridium difficile*, *Salmonella* sp, *B fragilis*	Adenovirus, cytomegalovirus, measles virus (rubeola virus)	*A lumbricoides, Enterobius vermicularis*, *Strongyloides stercoralis*, *Schistosomiasis haematobium*, *Entamoeba histolytica*, *Trichuris* sp	Mucormycosis, histoplasma capsulatum
Colorectal Cancer	*Helicobacter hepaticus*, *Enterococcus faecalis*, *Streptococcus bovis*, *H pylori*, *Clostridium septicum*, *E coli*, *Streptococcus sanguis*, *Streptococcus salivarius*	Human papillomavirus, JC virus, Epstein-Barr virus, cytomegalovirus	—	—

Table 4
Automatic nucleic acid extraction methods from bacteria

Instrument	Method	Number of Samples	Time Required
ABI PRISM 6100 nucleic acid PrepStation (Applied Biosystems)	Silica membrane bind/elute protocols with vacuum processing (RNA and DNA)	Up to 96	30 min
ABI PRISM 6700 automated nucleic acid workstation (Applied Biosystems)	Silica membrane bind/elute protocols with vacuum processing (RNA and DNA)	Up to 96	90 min
BioRobot EZ1 workstation (QIAGEN)	Silica membrane bind/elute protocols using magnetic-particle handling (RNA and DNA)	1–6	15–20 min
iPrep Purification Instrument (Invitrogen)	Based on a unique, ionizable nucleic acid-binding ligand whose charge can be switched based on the pH of the surrounding medium (DNA)	Up to 12	18 min
KingFisher ML/96 (Thermo Scientific)	Silica membrane bind/elute protocols using magnetic-particle handling (RNA and DNA)	1–96	20–30 min
MagNA pure compact/LC (Roche Applied Science)	Silica membrane bind/elute protocols using magnetic-particle handling (RNA and DNA)	1–32	15–40 min
Maxwell 16 Instrument (Promega)	Silica membrane bind/elute protocols using magnetic-particle handling (RNA and DNA)	Up to 16	30 min
NucliSens miniMAG (BioMérieux)	Silica membrane bind/elute protocols using magnetic-particle handling (RNA and DNA)	Up to 12	45 min
QIAcube (QIAGEN)	Silica membrane bind/elute protocols with built in centrifuge (RNA and DNA)	Up to 12	60 min, user-developed protocols
X-Tractor Gene RNA/DNA Extraction System (Corbett Life Science)	Silica membrane bind/elute protocols with vacuum processing (RNA and DNA)	8–96	1 h

Data from Barken KB, Haagensen JA, Tolker-Nielsen T. Advances in nucleic acid-based diagnostics of bacterial infections. Clin Chim Acta 2007;384:1–11.

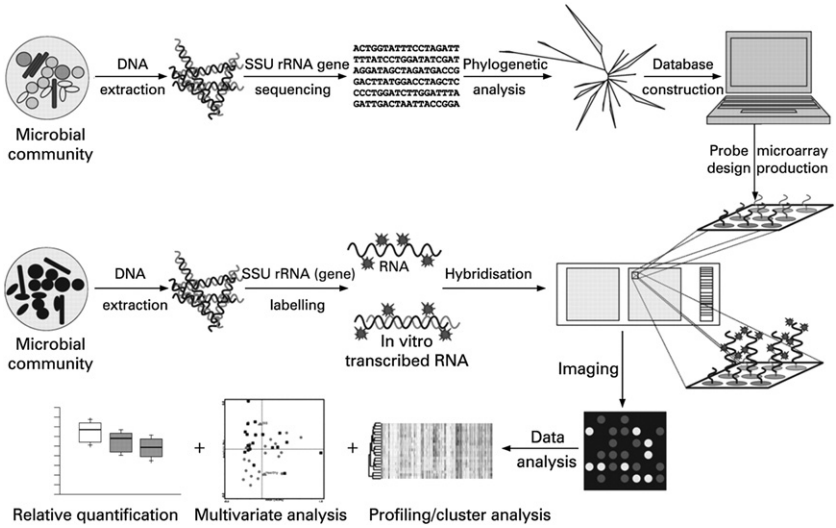

Fig. 3. High-throughput analysis of human GI tract microbiota via brute force sequencing and phylogenetic microarray analysis. SSU rRNA, small subunit ribosomal RNA. (*From* Zoetendal EG, Rajilic-Stojanovic M, de Vos WM. High-throughput diversity and functionality analysis of the gastrointestinal tract microbiota. Gut 2008;57:1605–15; with permission.)

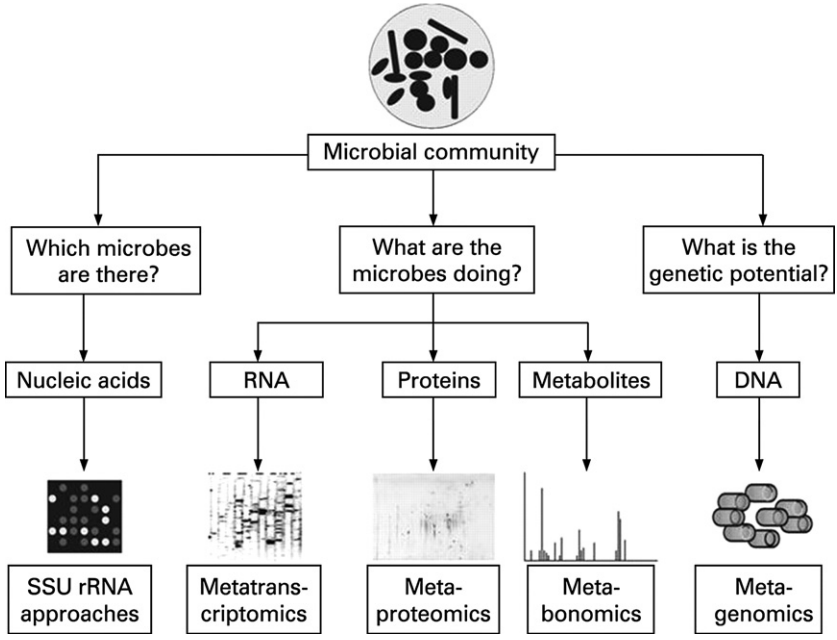

Fig. 4. Metagenomics and other community-based "omics" approaches. SSU rRNA, small subunit ribosomal RNA. (*From* Zoetendal EG, Rajilic-Stojanovic M, de Vos WM, High-throughput diversity and functionality analysis of the gastrointestinal tract microbiota. Gut 2008;57:1605–15, with permission.)

REFERENCES

1. Everhart JE editor. The burden of digestive diseases in the United States. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Washington, DC: US Government Printing Office. NIH Publication No. 09–6443; 2008. p. 1–12
2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA Cancer J Clin 2009; 59:225–49.
3. Goh KL. Changing trends in gastrointestinal disease in the Asia-Pacific region. J Dig Dis 2007;8:179–85.
4. Shaheen NJ, Hansen RA, Morgan DR, et al. The burden of gastrointestinal and liver diseases, 2006. Am J Gastroenterol 2006;101:2128–38.
5. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part I: overall and upper gastrointestinal diseases. Gastroenterology 2009;136:376–86.
6. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part II: lower gastrointestinal diseases. Gastroenterology 2009;136:741–54.
7. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part III: liver, biliary tract, and pancreas. Gastroenterology 2009;136:1134–44.
8. Hellier MD, Williams JG. The burden of gastrointestinal disease: implications for the provision of care in the UK. Gut 2007;56:165–6.
9. Schlenker C, Surawicz C. Emerging infections of the gastrointestinal tract. Best Pract Res Clin Gastroenterol 2009;23:89–99.
10. Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965;58:295–300.
11. Zoetendal EG, Rajilic-Stojanovic M, de Vos WM. High-throughput diversity and functionality analysis of the gastrointestinal tract microbiota. Gut 2008;57: 1605–15.
12. Barken KB, Haagensen JA, Tolker-Nielsen T. Advances in nucleic acid-based diagnostics of bacterial infections. Clin Chim Acta 2007;384:1–11.
13. Fan C, Plaxco KW, Heeger AJ. Electrochemical interrogation of conformational changes as a reagentless method for the sequence-specific detection of DNA3. Proc Natl Acad Sci U S A 2003;100:9134–7.
14. Kovatcheva-Datchary P, Zoetendal EG, Venema V, et al. Tools for the tract: understanding the functionality of the gastrointestinal tract. Therap Adv Gastroenterol 2009;2(Suppl 1):S9–22.