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GUT MICROBIOTA AND HUMAN HEALTH: INSIGHTS FROM ECOLOGICAL RESTORATION

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ABSTRACT

Dysbiosis of the gut facilitates chronic diseases such as cancer, obesity, and autoimmune disorders. Successful treatment may require restoration of functions performed by symbiotic microbes. The field of ecological restoration has restored species diversity and ecosystem function of natural habitats since the latter part of the 20th century, but its possible applications to medicine are unexplored. Here we show that approaches developed to restore natural ecosystems may aid in the treatment of chronic disease by helping to characterize target conditions for healthy microbe communities, by identifying the importance of donor diversity in fecal microbiota transplants, and by elevating the importance of diet, patient involvement, and personalized medicine in gut health. Dialogue between the fields of restoration ecology and medicine may help to guide future directions in gut research and clinical care.

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INTRODUCTION

THROUGHOUT history, humans have harmed beneficial species via inadvertent side effects of culture and technology. From stone points to the plow to petroleum, people have found ways to improve their well-being, but frequently failed to mitigate costly side effects such as megafauna extinction, topsoil loss, deforestation, and climate change (Lorenzen et al. 2011; Ruddiman et al. 2015), spurring what some have called a sixth major extinction (Dirzo et al. 2014). This propensity has affected not only the species around us, but also those inside us. Communities of human gut microbes have shifted in the wake of agriculture, industrial diets, sanitation, and antibiotics (De Filippo et al. 2010; Harper and Armelagos 2013; Gillings et al. 2015; Obregon-Tito et al. 2015), with changes linked to degraded health via chronic disease (Blumberg and Powrie 2012).

Insights into the importance of symbiotic microbes for human health, and calls to manipulate them for therapeutic purposes (Bäckhed et al. 2012), are accumulating in rough coincidence with what Roberts et al. call "the maturation of the young discipline of ecological restoration" (Roberts et al. 2009:555). Ecological restoration is defined as "the process of assisting the recovery of an ecosystem that has been degraded, damaged, or destroyed" (Society for Ecological Restoration International Science & Policy Working Group 2004:3). From the perspective of their gut microbes, humans are ecosystems (Box 1) because they host multiple interdependent species in a shared location, along with nonliving components, such as food substrates and bioelements. This emerging view of humans as ecosystems raises the question of whether approaches developed to improve the health of natural ecosystems may help to advance gut medicine.

To date, potential applications of restoration ecology to medicine remain unexplored. A keyword search in Web of Science with all combinations of "microbiome" or "microbiota" and "restoration ecology" or "ecological restoration" returns only four citations, none of which apply restoration ecology to medicine. Here we review the success of ecological restoration in natural systems, and apply its theories and practices to the human gut to highlight current approaches and identify new directions in gut research and clinical care.

SUCCESSES OF ECOLOGICAL RESTORATION

"Ecosystem services" are benefits that natural ecosystems provide to humans, such as regulation of climate and higher yields in fisheries (Cardinale et al. 2012; Table 1). Analogously, microbe symbionts provide ecosystem services to humans (Costello et al. 2012), such as nutrition and regulation of immunity and body mass (Tables 1 and 2). A principal goal of ecological restoration is to improve the ability of degraded, damaged, or destroyed ecosystems to deliver ecosystem services (Clewell and Aronson 2006). Medicine shares the same goal whenever perturbation of symbiotic microbes jeopardizes human health.

A minimum requirement for applying ecological restoration to medicine is for it to have demonstrated success in the systems it was originally developed to address. In 89 restoration projects across a range of natural systems, ecosystem services improved by an average of 25% while biodiversity rose by 44%, although it did not attain levels provided by undisturbed systems (Rey Benayas et al. 2009). Across 70 wetlands, ecosystem services were 36% higher in restored than degraded sites (Meli et al. 2014). In 54 studies of restored agroecosystems, biodiversity and many ecosystem services returned to preagricultural levels (Barral et al. 2015).

Restoring ecosystem services creates economic benefits. Across 200 projects, economic return was estimated by subtracting project costs from ecosystem services gained. Restoration always provided a positive rate of return in six of the nine biomes analyzed, even under worst-case estimates of highest restoration costs, lowest restoration success, and highest relapse toward a degraded state (De Groot et al. 2013). The success of ecological restoration in natural ecosystems encourages inquiry into whether its theories and practices may be applied to benefit human health.

BOX 1
Terms relevant to gut restoration

Active restoration: Manipulates species composition or ecosystem function by adding or removing species, introducing functions (e.g., fire), or manipulating land forms (e.g., river channels). In the gut, active restoration might involve probiotics or fecal microbiota transplants.
Biodiversity: The number and relative abundance of species in a community.
Community: A collection of different species occurring in the same location (e.g., fish or plankton in a lake or bacteria in a gut).
Ecological restoration: The process of assisting the recovery of an ecosystem that has been degraded, damaged, or destroyed.
Ecosystem: A community (see above) plus abiotic components such as soil, geology, and bioelements.
Ecosystem function: Things an ecosystem does, such as move nutrients, purify water, or capture and move energy. Functions performed by a gut ecosystem include: digestion of microbe-accessible carbohydrates and production of vitamins (Koropatkin et al. 2012: Sonnenburg and Sonnenburg 2014); regulation of neuroendocrine functions (Foster et al. 2016); development of gastrointestinal tissues; and shaping of T-cell differentiation (Hooper et al. 2012b).
Ecosystem service: Benefits extracted by humans from nature (see Table 1).
Ecosystem structure: Characteristics of the species present in an ecosystem (e.g., species composition, biodiversity or, less commonly, life stages and growth forms).
Kyoto Encyclopedia of Genes and Genomes (KEGG): Databases linking gene sequences to biological function.
Microbiota-accessible carbohydrate (MAC): A polysaccharide digestible by gut microbes but not their human host. High-MAC diets are associated with better gut health than high fat/high sugar diets (Janssen and Kersten 2015).
Microbiome: Genes of an individual's microbiota.
Microbiota: Microbe symbionts of an individual or body location.
Passive restoration: Restoration conducted by removing a disturbance without further intervention.
Reference condition: A community or ecosystem identified as a desired target state for restoration; may be an actual, undisturbed site or a theoretical construct derived from ecological sleuthing.

"A reference condition" identifies an end goal for restoration

What should a healthy ecosystem look like? What should a healthy gut microbiota look like? In ecological restoration, "reference conditions" provide a specific end goal for restoration (Egan and Howell 2001; Society for Ecological Restoration International Science & Policy Working Group 2004). The simplest and most direct way to identify reference conditions is to examine undisturbed remnant ecosystems. For example, in the dry ponderosa pine forests of Central Washington, an undisturbed forest occurs on an isolated plateau where steep terrain has impeded clearcutting and grazing. Tree sizes, stand densities, and understory species on the plateau yielded insights into predisturbance conditions (Rummell 1951). Analogously, researchers have explored reference conditions for the gut by examining traditional human societies whose culture and geography

TABLE 1
Gut microbiota may be viewed as a source of ecosystem services

Ecosystem service (ES) category	Examples in nature	Examples in the gut (details in Table 2)
1. Provisioning—produce products used by humans	Fisheries, fresh water, timber, pharmaceuticals	Microbes produce short-chain fatty acids (SCFAs) and vitamins, which serve as key nutritional sources (Koropatkin et al. 2012; Sonnenburg and Sonnenburg 2014)
2. Regulating—dampen extremes in ecosystem properties such as climate, flooding, and population sizes	Store carbon, store water, stabilize soil, biological control of crop pests and disease vectors	Microbes control blood sugar and weight (Clemente et al. 2012), prevent harmful bacteria overgrowth (Koropatkin et al. 2012), and reduce inflammation (Sokol et al. 2008; Clemente et al. 2012)
3. Supporting—allow ecosystem to function and thus indirectly provide all other services	Pollination, nutrient cycling, habitat provisioning	Microbes protect intestinal epithelia (Koropatkin et al. 2012), regulate immunity (Round and Mazmanian 2009), and improve mental health (Hsiao et al. 2013; Foster et al. 2016)
4. Cultural—provide spiritual, cultural, and recreational benefits	Sport fishing, ecotourism, spiritual renewal	Microbes support psychological well-being (Hsiao et al. 2013; Foster et al. 2016)

There are four categories of ecosystem services in nature, all of which have an analog in gut ecosystems.

renders them inaccessible to disturbances such as antibiotics and industrial diets. Such studies have found consistent differences between traditional and industrial gut microbiota. In every comparison we are aware of, gut microbiota species and gene richness are higher in traditional, usually uncontacted, cultures from Africa (De Filippo et al. 2010; Schnorr et al. 2014) and South America (Yatsunenko et al. 2012; Clemente et al. 2015; Obregon-Tito et al. 2015) than industrialized societies from Europe and North America. High diversity of gut microbes correlates with better health across numerous studies (Turnbaugh et al. 2009; Erickson et al. 2012; Cotillard et al. 2013; Le Chatelier et al. 2013; Colman and Rubin 2014; Kelly et al. 2015), although causative mechanisms, if they exist, are not yet well documented. High-fiber diets in traditional cultures may help to explain this difference (Sonnenburg and Sonnenburg 2014; Sonnenburg and Bäckhed 2016). Traditional societies also tend to have higher levels of specific taxa such as *Prevotella* (De Filippo et al. 2010; Yatsunenko et al. 2012; Schnorr et al. 2014; Clemente et al. 2015; Obregon-Tito et al. 2015) and *Treponema* (De Filippo et al. 2010; Schnorr et al. 2014; Obregon-Tito et al. 2015), and lower levels of *Bifidobacterium* (De Filippo et al. 2010; Schnorr et al. 2014; Obregon-Tito et al. 2015) and *Bacteroides* (Yatsunenko et al. 2012; Schnorr et al. 2014; Clemente et al. 2015; Obregon-Tito et al. 2015). The ratio of *Prevotella*:*Bacteroides* is correlated with health via glucose metabolism (Kovatcheva-Datchary et al. 2015). Mechanistic links between *Treponema, Bifidobacterium*, and health require further study.

"Functional" biomarkers, such as genes or metabolites, may identify reference conditions in the gut more reliably than taxon-based markers such as species and phyla because different taxa often perform the same functions for a host (Gilbert et al. 2016; Wang and Jia 2016) and, therefore, the absence of one taxon in a gut environment may not be important if its functions are performed by other taxa. Various functional biomarkers distinguish traditional from industrial societies. For example, rural African children from Burkina Faso have four times higher levels of propionic acid and butyric acid in their feces than European children (De Filippo et al. 2010). These two short-chain fatty acids (SCFAs) are produced exclusively by gut microbes, and affect physiological functions, including tumor suppression, colonocyte nutrition, gluconeogenesis,

TABLE 2
Microbe species present in the gut (i.e., ecosystem structure) affect human health (i.e., ecosystem function)

Structure	Function	Details	References
Faecalibacterium prausnitzii	Immunity	Reduces colitis[M/E]; reduced abundance is associated with postoperative recurrence of Crohn's disease[H/O]; secreted metabolites reduce inflammation[M/E†, CC/E†]	Sokol et al. (2008)
Christensenella minuta	Obesity	Both associates with[H/O] and causes[GFM/E] leanness	Goodrich et al. (2014)
Bacteroides fragilis	Psychology	Alters microbiota composition; corrects gut permeability; improves communicative, stereotypic, anxiety-like, and sensorimotor behaviors; improves serum metabolite profiles associated with behavioral abonormalities[MIAM/E†]	Hsiao et al. (2013)
Bacteroides thetaiotaomicron and many others	Digestion	Digests diet-derived polysaccharides from plants, animals, and breast milk that otherwise are undigestible by human enzymes[H/E†]	Koropatkin et al. (2012)

Superscripts prior to slash denote test subject (H = human, M = mouse, GFM = germ-free mouse, MIAM = maternal immune activation mouse, CC = cell culture); superscripts after slash denote experimental design (O = observational study, E = experimental study, E† = experimental study with mechanistic component demonstrated). More complete tables linking gut structure to function exist elsewhere (Qin et al. 2010:Table S11; Koropatkin et al. 2012:Table 1; Peterson et al. 2015:Table 2).

cell signaling, inflammation, obesity, and immunity (Koropatkin et al. 2012; Sonnenburg and Sonnenburg 2014; Wang and Jia 2016). Diets low in the plant polysaccharides that serve as precursors to SCFAs are associated with various chronic diseases (Sonnenburg and Sonnenburg 2014), and such diets and diseases are common in Western society.

Direct observations of predisturbance communities provide a convenient approach to assessing reference conditions, but natural ecosystems commonly suffer such widespread degradation that their original intact conditions no longer exist. In their absence, restoration ecologists resort to other clues to devise a reference ecosystem. For example, reference conditions for dry ponderosa pine forests in Arizona have been identified using photographs, stump records, historic survey records, and fire scars (Fulé et al. 1997). Analogously, many studies of gut health draw upon an entirely Westernized population, all of whose microbiota may deviate from their historic state. This does not mean, however, that all Westernized individuals are inherently sick, and microbiome-wide association studies (MWAS; Box 1; Gilbert et al. 2016; Wang and Jia 2016) may help to identify reference conditions in the gut within a Western population. MWAS associate characteristics of gut microbiota with host condition, and host health consistently associates with high genetic and taxonomic richness of gut microbes, high levels of butyric and propionic acid (Erickson et al. 2012; Sonnenburg and Bäckhed 2016; Wang and Jia 2016), and sometimes particular species (Gilbert et al. 2016; Wang and Jia 2016).

To infer desired reference conditions using MWAS, it is important to understand whether microbiota differences between healthy and diseased individuals are a cause or a consequence of disease (Gilbert et al. 2016; Wang and Jia 2016). Longitudinal studies that monitor gut microbiota during a course of treatment may help to ascertain causality (Gilbert et al. 2016; Wang and Jia 2016). For example, microbiota changes in type 2 diabetics in response to treatment with Chinese herbs both preceded and correlated with health-related improvements in fasting blood glucose, glycated hemoglobin, and postprandial blood glucose (Xu et al. 2015). Causation also can be tested by transferring stool from diseased and healthy humans to germ-free mice (Gilbert et al. 2016; Wang and Jia 2016). Symptoms of obesity (Ridaura et al. 2013) and kwashiorkor (Smith et al. 2013) have been transferred to experimental animals. Such studies also offer insight into the rela-

tive reliability of taxonomic versus genetic biomarkers in disease. In the kwashiorkor experiment (Smith et al. 2013) there was no signature of disease at any taxonomic level, from phylum through species; however, healthy and diseased individuals differed in microbial genes, measured using Kyoto Encyclopedia of Genes and Genomes (KEGG) enzyme commission (EC) numbers. In contrast, in a different study, taxonomic, metabolic, and transcriptional profiles all showed significant relationships to obesity in germ-free mice receiving stool from lean and obese humans (Ridaura et al. 2013).

Responses of microbiota biomarkers to treatment have been tracked using a microbial global positioning system. A microbial GPS uses principal coordinates analysis (PCoA) to plot biomarkers such as species, genes, gene products, or metabolites in n-dimensional space. Measurements are repeated during a course of treatment until the PCoA position of a sick individual either moves into the range occupied by healthy reference individuals (as in Gilbert et al. 2016) or out of the range occupied by diseased controls (as in Xu et al. 2015).

An "ecocentric" ideal of recreating historic landscapes for their own sake originally distinguished ecological restoration from other forms of land management (Jordan and Lubick 2011). Thus, a good reference condition was one that faithfully recreated predisturbance conditions. However, ecological restoration has begun to shift away from strict historic fidelity, in part because climate change is shifting the appropriateness of historic taxa to their current location, and in part because disturbance has become so pervasive that full restoration often is unrealistic (Shackelford et al. 2013; Higgs et al. 2014). Thus, history is increasingly viewed more as a guide than a template in ecosystem restoration (Higgs et al. 2014). The same could be said of the gut, since genetic, environmental, and cultural shifts in modern societies may make it inappropriate to try to restore gut communities with strict adherence to microbiota conditions found in traditional cultures. Nevertheless, both direct observations of traditional societies and other methods of inferring reference conditions for the human gut such as MWAS and microbial GPS have made headway in determining healthful states of the human gut biota, and identified some consistencies across techniques and study subjects, such as associations between high microbe diversity and better gut function. As we will argue later, however, such associations have not always been incorporated in medical interventions intended to improve gut health.

PASSIVE RESTORATION IS A FIRST PRIORITY

Disturbances in both nature (e.g., clearcutting, grazing, dams, species introductions, overharvesting) and the gut (e.g., diet, antibiotics) create the need for restoration. Restoration ecologists distinguish between two approaches to restoration: "passive restoration" and "active restoration." Passive restoration identifies and removes a disturbance without further intervention (Society for Ecological Restoration International Science & Policy Working Group 2004). For example, if a stream is degraded from browsing and bank trampling by cattle, then a passive approach would fence out the cows without further intervention, and will succeed if the system is capable of healing itself once disturbance ceases. Passive restoration will fail, however, if key species are no longer present or the system has moved to an alternative stable state, in which case "active restoration" is required. Restoration ecologists tend to prioritize passive restoration ahead of active restoration for two reasons, both of which apply in the gut. First, if a passive approach is sufficient to fix the problem, then active measures may introduce unneeded cost and redundancy. Second, active interventions are likely to fail if the source of the disturbance remains.

Removing a disturbance requires that it first be identified, which in a medical setting means taking a thorough patient history, including foreign travel, history of antibiotic use, sources of stress, and diet. Diet is an obvious target for passive restoration because diet-based disturbance is often chronic, and diet is increasingly recognized as a major factor affecting gut species composition (David et al. 2014) and its associated health effects

(Sonnenburg and Sonnenburg 2014; Sonnenburg and Bäckhed 2016; Wang and Jia 2016). Diets characterized by low microbe-accessible carbohydrates (MACs), high fructose, high calories, and/or high fat are associated with lower gut microbiota diversity (Ley et al. 2006b; Claesson et al. 2012; Sonnenburg et al. 2016) and, via their effects on gut microbiota, have been linked experimentally to obesity, endotoxemia (Janssen and Kersten 2015), and colitis (Devkota et al. 2012). Placing obese and overweight individuals on a calorie-restricted diet—a passive approach to restoration—increases gene richness, a parameter associated with decreased adiposity, blood cholesterol, and inflammation (Cotillard et al. 2013).

The timing of gut disturbances, both across generations and during an individual's development, may complicate passive, diet-based gut restoration. In mice, the ability of individuals fed an unhealthy low-MAC diet to recover a full complement of gut taxa after switching to a healthy high-MAC diet was increasingly compromised over each of four generations that mice spent on the unhealthy low-MAC diet (Sonnenburg et al. 2016). Subtherapeutic doses of antibiotics administered to mice early in life led to diet-induced obesity later in life (Cox et al. 2014). This sort of complexity may limit the efficacy of passive restoration in some patients.

If passive restoration is not sufficient to move a natural system satisfactorily toward reference conditions, then active restoration may be required, and could include physical manipulations of the landscape, exterminating undesired species, and introducing desired species. In the gut, active restoration might involve probiotics, antibiotics, or fecal microbiota transplants (FMT; Bäckhed et al. 2012). It is important to note, however, that if a passive approach does not solve the problem, then active measures should be applied *in addition to* continuing passive interventions, and *not instead* of them. We know this is true because healthy diets help to support microbe communities that are associated (De Filippo et al. 2010; Claesson et al. 2012), experimentally linked (Turnbaugh et al. 2008; Sonnenberg and Bäckhed 2016), and mechanistically linked (Sonnenberg and Sonnenberg 2014; Kovatcheva-Datchary et al. 2015) with good health. In terms of the stream analogy, it would not make sense to abandon passive measures and let cows back into a stream where active restoration has been implemented. In the next section, we discuss how mathematical models derived from ecology may offer insights into active restoration of the gut, particularly using FMT.

Structure-function models identify testable hypotheses in gut restoration

It is one thing to identify and remove a source of disturbance, but if that does not produce the desired outcome, and active restoration is required, then additional considerations arise. Field ecologists have repeatedly lamented that ecology is harder than rocket science (Hilborn and Ludwig 1993; Davis 2009). A plethora of interacting, often contingent, factors make ecosystems challenging to study—much less manipulate to desired end points. In ecology, active restoration frequently fails as early as the species establishment phase (Larson et al. 2015) due to factors ranging from annual variation in weather, properties inherent to individual species (e.g., seed mass), poorly adapted strains of a species, and insufficient understanding of biotic interactions, such as the role played by soil microbes in plant germination and establishment (Young et al. 2005; Larson et al. 2015).

Like natural ecosystems, guts are highly complex. Rob Knight, the head of the Human Microbiome Project, has echoed the ecologist's lament about complexity and rocket science (Knight and Buhler 2015:89). The human gut has the highest known cell densities of any microbial habitat on Earth (Ley et al. 2006a). An average European hosts as many as 160 of up to more than 1000 different gut bacterial species, and these harbor over 500,000 genes (Qin et al. 2010). Moreover, the gut microbiota's influence on health associates with variation at all levels of biological organization, from genes to phyla (Gilbert et al. 2016). To add to this complexity, many different host properties affect the species composition of gut microbiota, including mode of fetus delivery (vaginal versus

cesarean section), geography, genotype, age, diet, antibiotics (Bäckhed et al. 2012), and duration of symptoms (Moayyedi et al. 2015).

Ecologists use models to simplify complexity. A common ecological model, and one that is frequently utilized in restoration, employs a two-dimensional graph to relate the community of species present ("ecosystem structure") with how the system behaves ("ecosystem function"; Young et al. 2005; Cortina et al. 2006; Cardinale et al. 2011). Ecosystem structure is treated as the independent variable, and often is quantified as the number and/or relative abundance of species present. Ecosystem function is a dependent variable, and is measured as decomposition rates, nutrient flows, production of biomass, or other parameters (Cortina et al. 2006; Cardinale et al. 2011; Hooper et al. 2012a; Box 1; Figure 1). Figure 1A depicts three possible ways that structure and function can relate in an ecosystem: "immediate catastrophe," where a slight perturbation in species composition causes large losses in function; "proportional loss," where function declines linearly with structure; and "rivet-redundancy," where function declines little until large changes in species composition occur (Cardinale et al. 2011).

As in natural systems, structure-function relationships would appear to mediate interactions between gut microbes and human health (Bäckhed et al. 2012; Huttenhower et al. 2012). Five similarities between natural and gut ecosystems make structure-function models such as those in Figure 1A applicable to gut medicine. First, ecosystem structure is measured by recording species (or species attributes such as genes, transcripts, metabolites, and proteins) in both nature (Cardinale et al. 2011) and the gut (Erickson et al. 2012; Morgan et al. 2013; Shafquat et al. 2014). Second, the structure of gut communities associates with health-related functions, including obesity, metabolic syndrome, inflammatory bowel disease, diabetes, autism, allergies, asthma, cancer, and anorexia (Ley et al. 2006b; Turnbaugh et al. 2008; Qin et al. 2010; Bäckhed et al. 2012; Clemente et al. 2012; Koropatkin et al. 2012; Peterson et al. 2015; Table 2). Third, three common ways that function is measured in natural systems—

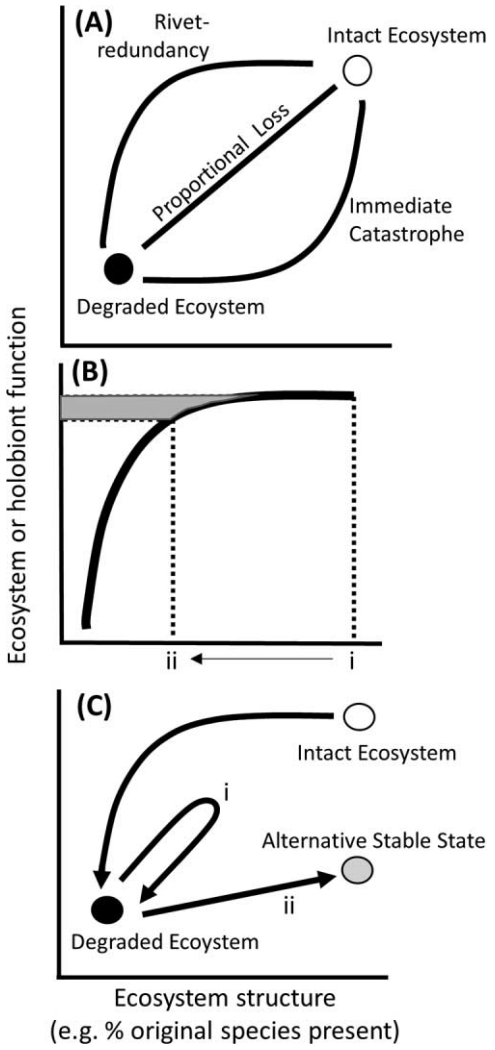

FIGURE 1. RELATIONSHIPS BETWEEN ECOSYSTEM STRUCTURE AND FUNCTION

(A) Three common structure-function relationships: *rivet-redundancy* (function is robust to diminished structure); *proportional loss* (function is lost linearly with structure); and *immediate catastrophe* (function declines rapidly after small losses in structure; Cardinale et al. 2011). (B) Under a rivet-redundancy model, gut-related health functions (y axis) remain robust (gray band) despite large declines in microbiota species diversity (from dotted line i to ii, x axis). Line ii represents a healthy but depleted individual, who may make a poor FMT donor (Figure 2). (C) In addition to those in Panel A, structure-function relationships may exhibit "irreversible change," where structure cannot be moved from the degraded state (arrow i), or an "alternative stable state," where function changes despite restoration of original structure (arrow ii; Cortina et al. 2006).

decomposition, nutrient flows, and biomass (Cardinale et al. 2011)—have human gut analogs: metabolism, energy harvest (Tilg and Kaser 2011; Koropatkin et al. 2012; Hsiao et al. 2013; Janssen and Kersten 2015), and body mass index (Ley et al. 2006b; Turnbaugh et al. 2008; Janssen and Kersten 2015). Fourth, when biodiversity is used as the metric for measuring ecosystem structure, it correlates positively with ecosystem function both in nature (Cardinale et al. 2012; Hooper et al. 2012a) and in the gut (Turnbaugh et al. 2009; Erickson et al. 2012; Cotillard et al. 2013; Le Chatelier et al. 2013; Colman and Rubin 2014; Kelly et al. 2015). Fifth, of the three structure-function models shown in Figure 1A, "rivet-redundancy" is most commonly observed in natural ecosystems (Cardinale et al. 2011, 2012), and would also appear to be the most common structure-function relationship in the gut.

In a rivet-redundancy model, function is robust to initial losses in species diversity because different species—sometimes many different species—perform the same function. Various lines of evidence suggest that a rivet-redundancy relationship predominates in the gut. First, hundreds of different human subjects harbored the same microbe-mediated gut metabolic pathways despite large differences in the microbe species present (Turnbaugh et al. 2009; Huttenhower et al. 2012), which points toward functional redundancy among gut taxa. Second, in both mice and humans, experimental subsets of microbiota appear to perform most of the functions present in the complete microbiota. For example, a subset of culturable species in stool from two human subjects produced more than 90% of the genes and proteins present in the complete (i.e., culturable + nonculturable) biota, and contained all of 14 of the genes for antibiotic resistance present in the complete biota, despite having only 56% of the complete species present (Goodman et al. 2011). Third, genes, rather than species, appear to form the functional core of ecosystem services provided by gut microbiota (Huttenhower et al. 2012), which provides a ready mechanism for functional redundancy because genes are commonly exchanged among human microbiota, with the highest rates of transfer in the gut (Liu et al. 2012). Fourth, Ley et al. (2006a) note that a wide range of functions can be restored by replacing as little as one microbe species in germ-free mice, which indicates that functional redundancy among species may occur because some species provide many overlapping functions. Fifth, functional redundancy will be favored at the host level because natural selection would be unlikely to select for host overreliance on one "keystone" microbe whose loss would devastate host fitness (Ley et al. 2006a). The application of structure-function models to gut medicine, and particularly the possibility that rivet-redundancy relationships predominate in human-microbe health relationships, leads to at least one conclusion that is not apparent without the models.

During fecal microbiota transplants, stool from a nominally healthy individual is transferred to a diseased individual to restore gut function. A rivet-redundancy relationship predicts that the biodiversity of donor gut microbes—which is currently ignored in FMT protocols—will influence FMT success. Under rivet-redundancy, seemingly "healthy" donors can harbor a depleted microbiota because their health remains relatively robust even after large losses in gut diversity (Figure 1B). However, as described in Figure 2, FMT may be less likely to succeed using a depleted donor than an intact donor. Depleted gut diversity is common in industrialized societies (De Filippo et al. 2010; Yatsunenko et al. 2012; Schnorr et al. 2014; Clemente et al. 2015; Obregon-Tito et al. 2015), which means that donor depletion may pose a common obstacle to FMT success.

Despite possible limitations posed by donor depletion, current FMT guidelines screen donors only for transmissible disease (Kelly et al. 2015). To our knowledge, no study has tested whether donor depletion reduces FMT success. The closest study we know of to associate individual donors with patient outcomes reported that, among 36 patients receiving FMT, seven of the nine recipients who underwent remission from ulcerative colitis received stool from one of the study's six donors, even though that donor was used for fewer than half of the patients in the

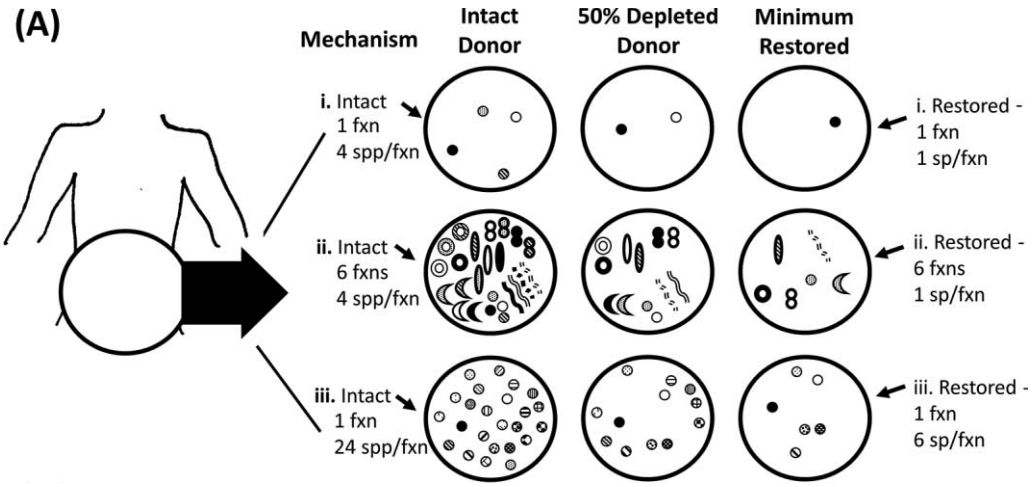

FIGURE 2. PANEL A. THREE POSSIBLE MECHANISMS (I–III) RELATING MICROBE COMMUNITY STRUCTURE TO HOST GUT FUNCTION

A population of a particular microbe species is present if its symbol is present. Every different shape-fill combination represents a different microbe species. Every different shape represents a different function performed by microbes. Mechanism i. Health is affected by just one function, and any one of N (in the diagram N = 4) different microbe species present in an intact donor would be sufficient to restore the function in a recipient—e.g., Hsiao et al. (2013); Sefik et al. (2015). Mechanism ii. Six different functions need to be restored to restore health, and an intact donor harbors N (in the diagram, N = 4) species per function. Mechanism iii. Assumes that from a pool of N competent donor species (in the diagram N = 24) affecting one function, any combination of six (or more) species needs to be established for health to be restored. Mechanisms ii and iii are based speculatively on Lawley et al. (2012) who found that six species needed to be administered simultaneously to overcome experimentally induced *Clostridium difficile* infection in mice. Each of the three mechanisms shown here has different implications for the efficacy of fecal microbiota transplants, as seen in Panel B.

study (Moayyedi et al. 2015). However, the association was not statistically significant (Moayyedi et al. 2015; despite data snooping, and possibly because of low statistical power), and no information on donor fecal diversity was reported.

Rivet-redundancy may affect not only the initial success of FMT but also the likelihood of relapse posttreatment. Replenishment of microbiota in an FMT recipient is more likely to be partial, and thus may place a recipient closer to relapse, if it comes from a depleted donor (Figure 1B, line ii) than a donor harboring high diversity (Figure 1B, line i). Relapse is common when FMT is used to treat inflammatory bowel disease, and FMT success has not been tracked over the long term in many studies of FMT for *Clostridium difficile* infection (Berg et al. 2015). Regardless of whether the issue is initial success or relapse, and regardless of whether physicians prescribe FMT or probiotics to replenish recipient biota, a rivet-redundancy model suggests that introducing a diversity of species with overlapping functions may improve patient outcomes.

The models in Figures 1A and B are not universal. Cortina et al. (2006) discuss additional relationships between structure and function in restoration, some of which may also be relevant to the gut (Figure 1C). An undesired community of species may become entrenched in a state of "irreversible change" if it alters the physical properties of an ecosystem in ways that help it to resist reestablishment of desired taxa. For example, invasive grasses alter fire, light, nutrients, soils, and water in ways that favor their continued competitive dominance (D'Antonio and Vitousek 1992). This may create an "alternative stable state" of degradation (Figure 1C)—or at least prolong the possibility of recovery.

Analogous processes in the gut merit consideration. Microbiota-accessible carbohydrates are carbohydrates resistant to digestion by human metabolism. They are metabolized

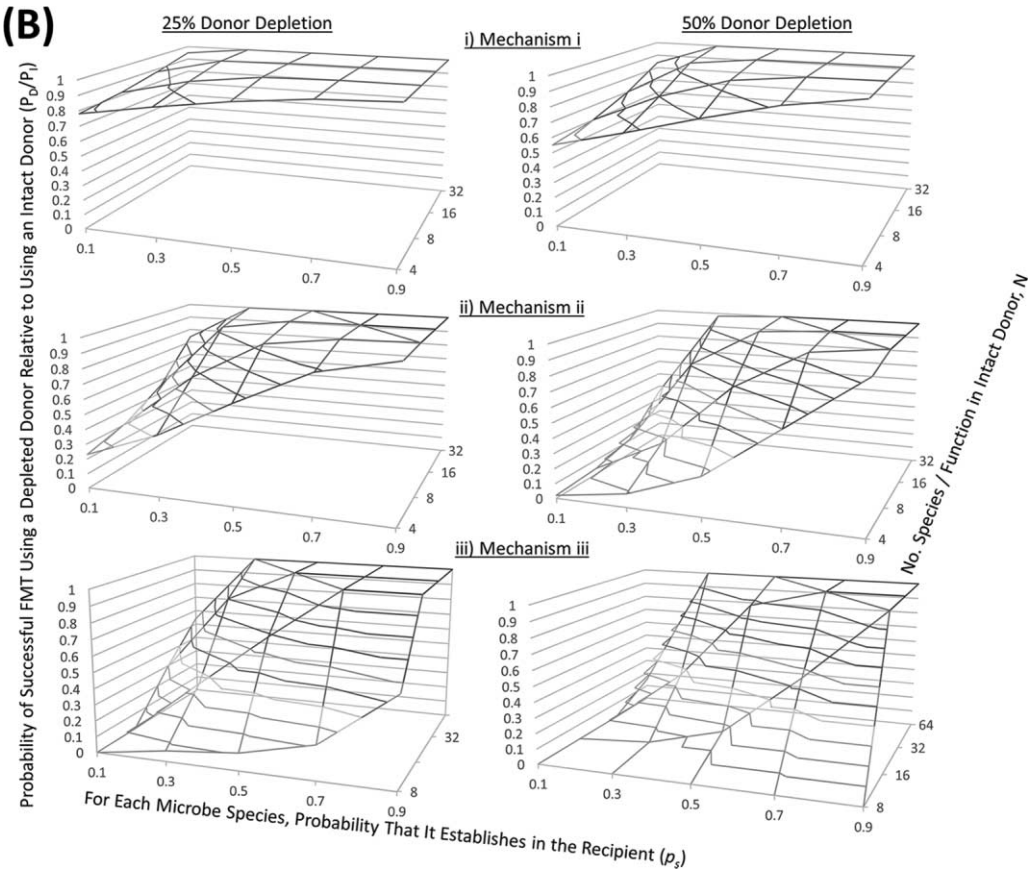

Figure 2. Panel B. Depleted Donors Jeopardize FMT Success

P is the probability of FMT success using a healthy donor with either a depleted (P_D) or intact (P_I) microbiome: their ratio, P_D/P_I (y axis), shows the proportional decrease in probability of FMT success using a depleted donor versus an intact donor. As the number (N) of different species providing a particular health function in an intact donor declines (z axis), and as the probability (p_s) of each species establishing in a recipient during FMT declines (x axis), P_D/P_I decreases, as shown by the surface falloff to the left of each panel. In the model, each of N species per function from an intact donor has a probability, $0 < p_s < 1$, of establishing in the recipient after FMT; p_s is the same for all N species; and $1 - p_s = q_s$ = the probability that a species does not establish in the recipient after FMT. Intact donors harbor N gut microbe species, while depleted donors harbor either 0.75N (left column; 25% donor depletion) or 0.5N (right column; 50% donor depletion) species. The mechanistic relationship between microbe structure and host function (described in Panel A), influences P_D/P_I, as seen in the different surfaces in the top, middle, and bottom rows. Under Mechanism i (top row), the probability that at least one species establishes, and health is restored = $1 - \phi$, where $\phi = q_1 * q_2 \ldots * q_N$. Mechanism ii is the same as i, except the probability that all six functions are reestablished and health is restored = $(1 - \phi_1)*(1 - \phi_2)\ldots(1 - \phi_6)$. Under Mechanism iii, the probability of six or more species from a pool of N species establishing in the recipient is given by the binomial expansion equation, $P = [N!/(x!(N - x)!]p^x q^{(N-x)}$. For each combination of N (y-axis) and p (x-axis), the probability that at least six functions are reestablished and health is restored = $\sum P$ for x = 6 to N.

Levels of depletion similar to or greater than those modeled here occur in response to diet, antibiotics, and disease. Changing from a diet high in microbiota-accessible carbohydrates to one high in fat and simple carbohydrates depleted biodiversity in mice by about 33% (Sonnenburg et al. 2016) and 50% (Turnbaugh et al. 2008). The relative abundance of gene sequences from the lean-associated phylum Bacteroidetes increased on average more than fivefold in individuals placed on a calorie-restricted diet (Ley et al. 2006b). In antibiotic studies, patients receiving the recommended therapeutic dose of clindamycin sustained a 50% depletion of Bacteroidetes clone types over two years (Jernberg et al. 2007), although ciprofloxacin had less of an effect (Dethlefsen and Relman 2011). Diseased Crohn's patients had a 75% reduction in the proportion of microbial genes expressed and identified as proteins (Erickson et al. 2012).

by microbes into compounds that benefit human health, including short-chain fatty acids (Sonnenburg and Sonnenburg 2014). A diet low in MACs lowers levels of butyrate, a short-chain fatty acid that is the preferred energy source of colonocytes (Koropatkin et al. 2012). MAC deficiency also may select for microbe species that glean energy from host mucosal polysaccharides (Koropatkin et al. 2012). Starved colonocytes and degraded mucosa could alter physical properties of the gut in ways that reduce the ability of preferred microbes to establish after being reinitroduced, or alter the functional effects of desired biota even if desired species are reestablished.

Together, structure-function models such as those in Figure 1 identify three potential causes of FMT failure—donor deficiency, relapse, and irreversible change. FMT trials have not been designed to compare the relative importance of these factors. Doing so would require time-sensitive experimental designs to discriminate between irreversible change and relapse, as well as designs to detect effects of donor stool diversity and recipient mucosal condition and diet. At present, FMT research does not consistently measure or control any of these parameters. For instance, among 18 FMT studies to treat inflammatory bowel disease (IBD), only one-third measured microbiota species compositions and only one looked for cellular changes using mucosal biopsies (Colman and Rubin 2014).

Like FMT studies, projects in restoration ecology commonly lack experimental and control treatments or are monitored insufficiently to identify causes of success and failure (Kondolf 1995; Michener 1997). Restoration ecology has been criticized for being ad hoc, site-specific, and conceptually ungrounded (Suding 2011). It is susceptible to such criticisms in part because its primary focus—one shared with medicine—is to restore a system's health, and when tradeoffs exist between investing in treatment versus implementing experiments and gathering data, experimental rigor can be deprioritized—even if its long-term benefits may outweigh its short-term costs. With regard to a possible weakness of being overly site-specific (i.e., study-specific), microbiome studies may benefit from the Microbiome Quality Control Project (Gilbert et al. 2016), which seeks to coordinate methods and metrics across studies.

STAKEHOLDERS AFFECT SUCCESS

Ecosystems in both nature and the gut function courtesy of an interconnected network of life. It is difficult to isolate a restoration project either biologically from adjacent habitat or sociologically from surrounding stakeholders, such as landowners, government agencies, and the public. Stakeholders include anyone affected by a project who has sufficient power or interest to influence its success. Because stakeholders may impede or expedite restoration, ecologists commonly consult them prior to embarking on a plan for restoration. Projects in watershed restoration have a particularly large emphasis on stakeholders (Oppenheimer et al. 2015) because what is done in one location is connected to others via stream flows.

For two reasons, physicians should view patients as important stakeholders in gut restoration. First, as discussed above, removing the disturbance that is causing degradation is the first logical step in restoration, and passive restoration of the gut often may require a modified diet. Diets high in fat and/or simple sugars have been tied to unhealthful changes in gut structure (Ley et al. 2006b; Devkota et al. 2012; Sonnenburg and Sonnenburg 2014) and function (Devkota et al. 2012), and therefore may impede physician-initiated active restoration, such as FMT or probiotics, if allowed to persist. Second, the target of gut restoration is not the entire individual but a specific organ system, the gut, which makes a neighboring organ—the brain—a stakeholder via a bidirectional physiological connection. In one direction, the brain controls what is put into the mouth, and therefore what appears "downstream" in the gut. Conversely, gut microbes are known to affect host behavioral and psychological states (Schmidt 2015), which may influence gut health via stress or food choices. Despite the importance of a patient's brain as a stake-

TABLE 3
Ten insights from ecological restoration, and their implications for research and clinical practice in gut medicine

Insights from ecological restoration	Implications for gut medicine
1. Restoration often has a net economic benefit	Estimating the economic benefits of restoring beneficial gut microbes may help to shift health care priorities and lower net medical costs
2. Undisturbed remnant intact ecosystems can help to define "reference conditions," an end goal for restoration	Gut species compositions of traditional cultures may help to identify target taxa, genes, or functions for gut restoration
3. When degradation is widespread and long-term, the correct reference ecosystem is not necessarily clear, and additional clues must be utilized to define it	Microbiome-wide association studies, as well as approaches that distinguish microbiota as causes versus consequences of disease, can provide clues about desirable taxa for restoration
4. History is more a guide than a template for restoration due to changing climate and the irreversibility of some disturbances	Chronic historic disturbance, genetic divergence, and permanent cultural shifts may make traditional cultures more of a guide than a template
5. Passive restoration (disturbance removal) is a prerequisite to active restoration (manipulating structure or function)	Sources of disturbance, especially high fat/high sugar industrial diets, should be removed as a prerequisite to treating gut disease
6. A rivet-redundancy model most often describes the relationship between ecosystem structure and function (Figure 1A)	Donors for fecal microbiota transplants should be screened not only for pathogens but also for microbe taxonomic or genetic diversity (Figures 1B and 2)
7. Restoration often is monitored insufficiently after implementation	To understand factors affecting FMT success, it is necessary to monitor donor-recipient relatedness and donor microbiota, as well as recipient colonic cell pathology and microbiota over time
8. Restoring ecosystem structure does not automatically restore function (Figure 1C)	
9. An appropriate range of stakeholders should be involved in restoration planning	Patient motivation, especially regarding diet, may augment the success of gut restoration
10. Restoration outcomes vary from site to site and year to year	Gut restoration should incorporate personalized medicine

holder in gut health, we know of only one study that even mentions the physician-patient relationship in treating microbiota-related gut disease (Chey et al. 2015).

site conditions fine-tune restoration

The steps required to reach a targeted reference condition may vary among sites. Prairie restorationist Chris Helzer asserts: "In some ways, prairie management is like parenting—each prairie (and child) has its own personality and needs to be treated in ways that match that personality" (Helzer 2013). Analogously, the emerging trend of "personalized medicine" (Schork 2015) tracks how individuals vary in response to medical treatments. Personalized approaches have tracked patient responses to diet-based passive restoration. A model using food diaries, blood parameters, anthropometrics, and microbiota biomarkers explained about 70% of the variation between subjects in glycemic responses to particular foods; it was equally predictive in an independent cohort, and helped to tailor personalized diets that lowered glycemia and altered gut microbiota (Zeevi et al. 2015). In another study, subjects who responded to a whole grain diet with lower blood glucose and insulin exhibited increased ratios of *Prevotella*:*Bacteroides*, while those who did not respond did not show changes in microbe ratios. This result was replicated experimentally in mice using FMT from responders and nonresponders. As a possible explanatory mechanism, *Prevotella*:*Bacteroides* ratios were experimentally linked to upregulation of genes associated with glucose metabolism and insulin signaling (Kovatcheva-Datchary et al. 2015). Like natural ecosystems, guts are likely

to require particularized approaches for individual patients, which could start with the sorts of studies cited here.

Conclusion

We close with one caveat: although many similarities exist between natural and gut ecosystems, there are also important differences. Foremost is the role of an immune system in the regulation of gut communities, whereas no analog exists in nature—unless one were to consider the practice of ecological restoration itself as a sort of immune system scanning for disrupted ecosystem function and endeavoring to reverse situations where ecosystem services are compromised. Nevertheless, long-term coevolution between human immune systems, microbes that facilitate proper immune function, and pathogens that stimulate immune responses have no exact analog in natural ecosystems. Moreover, whereas humans plus their microbes together constitute a "holobiont" (Bordenstein and Theis 2015), no analog exists between natural ecosystems and the humans who benefit from their services, despite increasing awareness of our dependence upon them.

Nineteenth-century research identified microbes as agents of disease, and set the stage for 20th-century breakthroughs in antibiotic therapies. However, antibiotic resistance is now a global crisis (Ventola 2015), along with increasing awareness that antimicrobials harm beneficial species (Jernberg et al. 2007; Dethlefsen and Relman 2011). Theories and practices that have restored ecosystem structure and function in nature may help to guide future directions in gut research and clinical care (Table 3). Harvard biologist E. O. Wilson, a leading advocate for biodiversity, predicted that the 21st century would be "the era of restoration in ecology" (Wilson 1992: 340). Might it also be the era of restoration in medicine?

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