

## **Trends**

Advances in research and medical practices have made significant inroads towards the treatment of diseases at the single patient level. This paradigm, precision medicine, holds the promise of reducing adverse effects, improving preventative care, and reducing costs by tailoring individual treatment based on highly detailed diagnostics.

Humans harbor trillions of microbes, termed the microbiome, which is now being appreciated as being a hugely substantial facet of health. Immune, metabolic, neurological, and other processes impact and are impacted by the microbiome.

The microbiome not only is a significant factor in health, but it is one that can be both readily assayed through DNA sequencing and directly modified by various targeted interventions. Therefore, the currently genetic information dominated field of precision medicine would be greatly enhanced by the introduction of the microbiome.

# 1 **Introducing the Microbiome into Precision Medicine**

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11

## 12 **Abstract**

13 Understanding how individual people respond to medical therapy is a key facet of  
14 improving the odd-ratio that interventions will have a positive impact. Reducing the non-  
15 responder rate for an intervention or reducing complications associated with a particular  
16 treatment or surgery is the next stage of medical advance. The Precision Medicine  
17 Initiative, launched in January 2015, set the stage for enhanced collaboration between  
18 researchers and medical professionals to develop next-generation techniques to aid  
19 patient treatment and recovery, and increased the opportunities for impactful preemptive  
20 care. The microbiome plays a crucial role in health and disease, as it influences  
21 endocrinology, physiology and even neurology, altering the outcome of many different  
22 disease states, and it augments drug responses and tolerance. We review the implications

23 of the microbiome on precision health initiatives and highlight excellent examples,  
24 whereby precision microbiome health has been implemented.  
25

26 **Introduction to Precision Medicine**

27 The sequencing of the human genome [1] in 2001 fostered advances in both our  
28 understanding of the genomic basis of disease and in the DNA sequencing technologies  
29 required to bring the results of this understanding to patients. This is often referred to as  
30 precision genomic medicine, which utilizes a patient’s individual genome to inform  
31 treatment and care, based on known genomic markers for disease [2]. The broader,  
32 inclusive field of precision medicine couples a person’s treatment with what is known  
33 about their population, life style, and medical history, by matching clinical data and  
34 genetic biomarkers. Since the genome is sometimes conceptualized as the core of human  
35 individuality, at least in terms of disease, the broader field of precision medicine is often  
36 conflated with genomic medicine. Precision medicine, however, includes aspects  
37 downstream from the genome, including gene expression and protein expression as well  
38 as metabolic markers. Nonetheless, genomic information is the most commonly used and  
39 has had great successes [3]. Cancer treatment in particular has been revolutionized by  
40 genomic medicine [4], which exemplifies that despite difficulties in implementing  
41 precision medicine, it is a deeply important development. In particular, achieving the  
42 goals of precision medicine, including diagnosing disease more accurately and reducing  
43 the relative risk of treatments, side effects, and non-responses to medications, will  
44 revolutionize both treatment courses — ideally at the single patient level [5] — and the  
45 structuring of medical care and costs, moving towards cheaper, preventative focused  
46 medicine.

47

48 **The Microbiome as a Precision Medicine Frontier**

49 In this review we focus on a more recent but in many ways analogous development, that  
50 of introducing the microbiome into precision medicine. The human microbiome is the  
51 “the ecological community of commensal, symbiotic, and pathogenic microorganisms  
52 that literally share our body space” [6]. These microorganisms, mainly bacteria, fungi,  
53 archaea, and viruses in the gastrointestinal tract, are slightly more abundant than the  
54 human cells in the body, leading some to classify them as an newly discovered organ [7].  
55 It is important to note however that the microbiome is compositionally and  
56 spatiotemporally far more fluid and mutable than human cells and organs. Therefore, the  
57 microbial “organ” may be better described as a “cloud” of genetic information accessory  
58 to the stable human genome [8]. Certainly, the influences of the microbiome on our  
59 physiology are significant and multitudinous, affecting immunology [9], neurology  
60 [10,11], endocrinology [12], and, importantly for precision medicine, disease states and  
61 clinical outcomes. Because microbiome science is a nascent but quickly developing field,  
62 additional important functions of the microbiome are likely still to be discovered. These  
63 discoveries are driven by similar sequencing technology as that which has enabled  
64 personal genomics, and this technology is decreasing rapidly in price [13], so much so  
65 that personal microbiome sequencing is already available to the consumer (e.g. American  
66 Gut - [americangut.org](http://americangut.org); uBiome - [ubiome.com](http://ubiome.com)). Furthermore, the well-developed analysis  
67 and statistical techniques of genomic medicine have commonalities with microbiome  
68 analysis. Since microbiome states are highly individual even between co-raised identical  
69 twins [14], but can be rapidly changed [15] (unlike genetics), there is a profound  
70 opportunity for individualized treatments. However, the microbiome, like any ecosystem  
71 is also profoundly complex, and so the goals of precision microbial medicine require

72 considerably more research before they are appropriately realized [16]. Nonetheless, the  
73 microbiome, as we shall exemplify here, is primed and ready for precision medicine, and  
74 therefore the clinical application of this new therapeutic area is on the immediate horizon.  
75 Various complementary routes of assaying and modifying the microbiome have been  
76 proposed and tentatively utilized towards this end; these will be laid out here in the  
77 following text as well as diagrammatically (Figure 1).

78

### 79 **Review of Microbiome Analysis Techniques**

80 How then could microbiome precision medicine be implemented? Currently two  
81 complementary analyses, both beginning with the extraction of microbial genomic DNA,  
82 are standard in the field: 16S rRNA sequencing and shotgun metagenomics. The 16S  
83 rRNA gene has both highly conserved regions, allowing for the usage of extremely  
84 bacterially nonspecific primers, and “hypervariable” regions, where base pair differences  
85 can often provide species level identification [17]. Thus, 16S rRNA amplicon sequencing  
86 provides a robust tool for identification as well as classification and even discovery of  
87 bacteria [18]. A typical 16S rRNA study utilizes the differences in observed communities  
88 of bacteria between differing samples to obtain statistically significant correlations  
89 between bacterial composition and sample description, for example to identify  
90 differences in the gut microbiomes of children born to obese mothers [19]. These studies  
91 have led to key insights into the human microbiome. While historically the majority of  
92 biomedical research on bacteria has focused on eliminating pathogens, many bacteria as  
93 well as communities of bacteria are important in both health and disease [6]. Though  
94 identifying causative bacteria in disease states will be an important facet of precision

95 medicine, understanding the overall ecology of the microbiome may be equally or even  
96 more vital.

97

98 Therefore, to go beyond bacterial identification and subsequent, limited patient  
99 stratification, it will be essential to understand the functional potential of the microbiome.  
100 Shotgun metagenomics enables the researcher to understand this function potential  
101 through analysis of the complete genomic repertoire of the community, by sequencing  
102 DNA extracted from that community, rather than relying on amplification of a marker  
103 gene. Taxonomy can still be determined from signature genes (including 16S rRNA), but  
104 it is also possible to assign phylogeny of the functional genes by comparing the DNA  
105 sequence against a library of genomes from close relatives [20]. In addition,  
106 metagenomics enables the assembly of genomes from organisms in the microbiome that  
107 are resistant to culture, providing a higher resolution exploration of the taxa associated  
108 with each person [21]. This enables us to determine the metabolic and signaling capacity  
109 of each taxon, to determine how it will interact with the rest of the body [22]. This clearly  
110 makes metagenomics of great interest for the development of precision medicine;  
111 however, one must be aware of the challenges this technique presents. Metagenomic  
112 studies are necessarily more expensive and computationally complex than 16S rRNA  
113 based studies. Possible contamination from undesired DNA and biases of analyses  
114 towards culturable organisms [23] further complicate matters. Ultimately metagenomics  
115 is an extremely useful tool, but the application of this technology to precision medicine  
116 will require a better understanding of the implications of these limitations, especially  
117 when scaling up to treatments of large patient populations.

118

119 Notably, both 16S sequencing and shotgun metagenomics are currently somewhat blunt  
120 tools, especially when describing the fluid nature of the microbiome. Evolution of  
121 microorganisms, horizontal transfer of genes, and subtleties in the characterization into  
122 types of microbiomes [24] problematize the microbiome snapshot style data often  
123 acquired. As sequencing costs continue to decrease, however, scientists can sample more  
124 densely in time to capture previously unobservable subtleties in microbial interactions  
125 and utilize time series techniques to uncover dynamic ecological phenomena [25].  
126 Additionally, the gut microbiome is known to be spatially inhomogeneous, in ways that  
127 influence function and disease states [26]. This limitation too might be surpassed in the  
128 near future, owing to emerging sampling techniques and protocols (e.g., laser  
129 microdissection of colonic crypt mucus [27]).

130

### 131 **Avenues Towards Microbiome-Based Precision Therapies**

#### 132 *Microbiome-xenobiotic interactions*

133 That gene polymorphisms can drive changes in drug metabolism has been known for  
134 some time; it was noted as early as 1957 that atypical forms of serum cholinesterase led  
135 to potentially fatal reactions to certain anesthetics [28]. This and other adverse drug  
136 reactions are estimated to cost from 30 to 130 billion dollars in the USA annually [29,30]  
137 and are a significant source of patient non-compliance and therapy failure [31]. Reducing  
138 these adverse reactions is a primary goal of precision medicine. While some interactions  
139 are idiosyncratic, a recent survey of adverse drug events observed that about 35% of  
140 these events were drug-gene or drug-drug-gene interactions involving cytochrome P450



141 oxidase (CYP) variants [32]. CYPs are generally considered the body's innate and  
142 primary general purpose drug metabolizers; they are involved in about 75% of total  
143 human drug modification [33].

144

145 However, microbial metabolism in the gut is also a significant factor in  
146 biotransformation, especially for low solubility, low permeability compounds [34].

147 Currently, more than 60 drugs have been identified to have microbiome interactions

148 according to the PharmacoMicrobiomics database [35], and given the vast number of

149 possible unique microbial metabolic transformations [36], many more interactions are

150 likely to be discovered compared with the apparently relatively limited number of human

151 genetic interactions. The plasticity of the microbiome may make these interactions

152 dynamic, necessitating precision medicine that is not only patient specific but temporarily

153 appropriate [37]. Importantly, the primary forms of xenobiotic metabolism are different

154 between human and bacterial cells: oxidation and conjugation dominate in the former

155 case, reduction and hydrolysis in the latter [34]. Metabolism of drugs is actually a key

156 component of many therapies; so-called "prodrugs" are essentially drugs that will be

157 metabolized into a pharmacologically active drug after consumption. Therefore,

158 production of active drug metabolites from prodrugs is sometimes dependent on the

159 microbiome, with the possibility to either improve or worsen outcomes [38]. This often

160 manifests as a modulation of bioavailability to the human, an important consideration for

161 prediction of appropriate dosing in precision medicine. Efficacy and side effects are also

162 altered directly by microbial metabolism. For example, acetaminophen toxicity shows

163 substantial variability within a given human population [39], and the microbiome has

164 been identified as playing a role in this variability. Members of the genus *Clostridium*, as  
165 well as other bacteria can produce *p*-cresol, which competes as a substrate for SULT1A1  
166 (a human liver enzyme) with acetaminophen [40]. A reduction in the breakdown of  
167 acetaminophen by SULT1A1 causes a build-up of NAPQI, which leads to hepatotoxicity.  
168 This general pattern of competition between bacterial metabolites and drugs for human  
169 enzyme modification constitutes a major challenge in pharmacology [41]. Directly  
170 harmful substances can also be formed by microbiota, as is the case in bacterial  $\beta$ -  
171 Glucuronidase mediated diarrhea in response to an antitumor camptothecin derivative  
172 [42]. Strikingly, in some cases even strain level differences can lead to altered  
173 metabolism, such as inactivation of digoxin by a non-universal *E. lenta* gene. Digoxin has  
174 a narrow therapeutic window, and thus a wrong dosage could lead to significant toxicity,  
175 highlighting the need for further study of metagenomic diagnostics and insights to  
176 adverse outcomes [43].

177

178 Furthermore, alternative mechanisms for xenobiotic-microbiome interaction including  
179 immune [9,44,45] and endocrine [12] modulation by bacteria are known to exist,  
180 complicating and enlarging the pool of possible drug-microbiome interactions. Lastly,  
181 there are possible reciprocal relations: drugs may both be altered by the microbiome and  
182 alter the microbiome. For example, antipsychotic medication has been shown to both  
183 alter the microbiome and have microbiome-dependent side effects [46]. While this  
184 greatly complicates endeavors to understand microbiota-xenobiotic interactions, it also  
185 points towards a different microbiome driven approach to precision medicine: directly  
186 targeting the microbiome for clinical results.

187

188 *Targeting the microbiome*

189 It is clear that medication is already utilized to have a direct effect on the microbiome;  
190 one needs to look no further than antibiotics. While these drugs are utilized for the  
191 eradication of pathogenic bacteria, they have widespread effects on the microbiome,  
192 possibly leading to adverse outcomes. Secondary infections caused by antibiotics are well  
193 known, most saliently *Clostridium difficile* [47], but it is often less appreciated that  
194 antibiotics can have side effects on the human, for instance fluoroquinolone associated  
195 cardiotoxic [48] and neuropsychiatric [49] reactions. Importantly, consequences of  
196 antibiotic usage, such as reduction of inflammation, are possibly not only human off-  
197 target drug effects, but also unintended consequences of microbial community disruption  
198 [50]. Studies using mouse models suggest that stress induced increases in circulating  
199 cytokines were abrogated by broad-spectrum antibiotic treatment [51]. Furthermore,  
200 these types of interactions are not limited to drugs classified as antibiotics; many other  
201 drugs have antibiotic and other microbial community structure and function modulating  
202 properties that are beginning to be appreciated [52,53]. While many of these  
203 perturbations to the microbiome are associated with poorer outcomes, some drugs may  
204 derive some or all of their beneficial qualities from alteration of the microbiome, thus  
205 they could be considered a form of discriminatory antibiotic.

206

207 A precision medicine therapy that leverages microbial community structural modulation  
208 could have beneficial clinical impact. Certainly if pathogen-specific antibiotics were  
209 developed, the odds ratio could be greatly increased compared to traditional antibiotics. A

210 clear approach is to design a species-specific enzyme inhibitor or other antimicrobial  
211 molecules. For example, a *Streptococcus mutans*-targeted drug based on the fusion of a  
212 species-specific targeting peptide domain with a wide-spectrum antimicrobial peptide  
213 domain has already been developed [54]. However, the bacterial community was also  
214 altered when using this peptide, despite its high specificity [55]. This is likely because the  
215 environment of *Streptococcus mutans*, the oral microbiome, presents significant  
216 structural and functional complexity [56]. It has been suggested that targeted antibiotics  
217 may shift the microbiome into a healthier state, but of course there is also the potential  
218 for negative ecological effects, although these may be less than for traditional antibiotics.

219

220 An intriguing approach that may largely avoid the problem of system scale changes in  
221 microbial community structure, as well as that of increasing antimicrobial resistance, is to  
222 non-lethally target specific enzymes in the bacteria. This has been realized at the multi-  
223 species level [57] through targeted inhibition of bacterial tri-methyl amine (TMA)  
224 formation by 3,3-Dimethyl-1-butanol (DMB, a structural analog of choline) ultimately  
225 attenuating atherosclerosis in a high choline diet mouse model. Surprisingly, slight  
226 alterations of bacterial composition were still observed, underscoring the extremely  
227 dynamic nature of the microbiome. Nonetheless, this study points towards a microbiome-  
228 based intervention for a specific (i.e., “Western”) diet-driven disease. In this case, a  
229 single target approach is undesirable, as reduction of global TMA formation is the goal,  
230 but given the availability of single isozyme inhibitors [58], precision, non-lethal drugs  
231 likely could be developed. These furthermore have the potential to be minimally  
232 bioavailable to the human, limiting side effects, and might be exploited not only to target

233 pathogens but also to reduce microbiota-drug interactions through selective elimination  
234 of problem microbes.

235

236 A final approach for targeted antimicrobials has been successfully employed for  
237 approximately 100 years, though not as popularly in the western world [59]. Phages were  
238 independently discovered in France and England, though developed as a therapy first in  
239 the former. Despite great successes in treatment, especially of cholera, commercialization  
240 of phage therapy failed due to production problems and other complications and so was  
241 subsequently ignored in the US and Europe after the development of antibiotics [60].  
242 Scientists in the Soviet Union (especially Georgia) continued to develop phage therapy,  
243 having been cut off from antibiotic advances due to World War II. Here it was effectively  
244 used it to control outbreaks of gastrointestinal diseases and refined further during the  
245 Cold War and afterwards [61]. The basic premise of this technique is that many bacterial  
246 species, and maybe even each strain (sub-species), are predated upon by a unique phage  
247 [62]. Phage target bacteria cell-membrane protein and sugar complexes that are unique to  
248 each bacterial taxon. Therefore, by identifying the correct phage it should be possible to  
249 precisely remove a specific bacterial species from an assemblage. This will enable  
250 accurate restructuring of a microbiome so as to precisely augment the functional  
251 properties of that consortium. In fact, recent evidence from the commercial sector  
252 suggests that the same mechanisms employed by phages to target and penetrate bacterial  
253 cells can be programmed into nano-particles that mimic these phage-properties to infect  
254 and kill specific cells (Pers. Comm. Jeffrey Miller, UCLA). In this new future, we may  
255 have ultimate control over the microbiome.

256

257 *Prebiotic treatments*

258 Conversely, instead of targeting the microbiome to reduce deleterious bacteria, one could  
259 aim to increase the levels of beneficial bacteria or otherwise positively alter the structure  
260 or function of the microbiome. Substances applied in this way are often referred to as  
261 prebiotics. However, the types of prebiotics currently studied are limited in scope, usually  
262 non-digestible fiber compounds that stimulate growth of *Bifidobacterium* and other taxa  
263 to produce short chain fatty acids (SCFA) including butyrate and propionate [63].  
264 Though this is promising as a broad treatments for several conditions [64], efforts for  
265 precision medicine in this sphere will require the expansion of the scope of prebiotics.  
266 Given that metagenomic and metabolomic advances continue to better characterize the  
267 metabolic potential of the microbiome, especially across groups with vastly different  
268 diets [65], prebiotic compounds that stimulate alternative beneficial bacteria towards  
269 useful metabolic endpoints will be discovered [66].

270

271 More audaciously, one might aim at fine-tuning the interactions between microbiota of  
272 the gut microbiome. The microbiome is a complex, human co-evolved ecosystem that  
273 produces many bioactive compounds, often for intercellular communication [26]. These  
274 compounds could be mined to find those which modulate the microbiome in a beneficial  
275 way, thus unearthing novel prebiotics [67]. While microbial community disruption is the  
276 consequence of both xenobiotic and microbiome targeted drug metabolism, these types of  
277 prebiotics might provide a more gentle perturbation than possible with the former by  
278 harnessing already existing biological pathways. This goal certainly seems distant, but as

279 dynamical systems approaches to studying the microbiome continue to develop, we may  
280 find that treating certain dysbiotic states require perturbations of varying magnitudes or  
281 delicate maintenance of the stability of the microbiome, especially in at-risk populations  
282 [68].

283

#### 284 *Precision probiotics*

285 Perhaps the most direct strategy for altering the microbiome is the usage of probiotics,  
286 live microbes administered for health benefits. This idea has been employed since at least  
287 1907 when Élie Metchnikoff hypothesized lactic acid producing bacteria could implant in  
288 the gastrointestinal tract to enhance longevity [69]. Today the probiotic landscape is still  
289 dominated by lactic acid bacteria, specifically genera *Lactobacillus*, though it is now  
290 appreciated that their beneficial properties are not limited to the production of a single  
291 metabolite and that other potential probiotic bacteria, perhaps isolated from healthy  
292 individuals [70], could affect various outcomes through multifarious means [71]. This  
293 opens the door to precision probiotic development since application of microorganisms is  
294 highly specific with regards to both applied agent and effect. Devices now exist for  
295 isolating microorganisms based on metabolic output [72], and work is being done to  
296 identify probiotic bacteria that produce particular compounds of therapeutic potential  
297 [73]. This may include compounds whose efficacies are contingent on route of  
298 administration, for example those that are inactive orally. Furthermore, probiotics are  
299 being bioengineered to expand their ranges and modes of actions as well as their  
300 robustness and incorporation [74]. However, it is important to keep in mind that  
301 interactions with diet, established microbiota, and genetics, are known to modulate

302 overall health outcomes if not specific effects and mechanisms of probiotics [71].  
303 Therefore effective patient classification and stratification is required for best results.  
304 Success of this program will require detailed insights into metagenomic potential and  
305 ecological interactions of presumptive probiotic bacteria, making precision probiotic  
306 development a task of considerable difficulty but one that has already seen demonstrable  
307 results, for example in enhancing resistance to *Clostridium difficile* infection [75] and  
308 suppressing hepatocellular carcinoma growth in mice [76].

309

### 310 **Regulation and Application**

311 Despite the therapeutic promise of the microbiome, its application to precision medicine  
312 requires overcoming considerable hurdles. One may anticipate that failure to successfully  
313 apply genomic medicine may lead to delays in the application of the microbiome as a  
314 precision therapy. For example, the current legal and R&D model is not well suited for  
315 development of genome-informed drugs [77]. Microbiome therapies likewise face  
316 difficulties, especially owing to the wide breadth of treatment options, many of which  
317 lack analogs in current medical practice. Furthermore, clinicians have been reticent to use  
318 the results of genomic information — and thus likely future microbiome data — in  
319 treatment due to both uncertainties on its importance and lack of understanding [78].  
320 These problems are highlighted in the case of Plavix® (clopidogrel), whereby despite an  
321 FDA box warning [79] indicating serious or fatal risk for those carrying certain  
322 CYP2C19 variants, this drug is still routinely used on genetically incompatible patients  
323 due to poor coverage by insurance and failure to clinically utilize genetic testing [80]. In  
324 the case of the microbiome, fecal transplant treatment for *Clostridium difficile* colitis is



325 known to be highly effective especially in recurrent infection [81]; however, this  
326 procedure still requires a licensed practitioner to have a protocol approved by their local  
327 Institutional Review Board, and therefore each patient needs to be consented prior to  
328 therapy. For a therapy with >90% success rate this is peculiar. However, it is because we  
329 still lack the ability to characterize the microbial community of donor stool appropriately.  
330 This means that we do not know the active components of the fecal transplant, and  
331 therefore it is very difficult to regulate this using standard legislation under FDA  
332 protocols. More importantly, we still don't fully understand the implications for  
333 microbiome therapy on a large scale. While fecal transplants are becoming extremely  
334 numerous with few legitimate side effects, it is still hard to predict the outcome across a  
335 broad population. The same is true for genomic medicine, whereby the interaction of  
336 genes with the environment is difficult to predict [82]. This requires enormous sample  
337 populations for any investigation to be statistically significant [83]. Though the future is  
338 bright for genomic medicine, particular issues currently impede efforts towards its  
339 development.

340

341 Fortunately, some of the difficulties in genomic medicine research and deployment might  
342 be lessened in precision microbiome medicine. Environmental-microbiome interactions  
343 are potentially more easily studied because there is a more direct interaction between the  
344 two, allowing for simpler identification of sample populations and achievement of  
345 statistical power. With the correct experimental design, genetic variation can be  
346 sufficiently decoupled from microbiome and environmental factors. In fact, studies of  
347 this nature already exist, both on humans [84] and especially on mice, where genetics can

348 be well controlled [85]. This bottom-up approach can then be extended by genomic  
349 studies which better account for confounding factors. Even where genetics is a significant  
350 factor, such as in mental health disorders, incorporating the microbiome greatly increases  
351 understanding and ultimately treatment of diseases [86]. Of course in disease states where  
352 the effects of genetic variation are either entirely or nearly absent, the microbiome is a  
353 great candidate for investigation. Conditions such as obesity [87] and inflammatory  
354 bowel disease [88] can in subsets of patients be driven by dysbiosis, a chronic, systemic  
355 maladaptation of the gut microbiome to the host. Unlike genomic medicine, there are  
356 possibilities especially for these conditions to do research in an *in vitro* environment,  
357 most excitingly in artificial gut paradigms [89]. Microbiome precision medicine also has  
358 the opportunity to break free of present R&D and legal hurdles to precision medicine.  
359 The regulation and marketing of these treatments will at least pose challenges for  
360 traditional models [90,91], as evidenced by the FDA's current stance on probiotics [92],  
361 which has led to faster product delivery to the public but also quality control and  
362 effectiveness issues [93]. Prioritizing treatments will be an important aspect of achieving  
363 R&D, FDA, and ultimately clinician support; unnecessary testing on low risk  
364 communities and for low benefit interventions, will only hamper the development of  
365 microbiome precision medicine.

366

#### 367 **Notable Application: Medically Underserved Communities**

368 Given the above unique assets of the microbiome modality of precision medicine, a  
369 promising potential area for its development is in low socio-economic status (SES) and  
370 other under-served communities. Low SES is associated with reduced diversity in the gut

371 microbiome [94]. Numerous factors are also present especially in urban communities that  
372 reduce immunoregulation, including reduced exposure to microbes in the natural  
373 environment [95] and increased stress [96], and increase obesity prevalence and  
374 dysbiosis, including increased density of fast-food restaurants [97] and lack of physical  
375 activity [98]. This is likely interrelated with microbiome-associated diseases such as  
376 asthma [99] and gastrointestinal symptoms [100]. The vast majority of genomic variants  
377 discovered are either rare with large effects or common with small effects, unlike in this  
378 situation where there is a possibility of appreciable effect size combined with biomarker  
379 occurrence. Therefore, these at-risk communities present a potentially illuminating cohort  
380 for microbiome.

381

382 Of course, great care must be taken to not draw inappropriate or invalid associations  
383 between microbiome [101] (or genome [102]) variations and minority status. Lack of  
384 cultural understanding and disparities in access to services have driven poor research  
385 trends in the past and continue to be a deep issue in the development of precision  
386 medicine. Access issues in particular have caused demonstrable problems; statistics on  
387 epidermal growth factor receptor testing, for example, show associations of lower  
388 educational attainment and income with reduced likelihood of testing [103], and studies  
389 suggest health insurance coverage alone does not explain this general effect [104,105].  
390 For precision medicine to succeed then, under-served populations must be both active  
391 participants and beneficiaries of research. Microbiome research in particular could lead to  
392 high impact clinical interventions for these communities, hopefully spurring its  
393 development. It is both an opportunity and imperative for microbiome precision medicine

394 to address social epidemiological trends, but this is only possible through the combined  
395 efforts of researchers, clinicians, the government, and perhaps most importantly the  
396 people at large.

397

### 398 **Concluding Remarks**

399 Here we have presented a collection of potential avenues towards introducing the  
400 microbiome into precision medicine. Though it is difficult to know if and when these  
401 techniques will ultimately make it to the clinic (see Outstanding Questions), there is  
402 substantial evidence that microbiome-based medicine holds great future potential to  
403 improve odds-ratios, reduce side effects, stratify patients, and precisely treat previously  
404 difficult or untreatable conditions. Ultimately, the microbiome must become an integral  
405 part of precision medicine as a whole, since so much of human functioning and  
406 metabolism is dependent upon it. If this is to happen in the near future, as it hopefully  
407 should, we must better understand the microbiome and its interactions with the human  
408 and the environment via a concerted effort and conversation between researchers,  
409 clinicians, patients, the government, and most importantly, the broader community.

410

### 411 **Figure 1**

412 A schematic of methods in precision microbiome medicine and their possible interplay:  
413 a) As an example, certain microbes, here represented in red, metabolize the compound  
414 cycasin to produce a carcinogenic compound methylazoxymethanol (MAM) [106]. This  
415 functional potential of the microbe might be discovered through metagenomic  
416 sequencing. b) If targeted removal of the red microorganism — identified in a patient via

417 16S sequencing — was desired, without harming commensal bacteria, represented in  
418 shades of blue, three approaches (green arrows) might be utilized. Direct removal of the  
419 deleterious microorganism through targeted antibiotics ideally would not affect  
420 commensal bacteria. Probiotic treatment introduces new beneficial microorganisms while  
421 prebiotic treatment favors the growth of existing beneficial microorganisms. Note that  
422 prebiotic and probiotic treatments do not directly remove the targeted microorganism, but  
423 in certain cases may shift the gut ecology such that it does not thrive [107]. In all three  
424 cases, the specific circumstances may affect which treatment is best employed and what  
425 residual outcomes there are on the microbiome.

426

#### 427 **References**

- 428 1 Venter, J.C. *et al.* (2001) The sequence of the human genome. *Science* 291, 1304–  
429 51
- 430 2 Guttmacher, A.E. *et al.* (2002) Genomic Medicine — A Primer. *N. Engl. J. Med.*  
431 347, 1512–1520
- 432 3 McCarthy, J.J. *et al.* (2013) Genomic Medicine: A Decade of Successes,  
433 Challenges, and Opportunities. *Sci. Transl. Med.* 5, 189sr4-189sr4
- 434 4 Garraway, L.A. *et al.* (2013) Precision Oncology: An Overview. *J. Clin. Oncol.*  
435 31, 1803–1805
- 436 5 Schork, N.J. (2015) Personalized medicine: Time for one-person trials. *Nature*  
437 520, 609–611
- 438 6 Lederberg, J. (2000) Infectious history. *Science* 288, 287–293
- 439 7 Sender, R. *et al.* (2016) Are We Really Vastly Outnumbered? Revisiting the Ratio

440 of Bacterial to Host Cells in Humans. *Cell* 164, 337–340

441 8 ElRakaiby, M. *et al.* (2014) Pharmacomicrobiomics: the impact of human  
442 microbiome variations on systems pharmacology and personalized therapeutics.  
443 *OMICS* 18, 402–14

444 9 Surana, N.K. en Kasper, D.L. (2014) Deciphering the tete-a-tete between the  
445 microbiota and the immune system. *J. Clin. Invest.* 124, 4197–4203

446 10 Sampson, T.R. en Mazmanian, S.K. (2015) Control of Brain Development,  
447 Function, and Behavior by the Microbiome. *Cell Host Microbe* 17, 565–576

448 11 Dinan, T.G. *et al.* (2015) Collective unconscious: How gut microbes shape human  
449 behavior. *J. Psychiatr. Res.* 63, 1–9

450 12 Clarke, G. *et al.* (2014) Minireview: Gut Microbiota: The Neglected Endocrine  
451 Organ. *Mol. Endocrinol.* 28, 1221–1238

452 13 (2010) Human genome at ten: The sequence explosion. *Nature* 464, 670–671

453 14 Franzosa, E.A. *et al.* (2015) Identifying personal microbiomes using metagenomic  
454 codes. *Proc. Natl. Acad. Sci.* 112, E2930–E2938

455 15 David, L.A. *et al.* (2013) Diet rapidly and reproducibly alters the human gut  
456 microbiome. *Nature* 505, 559–563

457 16 Gilbert, J.A. *et al.* (2016) Microbiome-wide association studies link dynamic  
458 microbial consortia to disease. *Nature* 535, 94–103

459 17 Clarridge, J.E. en Alerts, C. (2004) Impact of 16S rRNA gene sequence analysis  
460 for identification of bacteria on clinical microbiology and infectious diseases. *Clin.*  
461 *Microbiol. Rev.* 17, 840–862

462 18 Woo, P.C.Y. *et al.* (2008) Then and now: Use of 16S rDNA gene sequencing for

463 bacterial identification and discovery of novel bacteria in clinical microbiology  
464 laboratories. *Clin. Microbiol. Infect.* 14, 908–934

465 19 Galley, J.D. *et al.* (2014) Maternal obesity is associated with alterations in the gut  
466 microbiome in toddlers. *PLoS One* 9,

467 20 Sharpton, T.J. (2014) An introduction to the analysis of shotgun metagenomic  
468 data. *Front. Plant Sci.* 5, 209

469 21 Sangwan, N. *et al.* (2016) Differential Functional Constraints Cause Strain-Level  
470 Endemism in Polynucleobacter Populations. *mSystems* 1, e00003-16

471 22 Cardona, C. *et al.* (2016) Network-based metabolic analysis and microbial  
472 community modeling. *Curr. Opin. Microbiol.* 31, 124–131

473 23 Thomas, T. *et al.* (2012) Metagenomics - a guide from sampling to data analysis.  
474 *Microb. Inform. Exp.* 2, 3

475 24 Jeffery, I.B. *et al.* (2012) Categorization of the gut microbiota: enterotypes or  
476 gradients? *Nat. Rev. Microbiol.* 10, 591–2

477 25 Faust, K. *et al.* (2015) Metagenomics meets time series analysis: unraveling  
478 microbial community dynFaust, K., Lahti, L., Gonze, D., de Vos, W. M., & Raes,  
479 J. (2015). Metagenomics meets time series analysis: unraveling microbial  
480 community dynamics. *Current Opinion in Microbiology.* *Curr. Opin. Microbiol.*  
481 25, 56–66

482 26 Donaldson, G.P. *et al.* (2015) Gut biogeography of the bacterial microbiota. *Nat.*  
483 *Rev. Microbiol.* 14, 20–32

484 27 Rowan, F. *et al.* (2010) Bacterial Colonization of Colonic Crypt Mucous Gel and  
485 Disease Activity in Ulcerative Colitis. *Ann. Surg.* 252, 869–875

- 486 28 Kalow, W. en Genest, K. (1957) A METHOD FOR THE DETECTION OF  
487 ATYPICAL FORMS OF HUMAN SERUM CHOLINESTERASE.  
488 DETERMINATION OF DIBUCAINE NUMBERS. *Biochem. Cell Biol.* 35, 339–  
489 346
- 490 29 Sultana, J. *et al.* (2013) Clinical and economic burden of adverse drug reactions. *J.*  
491 *Pharmacol. Pharmacother.* 4, 73
- 492 30 Chan, A.L.F. *et al.* (2008) Cost evaluation of adverse drug reactions in  
493 hospitalized patients in Taiwan: A prospective, descriptive, observational study.  
494 *Curr. Ther. Res.* 69, 118–129
- 495 31 Edwards, I.R. en Aronson, J.K. (2000) Adverse drug reactions: definitions,  
496 diagnosis, and management. *Lancet* 356, 1255–1259
- 497 32 Verbeurgt, P. *et al.* (2014) How common are drug and gene interactions?  
498 Prevalence in a sample of 1143 patients with CYP2C9 , CYP2C19 and CYP2D6  
499 genotyping. *Pharmacogenomics* 15, 655–665
- 500 33 Guengerich, F.P. (2008) Cytochrome P450 and Chemical Toxicology. *Chem. Res.*  
501 *Toxicol.* 21, 70–83
- 502 34 Sousa, T. *et al.* (2008) The gastrointestinal microbiota as a site for the  
503 biotransformation of drugs. *Int. J. Pharm.* 363, 1–25
- 504 35 R. Rizkallah, M. *et al.* (2012) The PharmacoMicrobiomics Portal: A Database for  
505 Drug-Microbiome Interactions. *Curr. Pharmacogenomics Person. Med.* 10, 195–  
506 203
- 507 36 Carmody, R.N. en Turnbaugh, P.J. (2014) Host-microbial interactions in the  
508 metabolism of therapeutic and diet-derived xenobiotics. *J. Clin. Invest.* 124, 4173–



509 4181

510 37 Wilson, I.D. en Nicholson, J.K. (2015) The Modulation of Drug Efficacy and  
511 Toxicity by the Gut Microbiome. *bl* 323–341

512 38 Rautio, J. *et al.* (2008) Prodrugs: design and clinical applications. *Nat. Rev. Drug*  
513 *Discov.* 7, 255–270

514 39 Watkins, P.B. *et al.* (2006) Aminotransferase Elevations in Healthy Adults  
515 Receiving 4 Grams of Acetaminophen Daily. *JAMA* 296, 87

516 40 Clayton, T.A. *et al.* (2009) Pharmacometabonomic identification of a significant  
517 host-microbiome metabolic interaction affecting human drug metabolism. *Proc.*  
518 *Natl. Acad. Sci. U. S. A.* 106, 14728–14733

519 41 Swanson, H.I. (2015) Drug Metabolism by the Host and Gut Microbiota: A  
520 Partnership or Rivalry? *Drug Metab. Dispos.* 43, 1499–1504

521 42 Takasuna, K. *et al.* (1996) Involvement of beta-glucuronidase in intestinal  
522 microflora in the intestinal toxicity of the antitumor camptothecin derivative  
523 irinotecan hydrochloride (CPT-11) in rats. *Cancer Res.* 56, 3752–7

524 43 Haiser, H.J. en Turnbaugh, P.J. (2013) Developing a metagenomic view of  
525 xenobiotic metabolism. *Pharmacol. Res.* 69, 21–31

526 44 Shajib, M.S. en Khan, W.I. (2015) The role of serotonin and its receptors in  
527 activation of immune responses and inflammation. *Acta Physiol.* 213, 561–574

528 45 Viaud, S. *et al.* (2013) The intestinal microbiota modulates the anticancer immune  
529 effects of cyclophosphamide. *Science* 342, 971–6

530 46 Davey, K.J. *et al.* (2013) Antipsychotics and the gut microbiome: olanzapine-  
531 induced metabolic dysfunction is attenuated by antibiotic administration in the rat.

532 *Transl. Psychiatry* 3, e309

533 47 Worsley, M. a (1998) Infection control and prevention of *Clostridium difficile*  
534 infection. *J Antimicrob Chemother* 41 Suppl C, 59–66

535 48 Rubinstein, E. en Camm, J. (2002) Cardiotoxicity of fluoroquinolones. *J.*  
536 *Antimicrob. Chemother.* 49, 593–6

537 49 Galatti, L. *et al.* (2005) Neuropsychiatric reactions to drugs: an analysis of  
538 spontaneous reports from general practitioners in Italy. *Pharmacol. Res.* 51, 211–6

539 50 Rubin, B.K. en Tamaoki, J., reds (2005) *Antibiotics as Anti-Inflammatory and*  
540 *Immunomodulatory Agents*, Birkhäuser-Verlag.

541 51 Bailey, M.T. *et al.* (2011) Exposure to a social stressor alters the structure of the  
542 intestinal microbiota: Implications for stressor-induced immunomodulation. *Brain.*  
543 *Behav. Immun.* 25, 397–407

544 52 Wallace, B.D. en Redinbo, M.R. (2013) The human microbiome is a source of  
545 therapeutic drug targets. *Curr. Opin. Chem. Biol.* 17, 379–384

546 53 Maurice, C.F. *et al.* (2013) Xenobiotics shape the physiology and gene expression  
547 of the active human gut microbiome. *Cell* 152, 39–50

548 54 Eckert, R. *et al.* (2006) Targeted killing of *Streptococcus mutans* by a pheromone-  
549 guided “smart” antimicrobial peptide. *Antimicrob. Agents Chemother.* 50, 3651–7

550 55 Guo, L. *et al.* (2015) Precision-guided antimicrobial peptide as a targeted  
551 modulator of human microbial ecology. *Proc. Natl. Acad. Sci. U. S. A.* 112, 7569–  
552 7574

553 56 Belda-Ferre, P. *et al.* (2015) The human oral metaproteome reveals potential  
554 biomarkers for caries disease. *Proteomics* 15, 3497–507

555 57 Wang, Z. *et al.* (2015) Non-lethal Inhibition of Gut Microbial Trimethylamine  
556 Production for the Treatment of Atherosclerosis. *Cell* 163, 1585–1595

557 58 Yao, J. *et al.* (2016) A Pathogen-Selective Antibiotic Minimizes Disturbance to the  
558 Microbiome. *Antimicrob. Agents Chemother.* DOI: 10.1128/AAC.00535-16

559 59 Nobrega, F.L. *et al.* (2015) Revisiting phage therapy: new applications for old  
560 resources. *Trends Microbiol.* 23, 185–191

561 60 Kutter, E. *et al.* (2010) Phage Therapy in Clinical Practice: Treatment of Human  
562 Infections. *Curr. Pharm. Biotechnol.* 11, 69–86

563 61 Summers, W.C. (2012) The strange history of phage therapy. *Bacteriophage* 2,  
564 130–133

565 62 Koskella, B. en Meaden, S. (2013) Understanding Bacteriophage Specificity in  
566 Natural Microbial Communities. *Viruses* 5, 806–823

567 63 Petschow, B. *et al.* (2013) Probiotics, prebiotics, and the host microbiome: The  
568 science of translation. *Ann. N. Y. Acad. Sci.* 1306, 1–17

569 64 Candela, M. *et al.* (2010) Functional intestinal microbiome, new frontiers in  
570 prebiotic design. *Int. J. Food Microbiol.* 140, 93–101

571 65 O’Keefe, S.J.D. *et al.* (2015) Fat, fibre and cancer risk in African Americans and  
572 rural Africans. *Nat. Commun.* 6, 6342

573 66 Preidis, G.A. en Versalovic, J. (2009) Targeting the Human Microbiome With  
574 Antibiotics, Probiotics, and Prebiotics: Gastroenterology Enters the Metagenomics  
575 Era. *Gastroenterology* 136, 2015–2031

576 67 Garber, K. (2015) Drugging the gut microbiome. *Nat. Biotechnol.* 33, 228–231

577 68 Gerber, G.K. (2014) The dynamic microbiome. *FEBS Lett.* 588, 4131–4139

578 69 Gordon, S. (2008) Elie Metchnikoff: Father of natural immunity. *Eur. J. Immunol.*  
579 38, 3257–3264

580 70 Belda-Ferre, P. *et al.* (2012) The oral metagenome in health and disease. *ISME J.*  
581 6, 46–56

582 71 Bron, P. a. *et al.* (2011) Emerging molecular insights into the interaction between  
583 probiotics and the host intestinal mucosa. *Nat. Rev. Microbiol.* 10, 66–78

584 72 Gavrish, E. *et al.* Devices and methods for the selective isolation of  
585 microorganisms. . (2016) , Google Patents

586 73 Strandwitz, P. *et al.* GABA-Modulating Bacteria : Microbiome-Based  
587 Therapeutics for Depression? , *RISE.* (2015)

588 74 Amalaradjou, M.A.R. en Bhunia, A.K. (2013) Bioengineered probiotics, a  
589 strategic approach to control enteric infections. *Bioengineered* 4, 379–387

590 75 Buffie, C.G. *et al.* (2014) Precision microbiome reconstitution restores bile acid  
591 mediated resistance to *Clostridium difficile*. *Nature* 517, 205–8

592 76 Li, J. *et al.* (2016) Probiotics modulated gut microbiota suppresses hepatocellular  
593 carcinoma growth in mice. *Proc. Natl. Acad. Sci. U. S. A.* 113, E1306-15

594 77 Thompson, B.M. en Boiani, J. (2015) The Legal Environment for Precision  
595 Medicine. *Clin. Pharmacol. Ther.* [Accepted, 167–169

596 78 Ginsburg, G.S. (2013) Realizing the opportunities of genomics in health care.  
597 *JAMA* 309, 1463–4

598 79 Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership Plavix [package insert].  
599 . (2015) , 1–32

600 80 Johnson, J.A. *et al.* (2012) Clopidogrel: a case for indication-specific

601 pharmacogenetics. *Clin. Pharmacol. Ther.* 91, 774–6

602 81 van Nood Els *et al.* (2013) Duodenal Infusion of Donor Feces for Recurrent  
603 Clostridium difficile. *N. Engl. J. Med.* 368, 407–415

604 82 Manuck, S.B. en McCaffery, J.M. (2014) Gene-Environment Interaction. *Annu.*  
605 *Rev. Psychol.* 65, 41–70

606 83 Gauderman, W.J. (2002) Sample size requirements for matched case-control  
607 studies of gene-environment interaction. *Stat. Med.* 21, 35–50

608 84 Huang, Y.J. en Boushey, H.A. (2015) The microbiome in asthma. *J. Allergy Clin.*  
609 *Immunol.* 135, 25–30

610 85 Ellekilde, M. *et al.* (2014) Transfer of gut microbiota from lean and obese mice to  
611 antibiotic-treated mice. *Sci. Rep.* 4,

612 86 Foster, J. a. en McVey Neufeld, K.A. (2013) Gut-brain axis: How the microbiome  
613 influences anxiety and depression. *Trends Neurosci.* 36, 305–312

614 87 Turnbaugh, P.J. *et al.* (2006) An obesity-associated gut microbiome with increased  
615 capacity for energy harvest. *Nature* 444, 1027–31

616 88 Frank, D.N. *et al.* (2007) Molecular-phylogenetic characterization of microbial  
617 community imbalances in human inflammatory bowel diseases. *Proc. Natl. Acad.*  
618 *Sci.* 104, 13780–13785

619 89 Shah, P. *et al.* (2016) A microfluidics-based in vitro model of the gastrointestinal  
620 human–microbe interface. *Nat. Commun.* 7, 11535

621 90 Sun, X. *et al.* (2016) Patent watch: Modulating the human microbiome with live  
622 biotherapeutic products: intellectual property landscape. *Nat. Rev. Drug Discov.*  
623 15, 224–225

- 624 91 Morgan, B. (2016) Drug development: A healthy pipeline. *Nature* 533, S116–S117
- 625 92 Degnan, F.H. (2008) The US Food and Drug Administration and Probiotics:  
626 Regulatory Categorization. *Clin. Infect. Dis.* 46, S133–S136
- 627 93 Lewis, Z.T. *et al.* (2016) Validating bifidobacterial species and subspecies identity  
628 in commercial probiotic products. *Pediatr. Res.* 79, 445–452
- 629 94 Miller, G.E. *et al.* (2016) Lower Neighborhood Socioeconomic Status Associated  
630 with Reduced Diversity of the Colonic Microbiota in Healthy Adults. *PLoS One*  
631 11, e0148952
- 632 95 Rook, G.A.W. *et al.* (2014) Microbial “old friends”, immunoregulation and  
633 socioeconomic status. *Clin. Exp. Immunol.* 177, 1–12
- 634 96 Bailey, M.T. *et al.* (2011) Exposure to a social stressor alters the structure of the  
635 intestinal microbiota: Implications for stressor-induced immunomodulation. *Brain.*  
636 *Behav. Immun.* 25, 397–407
- 637 97 Block, J.P. *et al.* (2004) Fast food, race/ethnicity, and income: A geographic  
638 analysis. *Am. J. Prev. Med.* 27, 211–217
- 639 98 Powell, L.M. *et al.* (2006) Availability of Physical Activity–Related Facilities and  
640 Neighborhood Demographic and Socioeconomic Characteristics: A National  
641 Study. *Am. J. Public Health* 96, 1676–1680
- 642 99 Almqvist, C. *et al.* (2005) Low socioeconomic status as a risk factor for asthma,  
643 rhinitis and sensitization at 4 years in a birth cohort. *Clin. Exp. Allergy* 35, 612–8
- 644 100 Bytzer, P. (2001) Low socioeconomic class is a risk factor for upper and lower  
645 gastrointestinal symptoms: a population based study in 15 000 Australian adults.  
646 *Gut* 49, 66–72

647 101 McGuire, A.L. *et al.* (2008) Ethical, legal, and social considerations in conducting  
648 the Human Microbiome Project. *Genome Res.* 18, 1861–1864

649 102 Qureshi, N. en Kai, J. (2005) Genomic medicine for underserved minority  
650 populations in family medicine. *Am. Fam. Physician* 72, 386–7

651 103 Lynch, J.A. *et al.* (2013) Utilization of epidermal growth factor receptor (EGFR)  
652 testing in the United States: a case study of T3 translational research. *Genet. Med.*  
653 15, 630–638

654 104 Adler, N.E. (1993) Socioeconomic Inequalities in Health. *JAMA* 269, 3140

655 105 Penson, D.F. *et al.* (2001) The association between socioeconomic status, health  
656 insurance coverage, and quality of life in men with prostate cancer. *J. Clin.*  
657 *Epidemiol.* 54, 350–358

658 106 Spatz, M. *et al.* (1967) Role of intestinal microorganisms in determining cycasin  
659 toxicity. *Proc. Soc. Exp. Biol. Med.* 124, 691–7

660 107 Schoeni, J.L. en Wong, A.C. (1994) Inhibition of *Campylobacter jejuni*  
661 colonization in chicks by defined competitive exclusion bacteria. *Appl. Environ.*  
662 *Microbiol.* 60, 1191–7

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## **Outstanding Questions**

What is the relative significance of specific microbial actors versus whole microbiome ecology in disease states, and how will drugging specific bacteria affect ecological succession following this perturbation? How will this depend on the milieu in which a species is situated (e.g., presence of different taxa performing a similar ecological role)? Additionally, what roles might phages, fungi, viruses play?

How closely coupled are genetics and the microbiome, and how can these fields be integrated into a unified practice of precision medicine?

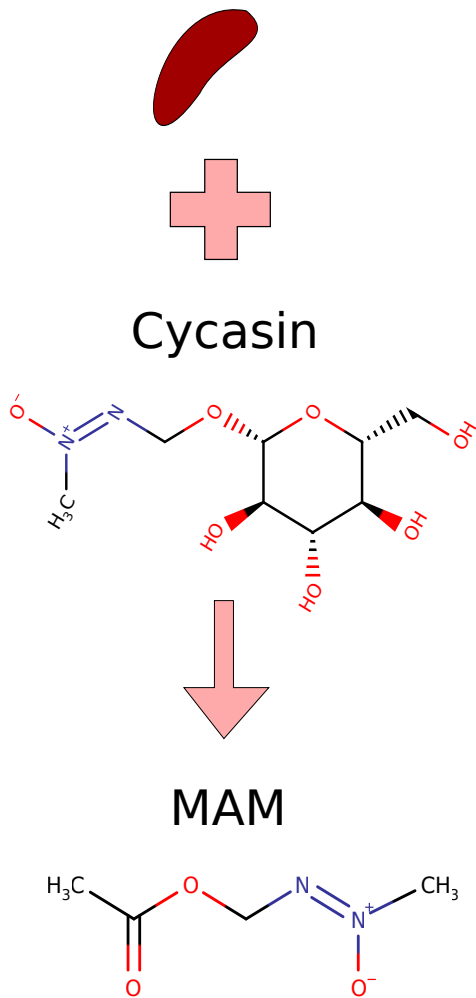
Which microbiome-driven disease states can be successfully cured? Which instead require prophylactic or palliative, noncurative therapy?

What is the best way to move precision microbiome medicine results out into the clinic? What changes in regulatory, governmental as well as research and development processes will need to occur for this to happen?

How will the needs of different groups be best addressed across diets, lifestyles, and environments? What interventions will ultimately require social change rather than medical therapy, and what will the interplay between these fields be?



Figure 1  
**(A)** *Metagenomic insight*



**(B)** *16S assay and diagnosis*

