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REVIEW

Consumer Safety Considerations of Skin and Oral Microbiome Perturbation

Andrew J. McBain,[a] Catherine A. O'Neill,[b] Alejandro Amezquita,[c] Laura J. Price,[c] Karoline Faust,[d] Adrian Tett,[e] Nicola Segata,[e] Jonathan R. Swann,[f] Adrian M. Smith,[g] Barry Murphy,[h] Michael Hoptroff,[h] Gordon James,[g] Yugandhar Reddy,[i] Anindya Dasgupta,[i] Tom Ross,[j] Iain L. Chapple,[k] William G. Wade,[l] Judith Fernandez-Piquer[c]*

[a]Division of Pharmacy & Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, United Kingdom
[b]Division of Musculoskeletal & Dermatological Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, United Kingdom
[c]Unilever, Safety & Environmental Assurance Centre (SEAC), Sharnbrook, United Kingdom
[d]Department of Microbiology, Immunology and Transplantation, Laboratory of Molecular Bacteriology, Rega Institute, Leuven, Belgium
[e]Department CIBIO, University of Trento, Trento, Italy
[f]Division of Integrative Systems Medicine and Digestive Diseases, Imperial College London, London, United Kingdom
[g]Unilever, Sharnbrook, United Kingdom
[h]Unilever, Port Sunlight, United Kingdom
[i]Unilever, Bangalore, India
[j]University of Tasmania, Hobart, Tasmania, Australia
[k]Periodontal Research Group, The University of Birmingham, Birmingham, United Kingdom
[l]Centre for Host-Microbiome Interactions, King's College London, London, United Kingdom

SUMMARY Microbiomes associated with human skin and the oral cavity are uniquely exposed to personal care regimes. Changes in the composition and activities of the microbial communities in these environments can be utilized to promote consumer health benefits, for example, by reducing the numbers, composition, or

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Address correspondence to Andrew J. McBain, andrew.mcbain@manchester.ac.uk.

* Present address: Judith Fernandez-Piquer, Upfield, Rotterdam, The Netherlands.

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activities of microbes implicated in conditions such as acne, axillary odor, dandruff, and oral diseases. It is, however, important to ensure that innovative approaches for microbiome manipulation do not unsafely disrupt the microbiome or compromise health, and where major changes in the composition or activities of the microbiome may occur, these require evaluation to ensure that critical biological functions are unaffected. This article is based on a 2-day workshop held at SEAC Unilever, Sharnbrook, United Kingdom, involving 31 specialists in microbial risk assessment, skin and oral microbiome research, microbial ecology, bioinformatics, mathematical modeling, and immunology. The first day focused on understanding the potential implications of skin and oral microbiome perturbation, while approaches to characterize those perturbations were discussed during the second day. This article discusses the factors that the panel recommends be considered for personal care products that target the microbiomes of the skin and the oral cavity.

KEYWORDS consumer safety, hygiene, oral microbiome, personal care, risk assessment, skin microbiome

INTRODUCTION

The last 2 decades have seen the effective application of culture-independent methods to study the human microbiota (the microbial cells) or microbiome (the associated DNA) (1). This has led to a deeper and more comprehensive analysis of the diverse range of organisms that inhabit the body, where a substantial proportion are not readily amenable to culture (2). In the process, some but certainly not all knowledge gaps have been addressed. High-throughput sequencing is currently performed using a range of platforms, including Illumina and Ion Torrent, which can rapidly sequence millions of fragments of DNA in parallel (3). Hypervariable regions of the bacterial 16S rRNA genes or whole-genome DNA is targeted to analyze complex microbial communities. For 16S amplicon sequencing in particular, bioinformatic analyses have been applied to cluster the generated sequences according to their similarity to define different operational taxonomic units (OTU), which are then compared to the sequences in databases to reveal community composition. However, tools such as DADA2 are being increasingly used to obtain exact sequence variants (4), giving greater resolution (5). The often short sequencing reads and the large data volumes generated through next-generation sequencing (NGS) present challenges, and taxonomic classification and relative abundances can vary depending on the bioinformatic pipeline used (3). Microbiome research has nevertheless identified microbial diversity considerably greater than that which had been previously characterized, overcoming some of the limitations of culture, including issues of nonculturability. While microbiome research in humans has focused primarily on the gut, studies of the oral cavity (6–9) and skin (10–14) have facilitated the deeper understanding of these sites, which are of particular relevance to personal care. The use of personal care products can result in changes in the microbiome that may be intentional or otherwise. It is, however, important to note that "oral microbiome" and "skin microbiome" are simplified terms referring to biogeography-dependent sets of communities where microbial composition and activities can vary markedly, depending on the site.

THE CHALLENGE OF ESTABLISHING CAUSALITY

The human microbiome provides protection against pathogenic organisms (14) and can stimulate the immune system (15, 16) and participate in the maintenance of different ecological niches present in the body (17). Fluctuations in microbiome composition may therefore perturb beneficial microbial functions with potential health implications for the host. The following paragraphs consider some notable diseases of the skin and the oral cavity where differentiating between cause and association for microbiome composition has been challenging.

Atopic dermatitis (AD) is a chronic, relapsing inflammatory condition characterized by pruritis (itchiness), wheels and flares, and, in severe cases, broken, bleeding skin. A high *Staphylococcus aureus* load has been reported to correlate with AD flares and vice

versa in clinical studies involving AD patients, where coagulase-negative staphylococci (CoNS) were more abundant in healthy controls (18). Colonization with commensal staphylococci early in life appears to be protective against the development of AD (19), and AD is also strongly associated with mutations in the barrier protein filaggrin (20). It has therefore been hypothesized that an abnormal epidermal environment caused by a leaky skin barrier predisposes the skin to infection by exposing environmental niches that would normally be inaccessible to *S. aureus*.

Unraveling the role of the microbiome in dermal diseases is confounded by the physiological changes in host tissues that characterize the pathology. Acne vulgaris, for example, has been associated with overgrowth of *Cutibacterium acnes* (formerly *Propionibacterium acnes*), but this association is not necessarily causal. In addition, acne vulgaris has been potentially linked to changes in the dermal environment proposed to be driven by factors including a Western-style diet, which may influence signaling in the hair follicle, resulting in the overproduction of sebum (21). The photodermatosis polymorphic light eruption (PLE), which is characterized by a rash on exposure to UV light, has been associated with the abnormal expression of antimicrobial peptides in the skin (22) distinct from that seen in psoriasis or AD, suggesting a microbiota involvement. PLE is, however, also associated with other changes in the immune system of the skin (23, 24). The common inflammatory skin condition psoriasis has been associated with changes in the skin microbiota (25, 26), but this association is not necessarily causal because the massive systemic inflammatory response that is a feature of psoriasis may also profoundly influence the composition of the skin microbiota (as reviewed in reference 27).

While the relationship between the oral microbiome and oral disease is, arguably, better understood, knowledge gaps remain. Common conditions such as dental caries, gingivitis, and periodontitis are closely associated with potentially harmful changes in the composition and activities of the oral microbiota (sometimes referred to as dysbiosis) (28, 29) that have environmental triggers. The development of caries, for example, is related to the high intake of sugary foods and the consequent production of lactic acid by caries-associated bacteria within the oral microbiome. This, in turn, favors the growth of acid-tolerant, acidogenic organisms, such as *Streptococcus mutans*, which, along with other oral bacteria, forms biofilms on the tooth surface (30). Acid produced by these organisms can alter the balance of enamel demineralization/remineralization of the tooth, leading to the loss of mineral and caries formation. In periodontitis, the persistent presence of subgingival biofilms associated with poor oral hygiene can lead to inflammation and bone loss (31). The pathology of periodontitis is largely caused by the host response, and the primary risk factor is host susceptibility (as reviewed by Wade [32]). However, certain species of bacteria, including *Porphyromonas gingivalis*, favor inflamed sites. These bacteria can subvert the host response, leading to a dysbiotic microbiota, which further exacerbates lesions (33). While the role of the host response in periodontitis is well established, the roles of the host response and the microbiome for gingivitis merit further research. Additionally, some reports suggest that oral bacteria can translocate from the mouth into the systemic circulation, and while causality has not been confirmed, periodontitis, for example, has been associated with other conditions, such as coronary artery disease (34), rheumatoid arthritis (35), and respiratory disease (36, 37).

TARGETING SPECIFIC MICROBES WITH PERSONAL CARE PRODUCTS

As well as investigating the role of the microorganisms present in health and disease, microbiome research is increasingly being applied to investigate the fundamental biology of various skin conditions (38), oral hygiene (39), dandruff (40), dental caries (41), acne (42), and periodontitis (28, 29) (Table 1). Recent advances in this field include improved knowledge of the bacterial and fungal composition of the scalp in individuals with and without dandruff (43) and the identification of bacteria involved in axillary (44) and oral (45) malodor. In addition, the importance of bacterial strain variability in acne is also now appreciated; although the overall relative abundance of

TABLE 1 Habitat parameters, microbiome functions, and intervention strategies for human skin and oral cavity[a]

Parameter	Skin				Oral cavity		
Conditions with microbiome associations	Atopic dermatitis, psoriasis	Acne	Dandruff	Axillary malodor	Caries	Gingivitis	Periodontitis
Routine perturbations	Cleansing; moisturizing; use of cream, gels, and lotions	Cleansing; use of cream, gels, and lotions	Cleansing, use of shampoo	Cleansing, use of antiperspirants and deodorants	Toothbrushing, flossing, use of toothpaste and mouthwash		
Microbiome understanding and potential target mode of action for microbial interventions	*S. aureus* load correlates with atopic dermatitis flares (18) Early colonization with commensal staphylococci provides protection (18, 19) Abnormal expression of antimicrobial peptides (22) Changes in the proportion of bacteria compared to healthy skin (25, 26) Associated with the fungus *Malassezia* (103)	Outgrowth of *C. acnes* and overproduction of sebum associated with acne (21, 90) Associated with specific strains of *C. acnes* (42, 116, 123) Decrease in the vitamin B_{12} biosynthesis pathway (125)	Associated with an imbalance of both bacterial and fungal species, with an increase in *Staphylococcus* spp. and *Malassezia restricta* (40). Severity of dandruff is dependent on the interactions between the host and microorganisms (43) Decreased *Propionibacterium* and increased *Staphylococcus* abundance (43)	Associated with *Corynebacterium* species (44) Malodor caused by short- and medium-chain volatile fatty acids (44)	Changes in oral microbiota composition (28, 29) Outgrowth of acid-tolerant *Streptococcus mutans* (30), *S. sobrinus* (92), and *Lactobacillus* and *Bifidobacterium* (28, 107–110) Increased glycan synthesis and carbohydrate metabolism and reduced lipid metabolism (67)	Changes in oral microbiota composition (28, 29) Subversion of host response at inflamed site, colonization of inflamed tissue by *Porphyromonas gingivalis* (33) Plaque load and maturity (60)	Changes in oral microbiota composition (28, 29) Subgingival biofilm formation is associated with inflammation and bone loss (31) Translocation of oral microbiome to systemic circulation (34–36) Increased metabolic degradation of nutrients and fatty acid metabolism (120, 122) Increased gene activity related to anaerobic growth conditions (122) Depletion of antioxidants, degradation of host cellular components, and accumulation of bacterial products (130, 131)
Ecological factors specific to the human body site	Bacteriocins and phenol-soluble modulins contribute to the maintenance of the niche (56) Skin has a mixture of secretions from different glands and microbiota (69) Host physiological conditions, such as sebum and water content, are relevant in the scalp (43) Higher exposure to moisture, changes in temperature and UV (84) Host factors, including skin barrier protein mutations, e.g., filaggrin in AD (20) and mTORC1 changes (increased sebum formation) due, in part, to diet (21) Host immune/inflammatory status (23–27)				Food intake, high intake of sugar correlated to production of lactic acid and acidification (30, 31) Biofilm formation by attaching to different surfaces (30, 31) Host susceptibility (32) Presence or absence of inflammation (33) Oxygen availability, mechanical stress, and saliva flow (6, 61, 82) Antibiotic use (60) Exposure to tobacco smoke (77)		
Selected microbiota functions	*S. epidermidis* produces AMPs to control the growth of *S. aureus* (16), serine proteases to inhibit biofilm (16), and fermentation products to inhibit *C. acnes* (46) *C. acnes* converts sebum to free fatty acids, inhibits colonization, and maintains acidic pH of the skin (46)				Some streptococci generate hydrogen peroxide to inhibit *S. mutans* (58) Nitrate-reducing bacteria can influence cardiovascular health and blood pressure (59) Some streptococci support enzymatic reactions for nutritional purposes (60)		

[a]For the categories with entries on multiple lines, there is not necessarily one-to-one correspondence between entries in the same row.

C. acnes is comparable between individuals with acne and healthy individuals, significant differences at the strain level have been observed (42). Manipulation of the compositional structure or function of skin and oral microbiomes can potentially counteract certain undesirable health conditions, where the use of probiotics, prebiotics, and targeted antimicrobials may provide opportunities to restore the healthy microbial composition of the skin (46) and oral cavity (47, 48). Manipulating the innate immunity of the skin and oral cavity is another route through which this could be achieved (39, 49).

AIMS AND OBJECTIVES

While differentiating between association and causality remains a key issue in microbiome research, the fact that in some cases interactions between the microbiome and the host play a role in health and disease has been established (as previously reviewed [50]). It is therefore important that the effect of personal care regimes on the microbiome receives adequate consideration. Understanding of the factors that cause fluctuations in the microbiome is likely to contribute to the development of novel approaches to understand potential links to undesirable health conditions and to the identification of microbiome-based biomarkers. It is in this context that the U.S. National Academy of Sciences has discussed the need to incorporate interactions between the microbiome and chemicals in assessing human health risks associated with environmental chemical exposure (51). As understanding of the functional significance of the human microbiome progresses and the exploration of host-microbial interactions advances, understanding the effects of intentional manipulation of the human microbiome in the context of human safety should be addressed.

In October 2016, a workshop was organized at Colworth Science Park in the United Kingdom including 31 specialists in the areas of microbial risk assessment, skin and the oral microbiome, microbial ecology, bioinformatics, bacterial modeling, and immunology. This review emerged from exploration of the areas discussed during the workshop. It considers factors that the panel agreed require consideration when evaluating the safety of personal care products that aim to benefit the consumer by affecting the composition or activities of the skin and oral microbiomes.

PROTECTION OF ORAL AND SKIN MICROBIOME FUNCTIONS TO PROMOTE HEALTH

The Human Microbiome in Health and Well-Being

Microbiotas associated with the oral mucosa and the skin help program the human immune system to recognize pathogens (52, 53), reduce the risk of invasion by undesired organisms (54), and produce vitamins and other metabolites, such as short-chain fatty acids (55). In skin, phenol-soluble modulins (PSMs) and bacteriocins (56) contribute to the ecological and structural maintenance of the niche (54). Commensal skin organisms, such as *Staphylococcus epidermidis* and *C. acnes*, use distinct mechanisms to inhibit pathogens and maintain a healthy skin barrier. *S. epidermidis* produces antimicrobial peptides which can reportedly control the growth of *S. aureus* (16), as well as serine proteases to inhibit biofilm formation (16); fermentation products, such as succinic acid, that may inhibit the overgrowth of the opportunistic pathogen *C. acnes* (46); and a unique form of lipoteichoic acid that can inhibit skin inflammation during skin injury (57). *C. acnes* also has a protective role as a commensal by converting sebum to free fatty acids, which in consequence inhibit colonization of opportunistic pathogens and contribute to the maintenance of an acidic skin pH (46).

In the oral cavity, some streptococci generate hydrogen peroxide, which can inhibit the caries-associated bacterium *S. mutans* (58). The oral microbiome also has nonantimicrobial functions of importance to health and disease, where nitrate-reducing oral bacteria can convert dietary nitrate into nitrites, which can influence cardiovascular health and blood pressure (59). Nutritional functions of the oral microbiota are delivered by complex communities via cross feeding and syntrophy. For example, streptococci have both glycosidic and endopeptidase activity, while species of *Prevotella* and

Porphyromonas have endopeptidase activity and species of *Fusobacterium* and *Peptostreptococcus* have aminopeptidase activity (60). Bearing in mind the roles of the skin and oral microbiome that are currently understood and the fact that other activities remain unknown, the maintenance and protection of the healthy functionality of the microbiome are important considerations when assessing the effect of personal care products.

Microbiome Composition versus Function

Initiatives such as the Human Microbiome Project (HMP) (13, 53, 55) and other studies (14, 52, 61) have enhanced our understanding of the baseline skin and oral microbial composition, but the search for attributes that define a healthy human microbiome continues. As part of the HMP, where 200 healthy individuals were examined, the core microbiome of different body sites, including saliva, plaque, tongue, and other oral tissues, ranged from 0 to 8 operational taxonomic units (OTUs) when analyzed for percent prevalence of 100%, compared to a higher range of 19 to 75 OTUs when the percentage was lowered to 50% (62). Interpretation of the core microbiome to measure the similarity of samples depends on the taxonomic resolution employed since samples may decrease in apparent similarity when analyzed to the genus or OTU level compared to the phylum level (8, 61, 63). While a specific group of microorganisms may be shared between individuals, interindividual variation may still be considerable at the species level and for the presence of rare microorganisms (8, 14, 61). Care is therefore required when classifying microbiome composition as healthy or otherwise, especially in the absence of species-level classification. This is of particular importance in the oral cavity, where different species within the same genera can have contrasting associations between health and disease.

The functions provided by compositionally different microbiomes can be relatively similar between individuals (55). Exploring which of these general functions are associated with health represents an alternative to the concept of "healthy composition" (64). A proposed functionality-based definition of a "healthy microbiome" involves three functions: those associated with health-related housekeeping functions, human functions, and specialized functions (53). Housekeeping functions involve energy production and the generation of metabolites and other requirements to maintain the microbial community itself; human-associated functions comprise interactions with the host, such as developing and influencing the activity of the immune system; and specialized functions include regulation of the pH in a specific body site. A functional core has been described for metabolic pathways detected in more than 75% of individuals (55). Pathway cores were identified for either multiple or single body sites, reflecting the fact that some core functions are broadly distributed and general to the human host, while others are an adaptation to a specific body site. It should be noted that core functions are not necessarily beneficial to the host. Among site-enriched pathways, nitrate reduction has been identified to be important in the oral cavity (55). These core pathways are generally associated with microbial consortia. Such functional observations may provide further insights when studied across populations and during longer temporal studies with a controlled microbial change. If functional characterization of the human microbiome can be achieved, measuring or predicting the loss of a beneficial function or the introduction of an undesired function could be used as a functional index during consumer safety assurance.

FACTORS THAT CONTRIBUTE TO PERTURBATION OF THE SKIN AND ORAL MICROBIOME

Microbiome Stability as an Indicator of Health

The variability of the microbiome over time in healthy individuals has been assessed and was found to be low (65). This "temporal stability" has been interpreted as a sign that the community is in equilibrium, regardless of the fact that some microbes may at the same time be changing as a response to disturbances (66). Stability in the classical sense, that is, the ability of the microbiome to remain at equilibrium when exposed to

a perturbation (resistance) or to return to it afterwards (resilience), has also been proposed to be a key feature of a healthy microbiome (53). When referring to a microbiota as stable, we include both of these two concepts of stability. Despite their importance for understanding microbial community dynamics and responses to perturbations, long-term longitudinal studies are still rare. However, based on the available evidence, the composition of the human microbiome is relatively stable over time, with the main variation within an individual being between body sites (13), and considerable temporal stability has also been reported for the microbiome in healthy skin. Oh and colleagues (14) generated metagenomic sequence data from longitudinal samples collected over 2 years and reported that bacterial, fungal, and viral communities were largely stable over that time, despite exposure to the external environment. This stability was observed to be site specific, with body sites harboring high microbiome diversity being more variable than low-diversity (sebaceous) body sites. Observations of temporal stability in the skin microbiome have been interpreted as evidence for colonization resistance and used as the basis for clinical studies exploring the skin microbiome in disease states, where compositional changes in the microbiome have been reported. Costello et al. (10) assessed the resilience of the skin microbiota by disinfecting plots on the forehead and left volar (i.e., underside of) forearms of volunteers and then inoculating them with foreign microbiotas (i.e., microbiotas taken from the tongue and skin of other individuals). The microbiotas of forearm plots ($n = 16$) that had been inoculated with tongue scrapings were more similar to tongue communities than to those normally associated with the forearm in relative abundance between 2 and 8 h after inoculation. However, communities more similar to those normally associated with the forehead developed on forehead plots that had been similarly inoculated with tongue material. It can be inferred, therefore, that for some reason (potentially the presence of sebaceous lipids), the forehead environment exerted a stronger selection pressure than the forearm. Furthermore, following interpersonal and intergender reciprocal swaps of forehead and forearm microbiotas, developing communities resembled those of the recipient rather than those of the donor, demonstrating the importance of the environment and, possibly, the action of endogenous mechanisms for individualization and microbiota perpetuation. The authors hypothesized that the stronger selection at forehead sites was due to sebaceous secretions, which, in contrast to dry sites like the volar forearm, (i) may have been more strongly selective and/or (ii) could have supported the more rapid recolonization from appendageal structures, which is in agreement with the hypothesis outlined above.

The oral microbiota may also remain stable over time in healthy individuals (6), although it is also sufficiently malleable to be beneficially manipulated through hygienic intervention (39). It is, however, important to consider what stability means when referring to a host-associated microbiota. Belstrom and colleagues collected saliva from five volunteers without oral disease every 4 h for 24 h, repeated this 7 days later (67), and profiled the salivary microbiome. While caution is necessary, given the small sample size, the author's tentative conclusion was that "little or no variation" within salivary microbiomes was observed over time. The oral cavity is a complex environment with various distinct areas, and saliva, often purported to contain microorganisms originating from multiple sites on the mouth, may vary less in terms of microbiome composition than, for example, a tooth surface, where, in individuals following the recommended oral health regime of twice-daily brushing, microbial abundance is very low immediately after cleaning but can exceed 10^7 bacteria per cm^2 following regrowth.

Maintaining microbiome stability in healthy individuals ensures that the beneficial microbial functions are maintained (68), so the measurement of microbiome stability and its recovery following disturbance is important in understanding potential risks. While the human microbiome is relatively stable, its composition can be altered both by pathologies, such as gingivitis and dandruff, and by treatment.

Consumer Products Can Alter Microbiome Composition or Function

The hypothesis that the skin microbiota, once established, is perpetuated by continuous endogenous inoculation is supported by an investigation by Grice et al. (12) in which the skin microbiota was sampled using swabs and biopsies and profiled by high-throughput sequencing. An attractive explanation is that secretions from sweat glands and the outward migration of differentiating skin cells could transport bacterial cells from within appendageal structures continuously onto the skin surface (as proposed by Kong [69]). Daily hygiene regimens may, however, affect the microbiome, and some routines, such as tooth brushing and hand washing, do this intentionally to control or reduce the risk of oral disease and to reduce the transmission of pathogens, respectively (54, 70). Exposure to antimicrobials through the use of household and personal care products has shown minimal long-term effects on the microbiome. In this respect, two human studies monitored how the use of toothpaste, liquid and bar soap, and dishwashing liquid with and without triclosan perturbed the microbiome. The first study, a crossover control study involving healthy individuals, showed no significant impact on the human oral or gut microbiome composition during 4 months of exposure to the antibacterial compound triclosan (71). A longitudinal survey of the gut microbiota in infants and mothers during the first year following birth also did not show major compositional changes or a loss of microbial diversity (72). It is highly likely that environmental modulation of the skin microbiota has been occurring since the ancient origins of the microbiome for the skin through UV irradiation, friction, and washing and for the oral cavity through diet, friction, and cleaning. In personal care, antiperspirants are used by approximately 50% of the global population and have been shown to reduce the bacterial load in the axilla. Individuals that do not use antiperspirants have been observed to harbor a greater axillary microbiome diversity than individuals that use antiperspirants do (73). For antiperspirant and deodorant users who ceased use of product, an increase in *Staphylococcaceae* was observed; in comparison, *Corynebacterium* species dominated in nonusers. In contrast, microbiome diversity was reported to be greater in antiperspirant users than in deodorant users or nonusers. In a separate study of nine cohorts, axillary diversity was similarly found to be greater in antiperspirant (and deodorant) users than in nonusers (74). A recent study on the effect of cosmetic products on the microbiome of facial skin of high- and low-hydration groups indicated that the baseline bacterial diversity was greater in the low-hydration group than in the high-hydration group and that the use of cosmetic products decreased the differences between the two groups (38).

Microbiome Individualization

Evidence suggests that both environment and host genetics play important roles in determining the composition of individual microbiomes. Salivary microbiome studies in twins indicate that overall microbial abundance and some aspects of the microbial population structure are influenced by heritability (75). With respect to the skin microbiome, Blekhman and colleagues (76) analyzed shotgun metagenomic data from the HMP, collecting data on host genetic variation for 93 individuals. They reported significant associations between host genetics and the microbiome composition for 10 of the 15 sites that they assessed, including the oral cavity and the skin. Thus, as well as extrinsic environmental factors, host genetics appears to play a role in the composition of the oral and skin microbiotas, probably through immunological and other mechanisms. These examples partly explain the variability between individuals observed in microbiome research (8) and highlight the need to separate a significant change from individual variation when assessing specific perturbations.

Extrinsic factors also influence the stability of the microbiome, since activities, such as smoking tobacco, have been shown to influence the composition of oral biofilms (77), suggesting that smoking promotes the acquisition and colonization of pathogenic bacteria. The development of gingivitis and its progression from gingivitis to periodontitis and the promotion of dental plaque biofilm colonization partly depend on the host immune response (78). Gomez and colleagues (79) illustrated the impact of host

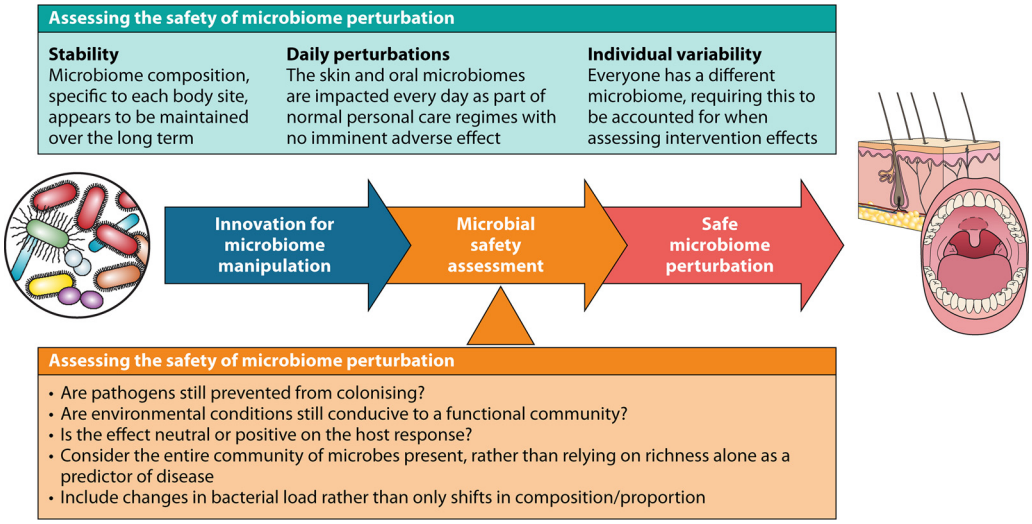

FIG 1 Assessing the safety of perturbations of the skin and oral microbiome.

genetics through a human volunteer study involving a large cohort of monozygotic and dizygotic twin children with and without active caries, with the aim of elucidating the contributions of host genotype and shared environment on the oral microbiomes (supragingival plaque) of children. They observed that the similarity in oral microbiomes was higher between monozygotic twins, regardless of caries state, with certain taxa being identified as highly heritable, but that most of the variation was determined by the specific growth microenvironment. The caries state, however, was not associated with the more highly heritable bacteria, suggesting that lifestyle, diet, and oral hygiene practices might outweigh parental heritability in establishment of a caries-associated microbiome. The more heritable species were detected at a lower abundance with increasing age and sugar consumption.

FACTORS TO CONSIDER DURING MICROBIOME PERTURBATION

Risks of Pathogen Colonization

One of the beneficial activities of the microbiotas of the skin and oral cavity is the protection of the host tissue from pathogens (as summarized in Fig. 1). Perturbation of commensal communities may therefore be a factor contributing to the pathogenesis of certain inflammatory conditions. In some circumstances, overgrowth of commensal microorganisms with pathogenic potential (pathobionts) or colonization by external pathogenic organisms (transients) can cause disease. The ability of transient organisms to colonize is likely to depend on the interactions with the commensals residing at each specific body site. In this respect, microbial communities with more competitive interactions than cooperative interactions are assumed to be more resilient, in the sense that cooperation causes coupling between species involving several species to change at the same time and destabilize the system (80). In the mouth, loss of colonization resistance through antibiotic use can lead to infections by opportunistic pathogens, such as *Candida* species and *S. aureus* (as reviewed in references 60 and 81). In this regard, microbial changes that do not increase the opportunity for pathogens to colonize are unlikely to adversely affect the well-being of the host.

The Human Body as a Microbial Niche

The skin and oral cavity present distinct environments, and ecological conditions *in situ* have a large influence on the compositional differences in microbiota between body sites. Oily, moist, and dry skin sites regulate nutrients and harbor specific microbial taxa (46, 52). The mouth can be broadly divided into different habitats, the gingiva and hard palate, the tongue and throat, and dental plaque, with each one being colonized by a microbiome characteristic of the specific site (60). The microbiota

present in the oral cavity forms biofilms by attaching to the different surfaces, which confer spatial structure and provide the conditions required for different organisms to survive within the community (9). The availability of oxygen is one of the drivers of microbiota composition, and in this context, a succession during the formation of dental plaque has been proposed whereby teeth are initially colonized by facultative genera, such as *Streptococcus*, with a shift to a microbial community better adapted to anaerobic conditions occurring as the biofilm matures. Bacterial succession on the tooth surface can also be strongly influenced by nutrient availability, mechanical stress, and saliva flow (6, 61, 82) and by binding of bacteria to proteins in the salivary pellicle coating the tooth surface (83).

Interactions with the external environment can also drive selection. For example, an increase in sugar intake or a reduction in saliva flow may induce a reduction in pH that allows the expansion of aciduric organisms (82). Loss of moisture, changes in temperature, and exposure to UV radiation can also result in microbiota alteration in the skin (84). Similarly, changes in the spatial structure may also influence the microbial community within a given body site (9, 84).

Microbial Diversity in Health

Several indices have been employed to differentiate microbiomes associated with health and disease. Among these, microbial (ecological) diversity is frequently measured. Ecological diversity can be measured as richness (the number of taxa present) and evenness (the abundance of microbial constituents). Although not universally applicable, higher diversity has been associated with health in specific contexts, when considering that more diverse microbes may supply the host with increased functional traits. However, microbial diversity on its own is not an accurate measure for determining disease etiology or health. While reduced microbial diversity has frequently been observed in conditions such as atopic dermatitis and psoriasis (85, 86), this is not always the case; for example, in both psoriatic and unaffected elbows (79), richness has been reported to be the same, while an increase in bacterial diversity due to the rise of species of minor abundance has been observed in gingivitis and periodontitis (63, 87). The measurement of diversity also does not account for interactions among species, and two microbiomes with the same level of diversity may be different. It may therefore be more pertinent to observe the entire community of microbes present and, by extension, how they function, rather than relying on richness alone as a predictor of disease (88).

The Importance of Bacterial Abundance

Compositional studies of the skin and oral microbiomes have suggested that the load or abundance of organisms can be more significant than their presence in the progression of disease. A 65% increase in the proportion of *S. aureus* in atopic dermatitis sufferers at flare sites and a partial correlation between *S. aureus* abundance and disease severity have been reported (106). Similarly, *S. epidermidis* was significantly more abundant during flares than after flares and in controls, although the underlying reasoning for the increase in *S. epidermidis* was not determined. Several studies have reported an increased *C. acnes* abundance in individuals with acne than in unaffected volunteers (90). While differences between the absolute numbers of bacteria between individuals with inflammatory acne, papules, and pustules have been reported, there appears to be progressively higher bacterial loads vis-à-vis the severity of the disease (91). The use of quantification methods, such as quantitative PCR, has revealed higher levels of *S. mutans* and *Streptococcus sobrinus* in children with caries than in caries-free children (92). In other oral diseases, such as gingivitis, severity is better correlated with the plaque load and maturity than with some specific bacteria (60). It should, however, be borne in mind that NGS is not well-suited to determining differences in bacterial absolute abundance (the quantified genetic or microbial load within a sample), such that two samples with an identical relative abundance (the genetic represen-

tation of microbes within a sample ranked against all taxa in the sample) could differ markedly in absolute abundance (93).

Host-Microbiota Interactions

Skin functions as a two-way barrier, which helps to preserve hydration levels and prevent entry of noxious substances into the body. Skin function may be shaped by the commensal organisms. and in this respect, Naik et al. (94) demonstrated that germfree mice had a weakened immune response to the parasite *Leishmania major* compared to mice raised under specific-pathogen-free conditions. The impaired response in the germfree mice could be rescued by colonization with *S. epidermidis* (94), implying a role for the microbiota in promoting host immunity. More recent evidence suggests that the microbiota is fundamental to skin structure. Conventionally reared mice showed altered gene expression compared with germfree mice. Meisel et al. (95) reported that 2,820 genes were differentially regulated by microbial colonization; these included genes associated not only with the host immune response but also with epidermal differentiation. Crucially, the expression of 9 genes involved in the epidermal differentiation complex (EDC), a collection of genes involved in terminal differentiation of keratinocytes (reviewed in refrence 89), was regulated by the microbiota. When the skin of conventionally raised mice was compared to that of germfree mice, differences in the balance of proliferation and differentiation were observed. These data support the view that the microbiome may be associated with the development of the skin architecture since the EDC has been implicated in dermatological diseases, such as psoriasis (reviewed in reference 96). Various studies have shown that the microbiota is associated with the outcome of the healing response when wounding breaches the skin barrier. In broken skin, the commensal microorganisms can behave as pathogens and colonization of wound sites can result in the release of microbial metabolites that can further damage host tissues (reviewed in reference 97). It is therefore unsurprising that accelerated wound healing has been observed in the absence of microbiota (98, 99), but it is also the case that the commensal microbiota can produce antimicrobial peptides (AMPs) that can inhibit the invasion of wound sites by pathogens (100). There is also evidence that *S. epidermidis* can inhibit the uncontrolled inflammation sometimes associated with wounding. Part of the mechanism for this may involve the inhibition of cytokine release by keratinocytes (57).

With respect to beneficial effects, *S. epidermidis* has been reported to augment tight junction function in keratinocytes (101), where the interaction of keratinocyte monolayers with *S. epidermidis* increased the transepithelial electrical resistance (a measure of tight junction function) within a short time of exposure to this bacterium. Furthermore, Toll-like receptor (TLR) ligands, such as lipoteichoic acid or peptidoglycan, may augment tight junction function in keratinocyte monolayers (102). These data suggest that skin commensals, like those of the gut, are probably involved in many aspects of epithelial barrier homeostasis.

MEASURING CHANGES IN THE MICROBIOME

Various data analysis methods that can objectively assess microbial changes are used in microbiome research. This section describes the information that each technique provides and how it is applied to characterize health and disease.

Metagenomic Profiling

Studies employing both ribosomal profiling and metagenomics have sought to identify microbes linked to either oral or cutaneous disease, whether it is at the community level or that of individual taxa. Several studies have reported changes in the proportion of bacteria on the skin in psoriasis (25, 26, 85). Gao et al. (26) and others (25), for example, reported that *Firmicutes* were significantly overrepresented in psoriasis lesions compared to uninvolved skin, while the *Actinobacteria* and *Propionibacterium* species were reportedly present at a significantly lower relative abundance in psoriatic lesions. Apart from bacteria, the fungal genus *Malassezia* has also been associated with

psoriasis (25, 26, 85, 103, 104). Altered microbial community profiles have also been reported in atopic dermatitis, where an increased proportion of *Staphylococcus* species, particularly *S. aureus* and *S. epidermidis*, was observed during disease flares in comparison to that at baseline or posttreatment and correlated with increased disease severity (19, 105, 106).

In terms of the oral microbiota, changes in microbial composition have long been associated with dental caries and periodontitis. For caries, sequence analysis has confirmed that bacteria other than *S. mutans* are correlated with active caries (*Lactobacillus* and *Bifidobacterium*), and likewise, several taxonomic groups of bacteria are associated with periodontitis (28, 107–110). It is also clear that the etiology of disease also involves a complex interplay between the host and the resident microbial communities that is yet to be fully explored. When applied to the study of psoriasis, such approaches indicate that strain-level features and associated functional variation may be pertinent to disease (111).

This exploration of host-microbe interactions has been hindered by the fact that virulence and pathogenic determinants could be partitioned at the subspecies or strain level. It is well established that intraspecies genomic features lead to phenotypic variability (106, 112–114). Ribosomal genus-based profiling approaches lack strain-level resolution. Several recent computational tools to taxonomically (115–117) and functionally (118, 119) characterize individual members of the microbiome at strain-level resolution in metagenomic data sets have become available.

Profiling of Functional Potential

While understanding the community structure of a microbiome and the relationship between specific taxa and health or disease can be informative, knowledge of community function will probably be most useful in understanding the effect of perturbing the microbiome. Shotgun metagenomics provides the potential to access strain-level taxonomic features and the potential functional characteristics of the community, which has, until recently, been computationally challenging. This approach can be used for the investigation of functional traits, although it can only reveal the functional potential of communities. It can also be used to profile viruses, which are not amenable to ribosome-based profiling. The oral microbiome has assessed disease states, such as caries or periodontal disease, compared to healthy controls. Shi et al. (120) and Wang et al. (121) reported that community function around bacterial chemotaxis and cell motility are increased in disease compared to periodontal health. It has also been shown that in periodontal disease there is an increase in metabolic pathway genes associated with fatty acid metabolism (122), as well as an increase in genes associated with the metabolic degradation of nutrients (120) and those required for growth under anaerobic conditions (122). Healthy communities have been shown to exhibit increased functions in the areas of fatty acid biosynthesis, aspartate and homoserine metabolism, membrane transport, and signal transduction. Metagenomic studies of the skin are more difficult due to the low bacterial density and small sample surfaces available (123). Mathieu et al. (124) consider the skin microbiota to be a complete organism, reporting a predominance of catabolic genes and the ability of the skin bacteria to use the sugars, lipids, and iron that are found on human skin. They also found genes related to antibiotic resistance, as well as some linked to acid resistance, clearly a mechanism for tolerance of the natural acidity of the skin. Oh et al. (17) have described a "functional core" of about 30% of the community that can vary depending on the diversity and biogeography of the different skin microenvironments, which drives the functional capacity that is required by that community. For example, dry sites were found to favor functional traits surrounding the citrate cycle, and sebaceous sites showed increased function around glycolysis and ATP/GTP/NADH dehydrogenase I. While these metagenomic approaches provide more than a simple inventory of taxa and provide information on function and health/disease interrelationships, making judgments of community functional traits by reference genome comparison should be undertaken with care. There is a large genomic diversity that is just starting to be understood, for

example, the association of only some *C. acnes* strains with acne vulgaris (116, 123). Further complicating the search for a functional understanding of the microbiome is the identification of new genes from metagenomic analysis approaches that are associated with health or disease but that cannot be assigned to any functional pathway.

Metatranscriptomic Analyses

Shotgun transcriptomics can be used to determine the active functions of a microbiome (125), especially as the community composition of a microbiome alone is not necessarily reflective of its active community members (126). This is an emerging research area with fewer data available, and challenges remain, for example, in sampling sufficient mRNA material to enable analysis. However, the transcriptomic profile of a community is dynamic and can easily change in the same biological sample at different times as the microbiome responds continually to changing environmental and host conditions. Metatranscriptomic studies applied to the human microbiome are more limited than metataxonomic/metagenomics surveys.

Metatranscriptomic studies of the skin are more challenging than those of the oral microbiome due to the limitations of the microbial biomass in the sample material. Kang and colleagues (125) analyzed the metatranscriptomics of patients with acne vulgaris versus those of healthy controls. *C. acnes* was reportedly the most transcriptionally active organism and was predominant in both the healthy and diseased samples. Further analysis of the gene expression profile of *C. acnes* in the samples identified that the organism's activity on acne-affected skin was distinct from its activity on healthy skin. Specifically, the vitamin B_{12} biosynthesis pathway was observed to be significantly downregulated in acne. Additionally, a model of how vitamin B_{12} modulates the transcriptional and metabolic activities of *C. acnes* in acne pathogenesis was suggested. The model underlined how shotgun metatranscriptomic approaches can enhance the understanding of disease pathogenesis. One of the limitations of metatranscriptome data is that the final metabolic products generated by a microbial community are not captured (126). In this respect, techniques such as proteomics, metabolomics, and lipidomics can help to have a deeper functional characterization of the microbiome.

Metatranscriptomics has been used in conjunction with metagenomics to investigate saliva from individuals with caries and periodontitis and to compare it with saliva from orally disease-free individuals. Belstrom et al. (67) identified 15 differentially expressed KEGG orthologs (KOs) between samples from patients with periodontitis or caries and samples from orally healthy controls. These included eight carbohydrate metabolism-associated KOs that were downregulated in periodontal disease and two KOs associated with glycan biosynthesis and carbohydrate metabolism that were upregulated in caries. In addition, the same study observed that lipid metabolism was increased in healthy samples compared with dental caries samples and concluded that longitudinal studies may reveal that screening for salivary metabolic gene expression can identify oral diseases preclinically. However, it is also clear that the development of such diagnostics is at a very early stage and that overcoming the very significant differences in complexity between the salivary and plaque microbiomes would be a substantial technical and clinical challenge.

Metabolomic Analyses

Microbial metabolites can have a direct impact on oral or skin health (e.g., short-chain fatty acids and sulfides in periodontal diseases, organic acids in dental caries), or they can enter and modulate host metabolic processes. As such, metabolite exchange between the microbiome and host represents one mechanism through which these systems communicate. Variation in the bacterial species present can modulate the genetic library of the microbiome, changing its overall functional capacity, its metabolite production, and the downstream impact on host health. However, different species are known to possess similar or even the same metabolic traits. This functional

redundancy means that studying composition alone may be insufficient to accurately determine the overall biotransformation capabilities of the microbiome and, therefore, its potential to modify host health. Metabolic profiling (metabolomics/metabonomics) has emerged as a powerful tool for studying the microbiota because it can ascertain the metabolic profile via low-molecular-weight compounds in a sample. These metabolic signatures contain thousands of molecular low-molecular-weight compounds reflecting biochemical events. These include host metabolic processes but also those performed by the resident microbes and products arising from interactions between the two. Studies using metabolomics to directly assess the functional status of the skin microbiota are limited. However, several studies have characterized the skin metabolome in a wider context. These have used a variety of sample types, including skin swabs, hydrogel micropatches (127), punch biopsy specimens, and sweat. In one study analyzing epidermal skin tissue, several bacterium-derived metabolites (128) and bacterial substrates were observed, including *p*-cresol, a product of bacterial tyrosine metabolism. This demonstrates that these tissue samples can be informative for studying the skin microbiome. Skin surface liquid extracts (sweat) represent another sample type of potential utility. These are complex mixtures of secretions derived from eccrine, apocrine, and/or sebaceous glands (depending on the body location) as well as from the microbiota inhabiting the skin (129). Attempts are being made to optimize and standardize the collection and analysis of sweat, and this may prove to be a useful resource for studying the skin microbiota.

Metabolic profiling of gingival crevicular fluid (GCF) has been used to study the importance of host-bacterium interactions in periodontal disease. Here, the depletion of antioxidants, degradation of host cellular components, and accumulation of bacterial products were seen in the disease state (130, 131). Attempts have been made to integrate salivary bacterial and metabolic data sets to identify metabolic products related to specific bacterial groups (132). Oral biofilms have also been studied by capillary electrophoresis-mass spectrometry (CE-MS)-based metabolomics. This has enabled the central carbon metabolic pathways to be investigated in the oral biofilm. One approach is to measure these pathways in supragingival plaque before and after a glucose rinse. Glucose can be degraded by bacteria to several metabolic products, including acetate, formate, lactate, and succinate. Assessing the metabolic content of this plaque after the rinse provides information on the functional capacity of the biofilm.

Mathematical Modeling

Oral and skin microbial community dynamics are shaped by three broad factors: the host, the environment, and the community. The human host provides the microenvironment for the community and may alter this environment through hygiene and other behaviors. The genetic makeup of the host also influences the community's microenvironment. The surrounding environment offers a large species pool from which immigration into the local community may take place. Finally, community composition (richness, evenness, and interactions) as well as history (e.g., previous exposure to perturbations) may impact its dynamics.

A community model expresses in mathematical terms how selected factors influence community dynamics. Community models thus allow prediction of the response of the community to short-term (pulse) perturbations and altered conditions (press perturbations). Models can be coarse grained or detailed, describing populations or individuals. A general distinction can be made between phenomenological models that predict community behavior on the basis of immigration and mortality rates, interaction strengths, growth rates, and other parameters and metabolic models that take underlying molecular mechanisms of interactions into account. The generalized Lotka-Volterra equation and its variants (133–135), but also individual-based models, such as the neutral model (136) and its extensions, are examples of the former.

In the oral cavity, these models have to deal with the complication that most community members can exist both in a free-floating planktonic state and as part of a

biofilm, which may have different growth rates and different access to nutrients and which may engage in different interactions. Previously, Schroeder and colleagues (137) proposed a discrete and continuous version of a model that describes the dynamics of both planktonic and sessile communities in drinking water pipes and that may be adapted to model community dynamics in the oral cavity. The programming language gro, which was designed for individual-based modeling of spatially structured microbial communities, may also be of interest in this respect (138). A range of factors, including growth rates, cell signaling, diffusing, and chemotaxis, can be factored in.

Metabolic models require the accurate reconstruction of each community member's metabolism (139), which is a major hurdle because of a lack of reliable and complete genome annotations and the large percentage of unknown gene functions. Metabolic reconstructions may be quickly generated automatically with tools such as ModelSEED or RAVEN (140, 141). This type of modeling presents some disadvantages, such as the requirement for a tedious manual curation to ensure an accurate reconstruction (142) and the assumption that community members are in a metabolic steady state. This assumption is relaxed by some dynamic metabolic models which require kinetic parameters, such as compound uptake rates (139). The dynamic individual-based metabolic modeling tools COMETS (143) and BacArena (144) additionally take spatial structure into account, which is important to model biofilms. Metabolic models can also exploit metaomics data as additional constraints on metabolic fluxes or as validation data (145). For example, gene expression data have been used to validate metabolic models (146). Despite their promise, to the best of our knowledge, metabolic models have been applied only to communities consisting of a small number of species. Metabolic models of species grown alone and in pairs can be exploited to predict ecological interactions (147). For instance, gut microbial interactions were predicted based on the semicurated reconstruction of 773 gut species (148). The extension of dynamic and spatial metabolic models to more complex microbial communities is a promising field for future research.

Community-level metabolic networks are a simpler form of metabolic models, where metabolites and reactions are represented as nodes and edges, respectively, but where stoichiometric coefficients are not taken into account (149). They offer a framework for the straightforward integration of metaomics data as node or edge weights (150). While metabolic networks can handle larger communities, they do not allow quantitative modeling (151).

Quantitative community models have parameters which need to be determined through measurements under well-controlled conditions. For instance, growth assays in mono- and coculture can provide growth rates and interaction strengths. Once a model is parameterized, it needs to be validated experimentally. Such a validation consists of comparing the outcomes of experimental perturbations with the outcomes predicted by the model. The model may undergo several rounds of adjustment and validation until it reaches sufficient accuracy, or it may fail to be predictive because important but unknown factors are not taken into account or the community dynamics are chaotic or predominantly stochastic. A model that predicts community dynamics to an acceptable level of accuracy can be applied to simulate the effects of yet untested perturbations on the community.

CONCLUSIONS

Perturbations of the microbiome can have positive and negative consequences for human health. However, more knowledge is required to understand the extent of change that corresponds to the maintenance of health and the establishment of disease states. Microbiome research is still in its early stages, and further studies to elucidate the nature of the functional and structural interactions among microorganisms and with the host are required. Analysis of the gut microbiome is advancing faster than that of the skin and oral microbiomes, where increasing research investment would help to understand better the dynamics of those two specific body niches. Although mankind has been manipulating its microbiome, often beneficially, through

diet, hand-washing, and oral hygiene practices, both modern and historic, for hundreds if not thousands of years, the risks of manipulating the microbiome through new technology innovation should be properly assessed, and the development of appropriate methods is required. Numerous factors should be considered when assessing the safety of novel approaches to microbiome perturbation, and approaches need to be developed to ensure that a compositional change delivers benefits while not compromising the stability, diversity, and immunological state required for the healthy functionality of the microbiome. These are summarized in Table 1 and Fig. 1. To increase our understanding of the safety of microbiome changes, multidisciplinary research needs to move to a mechanistic understanding to allow measurable elements specific to the oral and skin microbiome to be identified.

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Andrew J. McBain is a Professor of Microbiology at the University of Manchester, Manchester, United Kingdom. He was awarded his Ph.D. from the University of Cambridge, where he studied the human intestinal microbiota and pro-/prebiotics with the Medical Research Council at Addenbrookes Hospital. His interest in the human microbiome has diversified since moving to Manchester in 1999 to include body sites such as the skin and the oral cavity. He also maintains research programs in other areas of applied microbiology and particularly enjoys multidisciplinary research.

Catherine A. O'Neill received both her bachelor's degree and Ph.D. from the University of Wales, Bangor, where she studied bacterial biochemistry. Subsequently, she was a Research Fellow at the University of Leeds for 5 years before securing her first tenured appointment as a Lecturer at the University of Manchester. Subsequently, she was promoted to Senior Lecturer and then finally to Professor of Translational Dermatology, the post she currently holds at the University of Manchester. Professor O'Neill's interests are in using bacteria and their products for the treatment of skin in health and disease. The laboratory has a very translational focus and has a record in translating basic findings into human studies via technology transfer into commercial vehicles. Professor O'Neill has been involved in this area since 2011.

Alejandro Amezquita, Ph.D., graduated from the University of Nebraska—Lincoln (USA) and has more than 20 years of experience in various positions in academic (North Carolina State University, USA) and industrial (Unilever) research. Dr. Amezquita is working as Science & Technology Director within Unilever's R&D group and is interested in microbiome innovation in consumer goods and risk-based approaches to ensure product safety because of the importance of balancing the efficacy-safety continuum, using safety-by-design approaches as the foundation for safe innovation, He has been working in the microbiome innovation field for 4 years and in the consumer safety and microbiological risk assessment fields for 15 years.

Laura J. Price received her applied biology B.Sc. (Hons) from Staffordshire University in 2001. She started her career in microbiology quality assurance for CAMR in 2002. For the following 2 years, she was a Leukemia Research Associate for the MRC. Ms. Price started working at SEAC Unilever in 2004, where she is currently a Microbiology Risk Assessor. Her role is to independently assess the consumer safety of new technologies and formulations designed by Unilever R&D. With the increasing interest in the microbiome as a target for consumer products designed to improve health and well-being, she is part of the Human Microbiome Project, which is developing knowledge on how best to safety assess new technologies. Over the last 4 to 5 years the project has delivered a risk assessment framework, methods, and data. The interactions of the microbiome and immune system and dysbiosis manifesting as human disease are what particularly interest her.

Karoline Faust is a biologist turned bioinformatician who graduated at the Humboldt University in Berlin and earned her Ph.D. at the Université Libre de Bruxelles under the supervision of Professor J. van Helden. She worked as a postdoctoral researcher at KU Leuven and VIB in the group of Professor J. Raes. She is currently an Assistant Professor, heading the group of Microbial Systems Biology at KU Leuven since 2016. Her main research interests include the construction and analysis of microbial networks, the analysis of microbial sequencing data, and the investigation of microbial community dynamics *in silico* and *in vitro*. She therefore works at the intersection of microbial ecology, systems biology, and bioinformatics.

Adrian Tett is a Senior Research Associate in the Computational Metagenomics group (CIBIO, University of Trento). He received his Ph.D. from the NERC Centre for Ecology and Hydrology–Oxford in partnership with Cardiff University. As a microbiologist and bioinformatician he performed postdoctoral research at the BBSRC-funded institutes, the John Innes Centre, and the Institute of Food Research. His current work focuses on the microbial communities and subspecies strain-level determinants associated with human health and disease. He is also developing novel approaches to explore the population structure, evolutionary history, and subspecies diversification in abundant yet poorly characterized members of the human microbiome.

Nicola Segata, Ph.D., is Associate Professor at the CIBIO Department of the University of Trento (Italy). He earned his Ph.D. in computer science at the University of Trento in 2009 and he then moved to the Harvard School of Public Health for his postdoctoral training, where he started studying the human microbiome with computational metagenomics approaches. He came back to the University of Trento (Department CIBIO) where he started his laboratory in 2013. His laboratory employs experimental metaomic tools and novel computational approaches to study the diversity of the human microbiome across conditions and populations and its role in human diseases. His work is supported by the European Research Council and by several other European agencies. The projects in his laboratory bring together computer scientists, microbiologists, statisticians, and clinicians and focus on profiling microbiomes with strain-level resolution and on meta-analyzing very large sets of metagenomes with novel computational tools.

Continued next page

Jonathan R. Swann obtained a Ph.D. in biochemistry from the Department of Biomolecular Medicine at Imperial College London in 2008. Following his Ph.D., Dr. Swann continued as a research associate at Imperial College in the area of molecular epidemiology. In 2010, he joined the School of Chemistry, Food and Pharmacy at the University of Reading as a Lecturer in Metabonomics. In this role, he developed metabolic phenotyping strategies to study the impact of nutrition, the gut microbiota, and parasitic infections on mammalian health and disease. In 2015, Dr. Swann joined the Division of Computational and Systems Medicine at Imperial College as a Senior Lecturer in Human Development and Microbiomics. He was appointed Associate Professor in 2017. He leads a metabonomic-based research program to understand the influence of gene-environment interactions on the mammalian metabolic system and their implications for development, health, and disease. His research has a specific focus on the microbiome.

Adrian M. Smith was awarded a B.Sc. in biomedical sciences from Sheffield Hallam University in 2001 and an M.Sc. in bioinformatics from the same institution in 2002. He worked briefly for GSK before taking up his current position as Bioinformatician for Unilever R&D in 2005. He has had an interest in microbiomics for 9 years due to the initial disruptive nature of the science and the speed at which it continues to develop and reveal previously hidden microbial secrets. Most recently, he has had a particular focus on the development of bioinformatics analysis pipelines and visualization tools for microbial 'omics data analysis.

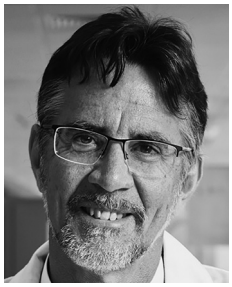
Barry Murphy has received education at University College Dublin with postdoctoral studies at the University of Leicester encompassing microbiology, molecular biology, and chemistry. A move to industry saw him establish and manage DNA sequencing laboratories across Europe before moving to Unilever to lead the microbiome capability group. Having held this position for 5 years, he has an interest in understanding human-associated microbial communities to investigate links between microbial metabolism and cosmetic conditions.

Michael Hoptroff is a Senior Project Manager at Unilever with responsibility leading Microbiome Science and Technology in the United Kingdom. He graduated in 1995 from the University of Sheffield and then moved to research posts in the United Kingdom and the United States prior to joining Unilever in 1998. Since joining Unilever, he has spent 21 years in Microbiology R&D initially as a research scientist and subsequently as a project manager. During this time he spent approximately 6 years working on skin cleansing and hand hygiene (2003 to 2008); 7 years on scalp microbiology (2009 to 2016), including 4 years leading Microbiology R&D in Unilever China; and 3 years on Oral Care microbiology research (2016 to the present). Mr. Hoptroff has 13 peer reviewed publications and has led the market delivery of numerous product technologies.

Gordon James originates from Glasgow in Scotland and was educated at the University of Glasgow, graduating with a B.Sc. and a Ph.D. in biochemistry in 1987 and 1991, respectively. He then did a postdoctoral fellowship at the University of Strathclyde in the area of environmental biotechnology, during which time he began practicing his favored disciplines of microbiology and biochemistry. Dr. James joined Unilever R&D in 1993, and in the time since, his main focus has been using his microbial biochemistry skills to probe the human skin microbiome, mainly to unravel the origins of axillary (underarm) odor. His current role is to provide scientific leadership to a United Kingdom-based team specializing in this topic on behalf of Unilever's Deodorants category and the global Science & Technology Platform, Human Microbiome.

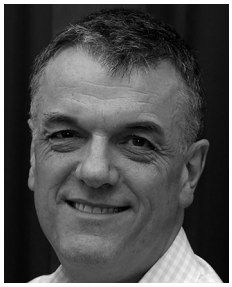
Yugandhar Reddy is a Research Scientist with Beauty & Personal Care, Unilever R&D. Dr. Reddy received his B.Sc. and M.Sc. in microbiology and later a Ph.D. at the Indian Institute of Science, Bangalore, India. He was a Postdoctoral Fellow at the Department of Microbiology & Molecular Genetics at the University of Pittsburgh. Prior to joining Unilever, Dr. Reddy worked as a Genomics Applications Scientist at Agilent Inc. His current interests are the human microbiome and its relevance for human health and well-being as well as building *in vitro* models to understand microbial community behavior. In a previous role at Unilever, Dr. Reddy worked at the Safety and Environmental Assurance Center of Unilever Plc, where he explored methods and approaches to risk assess microbiome-related technologies and led an S&T program on microbial ecology. He has been in this field for about 7 years to date.

Anindya Dasgupta has a Ph.D. in molecular biology, Albert Einstein College of Medicine, New York, NY, USA, and is based at Unilever R&D, Bangalore, India. He is currently exploring scientific insights that play a crucial role in the skin microbiome. The generation of these insights also helps in screening of actives and development of products that have a positive impact on the skin microbiome. A key factor in this activity is to look at the safety aspect of microbiome modulation.



Tom Ross is a Professor in Food Microbiology at the University of Tasmania. He was awarded his Ph.D. from the University of Tasmania in 1994. Since then he has been employed at the University of Tasmania as a researcher and teacher concerned with the quantitative microbial ecology of foods, leading to his current position. He has supervised ~25 Ph.D. graduates. He has published >150 international peer-reviewed papers/book chapters with his students and colleagues. His research has also led to numerous software tools that translate his research into decision-support tools for food safety and preservation that are used by governments and industry internationally. Those software tools are risk based and quantitative. He has been invited to contribute to many FAO/WHO scientific expert panels concerned with microbial food safety risk assessment. This background in quantitative risk assessment and microbial ecology led to his interest in the potential to modify the human skin microbiome and to assess the potentially associated risks.

Iain L. Chapple is Head of the School of Dentistry and Research Director of the Institute of Clinical Science, Birmingham University, Birmingham, United Kingdom. He graduated in 1986 from Newcastle University. Dr. Chapple is former Scientific Editor of the British Dental Journal, Associate Editor of the *Journal of Periodontal Research*, and current Associate Editor of the *Journal of Clinical Periodontology*. He has written 9 textbooks and 23 book chapters. Dr. Chapple served the IADR Periodontal Research Group (PRG) as President (2006 to 2007), Group Chair (2008 to 2015), and Counsellor (2016). He served the European Federation of Periodontology (EFP) as Treasurer (2007 to 2013), Workshop Cochair (2008 to the present), Chairman of Scientific Advisory Committee, Editor of *JCP Digest* (2014 to 2016), and Secretary General (2016-2019). He was British Society of Periodontology President in 2014 to 2015 and awarded the Tomes Medal of the Royal College of Surgeons (2011), the IADR PRG Rizzo Award (2001), IADR Distinguished Scientist in 2018, and a Special Citation Award of the American Academy of Periodontology in 2018. Dr. Chapple has >200 peer-reviewed manuscripts in the international literature.



William G. Wade obtained his B.Sc. in biological sciences at the University of East Anglia and a Ph.D. in microbiology at the University of Wales. He began his career as a Lecturer at the Welsh National School of Medicine in Cardiff and then moved to a Senior Lecturer appointment at the University of Bristol. He was appointed to the Richard Dickinson Chair of Oral Microbiology at UMDS (subsequently King's College London) in 1996. In 2013, he moved to Queen Mary University of London but returned to King's College London in 2018 to take up his current post of Professor of Oral Microbiology within the Centre for Host-Microbiome Interactions. He has played a major role in the characterization of the oral microbiome, culture of previously uncultivated bacteria, and the development of novel agents for the prevention and treatment of oral diseases. He has been active in microbiology research for 40 years.

Judith Fernandez-Piquer received her B.Sc. in chemical engineering and B.Sc. in food technology in Spain, her M.Sc. in food safety in the Netherlands in 2007, and her Ph.D. in food microbiology in Australia in 2012. Dr. Fernandez-Piquer has a broad knowledge of risk assessment and the integration of predictive microbiology for exposure assessment in foods. After her Ph.D., she was involved in projects for Dairy Australia, Walnuts Australia, and the Seafood CRC while at the University of Tasmania. Judith has a strong interest in protecting consumers' health. She joined Unilever SEAC in 2014 as a Risk Assessor and led the Human Microbiome Project, a program that aims to enhance the safety assessment of microbial reprofiling to support innovative technologies in personal care. Dr. Fernandez-Piquer started her current role as product safety manager with Upfield, a plant-based food company, in August 2018.