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Mapping the Microbiota in Hidradenitis Suppurativa

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2022

Dedications

I would like to dedicate this thesis to my husband Donal and to my family who have encouraged me from project conception and initiation, right up to submission. Your support is greatly appreciated.

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Declarations

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism and intellectual property.

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Abstract

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by the formation of nodules, abscesses, and fistula at intertriginous sites. Pain, pruritus, malodour, and suppuration have a significant impact on quality of life for HS patients. The skin-gut axis is an area of emerging research in inflammatory skin disease and is a potential contributory factor to the pathogenesis of HS. Skin microbiome alterations in HS have become an area of expanding research with its role in the pathogenesis of HS becoming clearer. Gut microbiome alterations have been described in many inflammatory diseases including inflammatory bowel disease, rheumatoid arthritis, and cancer, but little is known about the gut microbiome in HS. Our hypothesis is that gut, as well as skin, microbiota alterations and their metabolites, may be responsible for skin inflammation in HS.

The level of pain experienced by 150 patients with HS was measured using the visual analogue scale and EQ-5D-5L questionnaires. 59 patients with HS provided faecal samples, nasal and skin swabs of affected sites for analysis. These 59 patients also provided serum samples and completed questionnaires including the Dermatology Life Quality Index (DLQI), Morisky Medication Adherence Scale, International Physical Activity Questionnaire, and Food Frequency Questionnaire. 30 healthy controls provided fecal samples and 20 healthy controls provided nasal and skin swabs. We performed bacterial 16S rRNA gene amplicon sequencing on total DNA derived from the samples. Calprotectin was determined by enzyme-linked immunoassay (CALPROLAB™ Calprotectin ELISA (HRP). Complement C5a levels were assessed using enzyme-linked immunosorbent assay (Abcam ab193695 Complement C5a Human ELISA Kit).

Pain was widely reported in 134 responders to the visual analog scale questionnaire. 82.1% reported some level of pain and 35.8% reported high levels of pain. In the EQ-5D-5L questionnaire, 81.4% of responders indicated that they felt pain or discomfort, and 31.0% expressed “severe” or “extreme” pain/discomfort. Weak correlation was seen between levels of pain and one marker of gut microbiota alpha diversity (Chao1), but this failed to be repeated for all indices of microbiota species richness. A significant impact on quality of life with a mean DLQI score of 12.15 (SD 7.67) was observed in patients with HS, which is in line with other severe dermatoses. 59% of patients reported a large or extremely large impact on their quality of life. The DLQI score did not correlate with gut microbial diversity. In this study, over 40% of patients with HS also reported some difficulty remembering to take their medications with 20% reporting that they forgot to take their medication in the previous 2 weeks. Patients with HS also reported moderate-to-high levels of physical activity; however this may be overestimated. Alterations in gut microbiota diversity did not correlate with levels of physical activity. Microbiome alpha diversity was significantly lower in the faecal, skin and nasal samples of individuals with HS which may be secondary to disease biology or related to antibiotic usage. *Ruminococcus gnavus* was more abundant in the faecal microbiome of individuals with HS, which is also reported in Crohn’s disease (CD), suggesting comorbidity due to shared gut microbiota alterations. No significant difference in faecal microbiota composition or overall habitual diet was seen in the patients with HS and diet was not associated with disease severity. Diet in HS was significantly different to controls, and similar to patients with CD. *Finegoldia magna* was over-abundant in HS skin samples relative to healthy controls. It is possible local inflammation is driven by *F. magna* through promoting the formation of neutrophil extracellular

traps (NETs). 27.1% of patients with HS had a raised faecal calprotectin level of >50mg/kg with markedly elevated levels of >150mg/kg in 8.5% suggesting occult gastrointestinal inflammation. Median complement C5a level in patients with HS was elevated at 47 ng/ml (IQR 30.55 ng/ml) which is in keeping with prior studies.

These alterations in both the gut and skin microbiome in HS warrant further exploration, and therapeutic strategies including faecal microbiota transplant or bacteriotherapy could be of benefit. Faecal calprotectin is a simple test which should be considered in patients with HS, with further investigations warranted in patients with elevated levels. C5a may provide a therapeutic target in patients with HS and serum C5a may act a biomarker of the disease.

1. Introduction

1.1 Clinical Features of Hidradenitis Suppurativa (HS)

Hidradenitis suppurativa (HS), also known as Verneuil's disease and acne inversa in the past, was first described by a French Surgeon Aristide Verneuil in 1854 in his paper 'Etudes sur les tumeurs de la peau; de quelques maladies des glandes sudoripares'(1). HS is chronic debilitating inflammatory skin disorder of mainly flexural sites bearing apocrine glands, including the axilla, inframammary and anogenital regions. Typical early lesions are solitary, painful nodules that may persist for weeks to months, with a mean duration of 7 to 15 days (2). These nodules tend to be more rounded than common boils or abscesses, with which they are commonly mistaken, and they often present with initial burning, stinging, pain and pruritus (2). These nodules can fail to rupture and resolve spontaneously, 'silent nodules', or evolve into abscesses (2). Abscesses can rupture spontaneously, or after incision, with drainage of purulent material (2). Rupture can lead to a granulomatous, foreign-body like reaction. Chronic inflammation can result in chronic sinus formation with tunnelling into neighbouring skin, resulting in chronic discharge and malodour from anaerobic colonisation (2). Ulceration and pyogenic granulomas can also occur (2). Healing with hypertrophic scarring and multiporous or uniporous 'tombstone' open pseudocomedones is characteristic (2). These pseudocomedones represent superficial microfistulae. Folliculitis, or follicular pustules, can also co-occur but is not a diagnostic feature of HS (2).

Differences in topographical distribution of lesions has been described with women reporting more lesions in the anterior part of the body (axillae, breasts and genito-femoral area) and men reporting more involvement of the back of the body, atypical sites such as the ears and chest, and the presence of pilonidal sinus (3–6). An attempt

to describe three broad phenotypic groups in HS based on sites of predilection has been published in the literature: axillary-mammary, follicular and gluteal (7). In this cross-sectional study 'axillary-mammary' HS presented with breast and axillary lesions and hypertrophic scars (7). 'Follicular' HS presented with axillary, and mammary lesions as well as lesions in the ears, chest, back or legs, follicular lesions such as pilonidal sinus and comedones, severe acne, obesity, and a family history of HS (7). 'Follicular' HS was described most commonly in males and current smokers, with greater disease severity (7). 'Gluteal' HS was characterised by gluteal involvement, papules and folliculitis, and patients had less severe disease, smoked, and had lower body mass index values (7). A study of Mediterranean patients with HS which included serum biomarker analysis identified two clusters of presentation; cluster 1 which accounted for 65% of patients were male, non-obese, had early onset disease, nodular lesions of posterior sites, a history of pilonidal sinus, high levels of IL-10, and γ-secretase mutations (8). Cluster 2 which accounted for 35% of patients were either male or female, obese, with later onset HS, more sinuses and abscesses in anterior sites rather than nodules, and higher levels of IL-27 and IL-6 (8).



Figure 1: Severe Hurley stage III hidradenitis suppurativa of the buttocks. (Taken from McCarthy S, Foley CC, Dvorakova V, Quinlan C, Murphy M, Maher M. PASH syndrome with bony destruction. Clinical and Experimental Dermatology. 2019 Dec;44(8):918-20.)(9)

As the diagnosis of HS is made clinically, a standard disease definition is vital to accurately determine prevalence and incidence. It is agreed that three criteria must be met for hidradenitis suppurativa to be diagnosed: 1. Typical inflammatory skin lesions as described above, 2. Occurrence in one or more sites of predilection, predominantly flexural sites, in particular the axillae and groin, and 3. Chronic or recurrent bouts of inflammation (10).

Differential diagnoses of HS include common abscesses, carbuncles and furunculosis especially in those with early lesions, infected Bartholin's gland in the genital region of women, and infected or inflamed epidermoid cysts (2). Less common differentials include lymphogranuloma venereum, scrofuloderma, actinomycosis, developmental fistulae, nodular acne and pilonidal cyst, and cutaneous Crohn's disease (2).

1.2 Clinical Course, Assessment and Severity Grading of HS

HS is a chronic skin disease. Onset is typically after puberty with symptoms tending to abate in older age groups, however, there are rare reports of prepubertal and post-menopausal onset in the literature (11–14). Complete remission after menopause is usual in females, but HS in male patients may continue to be active in old age (2,5). Pre-pubertal onset should prompt endocrinological consultation and screening tests to rule out such conditions as hyperandrogenism, hyperinsulinism and precocious puberty (14). Disease onset tends to begin earlier if there is a positive family history of HS (2).

Assessment of severity is performed by clinical assessment of lesions and disease activity, and patient reported outcome measures. Imaging and biochemistry studies are rarely required, and these are not routinely used in routine clinical practice.

No ideal assessment tool for hidradenitis suppurativa exists and attempts are ongoing to develop valid and reliable severity assessments, particularly to measure outcomes in clinical trials (15).

Hurley staging is commonly used in assessing HS severity and is composed of three stages: I - Abscess formation, single, or multiple, without sinus tracts and cicatrisation, II - Recurrent abscesses with tract formation and cicatrisation, single or multiple, widely separated lesions, and III – Diffuse or near-diffuse involvement or

multiple interconnected tracts and abscesses across the entire area (16). Although stage I disease is the most common, most patients presenting to dermatology have Hurley stage II and III disease (10). The disadvantage of Hurley staging is that it is a static assessment which does not reflect disease activity, and does not evaluate the severity of each affected area which may differ. Despite these limitations Hurley staging remains the most commonly used clinical assessment of HS in routine clinical practice. The Refined Hurley score divides stage I and II into A, B and C based on number of areas involved and presence or absence of sinus tracts. Hurley stage I do not have sinus tracts and IA have $\leqslant$2 involved areas and <5 abscesses or nodules, IB have >2 body areas or $\geqslant$5 abscesses or nodules (predominantly fixed lesions) and IC: >2 body areas or $\geqslant$5 abscesses or nodules (migratory lesions). Hurley II have sinus tracts and Hurley IIA have <1% of BSA (body surface area), without abscesses or nodules, IB have <1% of BSA, with $\leqslant$2 affected body areas with abscesses or nodules and IC have <1% of BSA, with >2 affected body areas with abscesses or nodules. Hurley III is defined as $\geqslant$1% of BSA of the involved body site with interconnected inflammatory sinus tracts.

The Sartorius score and modified Sartorius score are more dynamic HS scores that are based on lesion counting, however they are used mainly in the setting of clinical trials (17). Lesions including nodules, abscesses, sinus tracts and scars are counted. The longest distance between two lesions in a region is measured to determine area involved and the presence or absence of normal skin between lesions is assessed. In severe disease counting of individual lesions can be difficult as lesions merge, however it is easier in milder disease with discrete lesions. As this score is time consuming, it is rarely used in routine clinical practice.

The HS-specific physician global assessment is also used to determine HS severity, but also generally only in the setting of clinical trials. Six stages of HS are described: 1 - Clear: no inflammatory or noninflammatory nodules, 2 - Minimal: only noninflammatory nodules are present, 3 - Mild: fewer than 5 inflammatory nodules without abscesses and draining fistulas, or 1 abscess or draining fistula without additional inflammatory nodules, 4 - Moderate: fewer than 5 inflammatory nodules or 1 abscess, or draining fistula and 1 or more inflammatory nodules, or 2 to 5 abscesses or draining fistulas and less than 10 inflammatory nodules, 5- Severe: 2 to 5 abscesses or draining fistulas and 10 or more inflammatory nodules, 6 - Very severe: more than 5 abscesses or draining fistulas (18).

Newer HS scoring systems include the hidradenitis suppurativa severity index (HSSI), and the hidradenitis suppurativa clinical response (HiSCR), which have been used in clinical trials, and the international hidradenitis suppurativa severity score system (IHS 4) and the hidradenitis suppurativa area and severity index (HASI) which have recently been developed in the hope of developing a more reliable and valid assessment tool (19–22).

A summary of the HS scoring systems is outlined in Table 1.

Table 1: Summary of the common HS scoring systems used in setting of clinical practice and clinical trials

Assessment tool	**Components of HS scoring system**						
Hidradenitis Suppurativa Severity Index (HSSI)	Composite score range 0-19		**No. of sites**	**Body surface area**	**No. of inflammatory lesions**	**No. of dressing changes in working hours**	**Pain (visual analog scale)**
		Stage 0	0	0	0	0	0-1
		Stage 1	1	1	1-2	0	0-1
		Stage 2	2	2-3	2-3	1	2-4
		Stage 3	3	4-5	4-5	>1	5-7
		Stage 4	≥4	>5	>5	>1	8-10
Hurley Score	I	Single or multiple abscesses					
	II	Recurrent abscesses, sinus tract formation and scarring. Single or multiple lesions, widely separated					
	III	Diffuse involvement of entire area, multiple interconnected tracts and abscesses					
Refined Hurley Score	Absence of sinus tracts	Hurley I A: ⩽2 involved areas and <5 abscesses or nodules B: >2 body areas or ⩾5 abscesses or nodules – predominantly fixed lesions C: >2 body areas or ⩾5 abscesses or nodules – migratory lesions					
	Presence of sinus tracts	Hurley II A: <1% of BSA, without abscesses or nodules B: <1% of BSA, with ⩽2 affected body areas with abscesses or nodules C: <1% of BSA, with >2 affected body areas with abscesses or nodules					

		Hurley III: ⩾1% of BSA of the involved body site with interconnected inflammatory sinus tracts
Sartorius Score		Assessing anatomical regions involved, distance between lesions, and scoring individual lesions.
Modified Sartorius Score	Anatomic regions affected	3 points per region affected: axilla, groin, gluteal, other
	No. and type of lesions (per region)	1 point for nodule 6 points for fistula
	Longest distance between 2 lesions	1 point <5cm 3 points 5-10cm 9 points >10cm
	Lesions clearly separated by normal skin	0 points if yes 9 points if no
HS-Physicians Global Assessment (HS-PGA)	Clear: 0	
	Minimal: 1	Presence of non-inflammatory nodules
	Mild: 2	<5 inflammatory nodules or 1 abscess/fistula
	Moderate: 3	≥ 5 inflammatory nodules 1 abscess or draining fistula and ≥ 1 inflammatory nodule 2-5 abscesses or draining fistulas and <10 inflammatory nodules

	Severe: 4 Very severe: 5	2-5 abscesses or draining fistulas and ≥10 inflammatory nodules >5 abscesses or draining fistulas
HS Clinical Response (HiSCR)		Achieving at least a 50% reduction from baseline in abscess and inflammatory nodule count with no increase in abscess/fistula counts
Hidradenitis Suppurativa Area and Severity Index (HASI)	HASI score 0-72	Modelled after the Psoriasis Activity and Severity Index (PASI) Erythema, thickness, drainage, and tenderness scored 0-3 for each body site involved, percentage body surface area (BSA) affected calculated for each body region using PASI approach (0 = none, 1 = 1–9%, 2 = 10–29%, 3 = 30–49%, 4 = 50–69%, 5 = 70–89%, 6 = 90–100%) The sum of the four clinical variable scores was multiplied by the area score of each involved region This value was then multiplied by the proportion of the BSA of that region, to give a regional HASI score Regional HASI scores were added together to give the cumulative total HASI score (range 0–72)
IHS4	Points = Mild Moderate Severe	(number of nodules x 1) +(number of abscesses x 2) _ (number of draining tunnels/fistulae/sinuses x 4) ≤3 points 4-10 points ≥11 points

Patient reported outcome measures can be useful in assessing disease severity in HS and its impact on quality of life. The dermatology life quality index (DLQI), EQ-5D-5L, and the Skindex-16 can be used to assess morbidity and impact on quality of life (23). Regular measurements over time are important to assess for impact of disease over time, disease activity and response to treatment. Visual analogue scales of pain and itch are also helpful in assessing patient symptoms (24).

Assessment of depression and anxiety is important in HS to ensure a holistic approach. Commonly used psychometric scales include the Beck depression inventory (BDI), patient health questionnaire-9 (PHQ9) and hospital anxiety and depression scale (HADS) (25). Furthermore, the HIDRAdisk, a short visual quality of life tool has been formulated to assess burden of HS on quality of life and shows strong correlation with Skindex-16 and DLQI (26).

Imaging is not routinely used in HS; however, several studies have reported the utility of ultrasound in determining extent of disease. Similarly, MRI has also been used to delineate the extent of disease, particularly prior to extensive surgery (27). Simple clinical photography can be useful in determining response to treatment and may be an easy adjunct in most clinical settings (28).

Biochemistry studies in HS are of limited use, but raised inflammatory markers such as C-reactive protein, and a raised leucocyte count may be detected (10). Generally, biochemistry studies in HS are used to monitor systemic treatment prescribed and in the assessment of the co-morbidities that are associated with HS (10).

1.3 Epidemiology of HS

Determination of HS prevalence and incidence is challenging as it is often under-recognised and a diagnostic delay is common (29). Prevalence figures vary greatly in the literature from 0.05% to 4.1% probably due to differing data sources used, and the varying levels of HS recognition between countries (30–32). Prevalence of HS in the USA is reported at 0.1% (33). Prevalence of up to 4.1% is reported in European populations with a prevalence of 1.4% in one Irish study (32,34). Although reported US prevalence is lower than European prevalence, this is likely due to the data sources used to estimate prevalence (30). Prevalence in African Americans is three times higher than in white individuals and thus higher prevalence in Europe is unlikely due to ethnicity and genetic differences (30,33). Information on prevalence in Asian populations is lacking with one study reporting a prevalence of 0.06% in the South Korean population (35). Reports from the rest of the world include a report of prevalence of 0.67% in Australia and 0.8% in Ghana (36,37).

Incidence of HS appears to be increasing, possibly due to increasing recognition of the condition (30). Annual incidence of 11.4 in the US and 28.3 in the UK per 100,000 population is reported (38,39).

Women are more commonly affected than men (32,40). In Europe and North America, HS has a female-to-male ratio of 3:1 (13,30,33,35,38). However, interestingly, in South Korean patients the ratio is 1:1.6 presenting more commonly in males (35). In Asian populations the buttocks are most frequently affected, whereas in Europe and the US it is the groin and axillae most affected (2,35,41,42). An association with lower socioeconomic status has also been reported. This may relate to the higher prevalence of risk factors for developing HS in this group, or could be a consequence of the illness itself (50).

1.4 Histology of HS lesions

Perilesional skin demonstrates psoriasiform hyperplasia with an increased number of CD3+ T-cells and CD138+ plasma cells, dendritic cells and mast cells observed (44). In early HS lesions, follicular occlusion with dilatation driven by endogenous and exogenous factors discussed below, is seen (45). On histology follicular hyperkeratosis is seen with plugging and dilatation of the hair follicle (44). Occlusion of the hair follicle is also thought to lead to dysregulation of keratinocytes and the microbiome of the skin (45).

Follicular occlusion is followed by rupture of follicular contents into the dermis which triggers an immune response (45). Histologically a dense cell infiltrate is seen, consisting of monocytes, neutrophils, multinucleated giant cells, B-cells, plasma cells, T-cells and natural killer (NK) cells leading to abscess formation (45). Keratin fibres and keratinocyte debris are seen, with multinucleated giant cells often contain keratin fibres (44). CD11c+ dendritic cells are abundant, as well as CD14+ monocytes, CD68+ macrophages and FXIIIa+ dermal dendritic cells (44). Granuloma formation has also been described (44).

Chronic lesions are characterised by expansion of the inflammatory infiltrate, with more pronounced neutrophilic inflammation (44). Chronic inflammation leads to formation of epithelialised fistula and sinus tracts, and scarring due to dysregulated matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinase (TIMPs), and increased tissue growth factor (TGF)-β1-2-3 which causes fibrosis (45–47). Furthermore, sinus tracts provide an ideal site for bacterial biofilm formation with subsequent maintenance of the inflammatory loop (48). Apocrinitis is not seen in all cases, confirming that apocrine involvement is a secondary phenomenon (49–53).

1.5 Aetiology of HS

Understanding the aetiology and pathogenesis of disease is of paramount importance in informing therapeutic options. Current therapies in HS are limited and treatment of severe cases can prove challenging (54). The current understanding of the aetiology and pathogenesis of HS is incomplete, with numerous hypotheses concerning the interplay of lifestyle factors, the skin microbiota, genetics, and a dysregulated immune system postulated (55).

1.5.1 Lifestyle Factors

Two widely accepted lifestyle factors which play a role in the development of HS are obesity and tobacco smoking, and higher smoking pack-year history and higher body mass index (BMI) are linked to increased disease severity (5,11,35,39,51–54). In one study assessing clinical course and prognosis in HS, it was noted non-smokers were more likely to report remission than active smokers, and similarly more non-obese patients reported remission compared to obese patients (60).

Obesity is reported in approximately 60% of patients with HS, particularly central obesity (43). An odds ratio of 3.45 (95% CI 2.20-5.38, $P < 0.001$) for HS and obesity has been reported (59). Obesity appears to predispose patients to the development of HS in a number of ways. Firstly, it enlarges the skinfolds of the body providing sites of repeated mechanical stress and friction, maceration, and anaerobic bacterial colonisation (44,45). Mechanical stress and friction are thought to contribute to the development of HS by promoting follicular occlusion and rupture in a susceptible individual (44). Mechanical stress may provoke the release of damage-associated molecules (DAMPS) and allow for entry of microbes promoting inflammation (55).

Skin-to-skin contact leads to a higher skin temperature, and humidity from sweat retention in large skin folds, with reduced oxygen availability promoting anaerobic bacterial growth and maceration (44). Obesity also creates a subclinical proinflammatory state, producing proinflammatory cytokines and dysregulated adipokines which promote the development of inflammatory disorders, including skin disease (46–50). IL-1β and TNF-α are secreted by macrophages in visceral fat and upregulation of IL-6 and TNF-α gene expression is seen (69,70). Circulating palmitate levels are also increased in obesity and interact with toll like receptors (TLRs) to activate the innate immune system and result in inflammation (71). Furthermore, obesity increases the risk of developing metabolic syndrome and insulin-resistance, which have also been associated with HS, and contribute to the proinflammatory state (51). Weight reduction has a proven beneficial effect on morbidity and prognosis in HS and response to treatment. Obesity is associated in the literature with abnormal gut microbiota, and attempts are being made to modulate the gut microbiota for treating obesity (72).

Cigarette smoking is a common association in HS and has been attributed to the development and severity of disease (13,42,73,74). Reports of current or former cigarette smoking in HS ranges between 30% to 98% (75). A systematic review calculated an odds ratio (OR) of 4.34 (95% confidence interval (CI) 2.48-7.60, $P < 0.001$) for HS and current smoking (59). Tobacco is composed of thousands of chemicals including nicotine, and polyaromatic hydrocarbons (76). It is thought that nicotine in cigarettes may activate keratinocytes via nicotinic acetylcholine receptors and induce acanthosis, and epidermal hyperplasia (77,78). Smoking also creates an altered skin microbiome, with increased virulence of *Staphylococcus aureus* through enhanced cellular adhesion and biofilm formation (79,80). Nicotine also reduces

anti-microbial peptides, such as human-beta-defensin-2 (hβD-2) increasing susceptibility to bacteria (81,82). Smoking is proinflammatory, and has been seen to increase intracellular cAMP levels and increase IL-1α, IL-1β, IL-8, IL-10, IL-17 and TNF-α resulting in neutrophil chemotaxis and TH17 cell inflammatory responses (62,83,84). Altered chemotaxis of neutrophils has also been postulated in palmoplantar pustulosis to explain the predilection in smokers (85). Acquired downregulation of Notch signalling has also been reported in smokers, and this pathway plays a role in development of HS (86). Furthermore, smoking reduces blood circulation resulting in impaired wound healing from reduced tissue oxygenation, and this potentially results in poor healing of lesions in HS (87). Smoking is also associated with an altered skin and gut microbiota in the literature (88,89).

1.5.2 Hormonal Influence

HS demonstrates a female predominance, presents after puberty, and patients often report premenstrual flares when progesterone levels are high (90). Reports of improvement in HS during pregnancy or after menopause further supports the role of hormones in HS pathogenesis (90). However, one study surveying 85 women with HS reported the majority had no effect of pregnancy on their HS (72%) with 20% reporting an improvement and 8% a deterioration (60). In this study menopause was associated with an improvement in HS for the majority (48%), no difference in 38% and worsening in 15% in 61 women surveyed (60). Basal levels of major sex hormones such as oestrogen, progesterone, testosterone and dehydroepiandrosterone sulphate also do not appear to be altered compared to controls (91). However, response to anti-androgen therapy in HS has been reported (92).

1.5.3 Genetic Predisposition

A family history of HS is reported in approximately 40% of cases (93). Familial HS tends towards more severe disease and lower remission rates, implying the importance of genetic factors. Interestingly patients with no family history of HS tend to be more overweight and smoke more, suggesting different subpopulations exist in HS (7).

Early Genetic Studies

Fitzsimmons et al. provided an initial report on 3 families with 21 members affected by HS, with all three generations of one family affected (94). This report was followed by a study on HS in 23 families with 62 members affected; 3 generations affected in 5 families and 2 generations affected in 6 families (95). This prompted discussion as to whether an autosomal dominant pattern of inheritance was present in HS, despite only 34% of first-degree relatives being affected, compared to 50% in confirmed autosomal dominant conditions (95). It was postulated that incomplete penetrance or missed cases resulted in the lower familial cases (95).

Defects in Notch and γ-secretase pathways

Gao et al. assessed families exhibiting autosomal dominant inheritance of HS in a large Han Chinese family with a genome wide scan (96). Linkage to chromosome 1 was demonstrated in affected members of this family with HS (1p21.1-1q25.3) (96). This linkage was not demonstrated in a further familial HS study by Saleh Al-Ali et al. in 2010 (97).

Wang et al. first identified a mutation in the PSENEN gene in affected members of 2 families demonstrating autosomal dominant inheritance (98). This was not present in

unaffected members of the family or in a control population (98). PSENEN encodes a subunit of γ-secretase protein. In four other families, mutations in NCSTN or PSEN1 genes were seen that encode other γ-secretase subunits (98). The NCSTN gene is located at 1q22-23, which is within the region identified by the early study by Gao et al (96,98). γ-secretase is a protease that targets type-1 transmembrane proteins such as Notch, E-cadherin, or CD44 (99).

Notch signaling in particular plays a role in hair follicle development, in modulating T-cell-mediated immune responses and in suppressing Toll-like receptor-4 induced cytokine responses (98–100). Mutations in PSEN1 and PSEN2, which also encode γ-secretase subunits, have been identified in familial Alzheimer disease, with accumulation of β-amyloid peptides due to abnormal cleavage of amyloid precursor protein, a type-1 transmembrane protein (101). A link between HS and Alzheimer disease has not been found to date. In mouse models, deficiency of γ-secretase results in the development of epidermal cysts from hair follicles and an absence of sebaceous glands, mediated via the Notch signaling pathway (102). Reduced sebaceous gland number and volume are seen in HS (103). Deficiency of Nicastrin, a protein in the γ-secretase protein complex, has been shown to cause follicular and cystic hyperkeratosis (104). Further studies, however, demonstrated that γ-secretase mutations appear to represent only a minority of cases of HS, even in those with a family history (105,106). It has also been demonstrated that mutations in γ-secretase can be present in unaffected family members suggesting incomplete penetrance, and epigenetics, such as the impact of smoking, may be important in the development of HS these cases (107). Furthermore, it appears that those with γ-secretase mutations tend towards more severe disease, an atypical phenotype, and prove refractory to treatment (106).

Mutations in Proline-Serine-Threonine Phosphatase Interacting Protein 1

Proline-serine-threonine phosphatase interacting protein 1 (PSTPIP1) mutations have been identified in syndromic cases of HS. Genetics of HS with defects in inflammasome function in the setting of inflammatory syndromes will be discussed in associated conditions.

Twin studies

Twin studies give important information on the contribution of genetics and environment to the development of disease (108). One early study on the genetics of HS included a pair of female monozygotic twins who developed HS in their 20s (94). A recent Dutch study reported a prevalence of HS among twin pairs of 1.2%, with a mean age of 32.7 years (108). The calculated heritability of HS was 77% (95% CI 54-90%) suggesting a strong contribution of genetic factors in the development of HS, and was higher than in psoriasis and rheumatoid arthritis (108). Interestingly the heritability of HS was similar to Crohn's disease (108). The variance seen in this study also supports a multifactorial cause, with environmental factors contributing (108).

Other genes associated with HS

Sphingolipids are membrane lipids involved in growth regulation, cell migration, adhesion, apoptosis, senescence, and inflammatory responses in tissues (109). Aberrant expression of the genes Ceramide synthase-2 (CerS2) and Sphingosine kinase-2 (SPHK2), involved in sphingolipid synthesis, are significantly downregulated in HS when compared with unaffected skin resulting in decreased levels of ceramide generating enzymes (110). Furthermore, galactosylceramides and

gangliosides, products of the sphingolipid pathway, are elevated in lesions of HS (110). Galactosylceramide activates natural killer cells and promotes inflammation (110).

In one study a single nucleotide polymorphism of the *IL-12Rb1* gene coding for the IL-12Rb1 receptor subunit did not genetically predispose to HS, however, this polymorphism was associated with later disease presentation in the h1 haplotype and higher risk of severe disease in the h2 haplotype, suggesting the IL-12/IL-23 pathway may be important in the pathogenesis of HS (111).

The copy number of the β-defensin gene cluster (DEFB) was found to increase risk of developing HS and determine disease phenotype in one case control study (112).

HS lesions have also demonstrated higher lipocalin 2 (LCN2) mRNA expression levels compared to healthy controls and this may serve as a blood biomarker to assess activity of disease (113).

Genome Wide Association Studies

A paucity of genome wide association studies (GWAS) exists in HS. A single GWAS in HS has been undertaken in patients enrolled in two phase 3 hidradenitis suppurativa trials (PIONEER I and II) and who were responders to adalimumab (114). An intron of the BCL2 gene was discovered which reached genome-wide significance suggests that BCL2 may be repressed in HS affected tissues by adalimumab (114). A GWAS to elucidate the genetic aetiology of HS is currently being undertaken by the National Institute of Health in the United States utilising the Genetic Epidemiology Research in Adult Health and Aging (GERA) cohort and Partners Healthcare Biobank cohort and is due for completion in 2022 (115).

1.5.4 Follicular Occlusion

HS was once believed to be a disease of the apocrine gland. However, it is now known that it is primarily a disease of the hair follicle (116). The primary event in HS is follicular occlusion with infundibular hyperkeratosis of the follicle and hyperplasia of the follicular epithelium lead to collection of cellular debris, dilation of the hair follicle, rupture, an inflammatory response, abscess and sinus tract formation and scarring (117). Apocrine glands can be inflamed secondary to dermal inflammation however apocrine gland morphology, density and distribution is similar to healthy controls (117,118). A reduction in sebaceous gland volume is seen (103). Thinning of the basement membrane zone around the sebofollicular junction in HS skin has been observed and this may predispose to the rupture of follicular contents into the dermis causing inflammation (119). This is a primary phenomenon which is not caused by prior inflammation (119). Mechanical trauma, as discussed in association with obesity, contributes to follicular disruption in these weakened pilosebaceous units (119).

1.5.5 Immunopathogenesis of HS

HS was largely thought to be an infectious disease until the 1980s when early studies suggested the role of immune dysfunction, in particular the role of T-lymphocytes, in its pathogenesis (120,121). In the early 2000s, host-defence defects in HS and possible response to immunosuppression were reported in the literature (122,123). Lapins et al. noted dysfunctional neutrophils in patients with HS compared to controls (122). Links between HS and inflammatory bowel disease had been made and Martinez et al noted improvement in HS in a patient who was treated with

infliximab for Crohn's disease (123,124). Since this time it has become widely accepted that HS is an autoinflammatory disorder with alterations in the immune system (45). In the primary lesion the release of follicular contents into the dermis activates several inflammatory pathways, in particular the Th17/IL-23, NOD-like receptor protein 3 (NLRP3) and innate toll-like receptors (TLR), creating skin inflammation and an inflammatory loop (45). Resulting influx of dysregulated immune cells and the production of keratinocyte-mediated products is key to the development and maintenance of inflammation in HS (125,126).

Alterations of the innate immune system are noted in HS (127). Antimicrobial peptides (AMPs) are produced as part of the body's response to pathogens and play a role in the modulation of inflammatory responses, wound healing, and skin barrier homeostasis (128,129). Examples include the human β-defensins (hβD)1- 3, cathelicidin LL-37, ribonuclease 7, psoriasin (S100A7), calgranulin-A (S100A8), calgranulin-B (S100A9), koebnerisin (S100A15 or S100A7A), and dermcidin. The role of AMPs in HS is under investigation, with mixed results in the literature. Wolk et al. confirmed an upregulation of the AMPs hβD 2 and 3, S100A7, S100A8 and S100A9 compared to controls suggesting a role of AMPs in HS development (130). However the levels of AMPs were not as high as in psoriasis and atopic dermatitis, in particular for hβD 2 and 3 (130). Hofmann et al. noted reduced levels of hβD3 in severe HS and reduced ribonuclease 7 (131). However, a further study demonstrated elevated levels of ribonuclease 7, S100A7 and S100A8 compared to controls (132). Cathelicidin LL-37 is also elevated in HS compared to controls and correlates with the presence of inflammatory cells and cytokines (133,134). Dermcidin was downregulated in HS compared to controls in two further studies (135,136).

Lipocalin 2 (LCN2) is also increased in serum and affected skin of patients with HS as previously discussed (113).

The role of the complement cascade is another area of research in HS and recent studies have noted several complement abnormalities in HS (137). The complement system plays an important role in the innate immune system, defending against pathogens. There are three pathways in the complement cascade: the classical, lectin and alternative pathways which all converge to generate C3 convertase, which in turn generates C5 convertase, which generates C5a and C5b-9 production (137). Complement facilitates removal of pathogens through opsonization and lysis, and it also plays a role in the adaptive immune system through B and T-cell activation (137). The role of complement activation in the pathogenesis of HS is unclear and may be as a consequence of the disease (137). Elevated levels of C5a and C5b-9 are found in HS (138,139). It is thought that an altered microbiome in HS may activate C3a and C5a pathways which may result in NLRP3 inflammasome activation (nucleotide-binding oligomerization domain (NOD)-, leucine-rich repeat (LRR)-, and pyrin domain (PYD)-containing protein 3) (140). In the study by Kanni et al., which demonstrated elevated levels of C5a and C5b-9 in HS, a C5a inhibitor IFX-1 reduced TNF-α levels produced by peripheral blood mononuclear cells (PBMCs) taken from HS affected patients (138). This suggests the role of C5a in promoting cytokine production by monocytes. Furthermore, a study on IFX-1 demonstrated a significant reduction in neutrophil and serum calprotectin levels (139).

Studies determining the levels of cytokines in serum and skin, both affected and non-affected, have led to a greater understanding of HS pathogenesis. Elevated cytokines have been noted in the affected and unaffected skin, serum, and exudate of HS patients (125,126). Cytokines can contribute to follicular occlusion in the primary

lesions by contributing to hyperkeratinisation and hyperplasia of the follicular infundibulum (53). Furthermore, it is thought circulating cytokines and chemokines can prompt development of HS in distant predilection sites (45). A number of cytokines have been found to be elevated in HS.

Both IL-1α and IL-1β levels are elevated in HS (126,141). High IL-1β levels result in production of neutrophil-attracting chemokines (chemokine ligand-1 (CXCL1), CXCL6 and CXCL8) and matrix metalloproteins (MMP1, MMP3, MMP10) resulting in neutrophil chemotaxis and subsequent inflammation (55). IL-36 α, β and γ, members of the IL-1 cytokine family, are also elevated in HS, particularly in established or chronic lesions (142). IL-36 cytokines play an important role in the modulation of T-helper (Th)1 and Th17 responses (142). Tumour necrosis factor-α (TNF- α) plays an important role in the pathogenesis of HS, as evidenced by the efficacy of TNF- α inhibitors in the disease (18,21,143,144). Elevated TNF- α has been reported in HS and correlate with severity (126,141). TNF- α recruits and activates neutrophils and lymphocytes and promotes the production of other inflammatory cytokines (145). Moran et al. observed T-cells with a Th17 skewed cytokine profile (expressing IL-17, as well as CM-CSF, IL-22, IFN-γ and TNF- α) and elevated regulatory T-cells (Treg) in lesional skin, which normalized on the introduction of a TNF- α inhibitor. This suggests that IL-17 inhibition via TNF blockade leads to clinical improvement (146). In another study Th17 inflammatory serum markers (Il-1β, IL-6, IL-8, IL-10, IL-17A, and TNF-α), CRP and ESR were reduced significantly after 36 weeks of adalimumab, a TNF-α inhibitor (147). Mechanistic target of rapamycin complex 1 (mTORC1) pathway is upregulated in HS lesions, and this also responds to TNF-α inhibition (148).

Interferon (IFN)-γ, a cytokine predominantly secreted by natural killer (NK) cells, CD4+ Th1 cells, and CD8 cytotoxic cells, are also elevated in HS and appear to be a dominant response by keratinocytes in HS (149,150). IFN-γ activates macrophages and plays a synergistic role with TNF-α in mediating immune response (151).

IL-10 is highly expressed in HS lesions, both lesional and perilesional, compared to healthy control skin (126). IL-10 is an anti-inflammatory cytokine; however, it exerts a negative effect on IL-22 expression, an important stimulator of keratinocyte antimicrobial peptide (AMP) expression (152). These decreased levels of IL-22 are postulated to contribute to HS pathogenesis (152).

The IL-12/23 pathway is also thought to be important in the pathogenesis of HS. IL-23 is necessary for development of Th17 cells to produce IL-17. IL12/Th1 and IL-23/Th17 pathways are upregulated in HS (153). Clinical improvements noted by patients with HS treated with the IL-12/23 inhibitor ustekinumab further support the role of IL-12 and IL-23 in HS (154).

IL-17, mainly produced by Th17 cells and neutrophils, is significantly elevated in HS (141,155,156)IL-17 exerts a pro-inflammatory effect on the skin, promoting influx of monocytes, neutrophil, Th17 cells and myeloid cells, and feeding an inflammatory loop resulting in increased IL-17 production and further inflammatory cell infiltration (141). The role of Th17/IL-17 in HS is further supported by the fact the levels decrease after effective treatment of HS, including the use of IL-17 inhibitors (156,157).

Elevated levels of IL-36α, β and γ is also reported in lesions of HS and is known to induce neutrophil-attracting chemokines, cytokines, and AMPs (55).

1.5.6 Role of the Microbiota in HS

The role of the skin microbiota in the development of HS is an area of expanding research. However, its role in the development of HS is controversial (158). A number of studies reported that the microbiome of HS lesional and non-lesional skin differs from healthy controls, and support its role in disease pathogenesis (159). Nevertheless, HS does not appear to be a primarily infectious disease, evidenced by the failure in most cases to develop infectious complications such as cellulitis, lymphadenopathy and systemic symptoms (160). The response to immunosuppression also suggests that the role of the microbiota is not the primary cause in HS but rather a contributing factor (161). Furthermore, it is unknown if antibiotics are effective in HS due to their anti-bacterial or anti-inflammatory properties (162). It is thought that antibiotics may attenuate the inflammatory response in HS by removing bacteria from ruptured follicles which are thought to trigger an immune response (163). Detailed discussion of the altered microbiome in HS will be provided later in this chapter.

1.5.7 Diet and HS

The gut-skin axis is an expanding area of research, and several skin conditions including HS, have gut comorbidities (164–166). An abnormal gut microbiota, or dysbiosis, has been linked to the development of skin disease (166). Diet has a significant impact on the gut microbiota composition (166,167). Study on the role of dietary factors in the development of HS is lacking (168). It has been suggested that a dairy-free diet and avoidance of high glycaemic load foods can result in improvement in HS (168,169). It is postulated that dairy products and high

glycaemic foods can act through hormonal mechanisms by triggering androgen-driven obstruction of follicles (169). Other studies suggested avoiding nightshades (Solanaceae) and foods and drinks containing brewer's yeast such as bread and beer (168). One study reported lesser severity of HS in those who follow a Mediterranean diet (170). These studies, however, provide little commentary on the effect of diet on the microbiota as a potential aetiological factor. More detailed discussion of the gut-skin axis in HS will be provided later in this chapter.

1.5.8 Drug-induced HS

HS is rarely associated with medications, however it has been reported to flare with lithium therapy and reports of 'de novo' HS with sirolimus therapy are present in the literature (2,171,172). Further reports implicated ciclosporin, vemurafenib, adalimumab, etanercept, infliximab, secukinumab, ustekinumab, tocilizumab, rituximab, and the oral contraceptive pill therapy in the development of HS, however, a systematic review found the evidence for drug-induced HS low (173,174).

1.6 HS, Associations, and Disease Complications

1.6.1 HS and Autoinflammatory Syndromes

Autoinflammatory diseases are a heterogenous group of systemic disorders characterised by exaggerated innate immune system response with abnormal interleukin (IL)-1 signalling (175). The four recognised autoinflammatory syndromes presenting with HS as part of the spectrum of disease are PASH (Pyoderma gangrenosum, acne, and hidradenitis suppurativa), PAPASH (Pyogenic arthritis, pyoderma gangrenosum, acne, and hidradenitis suppurativa), PsAPASH (Psoriatic arthritis, pyoderma gangrenosum, acne, hidradenitis suppurativa) and PASS (Pyoderma gangrenosum, acne, and ankylosing spondylitis, with or without hidradenitis suppurativa) and have been associated with mutations related to the inflammasome, which regulates innate immunity. Diagnosis of syndromic HS is often made on clinical features, which may be atypical, severe, and resistant to treatment, and the presence of systemic inflammation. Mutations in the gene encoding PSTPIP1 (proline-serine-threonine phosphatase-interacting protein 1), which interacts with pyrin, have been found in the autosomal dominantly inherited PAPA syndrome which presents with pyogenic arthritis, acne and pyoderma gangrenosum (176). The genetic basis of PASH, and PAPASH is less understood and appears to be heterogenous, with mutations in several genes including PSTPIP1, MEFV(Mediterranean fever), NOD (Nucleotide binding oligomerization domain containing)-2, NCSTN (Nicastrin), and NOD-like receptor protein (NRPL)-3 described (177–181). The genetic basis of PsAPASH and PASS has not been described (182–184).

An association between Familial Mediterranean Fever (FMF) and HS has been described in the literature. FMF is an autosomal recessive condition characterised by recurrent attacks of fever, peritonitis, arthritis and amyloidosis and may result in end-stage renal disease (185). The MEFV gene is mutated in FMF which encodes pyrin. Several case series report a link between FMF and HS, with an increased prevalence of 0.7% in patients with HS vs. 0.1% in controls (43–45). An association has also been seen with SAPHO syndrome (Synovitis, acne, pustulosis, hyperostosis and osteitis) (187,188). The genetics of SAPHO is still unknown, however one case report demonstrated a mutation in NCSTN in a patient with concurrent HS (189).

HS can be challenging to treat and syndromic HS, which often presents with more severe disease, can prove very resistant to standard treatment. Although standard HS treatment, such as the TNF-α inhibitors, are reported to be effective, consideration for targeting IL-1 such as Anakinra and Canakinumab should be made if patients fail first line therapies (190–192). Due to the chronicity and severity of syndromic HS, combination therapy with biologics, immunomodulating agents such as dapsone, and surgery is often required (190).

Of note, an abnormal gut microbiota has been suggested in small studies on FMF and SAPHO, with no studies exploring the microbiota in the autoinflammatory conditions in which HS forms part of the spectrum (193,194).

1.6.2 HS and Follicular Occlusion Syndrome

Follicular occlusion syndrome is an umbrella term that includes the conditions acne, HS, pilonidal sinus and dissecting cellulitis of the scalp.

A strong association is seen between HS and acne vulgaris, independent of the auto-inflammatory syndromes discussed above (38). As discussed previously, hyperkeratinisation and hyperplasia of the terminal part of the hair follicle is seen in early lesions in HS, leading to occlusion, dilatation, and rupture of the hair follicle triggering an inflammatory response (195). Similar features are seen in acne vulgaris (196). Toll-like receptor (TLR)-2 is raised in HS and acne triggering inflammation (197,198). Elevated interleukin 1ß is also seen in both conditions, driving neutrophilia and type 17 helper (Th17) T-cell response (163). Prevalence of acne vulgaris in patients with HS has been reported as 15.2% in a large cross-sectional study with a prevalence of only 2.9% in those without HS ($p<0.001$) (199). Prevalence was greatest in females, those aged 18 to 44, non-white, obese, and in those who had polycystic ovarian syndrome (199). Acne conglobata, presenting with severe nodulocystic acne with extensive scarring, is also strongly associated with HS, with a prevalence of 4.5% (OR 5.07, 95% CI 4.69-5.49) seen in Korean patients (35,200). Acne treatments have some success in HS including the use of antibiotics and retinoids, however their efficacy is less than in acne vulgaris with mixed benefit in particular with isotretinoin (163).

An altered skin microbiome is well described in acne with an abundance of *Cutibacterium* (previously known as *Propionibacterium*) *acnes* found in the acne-prone sebum rich areas of skin (201). Other bacteria and fungi may also play a role in development of acne including *Staphylococcus epidermidis, Cutibacterium granulosum, Proteobacteria* and *Firmicutes,* and *Malassezia species* (201). The use of antibiotics in acne suppresses *C. acnes,* with an increase seen in alpha diversity or bacterial species richness, and also has an anti-inflammatory effect (201–203). An altered gut microbiome has also been described in acne, with lower gut microbiota

diversity and a higher ratio of Bacteroidetes to Firmicutes, and lower levels of beneficial bacteria Lactobacillus and Bifidobacterium (204,205). Clinical trials have demonstrated some beneficial effects of modulating the skin and gut microbiota in acne via the use of probiotics (helpful bacteria) but further study is required (201,206,207).

Pilonidal sinus (PS) is an abscess of the sacrococcygeal region which can present acutely, when inflamed and under tension, with severe pain and suppuration (208). It is more common in men, and presents usually between the ages of 25 to 30, and similar to HS rarely presents before puberty or in old age (209). Treatment in symptomatic cases is surgical, to remove the fistulating abscess, with healing by primary or secondary intention (208). PS has been associated with HS with five-fold higher odds of developing the condition in HS compared to controls (28,31,49). Similar risk factors for development are seen in both conditions including friction, increased BMI, and a positive family history (209). Anaerobic bacteria, dominate in skin samples taken from pilonidal sinus, similar to HS (211). It is thought PS may represent part of the disease spectrum in HS.

Dissecting cellulitis (DC), also known as ‘folliculitis et perifolliculitis capitis abscedens et suffoidens’, presents with perifolliculitis (inflammatory cells in skin around hair follicles), dermal abscesses, and sinus tract formation in the scalp resulting in a secondary scarring alopecia (212). An overlap of clinical features is seen with HS and the association of DC, HS, and acne conglobata is known as the follicular occlusion triad, or tetrad if pilonidal sinus is also present (212). DC presents more often in men, African-Americans and in those who are overweight or obese (212,213). Similar to HS, DC is often made worse by smoking, and hair

shaving can be a trigger (212). DC has also been associated with Crohn's disease, pyoderma gangrenosum, axial arthropathy, and SAPHO syndrome discussed previously (213–216). Again similarities between DC and HS have led some to conclude they are different localisations of the same disease (212). *Staphylococcus aureus* is the predominant bacterium found on swabs of DC, and bacterial biofilm formation, similar to the process in HS, has been described (217). Treatment of DC includes retinoids, antibiotics, steroids, and dapsone.(212). Based on its similarity to HS, biologic therapy with anti-TNFα has been trialled with reports of some success in the literature (218).

1.6.3 HS and Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a chronic relapsing inflammatory disease of the gastrointestinal tract and includes the diagnoses of Crohn's disease (CD) and ulcerative colitis (UC). HS and inflammatory bowel disease, in particular CD, share clinical and pathogenic similarities, and an association has been proven (219,220). A prevalence of Crohn's disease of 2% in patients with HS has been reported in the USA, compared with 0.6% in controls, and a higher prevalence of 2.5% in European patients with HS (221,222). In Korean patients an association between HS and Crohn's disease was not found, but an association with UC was present (35). Meta-analysis data demonstrates a 2.12-fold increased odds for developing CD and 1.51-fold increased odds for developing UC, with one cohort demonstrating a 5.6-fold increased risk of IBD, in patients with HS (219).

Both CD and HS present with sterile abscesses, scarring, and sinus tract formation (219). Perianal HS and perianal CD are clinically similar with inflammatory fistulae

and suppuration and HS is likely to be misdiagnosed as cutaneous CD, although true cutaneous CD is very rare (220). Histology is often not helpful in distinguishing between HS and CD with granuloma formation and lymphoid follicles seen in both (220). Both HS and IBD are associated with spondyloarthropathy, smoking, and obesity, and both respond to TNF-a inhibitors (74,223–229).

HS and IBD also share genetic susceptibility with the genes SULT1B1 and SULT1E1 associated with both (220). HS and IBD also have an immunopathogenic link with an aberrant immune response playing a central role in both diseases. Elevated levels of cytokines such as IL-1, IL-6, IL-17, IL-23, and TNF have been described in HS and IBD (230,231). Conventional treatment of IBD and HS includes biologic therapies, in particular TNF-a inhibitors (225,232). IBD is associated with an altered gut microbiota compared to healthy controls, known as dysbiosis, and it is thought that inflammation is as a result of abnormal immune responses in susceptible individuals to this dysbiosis (233). Although an altered skin microbiota has been described in HS compared to controls, research on the gut microbiota is lacking (227–234). The interaction between the gut and skin microbiome and the immune system, known as the gut-skin axis, is an area of emerging interest, particularly in gut pathologies that have skin co-morbidities (235). Given the role of the microbiota in driving inflammation in IBD, studies assessing the manipulation of the microbiota have also been undertaken. The use of probiotics (health-promoting gut microbiota), prebiotics (non-digestible fibres that help microbiota grow) and synbiotics (mixture of prebiotics and probiotics) in IBD have shown mixed results, with most evidence for supplementing with *Lactobacillus* and *Bifidobacterium* (236). Faecal microbiota transplantation (FMT) is the transplantation of healthy donor gut microbiota via a liquid stool suspension to the small intestine of an affected individual, with the aim

of restoring a healthy intestinal microbiota. This has proven effective in treating refractory and recurrent *Clostridium (Clostridioides) difficile* infection (237). FMT has also been used with some success in IBD (238,239). It is possible that such strategies could be effective in HS also, if an altered gut microbiome is confirmed.

1.6.4 HS, Metabolic Syndrome, and Cardiovascular Disease

HS has been associated with the metabolic syndrome. Metabolic syndrome is defined by at least three of: high serum triglycerides, low serum high density lipoprotein (HDL), hypertension, elevated fasting blood glucose, and abdominal obesity. The association between obesity and HS has been discussed above. An association between HS and hypertriglyceridaemia (OR 1.67 (95% CI 1.14-2.47)) and low HDL (OR 2.48, 95% CI 1.49-4.16) (54). An association with type 2 diabetes has also been described with an adjusted odds ratio of 1.69 (95% CI 1.50-1.91) in one review and odds ratio of 2.85 (95% CI 1.34-6.08) in another (40,46). Insulin resistance is also increased in HS, seen in 43% of patients with HS in one study (47). Hypertension has been associated with HS in case-control studies, however a significant association was not seen in the meta-analysis of these studies (OR 1.5, 95% CI 0.63-3.58) (54). Cardiovascular disease (CVD) associated mortality is significantly higher in patients with HS when compared to severe psoriasis and healthy controls with double the risk of death from CVD compared to those without HS and 1.5 times the risk compared to patients with psoriasis (48). The incidence rate ratios (95% CI) compared to healthy controls were 1.57 (1.14-2.17) for MI, 1.33 (1.01-1.76) for ischaemic stroke and 1.95 (1.42-2.67) for CV-associated death, 1.53 (1.27-1.86) for major adverse CV events (MACE) and 1.35 (1.15-1.59) for all-cause mortality (48). The incidence rate ratios (95% CI) in patients with HS were 1.00

(0.74-1.35) for MI, 0.93 (0.71-1.22) for ischemic stroke, 1.58 (1.17-2.12) for CV-associated death, 1.08 (0.90-1.29) for MACE, and 1.09 (0.94-1.28) for all-cause mortality when compared to patients with severe psoriasis (48).

The gut microbiota plays a role in the pathogenesis of the metabolic syndrome and studies have shown a transient improvement in insulin levels with faecal transplantation from lean healthy donors (245–247). Furthermore, a connection between an altered gut microbiota and atherosclerosis has been described (248,249).

1.6.5 HS and Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS) is a common endocrine and metabolic disorder of women which may present with irregular menses, clinical hyperandrogenism, obesity, and polycystic ovaries (250,251). An association between PCOS and HS is recognised with anti-androgen therapy used in both conditions (250,252). A pooled OR of 2.64 (95% CI 1.69-4.11; $p<0.00001$) of PCOS has been reported in patients with HS, however literature studying the link is lacking (252). Co-morbidities including obesity, diabetes, metabolic syndrome are seen in both conditions (252). An altered gut and vaginal microbiome has been described in PCOS, but further study is required to demonstrate on how this impacts on its pathogenesis (253,254).

1.6.6 HS and Obstructive Sleep Apnoea

HS is also associated with obstructive sleep apnoea (OSA) with a prevalence of 3.5% and an odds ratio of 1.45 compared to controls (95% CI 1.33-1.57) (255). As this association is under-recognised, screening for sleep disturbance in HS cohorts is

recommended (255). Disruption of sleep in the context of OSA has also been associated with alterations in gut microbiota (256).

1.6.7 HS and Psoriasis

An association between HS and psoriasis has been reported in the literature. A study from South Korea reported an odds ratio (OR) of 4.58 (95% CI 4.21-4.97), a study from Israel an OR of 1.8 (95% CI 1.4-2.2), and a study from Denmark an OR of 2.99 (95% CI 2.04–4.38) (35,257,258). Both HS and psoriasis share similar aggravating factors and comorbidities including smoking, obesity, cardiovascular disease, and metabolic syndrome (30,259–262). Shared inflammatory pathways including the IL-23/Th17 pathway have been implicated, and elevated levels of TNF-α are seen in both conditions (55,263). Both conditions respond to similar biological therapy, although more effectively in psoriasis (161,264). Treatment of psoriasis with biological therapy can be associated with paradoxical development of HS and vice versa (265,266). The exact pathophysiology of paradoxical eruptions is unknown, however, it is likely genetic susceptibility, and multiple immunological pathways with cytokine imbalance are involved (265). Also psoriasis and HS can co-occur in the rare autoinflammatory syndrome PsAPASH (Psoriatic arthritis, pyoderma gangrenosum, acne, hidradenitis suppurativa) (267).

The role of bacteria, in particular the role of *Steptococci* in triggering flares of psoriasis, is well recognised (268,269). An altered skin microbiome has been described in psoriasis, however, studies on the gut microbiome have yielded mixed results (270). Although alpha-diversity (a measure of species richness) was not significantly lower in psoriasis in the majority of studies, an altered microbiota or dysbiosis was seen in all studies (270).

1.6.8 HS, Alopecia Areata, and Vitiligo

An association between HS and alopecia areata (AA) has been described with an odds ratio (OR) of 1.352 (95% CI 1.235-1.481) in a population-based study from South Korea (35). In that study an association between HS and vitiligo (OR 1.233, 95% CI 1.007-1.511) was also found (35). A study from the US also confirmed a link with alopecia areata with a relative risk (RR) of 2.22 (271). The primary event in both AA and HS is hair follicle disruption, leading to subsequent inflammation (271). An altered gut microbiome was not found in one study on AA, and another described a distinct microbiome in AA compared to controls with no difference in alpha diversity (species richness) (272,273). Several cases of hair regrowth following faecal microbiota transplantation have been reported suggesting a link does exist and could provide a novel therapeutic target in AA (274,275).

1.6.9 HS and Rheumatological Disease

HS has been associated with ankylosing spondylitis, rheumatoid arthritis and psoriatic arthritis (30). An odds ratio (OR) of 1.47 for ankylosing spondylitis (95% CI1.14-1.89), and 1.31 for rheumatoid arthritis (95% CI 1.16-1.47) has been reported in South Korean patients (35). A US study confirmed the increased link of developing ankylosing spondylitis and rheumatoid arthritis, and also confirmed a link with psoriatic arthritis (Hazard ratio 1.44, 95% CI 1.08-1.93) (276). Furthermore, an altered gut microbiome has also been reported in spondyloarthritis, rheumatoid and psoriatic arthritis (277–279).

1.6.10 HS and Pyoderma Gangrenosum

Pyoderma gangrenosum is a rare inflammatory skin condition which presents in the classical form with a painful nodule or pustule than breaks down and evolves into a painful enlarging ulcer with undermined border (280). Concomitant pyoderma gangrenosum (PG) and HS is well described in the literature and can present in the context of several autoinflammatory syndromes, as discussed above (281). HS and PG have been associated with Crohn's disease (CD) and ulcerative colitis, and both respond to treatment with TNF-α inhibitors (221,222,282–288). An odds ratio of 21.14 (95% CI 17.51-25.51) has been reported in the US of PG in patients with HS. The prevalence of PG is higher (3.68%) in those who have both HS and CD, than in those who have HS alone (0.12%), however when patients with CD are excluded the odds ratio remained high at 26.51 (95% CI 21.07-33.36) for PG in HS (289).

1.6.11 HS, Dowling-Degos disease

Dowling-Degos disease (DDD) is a rare autosomal dominant genodermatosis, characterized by reticulate pigmentation of the flexures and has been associated with HS (290). Loss of function mutations in KRT5 (keratin 5), POFUT1 (protein O-fucosyltransferase 1) and POGLUT1 (protein O-glucosyltrans-ferase 1) have been implicated in DDD (291–293). Mutations in γ-secretase subunit encoding PSENEN have been described in DDD associated with HS, in those negative for the above mutations (294). Mutations lead to defective Notch signalling, which is important in follicular epithelial differentiation. Similar to HS, DDD has a predilection for flexural skin and also involves the hair follicle (295). The clinical presentation of DDD can also include follicular hyperkeratotic lesions, epidermoid cysts, comedo-like lesions, and pilonidal sinus (296). In patients with HS and DDD, there is often a

family history of HS, a follicular pattern and involvement of the trunk and nape of the neck (290,297).

1.6.12 HS and Down Syndrome

Down syndrome patients have been reported to have increased rates of follicular occlusion disorders (298). An association between HS and Down syndrome is well established, and is associated with earlier onset of disease (299). One meta-analysis demonstrated an odds ratio of 9.61 (95% CI 5.70-16.20) of developing HS in Down syndrome patients (299). Obesity is often associated with Down syndrome and is a risk factor for development of HS as discussed previously (40,299). However, studies have shown that Down syndrome is an risk factor for HS, independent of increased body mass index (299). Genetic factors may explain this link, with overexpression of amyloid precursor protein on chromosome 21 in Down syndrome resulting in a decline in notch signalling proposed (300). Excess amyloid precursor protein also leads to follicular plugging and keratinocyte proliferation seen in HS (301).

1.6.13 HS and Skin Cancer

A rare complication of the chronic inflammation seen in HS is the development of cutaneous squamous cell carcinoma (SCC). Higher risk of developing SCC in HS is seen in men, and in older age groups and nearly all cases of SCC in the literature involved the perianal or buttock regions (302). Patients often presented late due to difficulty distinguishing early SCC with HS lesions, and over half the cases in the literature presented with metastases (302). It is imperative that patients are

monitored for malignant transformation of chronic lesions to ensure early diagnosis and treatment.

1.6.14 HS and Lymphoedema

Lymphoedema, presenting with swelling and induration of the skin, is a recognised complication of HS which can prove difficult to treat (303). Lymphoedema most commonly complicates HS of the genital area and buttocks (303). Once lymphoedema is established, it responds poorly to HS medical management (303). Early intervention in HS should be undertaken to prevent the complication of lymphoedema, and once present early surgical intervention should be considered (303).

1.6.15 HS, Depression, and Anxiety

HS is a debilitating, painful, and chronic skin condition, and the drainage and odour from suppurating lesions can cause embarrassment and social isolation. It is therefore unsurprising that a high prevalence of depression and anxiety is seen in HS. A meta-analysis reported a prevalence of depression of 21% in HS, with an odds ratio of 1.99 (95% CI 1.63-2.43), and a prevalence of anxiety of 12% in HS, with an odds ratio of 1.97 (95% CI 1.65-2.35) (304). A higher risk of suicide was also found in the literature, with a hazard ratio for completed suicide in HS patients of 2.42 (95% CI 1.07-5.45) reported in a Danish national registry study (305).

The microbiota are a key regulator of gut-brain function, and the microbiota-gut-brain axis is an area of expanding research in determining the biological and physiological basis of psychiatric disorders (306). Gut microbiome dysbiosis has

been described in anxiety and depression, and mouse models have proven that anxiety and depressive behaviour can be transferred by faecal transplant from an affected individual (307,308). Efforts are underway to target this altered microbiota in depression and anxiety, via the use of antibiotics, faecal transplantation of a healthy microbiome, and the use of prebiotics, probiotics (or 'psychobiotics') and fermented foods (307).

1.6.16 HS, Body Image and Sexual Dysfunction

A further consequence of the disfigurement and painful inflammation of HS is poor body image and sexual dysfunction. Body image is significantly diminished in patients with HS compared to BMI matched controls (309). Sexual dysfunction is markedly raised in HS with a prevalence ranging between 51-62% in the literature (310). Risk factors for sexual dysfunction in HS included female sex, more severe disease activity with active lesions in the genital area, higher intensity of pain, presence of malodour, and presence of mood disorders (310).

1.7 Management of HS

Due to the phenotypic heterogeneity of HS and its multifactorial pathogenesis, it is unsurprising that HS is a complex disease which can prove challenging to manage.

1.7.1 Lifestyle measures in HS

Mild disease may respond to lifestyle modifications such as weight loss, smoking cessation, and wearing loose clothing which reduces friction (311,312).

1.7.2 Topical Therapies in HS

Treatment of HS includes the use of topical antiseptics, keratolytics or antibiotics. Monotherapy with topical treatment is considered for mild or localised disease, however topical therapy is generally recommended as an adjunct to systemic therapy (313).

Anti-bacterial cleansers, for example those containing chlorhexidine, iodine or benzalkonium chloride, are frequently prescribed in HS to reduce the bacterial colonization in affected areas; however there are no studies of their efficacy (225,313,314). A phase II open-label study is currently evaluating topical gentian violet as an antiseptic in HS (NCT04388163) and a topical anti-biofilm surfactant wound gel is also being evaluated (NCT04648631) (315).

Topical clindamycin is recommended by the European S1 for localised Hurley stage I or mild Hurley stage II disease, twice daily for three months (311). An early study Clemmensen et al. proved that topical clindamycin reduced symptom recurrence and reduced lesion count compared to placebo (316) Topical clindamycin is well tolerated, however it increases rates of *Staphylococcus aureus* resistance (317).

Topical resorcinol (15%) is a keratolytic or exfoliant which has been proven effective in mild Hurley stage I or II disease, and also has antipruritic and antiseptic properties (318). Several small studies have demonstrated efficacy in stage I and II disease, with reduction in pain noted, and was well tolerated (318–321). Recommended dosing is twice daily for flares, reducing to once daily for maintenance treatment (311,318).

Topical ichthammol 10% has also been trialled in HS with patients reporting some improvement (322). Topical benzoyl peroxide (5-10%) can also be used in HS, and may reduce antibiotic resistance when used in combination as seen in acne (323). Weak evidence also exists for the use of azelaic acid and topical isotretinoin in HS (324).

A phase-II open label trial of the JAK1/2 inhibitor ruxolitinib as a topical cream (1.5%) is also currently in progress (NCT04414514)(325).

Table 2: Studies of topical therapies in HS

Study	Therapy used	Number of participants	Outcome measure	Result
Topical clindamycin				
Clemmensen et al. (1983): (316)	Topical clindamycin hydrochloride 1% in isopropanol 80%, propylene glycol 10% and water 9% versus placebo	27 participants: 13 clindamycin 14 placebo	1. Patient assessment: diary of frequency and duration of recurrences. Ranked as much improved (+2), improved (+1), unaltered (0), worse (-1), much worse (-2) 2. Lesion count	Clindamycin treatment significantly better than placebo ($p < 0.01$)
Jemec et al. (1998): (326)	Topical clindamycin 1% twice daily versus Tetracycline 500mg twice daily	44 participants with Hurley Stage I-II disease: 22 clindamycin 22 tetracycline	1. Visual analog scale (VAS): patient global evaluation, soreness 2. Lesion count	No significant difference seen between two treatment arms
Topical Resorcinol				
Boer et al. (2009): (318)	Resorcinol 15% once daily	12 participants Hurley stage I-II	Reduction in pain by VAS over 1 year	Reduction in pain by VAS noted in all 12 participants
Pascual et al. (2017): (321)	Resorcinol 15% twice daily	32 participants Hurley stage I-II	1. Lesion size on ultrasound at day 30 2. Clinical resolution of lesions at day 30 3. Ultrasonographic (US) resolution of lesions at day 30 4. Reduction in pain by VAS at day 30	1. Reduction in lesion size ($p<0.001$) 2. Clinical resolution in 84.4% 3. US resolution in 65.5% 4. Reduction in mean pain score ($p < 0.001$)

Molinelli et al. (2020): (320)	Resorcinol 15% once daily	61 participants with Hurley Stage I-II	1. HiSCR at 12 weeks 2. IHS4 at 12 weeks 3. VAS and DLQI at 12 weeks 4.Ultrasonography at baseline, 4 and 12 weeks	1.Clinical response (HiSCR) in 85.2% at 12 weeks ($p < 0.001$ 2. Reduction in IHS4 ($p<0.05$) 3. Reduction in VAS and DLQI ($p<0.001$) 4. Reduction in lesion numbers on ultrasound by 80.4% for nodules and 87.1% for abscesses ($p<0.001$)
Docampo-Simón et al. (2022): (319)	Resorcinol 15% twice daily for flares, once daily maintenance	92 participants with Hurley stage I-II	Treatment Satisfaction Questionnaire for Medication (TQSM)	Mean TQSM score 317.5 out of a possible 400 with 84.4% recommending the topical treatment to others with HS
Topical ichthammol				
Fisher et al. (2020): (322)	Ichthammol 10% in soft yellow paraffin twice daily	20 participants	Patient reported improvement	90% reported some improvement

1.7.3 Systemic Antibiotic Therapy in HS

Systemic antibiotics are indicated in patients with mild disease which fails to respond to topical or lifestyle measures, moderate-to-severe disease, and when multiple body sites are affected (311,313,327). Monotherapy may be effective in mild-to-moderate disease, however, in more advanced disease it is used as an adjunct to other therapies. Antibiotics are thought to be effective in HS due to their anti-inflammatory properties, however antibiotics which lack an anti-inflammatory action such as ertapenem and ceftriaxone have also been shown to be effective in HS (328,329). Tetracycline antibiotics and rifampicin are the mainstay of antibiotic therapy in HS. Tetracyclines interfere with protein synthesis in bacteria at the ribosomal level (330). Inhibition of inflammation by tetracyclines is due to inhibition of mitogen-induced human lymphocytic proliferation, suppression of neutrophil migration and chemotaxis, inhibition of T-cell proliferation, inhibition of phospholipase A2, and inhibition of expression of nitric oxide synthetase (330). Rifampicin has a bacteriostatic effect via its inhibition of DNA-dependent RNA polymerase in bacteria, however its immunomodulatory effects are thought to be important in HS(331). A recent *ex vivo* culture study of rifampicin in HS noted its effect on cytokine production with decreased IL-1β, IL-6, IL-8, IL-10 and TNF-α, and reduced expression of Toll-like receptor 2 (331).

Tetracycline antibiotics or combination therapy with rifampicin and clindamycin for a 12 week period are the usual first line choices as monotherapy for HS, or used as an adjunct in more severe disease (311). The first randomised control trial of systemic tetracyclines by Jemec et al. showed no difference between oral tetracycline 500mg twice daily and topical clindamycin twice daily (326). Minocycline (100mg once daily) was evaluated in combination with colchicine

(0.5mg twice daily) with a significant improvement noted; however the efficacy of minocycline alone cannot be extrapolated from this (332). Doxycycline or minocycline 100mg twice daily used in a subset of patients enrolled in the PIONEER trials of adalimumab, was not linked to better outcomes (143). A small retrospective study demonstrated a marked response to doxycycline 100mg twice daily with 60% achieving HiSCR, however, numbers were small (333). A recent study by Jørgensen et al. compared oral tetracycline 500mg twice daily, doxycycline 100mg twice daily, or lymecycline therapy 300mg twice daily in HS (334). Treatment with tetracycline, doxycycline and lymecycline was effective, with a statistically significant mean improvement in Sartorius HS score (HSS), and safe in this study with greatest clinical improvement with tetracycline therapy, as measured by the HSS (334). Van Straalen et al. assessed efficacy and tolerability tetracycline, doxycycline, minocycline and lymecycline in HS and noted a significant decrease in IHS4 and 40.1% HiSCR achievement with 12 weeks treatment with a tetracycline (335). Combination therapy with clindamycin and rifampicin (300mg twice daily) has been proved to be effective in several studies, with response rates of 71% to 93% (336–340). Clindamycin is added to reduce the development of resistance to rifampicin as it is highly mutagenic; however, rifampicin significantly reduces clindamycin levels via the cytochrome p450 3A4 pathway which can explain secondary resistance (341,342). Caposiena et al. evaluated the efficacy of clindamycin alone versus combination therapy with rifampicin, and found no difference between the treatment groups, suggesting monotherapy with clindamycin as an effective alternative therapy in HS (343). In contrast, Iannone et al. noted better efficacy in patients treated with combination therapy versus clindamycin alone (344).

Join-Lambert et al. also assessed the efficacy of combination rifampicin (10mg/kg once daily), moxifloxacin (400mg once daily) and metronidazole (250 to 500mg three times daily) for 6 weeks followed by rifampicin and moxifloxacin therapy until remission to treat Hurley stage I, II, and III HS (345). Once remission was noted rifampicin and moxifloxacin was continued for a further 6-12 weeks and some were prescribed secondary prophylaxis with trimethoprim-sulfamethoxazole or doxycycline (345). Of note 50% of the participants also had induction treatment with ceftriaxone IV with oral metronidazole for 2 weeks (345). Complete remission was obtained in 57% of patients (345).

Delage et al. assessed the use of this combination therapy to treat severe Hurley stage I HS, with complete and prolonged remission noted in 75% of patients, suggesting early broad spectrum antimicrobial treatment may induce clinical remission (346). Pristinamycin was used in those who did not tolerate moxifloxacin, or had a history of tendonitis or joint pain, with no difference in outcomes (346). A retrospective study assessed efficacy of adalimumab alone versus rifampicin and clindamycin (347). Both groups achieved a significant reduction in modified Sartorius score but with a greater efficacy noted in the adalimumab group (347). A study assessing efficacy of daily ofloxacin (200-400mg) and clindamycin (600-1800mg) demonstrated similar response rates to rifampicin and clindamycin combination treatment (348).

Intravenous antibiotics have also been used in HS, such as the induction therapy with IV ceftriaxone seen in the 2011 study by Join-Lambert el al. (345). Intravenous ertapenem daily for 6 weeks was also assessed in a study by Join-Lambert et al., and was effective in 17 of 30 patients with dramatic improvement in severe cases (328). This has led to its use as a bridge to biologic or surgical treatment of severe HS.(328)

IV clindamycin for 5 days (600mg three times daily) followed by rifampicin and clindamycin combination therapy for 10 to 12 weeks, in a study by Nikolakis et al. in 2021, achieved rapid response with improved quality of life (349).

Table 3: Studies of systemic antibiotic therapy in HS

Study	Therapy used	Participants	Outcome measure used	Results
Tetracycline antibiotics				
Jemec et al. (1998): (326)	Topical clindamycin 1% twice daily versus Tetracycline 500mg twice daily	44 participants with Hurley Stage I-II disease: 22 clindamycin 22 tetracycline	1. Visual analog scale (VAS): patient global evaluation, soreness 2. Lesion count	No significant difference seen between two treatment arms
Armyra et al. (2017): (332)	Minocycline 100mg once daily with colchicine 500mcg twice daily	20 participants with Hurley stage I-III	1. Physician's global assessment (PGA) 2.Hurley score 3. Dermatology Life Quality Index (DLQI)	Significant improvement in 1. PGA 2. Hurley score 3. DLQI
Vural et al. (2019): (333)	Doxycycline 100mg twice daily	10 participants with Hurley stage I-III	HiSCR	60% achievement HiSCR
Jørgensen et al. (2021): (334)	Tetracycline 500mg twice daily, doxycycline 100mg twice daily, or lymecycline therapy 300mg twice daily	108 patients with Hurley stage I-III	1. Sartorius HS score (HSS) 2. DLQI 3. PGA 4. Pain numerical rating scale (NRS)	1. Mean HSS decreased by 8.13 from baseline ($p < 0.001$) 2. Mean DLQI decreased by 3 ($p < 0.001$) 3. Median PGA 'small improvement (1-29%) 4. Mean pain NRS decreased by 1 ($p < 0.001$)

Van Straalen et al. (2021): (335)	Tetracycline 500mg twice daily, doxycycline 100mg once daily, minocycline 100mg once daily	108 participants: 42 received tetracycline, 121 received doxycycline, 17 received minocycline	1. HiSCR 2. IHS4 3. DLQI 4. Pain NRS	1. 40.1% attainment of HiSCR 2. Significant reduction in IHS4 (P < 0.001) 3. Significant reduction in DLQI (p < 0.001) 4. Significant reduction in pain (p = 0.001)
Caposiena et al. (2021): (350)	Group A: Lymecycline 300mg daily versus Group B: rifampicin 300mg twice daily and clindamycin 150mg four times daily for 10 weeks	52 participants with HS Group A: 26 Group B: 26	1. Sonographic score of HS 2. IHS4 3. VAS pain 4. DLQI	Significant improvement in IHS4, pain VAS and DLQI in both groups (p <0.001) No significant difference in response rates in both groups (p= 0.78) IHS4 did not differ significantly between groups Ultrasound nodule and abscess count was lower in Group A than Group B after treatment, draining tunnel count was lower in Group B than Group A Group A had higher improvement in pain VAS (p<0.001) and DLQI (p<0.05)

Rifampicin and Clindamycin				
Mendonça et al. (2006): (337)	Rifampicin and clindamycin 300mg twice daily for 10 weeks (minocycline 100mg once daily substituted if developed diarrhoea on clindamycin)	14 participants	Retrospective review of clinical remission	10 of 14 (71%) achieved remission
Gener et al. (2009): (340)	Rifampicin 600mg daily and clindamycin 300mg twice daily for 10 weeks	70 participants with Hurley stage I-III disease	1. Sartorius score 2. Hurley stage at 10 weeks 3. Pain VAS	1. Dramatic decrease in Sartorius score ($p < 0.001$) 2. Decrease in Hurley score noted ($p=0.018$) 3. Median pain reduction from 7 to 3 ($p < 0.001$)
Van Der Zee et al. (2009): (339)	Rifampicin and clindamycin 600mg daily for 10 weeks	34 participants with Hurley stage I-III disease	1. Hurley score 2. Investigator global assessment with partial improvement: <75% clinical improvement from baseline, and total remission: > 75% improvement or total clearance	28/34 (82%) showed at least partial improvement 16/34 (47%) showed total remission
Bettoli et al. (2014): (338)	Rifampicin and clindamycin 600mg daily for 10 weeks	20 participants with Hurley stage I-III disease	1. 25% improvement in Sartorius score 2. Number of exacerbations	1. 17/20 (85%) had >25% improvement in Sartorius score ($p = 0.00098$) 2. Reduction in exacerbations ($p = 0.0091$)

Dessinioti et al. (2016): (336)	Rifampicin and clindamycin 600mg daily for 12 weeks	26 participants with Hurley stage I-III disease	Clinical response	Clinical response in 19/26 (73%) with sustained efficacy at 1 year in 7/17 (41%) and disease relapse in 10/17 (59) after a mean of 4.2 months
Ochi et al. (2018): (351)	Rifampicin and clindamycin 300mg twice daily for 10 weeks	11 participants with HS	Clinical response HS-PGA in 4 participants	63.6% reported clinical improvement 3 of 4 had improvement in HS-PGA
Caposiena et al. (2019): (343)	Group A: Clindamycin 150mg four times daily with rifampicin 300mg twice daily for 8 weeks versus Group B: Clindamycin 150mg four times daily for 8 weeks	60 participants: 30 in group A 30 in group B	Hidradenitis Suppurativa Clinical Response (HiSCR) – at least a 50% reduction from baseline in total abscess or inflammatory nodule count	17/30 (56.7%) in group A, and 19/30 (63.3%) achieved HiSCR with no significant difference between groups ($p = 0.598$)
Marasca et al. (2019): (347)	Adalimumab versus rifampicin and clindamycin for 10 weeks	30 participants	1. Modified Sartorius score 2. Hidradisk QOL assessment	1. Reduction in modified Sartorius score ($p = 0.0052$) 2. Reduction in Hidradisk ($p = 0.0095$)
Vural et al. (2019): (333)	Rifampicin and clindamycin 300mg twice daily for 3 months	28 participants with Hurley stage I-III disease	HiSCR	46.6% achievement HiSCR
Yao Y et al. (2021): (352)	Rifampicin and clindamycin 300mg twice daily for 6 months	54 participants with HS	1.Hidradenitis Suppurativa Score (HSS) 2.DLQI 3.VAS pain 4.HS-PGA	1. 79.6% showed improvement in HSS, with 37% achieving >50% improvement from baseline, and 13% full remission 2. Median DLQI decreased from 14.5 to 10 ($p<0.0001$)

				3. Median VAS decreased from 9.1 to 5.9 (p<0.0001) 4. Median PGA corresponded to 'small improvement' (1-29%)
Iannone et al. (2021): (344)	Rifampicin 300mg twice daily and clindamycin 150mg four times daily for 12 weeks versus clindamycin 150mg four times daily for 12 weeks	36 participants with moderate to severe HS: 19 on clindamycin plus rifampicin, 17 on clindamycin alone	1. Modified Sartorius score 2. Acne inversa severity score (AISI) 3. DLQI	1. Greater reduction in modified Sartorius score in clindamycin plus rifampicin group (p = 0.058) 2. Significant reduction in AISI in clindamycin plus rifampicin group (p = 0.034) 3. Non-significant reduction in DLQI between groups (p = 0.207)
Van Straalen et al. (2021): (335)	Rifampicin and clindamycin 600mg daily for 12 weeks	103 participants with Hurley stage I-III disease	1. HiSCR 2. IHS4 3. DLQI 4. Pain NRS	1. 48.2% attainment of HiSCR 2. Significant reduction in IHS4 (P < 0.001) 3. Significant reduction in DLQI (p < 0.001) 4. Significant reduction in pain (p = 0.001)
Caposiena et al. (2021): (350)	Group A: Lymecycline 300mg daily versus Group B: rifampicin 300mg twice daily and clindamycin 150mg four times daily for 10 weeks	52 participants with HS Group A: 26 Group B: 26	1. Sonographic score of HS 2. IHS4 3. VAS pain 4. DLQI	Significant improvement in IHS4, pain VAS and DLQI in both groups (p <0.001) No significant difference in response rates in both groups (p= 0.78) IHS4 did not differ significantly between groups Ultrasound nodule and abscess count was lower in Group A than Group B

				after treatment, draining tunnel count was lower in Group B than Group A Group A had higher improvement in pain VAS ($p<0.001$) and DLQI ($p<0.05$)
Bettoli et al. (2021): (353)	Rifampicin and clindamycin 300mg twice daily for 10 weeks	20 participants aged ≤ 16 years with HS	1. Sartorius Score 2. No of exacerbations during treatment compared to prior 3 months	1. Sartorius score mean reduction of 52.8% with 60% achieving >50% improvement ($p= 0.001$) 2. 37.1% mean reduction in number of exacerbations ($p = 0.001$)
Rifampicin				
Join Lambert et al. (2011): (345)	Rifampicin (10mg/kg/day), moxifloxacin (400mg daily) and metronidazole (500mg three times daily) and 50% received pre-treatment with IV ceftriaxone (1g daily) and metronidazole (500mg three times daily) for 2 weeks. Median duration was 2.4 – 12 months depending on stage.	28 participants with Hurley stage I-III disease	Remission of HS	57% achieved complete remission
Vural et al. (2019): (333)	Rifampicin, moxifloxacin and metronidazole for 3 months	2 participants with Hurley stage I disease	HiSCR	100% achievement HiSCR
Delage et al. (2020): (346)	Rifampicin (10mg/kg once daily), moxifloxacin (400mg once daily) and metronidazole (250-500mg three times daily) for 6 weeks then Rifampicin and moxifloxacin alone	28 participants with Hurley Stage 1 HS	Sartorius score	Median Sartorius score dropped from 14 to 0 ($p=6 \times 10^{-6}$) at week 12 75% reached clinical remission (Sartorius score = 0)

	for 4 weeks. (Pristinamycin 1g three times daily in those with contra-indications or intolerant of moxifloxacin)			
Clindamycin				
Delaunay et al. (2018): (348)	Ofloxacin (200-400mg) and clindamycin (600-1800mg daily) as per patients' weight with mean duration of treatment of 4.3 months	65 participants with Hurley stage I-III disease	Patient reported improvement	58.4% reported improvement in HS
Caposiena et al. (2019): (343)	Group A: Clindamycin 150mg four times daily with rifampicin 300mg twice daily for 8 weeks versus Group B: Clindamycin 150mg four times daily for 8 weeks	60 participants: 30 in group A 30 in group B	Hidradenitis Suppurativa Clinical Response (HiSCR) – at least a 50% reduction from baseline in total abscess or inflammatory nodule count	17/30 (56.7%) in group A, and 19/30 (63.3%) achieved HiSCR with no significant difference between groups ($p = 0.598$)
Rosi et al. (2019): (354)	Clindamycin 300mg twice daily for 12 weeks	31 participants	1. Sartorius score 2. HS-PGA 3. IHS4 4. VAS pain	1.Mean reduction of 15 in sartorius score ($p \leq 0.01$) 2. Mean reduction of 1 in HS-PGA ($p \leq 0.01$) 3. Mean reduction of 6 in IHS4 ($p \leq 0.01$) 4. Mean reduction of 3 in VAS pain ($p \leq 0.01$)

An et al. (2021): (355)	Clindamycin monotherapy (dose not specified) for 8 weeks	50 participants: 34 eligible for evaluation at 8 weeks	1. HISCR - at least a 50% reduction from baseline in total abscess or inflammatory nodule count 2. HS-PGA	1. 61.76% achieved HiSCR 2. Mean HS-PGA decreased from 3.24 to 2.15 (p=0.001)

Antibiotic side-effects can be numerous and care should be taken to minimise these. Apart from specific side effects to particular antibiotics (for example photosensitivity with tetracyclines), side effects common to all antibiotics include candidiasis, and allergic reactions (329). The negative impact of antibiotic therapy on gut microbiome diversity has been established in multiple studies with repeated and prolonged courses leading to dysbiosis (356,357). Acute *Clostridioides difficile* infection can also occur with antibiotic use, and is a particular risk with clindamycin (342). *C. difficile* risk is higher in patients with inflammatory bowel disease with one study reporting a higher prevalence among patients with ulcerative colitis (3.7%) and Crohn's disease (1.1%) compared to the general population (0.5%) (358). Interestingly, this increased risk is not borne out in cases of HS treated with clindamycin. A study by Kwak et al. found no increased risk of *C. difficile* infection in patients treated with IV or oral clindamycin in HS (359). Co-prescription with rifampicin (over 75% in this study) may explain the low incidence of *C. difficile* infection, as it reduces serum clindamycin levels, and also treats the infection (341,342,359). Antibiotic resistance is also a growing concern, and prolonged use of antibiotics in HS should be discouraged. Treatment of flares with antibiotics or induction treatment with antibiotics prior to surgery or commencement of a biologic is recommended, with long-term maintenance therapy with antibiotics discouraged (329).

1.7.4 The Use of Biologic Drugs in HS

Targeted biologic therapy is now the mainstay of treatment of moderate to severe HS.

Anti-TNF-α therapy

As discussed previously TNF-α is elevated in HS. Several biologics targeting TNF-α have been trialled in HS.

Adalimumab is the first and only biologic approved (by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA)) for the treatment of HS. This is based on the results of two phase III double-blind placebo-controlled trials (PIONEER I and II) (143). In these studies 633 participants with HS received either a loading subcutaneous adalimumab dose of 160mg on week 0, and 80mg on week 2 followed by 40mg weekly maintenance dose from week 4, or placebo. In PIONEER II tetracycline antibiotics were continued if required (143). The HiSCR (at least a 50% reduction from baseline in total abscess or inflammatory nodule count) was achieved in 50.6% of participants on adalimumab, versus 26.8% receiving placebo ($p<0.001$), and Dermatology Life Quality Index (DLQI) scores also improved in the treatment arm (143). 88 participants entered the open-label extension study of adalimumab 40mg weekly with HISCR achieved in 52.3% at week 12, 62.5% at week 36, and 52.3% at week 168 (288). Adalimumab was well tolerated in these studies. Adverse events were 4.6% or less in both PIONEER studies, with one incidence of non-melanoma skin cancer and one incidence of breast cancer, and no serious infections reported (143). Four serious infections and no adverse events of opportunistic infections excluding oral candidiasis, no active tuberculosis, lymphomas, cancers or demyelinating disorders were reported in the

open label study (288). In practice doses of 80mg weekly can be introduced in those with partial response or loss of efficacy to 40mg weekly of adalimumab (360). Studies in Crohn's disease and ankylosing spondylitis suggest an improvement in gut microbiota composition results from adalimumab therapy (361,362). Furthermore studies in spondyloarthritis have suggested certain microbiota patterns can predict response to TNF-α treatment (361,363). A small study assessed the gut microbiota before and after 12 weeks of adalimumab therapy in 10 patients with HS (364). It showed a shift in composition and function of the gut microbiota after adalimumab therapy, with more beneficial metabolites such as short-chain fatty acids detected (364).

Infliximab, a chimeric monoclonal antibody targeting TNF- α, was studied in a phase II randomised, placebo-controlled, double-blind study in moderate to severe HS (21). 38 patients with moderate to severe HS received 5mg/kg of infliximab on weeks 0, 2, 4, 6, 14, and 22 (21). At 8 weeks, 57% had a $>$ 50% decrease in their HS Severity Index (HSSI) versus 5% in the placebo group ($p=0.092$), 60% had a 25-50% decrease in HSSI compared to 5.6% receiving placebo ($p<0.001$) (21). DLQI and visual analog scores of pain also improved in the treatment arm (21). Infliximab was well tolerated in the treatment group, with no serious adverse events reported (21). Higher doses of infliximab have been proposed (7.5-10mg/kg) with good control of disease (123,365).

Etanercept is a recombinant human TNF-α receptor fusion protein that binds membrane bound TNF- α receptors. No improvement was achieved in HS patients treated with etanercept in one phase II open-label, randomised controlled trial (366).

Golimumab is a fully human anti-TNF-α monoclonal antibody that binds to TNF-α. Case reports have shown some efficacy in HS (367,368).

Certolizumab Pegol, is a pegylated humanised monoclonal antigen-binding fragment of IgG which binds to TNF-α. A case series of certolizumab use in 2 patients (200mg every 2 weeks) showed no efficacy, however several case reports show improvement at higher doses (400mg every 2 weeks) (369–372). As certolizumab is pegylated it does not cross the placental barrier, therefore it has been used off-licence in pregnancy (370).

Anti-IL-1

The IL-1 pathway has been found to be hyperactive in HS, leading to skin infiltration and destruction (373). Targeting this pathway has been trialled in HS.

Anakinra is a recombinant interleukin-1 receptor antagonist, competitively inhibiting IL-1α and IL-1β receptor interaction. An open label study of anakinra 100mg subcutaneously for 8 weeks in patients with moderate to severe HS showed a significant mean decrease of 34.8 in their modified Sartorius score, as well as a reduction in patient and physician global assessments. Furthermore an improvement in DLQI was seen. However, rebound of HS was seen in all patients during the 8-week follow up period (374). Tzanetakou et al. reported 78% of patients treated with anakinra achieved HiSCR (at least a 50% reduction from baseline in total abscess or inflammatory nodule count) compared to 30% receiving placebo at week 12 ($p=0.04$) (192). Again, in the 12 week follow-up period control of HS was lost, with no difference in HiSCR between the groups (192). A study of long-term efficacy of anakinra followed three patients treated with anakinra for between 6 months and 7 years (375). In this study all required switching to another biologic agent due to

relapse (375). As anakinra has had mixed results in HS, and also requires daily subcutaneous injections, its use in HS is limited. However, anakinra may be an appropriate option in those with other autoinflammatory syndromes (281).

Canakinumab is a human IgGκ monoclonal antibody targeting IL-1β with mixed evidence of efficacy in HS in the literature. Case reports have shown some efficacy in HS, however failures have also been reported (376–379).

Bermekimab (MABp1) is a recombinant human IgG1 monoclonal antibody which binds IL-1α. In a study by Kanni et al. 60% (6/10) of patients achieved HiSCR (at least a 50% reduction from baseline in total abscess or inflammatory nodule count) after receiving bermekimab 7.5mg/kg every 2 weeks versus 10% (1/10) of those receiving placebo at 12 weeks (380). In the open label extension study 75% of those transitioned (8 patients) achieved HiSCR at week 12 (381). A further open-label phase II study of bermekimab 400mg subcutaneously weekly showed a significant reduction in lesion count and visual analog scale pain scores in patients with moderate to severe HS who were anti-TNF naïve and those who failed anti-TNF treatment (382).

A phase II trial is ongoing of lutikizumab, an anti-IL1α/β dual variable domain immunoglobulin in HS (383). Another phase II trial is assessing MEDI8968, a fully human monoclonal antibody which binds to IL-1R1 in HS (384).

Anti-IL17

Serum IL-17 levels are elevated in patients with HS and correlate with disease severity (156). A number of biologic agents targeting IL-17 have been used to treat HS.

Secukinumab, a human monoclonal IgG1κ antibody that binds IL-17A, has shown some efficacy in HS. A pilot trial in 9 patients with moderate to severe HS found 67% achieved HiSCR when treated with secukinumab 300mg weekly for 5 weeks then every 4 weeks for 24 weeks (385). An open label study in 20 patients with moderate to severe HS found 70% achieved HiSCR when treated with secukinumab 300mg subcutaneously weekly for 5 weeks then every 4 weeks in 9 patients, or every 2 weeks in 11 patients up to 24 weeks (386). A retrospective study of secukinumab 300mg weekly for 5 weeks then every 4 weeks up to 16 weeks in 20 patients with HS found 75% achieved HiSCR response (387). In this study, 2 of the 20 patients developed Crohn's disease after 3 and 5 months of treatment (387). HS has been associated with inflammatory bowel disease as discussed previously, and careful clinical examination to detect possible susceptibility to IBD prior to secukinumab therapy should be advised (388). It should also be avoided in those with active inflammatory bowel disease. An Italian retrospective study in 31 patients with HS treated with secukinumab 300mg weekly for 5 weeks, followed by 300mg every 4 weeks, found 41% achieved HiSCR at week 28 which was lower than previously reported (389). Several clinical trials are in progress to determine if there is a benefit to treatment with secukinumab in HS (NCT03099980, NCT04179175, NCT03713632, NCT03713619) (390).

Brodalumab is a monoclonal antibody that binds with high affinity to the IL-17RA subunit of the IL-17 receptor and blocks signalling of the pro-inflammatory cytokines IL-17A, IL-17C and IL-17F. An open label study of brodalumab 210mg subcutaneously on week 0, 1, 2, and every 2 weeks thereafter in 10 patients with moderate to severe HS found 100% achieved HiSCR at 12 weeks (391). In the maintenance period 2 patients had recurrence of drainage from their gluteal sinus tracts, and suggested higher doses for some patients with more severe disease may be required (391). Weekly brodalumab 210mg subcutaneously was then trialled in 10 patients with draining tunnels, with 100% achieving HiSCR by week 4 and sustained up to week 24 (392). Therefore weekly dosing may be indicated in those with more severe disease with tunnels and sinus tracts.

Ixekizumab is an IgG4 monoclonal antibody that binds with high affinity to IL-17A and IL-17A/F. Three case reports in the literature have suggest ixekizumab may also be effective in HS but no case series or trials have been published (393–395).

Bimekizumab is a monoclonal IgG1 antibody that inhibits ILA and IL17F. A phase II, double-blind, placebo-controlled trial was carried out, comparing bimekizumab 640mg week 0, then 320mg every 2 weeks, to placebo, and to adalimumab 160mg week 0, 80mg week 2 and then 40mg weekly from week 4 (396). 57.3% of patients receiving bimekizumab achieved HiSCR at week 12, versus 26.1% in the placebo group. 46% bimekizumab-treated patients achieved $HiSCR_{75}$ and 32% achieved $HiSCR_{90}$, 10% of placebo-treated patients achieved $HiSCR_{75}$ and none achieved $HiSCR_{90,}$ and 35% of adalimumab-treated patients achieved $HiSCR_{75}$ and 15% achieved $HiSCR_{90}$ (396). Results of two phase III trials and an extension study are awaited (NCT04242446, NCT04242498, NCT04901195) (397).

CJM112 is an anti-IL17A and IL-17A/F IgG1κ monoclonal antibody. In a phase II randomised controlled trial HS-PGA response rate was 32.3% in those treated with CJM112 300mg weekly for 5 weeks then every 2 weeks (33 patients) compared to 12.5% in those who received placebo (33 patients) at week 16 (398).
Izokibep is a potent and selective inhibitor of IL-17A that is being developed for HS and is currently in phase II trials (399). The IL17A/F nanobody sonelokimab is also being studied in HS (400).

Anti-IL12/23

Ustekinumab is a fully human IgG1κ monoclonal antibody that binds to the shared p40 protein subunit of IL-12 and IL-23. A phase II open label study found that patients treated with ustekinumab (45mg if <100kg, 90mg if >100kg) at week 0, 4, 16, and 28 with an observation period to 40 weeks, had a marked improvement in modified Sartorius score in 35% and a moderate improvement in 47%. Furthermore 47% achieved HiSCR at week 40 (401). Several case series and case reports have reported efficacy of ustekinumab in HS (402–410). However drug survival was variable (402–410). Higher doses as used in Crohn's disease has also been trialled in HS (411–413). Romani et al evaluated an initial iv infusion of ustekinumab adjusted by weight ($\leqslant$55 kg, 260 mg; 56–85 kg, 390 mg; $\geqslant$86 kg, 520 mg) followed by a maintenance subcutaneous dose of 90mg every 8 weeks in 14 patients (413). 50% had achieved HiSCR at 16 weeks (413). A retrospective study in 6 patients with the same regimen also found 50% achieved HiSCR at week 12 (411). In another retrospective case series of 10 patients 90% achieved HiSCR with 90mg subcutaneous ustekinumab with no induction therapy (412).

Anti-IL23

Guselkumab is a recombinant human monoclonal antibody that binds to the p19 subunit of IL-23. Case reports and case series have reported efficacy with guselkumab 100mg subcutaneously at weeks 0, 4, then every 8 weeks (414–418). A retrospective study of 11 patients reported that 63.6% achieved HiSCR at week 16 ± 4 weeks, with mean drug survival of 24.54 months (419). However, one case series reported poor outcomes with a higher dosing regimen (100mg sc week 0, 4, then every 4 weeks) in 4 patients (420).

Tildrakizumab is a recombinant human monoclonal antibody to the p19 subunit of IL-23. One case series in 5 patients of Tildrakizumab 100mg week 0, 4 then 200mg every 4 weeks thereafter reported improvement in abscess and nodule count at week 8 in all patients and ongoing improvement at week 20 in 3 of the 5 patients (1 discontinued at week 8 due to pregnancy)(421)

Rizankizumab is a humanised monoclonal antibody that binds to IL-23. Clinical response has been reported in cases in the literature at a dose of 150mg on week 0, and week 4, then every 12 weeks thereafter (422–424).

Anti-IL36

IL-36 is involved in neutrophil recruitment and activation, and elevated levels of IL-36 has been found in HS lesions (425). Imsidolimab and spesolimab are monoclonal antibody that bind to IL-36 which have been developed for the treatment of pustular psoriasis (426,427). Their use in HS is being trialled currently (428,429).

Janus Kinase (JAK) inhibitors

Janus Kinase inhibitors block IL-6 signalling through the JAK-STAT pathway (430). IL-6 is known to be involved in the pathogenesis of HS (373). Tofacitinib is a JAK-1 and -3 inhibitor with reports of success in the treatment of 2 patients with HS (430). INCB054707 is a JAK1 inhibitor which was studied in 2 phase II trials in patients with moderate to severe HS (431). Ten patients received 15mg in study 1 and 9 received 30mg, 9 received 60mg, 8 received 90mg patients and 9 received placebo in study 2 (431). 70% of patients in study 1 and 81% of patients in study 2 had treatment related adverse events, with 30% in study 1 and 42% in study 2 having grade 3 adverse events (431). Of those patients eligible for evaluation, 3(43%) in study 1 and 17(65%; 30mg, 56%; 60mg, 56%;90mg, 88%) in study 2 achieved HiSCR (431). A further study evaluating efficacy and safety of INCB054707 is ongoing currently (432). Upadacitinib, a JAK1 inhibitor has been studied in HS and results are awaiting publication (433).

C5a inhibitors

IFX-1 is a monoclonal IgG4κ antibody that selectively binds to C5a (139). A phase II study assessed efficacy of IFX-1 800mg day I, 4, 8, 15, 22, 29, 36, 43 and 50 in patients with HS (139). 12 patients were enrolled and 75% achieved positive HiSCR on day 50, and 83.3% on day 134 (139). IFX-1 was well tolerated (139). A randomised, double-blind, placebo controlled trial in 175 patients with HS, demonstrated HiSCR achievement in 40.4% receiving 400mg every 4 weeks, 51.5% receiving 800mg every 4 weeks, 38.7% receiving 800mg every 2 weeks and 35.5% receiving 1200mg every 2 weeks (434). 47.1% of those receiving placebo achieved HiSCR (434). It is thought that using HiSCR contributed to the high placebo

response rate as the data collected on draining tunnels demonstrated significant efficacy of IFX-1 compared to placebo (434,435). Avacopan is an oral C5a receptor antagonist which is also under study in HS (436).

Others

Several other treatments in HS are under study currently:

- LY3041658 is a monoclonal antibody that inhibits chemokines which bind to CXCR1 and CXCR2 which is currently in a phase II trial in HS (437).
- PF-06650833, an IL-1 receptor-associated kinase 4 (IRAK4) inhibitor (438).
- PF-06700841, a tyrosine kinase (TYK2) and JAK1 inhibitor that blocks IL-12/23 signalling (438).
- PF-06826647, a tyrosine kinase inhibitor (TYK2)(438).
- Fostamatinib, a spleen tyrosine kinase enzyme inhibitor (SYK)(439).
- KT-474, an IRAK4 inhibitor is recruiting to a phase 1 study (440).
- Iscalimab (CFZ533) is an anti-CD40 IgG1 monoclonal antibody that blocks the CD40-CD154 pathway (441).
- LYS006, a leukotriene A4 (LTA4) hydrolase inhibitor (442).
- CSL324, a recombinant anti-granulocyte colony-stimulating factor (G-CSF) receptor monoclonal antibody (443).
- RIST4721, an oral CXCR2 antagonist (444).
- BDB-001, a toll-like receptor 7 and 8 agonist (445).
- ATI-450, a small molecule inhibitor of p38a mitogen-activated protein kinase (MAPK)/MAPK-activated protein kinase 2 (MK2)(446).

1.7.4 Other Systemic Treatments

Steroid therapy

Systemic corticosteroids produce pan-cytokine inhibition and are thus effective in HS (447). However, high dose and protracted courses of oral corticosteroids are not recommended due to side effects, and due to the chronicity of HS it is not recommended to prescribe them routinely. They may however be a useful adjunct as short-term rescue therapy for flares or as a bridge to other long-term systemic therapies (313).

Intralesional steroids, however, are widely used to treat individual lesions in HS (448–452). Intralesional corticosteroids administered to inflammatory nodules can lead to rapid resolution and can be useful in treating flares (452,453). One study compared two different doses of intralesional triamcinolone, 10mg and 40mg/ml and showed no statistical difference when compared to placebo (449). Varying doses of intralesional steroid is used in the published studies, thus optimal dosing is unknown (448–454). A clinical trial is being undertaken to determine this (455).

Oral retinoid therapy

There is some evidence in the literature for the use of retinoids in HS. Acitretin at doses of 0.5-0.6mg/kg/day for 3 to 12 months have been trialled with variable outcomes in HS (456,457). Response rates are reported to be approximately 50% with high recurrence rates seen, and as such it should only be considered as a second- or third-line treatment (313,456,457). Isotretinoin may be helpful in mild disease at low doses (<1mg/kg/day) and can be considered if the patient has severe concomitant acne or as second- or third-line therapy (313,458). Alitretinoin at a dose of 10mg/kg/day has been assessed in 14 women for a period of 24 weeks in one

study with 78.5% patients having significant improvement in their modified Sartorius score (459). Alitretinoin is not available to prescribe in Ireland.

Selective PDE-4 inhibitor therapy

Apremilast is a phosphodiesterase-4 (PDE-4) inhibitor which has been studied in a placebo-controlled trial in HS (460). In this study 20 patients with moderate HS received apremilast 30mg twice daily or placebo for 16 weeks (460). HiSCR was achieved in 53.3% of those receiving apremilast and in none of those receiving placebo (460). Four of the eight responders continued apremilast in a 2 year follow-up study (2 discontinued due to pregnancy, one due to intolerable nausea, and one due to quiescence of HS)(461). Orismilast, is another PDE-4 inhibitor currently being trialled in HS (462).

Hormonal and endocrine therapies

Due to the onset of HS after puberty, presence of premenstrual flares, and the rarity of cases in postmenopausal patients hormonal therapies have been trialled in HS (463). In particular patients with polycystic ovarian syndrome (PCOS), discussed above, may benefit from hormonal therapy for their HS, although robust evidence for the use of anti-androgens does not exist in the literature due to the limited small studies (92).

Cyproterone acetate with ethinyloestradiol (50mg/50µg) versus ethinyloestradiol/norgestrel (50µg/500µg) has been evaluated in 24 patients with HS showing clinical improvement, with no difference noted between the two treatments (464).

Spironolactone (100 to 150mg daily) has also been used to some success in HS in a case series (465). A further retrospective study of spironolactone 75mg daily found that it reduced lesion count, HS-PGA score and pain (466).

Metformin 1.5g/day has also been used in HS as it has anti-androgen, and anti-inflammatory effects, and can treat concomitant PCOS and metabolic syndrome if present (467). In this retrospective study subjective clinical response was seen in 68% with 19% experiencing quiescence of disease with metformin monotherapy (467). However drug survival in this study at 12-months was 39% (467). A further study of metformin (500mg to 1500mg) in 25 patients with HS showed significant reduction in Sartorius score in 76%, as well as a significant improvement in DLQI in 64% at week 24 (468). A phase III trial is currently evaluating the efficacy of metformin and doxycycline versus doxycycline alone (469).

Finasteride, a type II 5-α reductase inhibitor has also been used with some effect in HS (470–473). Doses of between 1 and 5 mg have been trialled with success reported but relapse is common (473). A study of 7 patients who failed antibiotic therapy, treated with 5mg a day of finasteride reported improvement in 6 of 7 patients with complete healing in 3 cases (472). 2 case series report improvement in paediatric cases of HS with finasteride (470,471).

Dapsone

Dapsone has been used in HS with some success but evidence available is weak (474). A retrospective review evaluated dapsone (50-200mg/day) in 24 patients with HS with improvement noted in 38%, however none of the Hurley Stage III patients responded (475). A retrospective case series of dapsone 25-150mg/day also showed positive response in all 5 patients (476). A series of 19 patients with moderate to

severe HS taking 25-100mg/day showed clinically significant improvement in 15.8%, slight improvement in 52.6% and no improvement in 31.6% (477). A retrospective review in 25 patients receiving dapsone 50mg-200mg showed subjective clinical improvement in 64% (478). Again this study showed no improvement in Hurley Stage III disease with responders having mild to moderate HS (478). A larger case series in 56 patients with mild to moderate HS showed 62.5% of patients achieved HiSCR at 12 weeks on doses of 50-150mg/day (479). Dapsone is designated as third line treatment in mild to moderate HS (313).

Colchicine

Colchicine has been trialled in small series at a dose of 0.5mg twice daily with little effect (332). In a prospective pilot study of 8 patients with HS only 2 continued treatment at 4 months, with only 1 showing slight improvement in HS-PGA (480). When used in combination with minocycline 100mg once daily for 3 months, followed by colchicine alone for 3 months a significant improvement was noted in 20 patients (332). However, this does not support its use as monotherapy in HS (332).

Finally, a study of 44 patients who received colchicine as monotherapy, or in combination with doxycycline 100mg daily or doxycycline 40mg daily, showed significant improvement in DLQI and IHS4 scores in all groups ($p<0.001$)(481).

Methotrexate

Methotrexate, a folate antagonist, has been shown not to be effective in HS in a single series of 3 patients treated with doses of 12.5-15mg weekly for 6-24 weeks (482). However, a review in 2020 of 15 patients suggests methotrexate may be

effective in a subset of patients with HS, in particular older patients with lower body mass index, but did not show benefit when taking concurrent biologic therapy (483). Low dose methotrexate however may be beneficial in treating anti-drug antibodies in infliximab therapy (484).

Azathioprine

Azathioprine, a disease modifying anti-rheumatic drug, is deemed to be poorly effective in treating HS (313). One series in 9 patients with HS receiving low doses of azathioprine 0.5-1mg/kg for 1-8 months showed slight improvement in 4 of the cases (485).

Ciclosporin

Ciclosporin has been reported as having poor efficacy in HS in patients receiving doses up to 5mg/kg day (486). Doses of 6mg/kg have shown some improvement in HS but relapse on discontinuing the ciclosporin and side effects make it an unpopular option in HS (487–489).

Sirolimus

Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, has been reported to be effective in one case series of 9 patients as combination rescue therapy with a TNF-α inhibitor in severe, refractory HS (490).

1.7.5 Surgery for HS

Evidence for surgical management of HS is mainly based on case series and reports. Incision and drainage is often performed to give rapid relief of acute lesions but

recurrence usually occurs (491). Deroofing is associated with less recurrence and can be performed on localised HS (492). Seton suturing of tunnels and fistulae is well tolerated and has shown some benefit for perianal disease in HS, but there is little evidence of its efficacy in the literature, in particular for axillary disease (415,493). Wide excision is recommended in those with scarring, and tunnel formation with lower recurrence rates compared to marginal excision (491). With regard to reconstruction practices, recurrence rates in one study were 22% with primary intention healing, 11% with secondary intention healing, and 2% each with flaps and grafts in a systematic review of the literature (494). Combination therapy with biologic therapy is recommended to prevent higher recurrence rates (495).

1.7.6 Laser, Light and Radiation Therapy for HS

Neodymium-doped yttrium-aluminium-garnet (Nd:YAG) laser was trialled in studies and case reports showing efficacy in HS (496). CO_2 lasers have been used in the excision of affected skin with positive outcomes (497–503). Long-pulsed alexandrite, diode lasers and intense pulsed light has been reported to be effective in causing follicular destruction and improvement in HS in case reports (504–507). Both topical and intralesional photodynamic therapy has been trialled in several series in HS with variable results (508–510). External beam radiation has shown equivocal results in the literature and thus is not recommended routinely in HS but may be an option in severe recalcitrant HS not suitable for surgery (511).

1.7.8 Wound dressings

Evidence on wound care in HS is limited. Absorptive dressings are most often used in HS but these can be costly (512). A prospective study found some benefit to using gentamicin-collagen sponges over primary closure in 124 patients, however recurrence and complication rates were similar at 3 months (513). Manuka honey with silver alginate dressings, hydrofiber, and silastic foam dressings were also found to be well tolerated by patients in 2 studies (514,515). Negative-pressure wound therapy has been used with success in surgical wounds in HS to shorten healing time and as a bridge to skin grafting or use of a dermal regeneration template (Integra®)(516–518). Several studies are in progress to determine ideal wound care in HS (519).

1.8 The Microbiome in HS

1.8.1 The Human Microbiome

The microbiome is defined as 'the collective genetic information contained within the microbiota, including bacteria, viruses and fungi, residing in and on the human body' (520). The microbiome and its links to health and disease is an area of rapidly expanding research. The microbiome varies from person-to-person; however, the overall functional characteristics and higher-level taxonomy is largely preserved in health (521). Factors which impact the microbiome composition include vertical mother-to-infant transmission of the microbiome (via vaginal mode of delivery at birth and breastfeeding), host genetics, ageing, diet, ethnicity, medications, and lifestyle factors such as smoking (520,521).

The gut microbiota contributes to host defence via its influence on the maturation of the immune system, however, in some susceptible groups the gut microbiota can lead to inflammation (522). Variant microbe populations in the gut have been described in many disease states including inflammatory bowel disease, colorectal cancer, Type-2 diabetes, and rheumatoid arthritis (521). However, causal relationships for many of these associations have not been proven, and the question remains whether this is 'cause or effect?'(520). Nevertheless, describing the gut microbiome in disease states may provide therapeutic options to improve health. Examples of this includes the successful use of healthy donor faecal transplants in patients with *Clostridiodes difficile* infection as a consequence of antibiotic use, to restore intestinal microbial diversity and reduce inflammation (523).

The human skin is the body's largest organ and is a physical and immunological barrier against external agents (524). Human skin is colonised by countless microorganisms, most of which are harmless or sometimes beneficial (524,525). The innate and adaptive immune systems play key roles in determining skin microbiome composition and homeostasis; however, a bidirectional relationship exists with the microbiota also informing the immune system (524,526). Studies profiling the healthy skin microbiome have been undertaken (527). The skin is colonised by a diverse microbiota, which varies greatly across and within individuals, dependent on anatomical site, and host and environmental factors such as temperature, humidity, antibiotic use, soaps, cosmetics, and UV exposure (528). Abundant microbes are found in moist skin areas, with Staphylococcus and Corynebacterium found preferentially in these areas (524). Sebaceous areas are colonised with more *Cutibacterium acnes*, and dry sites have a diverse microbial composition (524). Some skin diseases are associated with an imbalance in the skin microbiome, for example the overabundance of *C. acnes* seen in acne vulgaris, and treatment of dysbiosis can be effective in treating the disease (528).

Early studies on skin and gut microbiota in disease used culture-based methods which underestimate the total microbial diversity, as easily cultured bacteria were favoured (529). As sequencing technology has advanced, our understanding of the microbiome is greatly improved, and the complete diversity of the microbiome can be captured using sequence variation in conserved taxonomic markers to identify microbes. In our study we will focus on bacteria, and thus 16S ribosomal RNA (rRNA) gene sequencing will be used.

1.8.2 The Skin Microbiome in HS

Several attempts to profile the skin microbiome in HS has been undertaken, with more recent studies suggesting its potential role in the pathogenesis of HS (530,531). It is hypothesized that HS may be initiated by an abnormal immune response to bacteria in the skin which are released after follicular rupture, promoting inflammation via toll-like receptors, NOD-like receptors and the inflammasome (526). The majority of studies on the skin microbiome in HS utilised aerobic and anaerobic culture techniques on swab, aspirate or biopsy samples (532–545). These studies often noted a high proportion of sterile samples and *Staphylococcus aureus*, coagulase-negative Staphylococcus, gram-positive cocci, and Enterobacteriaceae dominated (532–545). Next generation sequencing techniques were introduced in recent years targeting pooled amplicons of 16S and 18S ribosomal RNA demonstrating a previously undiscovered microbiome alteration in the affected and non-affected skin of patients with HS compared to controls which has expanded our knowledge of the microbiota role in the pathogenesis of HS (546). *Porphyromonas, Prevotella,* and *Corynebacterium* were found in abundance (546). Reduced levels of *Cutibacterium acnes* was noted, as well as reduced coagulase-negative staphylococci (159,547,548). *C. acnes* is a beneficial bacterium, which helps to maintain a low skin pH (via the release of free fatty acids), and as a commensal it blocks colonisation by pathogenic *Staphylococcus aureus* and Streptococci (525). However, elevated levels of *C. acnes* appear to be pathogenic in acne vulgaris (163). Extensive bacterial biofilm formation is also seen in the chronic lesions of the disease, in particular in the sinus tracts (530).

Of note, only three of these studies on the skin microbiome in HS had matched control groups (546–548). Furthermore, only six of these studies used skin biopsies

or deep swabs during CO_2 laser ablation or deroofing procedures to describe the microbiome in HS, with superficial sampling with swabs or aspirates of lesions the most common method of sample collection (530,533,536,540,545,546,549).

Acquiring an accurate and representative sample of the microbiome of the skin is challenging and approaches adopted include swabbing, tape stripping, skin biopsies and scraping. Swabbing is the easiest and least invasive approach, however, it may not represent the microbiome of the deeper skin layers. The addition of skin scraping with swabbing increases yield and this is the approach we will adopt in this study. Biopsies are most likely the best approach to profile the microbiome as they provide all layers of skin, however, they result in scarring and thus are generally taken during surgical treatment of HS in the literature (533,536). Tape stripping and pore stripping can be helpful in sampling the superficial and follicular microbiome. Grice et al. compared these sampling techniques and found similar microbial populations regardless of sampling method used, however Prast-Nielsen showed that biopsy specimens were superior to swabs (550,551).

Although bacteria appear to play a key role in the development of HS, HS is not a primary infectious disease, as evidenced by the low rates of cellulitis and lymph node enlargement, and the response of HS to immunosuppression (160,552). A matter for debate, however, is how antibiotic therapy works in HS, whether it is via it anti-inflammatory or anti-microbial effect.

This study of the skin microbiota in HS will add to the expanding literature in this area using next generation sequencing with a control to further elucidate the alterations seen and characterise their role in HS pathogenesis and propagating inflammation.

Alterations in the cutaneous microbiome in the studies of patients with HS are listed in Table 3.

Table 3: Skin microbiome in HS in culture and next generation sequencing studies

Methods used	Study	Samples taken	No of patients	Control group	Results
Culture studies	Highet et al. (1988):(532)	Swabs from perineum	32	No	*Streptococcus milleri, S. aureus* & anaerobic streptococci
	Jemec et al. (1996):(535)	Lesion aspirates from axilla, inframammary and genital area	41	No	*S. epidermidis, S. aureus* & anaerobes
	Brook et al. (1999):(553)	Lesion aspirates and swabs from axilla	17	No	*S. aureus, Prevotella melaninogenica, Peptostreptococcus, Streptococcus pyogenesis*
	Lapins et al. (1999):(533)	Biopsies and swabs post CO_2 laser ablation from axillae and perineum	25	No	*S. aureus, Prevotella, Peptostreptococcus, C. acnes, Lactobacillus, Bacteroides,* group c streptococci, *Enterobacteriacea*
	Sartorius et al. (2012):(536)	Biopsies post CO_2 laser ablation from axilla and groin	10	No	Coagulase-negative staphylococcus, anaerobes & *Corynebacterium*
	Matusiak et al. (2014): (537)	Swabs from axilla and perineum	69	No	*S. aureus, S. epidermidis, Proteus mirabilis, & Entercoccus faecalis*

	Katoulis et al. (2015): (540)	Lesion aspirates from axilla, breast, perianal, groin, buttocks, and scalp	22	No	Staphylococcus *& P. mirabilis*
	Hessam et al. (2016):(539)	Swabs from axilla, groin, gluteal cleft, and perineum	113	No	*S. aureus, P. mirabilis, E-coli,&* Coagulase-negative staphylococcus
	Thomas et al. (2016):(538)	Samples taken from neck, occiput, chest, face, axilla, breast, groin, perineum, gluteal cleft and perianal area, and genitals	76	No	*S. aureus, Prevotella, Corynebacterium, & S. epidermidis*
	Nikolakis et al. (2017):(544)	Swabs from axilla, breast, inguinal area, buttock and perianal area	50	No	*S. aureus,* coagulase-negative staphylococci, streptococci, Enterobacteriaceae
	Bettoli et al. (2018):(542)	Swabs from axilla, groin & perianal area	137	No	*S. epidermidis, S. haemolyticus, Proteus, E-coli, Streptococcus agalactiae*
	Jamalpour et al. (2018):(543)	Swabs from axilla, groin, scalp, neck, buttock, breast and perianal area	26	No	*S. aureus, E-coli &* diphtheroids

	Benzecry et al. (2018):(541)	Swabs from axilla, breast, groin, genitals, perineum, and buttocks	46	No	Staphylococcus, Steptococcus, Corynebacterium & Enterobacteriacea
	Barmatz et al. (2022):(554)	Samples from genitalia, gluteal/perianal area, and axilla	97	No	Enterobacterales and coagulase-negative staphylococci higher in those prescribed antibiotics in community
Culture & Next Generation Sequencing (NGS)	Guet-Revillet et al. (2014):(545)	Swabs, aspirates, and biopsies from axilla, breast, trunk and neck, gluteal cleft, buttocks, and inguinal crease	82	No	*Staphylococcus lugdenesis,* actinomycetes, milleri group streptococci, anaerobes
Next Generation sequencing (NGS)	Ring et al. (2017):(546)	Biopsies of affected and unaffected skin groin and axilla	30	Yes – 24 controls	Increased *Corynebacterium, Porphyromonas, & Peptoniphilus* compared to controls Decreased *Cutibacterium acnes*
	Guet-Revillet et al. (2017):(549)	Swabs, aspirates and biopsies from affected areas – axilla, inguinal fold, buttocks and breast, and swabs of unaffected areas	65	No	*Prevotella, Porphyromonas,* anaerobes, *Fusobacterium & Parvimonas*
	Ring et al. (2019):(530)	Swabs of HS tunnels during deroofing of axilla and groin	32	No	*Prevotella, Porphyromonas, & Corynebacterium*

	Naik et al. (2020):(548)	Swab from axilla, gluteal cleft, and inframammary fold	12	Yes – 5 controls	Increased Anaerobes Decreased *C. acnes*
	Riverain-Gillet et al. (2020):(547)	Swabs of unaffected axilla, inguinal crease and gluteal cleft	60	Yes -17 controls	Increased anaerobes, *Prevotella, Actinomyces, Campylobacter ureolyticus, & Mobilinucus* Decreased *S. epidermidis, S. hominis, C. acnes* & coagulase-negative staphylococci
	Lam et al. (2021): (555)	Swabs of axilla	6	7	

1.8.3 The Gut Microbiome in HS

There are limited studies on the gut microbiome in HS (236,556). As discussed previously, HS is associated with many other disease states, including spondyloarthritis, inflammatory bowel disease (IBD), and metabolic syndrome, and an altered gut microbiome has been associated with these conditions (56,219,224,247,557–562). In Crohn's disease shifts in gut microbiota composition, in a genetically susceptible individual, are associated with a dysregulated immune system resulting in inflammation (563,564). Manipulation of the gut microbiota in IBD is a focus of current research, with the aim of reducing inflammation (240). We hypothesize that similar shifts in the gut microbiome exist in patients with HS, and could result in the immune dysregulation seen, leading to skin inflammation (564). Thus, exploration of the gut microbiome in HS is of interest, particularly as it may inform future therapies.

Three other studies on the gut microbiota composition in HS have been carried out (236,556). Eppinga et al. characterised the gut microbiome using taxon-specific quantitative polymerase chain reaction (PCR) in 17 patients with HS, 17 patients with HS and IBD, 29 patients with psoriasis, 31 patients with IBD, 13 patients with IBD and psoriasis, and 33 controls (235). In psoriasis, IBD, psoriasis and IBD, and HS and IBD groups lower abundance of the anti-inflammatory bacterium *Faecalibacterium prausnitzii* was found, with an increased relative abundance of pathogenic strains of *Escherichia coli* (556). This altered microbiome was not noted in the patients with HS alone (556). Kam et al. profiled the gut microbiome in 3 patients with HS and compared to 3 healthy controls (236). Increased levels of *Bilophila* and *Holdemania* were found, with lower relative abundance of Firmicutes, Lachnobacterium, and Veillonella in patients with HS when compared to controls

(236). Lam et al. profiled the gut microbiome in 17 patients with HS and 20 healthy controls, and the axillary skin microbiome from 6 patients with HS and 7 healthy controls via 16S ribosomal RNA amplicon sequencing (555). No difference in bacterial richness (p=0.483), Shannon (p=0.082) and inverse Simpson (p=0.916) indices nor in bacterial community structure was seen (555). No differences in α- and β- diversity were found in this study.(555) *Robinsoniella* was found in the majority of HS patients (59%) and in none of the healthy controls, and could be a potential pathogen (555,565). *Sellimonas* was also more common in patients with HS than in controls and overabundance of *Sellimonas* has also been found in the gut microbiome of patients with rheumatoid arthritis and ankylosing spondylitis (555,566,567). *Christensenellaceae* was depleted in faeces of patients with HS, a phenomenon which has also been described in psoriasis (555,568). No differences were found in this study in α- and β- diversity of skin samples, however Mesorhizobium (a soil and environment microbe) was present in all affected skin samples (555). A recent study in 2022 has described a shift in gut microbiota composition, function, and metabolic profile after adalimumab therapy and has been discussed previously (364). Baseline gut microbial samples showed reduced alpha-diversity with a shift towards control samples after 12 weeks of adalimumab therapy with no differences noted between the two groups (364). At baseline HS patient had reduced Firmicutes and Euryarchaeota, and increased Actinobacteria and Bacteroidetes, with higher abundance of *Ruminococcus bromii* and *Coprococcus eutactus* in healthy controls (364). After Adalimumab therapy *Bifidobacterium, Bacteroides, Agathobacter, Prevotella_9, Faecalibacterium,* and *Blautia* were noted in the gut microbiota of patients with HS (364).

To date the nasal and oral microbiome have not been described in HS.

1.8.4 Peripheral Blood Bacteria in HS

A study by Ring et al. did not demonstrate a peripheral bacteraemia in 27 patients with moderate to severe HS compared to 26 healthy controls via Next Generation 16s rRNA gene Sequencing (NGS)(569).

1.9 Outline of Thesis

As discussed above, HS is a chronic, debilitating disease which can prove challenging to treat, and which has a significant impact on quality of life. In **Chapter 2** I sought to examine the limited placebo controlled trials to date in HS and the heterogeneity of outcome measures used, and to assess the placebo response rate in these trials in an attempt to determine true drug efficacy. Knowledge of placebo response will be vital in clinical trial design of microbiota based interventions in HS in future, which is of particular interest to me. In **Chapter 3** I studied pain in a cohort of patients with HS, adherence to prescribed treatment, exercise patterns, and examined the impact of HS on quality of life. I also assessed correlations between levels of pain and physical activity, and impact on quality of life with measures of gut microbiota diversity. In **Chapter 4** I described the skin microbial composition in a cohort of patients with HS compared to healthy controls, to determine if a dysbiosis or an altered skin microbiome was noted which may contribute to disease pathogenesis. In **Chapter 5** I described the gut microbial composition in a cohort of patients with HS compared to healthy controls, to determine if a dysbiosis was noted which may contribyte to disease pathogenesis and may provide a therapeutic target. In **Chapter 6** I described the inflammatory markers, faecal calprotectin and serum C5a levels, in a cohort of patients with HS and correlated these to microbiota diversity. Finally in **Chapter 7** I described the diet of a cohort of patients with HS and its relationship to the gut and skin microbiome, inflammatory markers and clinical characteristics. I compared the habitual diet of those with HS to healthy controls and patients with Crohn's disease.

2. Placebo Response Rates in Hidradenitis Suppurativa

Abstract publication in the British Journal of Dermatology, 2016

A review of the placebo-controlled trials in hidradenitis suppurativa. S. McCarthy, D. Sheehan, M. Murphy, F. Shanahan (2016), Bristol Cup Posters. Br J Dermatol, 175: 25-78.

Presentation at British Association of Dermatologists Annual Meeting, 2016 and Irish Association of Dermatologists Spring Meeting, 2016

Abstract

Background

Knowledge of placebo effect is important in evaluating therapies and in planning future clinical trials. Patients with hidradenitis suppurativa (HS) experience clinical improvement without medical intervention, as in many other chronic inflammatory diseases. Due to the relapsing remitting nature of HS placebo response is likely to be high. Knowledge of placebo response will be vital in planning future microbiota based interventional trials in future.

Aim

The aim of this study was to review the literature to describe the placebo response rates in the controlled trials of hidradenitis suppurativa.

Methods

A search for placebo-controlled, randomised controlled trials (RCT) of interventions for hidradenitis suppurativa was undertaken and placebo response rates documented.

Results

The placebo rates across the studies varied greatly (range 0 to 30%). There was a significant trend for higher response rates to be associated with higher placebo rates (P-value < 0.05). Placebo rates were dependent on the scoring system used to assess severity of disease.

Conclusion

The placebo response rate in clinical trials of hidradenitis suppurativa was variable. The use of standardised validated outcome measures to assess response is essential in the future trials of hidradenitis suppurativa to compare efficacy of systemic treatments as well as placebo response.

2.1 Introduction

Knowledge of placebo response rates is important in evaluating therapies and for the design of further therapeutic trials. Studies of placebo effects in medical trials of inflammatory conditions indicate significant clinical improvement occurs in approximately 30% of patients in inactive treatment groups, and modulate active treatment outcomes (570–572). The determinants of the placebo-response are varied but include the natural history of the disease, the behaviour of clinicians, cognitive emotional biases, and the study design (570). Placebo response can be a result of the patient's expectations and beliefs about a beneficial outcome, and optimised doctor-patient relationships in the setting of a trial. Furthermore, since the natural history of chronic inflammatory diseases is characterised by recurring periods of relapse and remission, this can have a profound influence on the results of therapeutic trials. Knowledge of the impact of placebo response and its determinants can improve clinical trial design, and of particular interest to us in the design of microbiota based interventions in future. When assessed in terms of remission and response, the placebo rates for inflammatory bowel disease have been estimated at 18-19% for Crohn's disease, and 13-28% for ulcerative colitis (573,574). Similarly, mean improvements of 14-28% were reported in the placebo limbs in treatment trials for atopic dermatitis, with lower placebo response rates of ~4% in psoriasis (575,576).

Hidradenitis suppurativa is a debilitating chronic inflammatory disease characterised by recurrent abscesses in flexural sites including the axilla, groin, and inframammary area. Progress in hidradenitis suppurativa research and treatment has been limited, in part, by disease heterogeneity but also by insufficient knowledge of placebo rates and its implication on sample size and study design. Furthermore, a standardised

definition of clinical response in hidradenitis suppurativa is lacking and has resulted in significant heterogeneity between the primary and secondary outcome assessments used in HS studies (15).

Here, we review the placebo response rates in the published controlled trials in hidradenitis suppurativa.

2.2 Methods

Literature search

A search of PUBMED/MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) was performed. Placebo-controlled, randomised controlled trials (RCT) of interventions for hidradenitis suppurativa were included. The literature search used the following combination of terms ‘hidradenitis suppurativa’, ‘acne inversa’, ‘placebo’, ‘placebo-controlled’, ‘double-blind’, ‘randomised-controlled trial’ and ‘clinical trial’.

Selection criteria

Studies were included for analysis if all the following criteria were fulfilled: 1. the study was a placebo-controlled trial, 2. all patients in the study had active disease at entry, 3. the active treatment was a systemic therapy, 4. the study reported the methodology of defining clinical response and 5. data on response or remission in patients receiving placebo was available. Ten RCT were identified (18,21,143,144,192,316,366,380,577). Eight were eligible for inclusion to the review (18,21,143,144,192,380,577). One trial was excluded because a topical therapy was used (316) and another was excluded because the placebo response was not

documented (366) and unavailable from the authors on request. We assessed the intervention response rate and the placebo-response rate in each study.

Data abstraction

Data abstraction was performed by two independent reviewers (SM and MM). Data abstracted included study design, outcome measures employed, sample size of active and placebo groups, duration of follow up and response rates.

Statistical analysis

Statistical analysis was carried out using R software (2019 r-project.org).

2.3 Results

Eight studies were included in this review (18,21,143,144,192,380,460). These studies used varying outcome measures to determine response. Characteristics of studies, outcome measures used, and placebo response rates are shown in Table 1. The components of the outcome measures used are summarised in Table 2.

Table 1: Characteristics of studies containing placebo response data

Authors	**Year**	**Active Treatment size (N)**	**Placebo size (N)**	**Active Therapy**	**Follow up to placebo response**	**Outcome measures used and definition of response**		**Active Treatment Response rate**	**Placebo response rate**	***p-value***
Grant et al.:(21)	2010	15	18	Infliximab (5mg/kg week 0,2,6)	8 weeks	1°:	50% decrease in HSSI	**~27%**	**5.6%**	**0.092**
						2°:	25-50% decrease in HSSI	60%	5.6%	<0.001
							Mean PGA	~1.7	~4.6	<0.001
							Mean change in DLQI	-10	~-<2	0.03
							Mean change in VAS for pain	-39.8	-0.6	<0.001
							Mean change in ESR	~ -12	~ +6.0	0.012
							Mean change in CRP	-1.0	~ + 0.4	0.062

Miller et al.:(144)	2011	15	6	Adalimumab 80mg at baseline then 40mg alternate weeks	12 weeks	1°:	Mean change in Sartorius Mean change in Hurley score	**-11.27** **-0.13**	**+ 5.83** **0**	0.074 0.4
						2°:	Mean change in % of days with lesions	-38.89	-32.14	0.4
							Mean change in VAS for pain	-13.4	+3.17	0.4
							Mean change in DLQI	-3.67	+1.00	0.06
Kimball et al.:(18)	2012	103	51	Adalimumab 40mg weekly or 40mg EOW	16 weeks	1°:	HS-PGA with at least a 2-grade improvement relative to baseline	EOW **9.6%** Weekly **17.6%**	**3.9%**	EOW 0.25 Weekly 0.025
						2°:	HS-PGA OF Clear/Minimal/Mild %	EOW 21.2% Weekly 49.0%	23.5%	0.004 (vs. weekly)
							Mean % improvement from baseline: Inflammatory nodules	EOW 30.4% ± 11.8 Weekly 43.3% ± 11.9	13.2% ± 12.9	0.089 (vs. weekly)

							Mean % improvement from baseline: Abscesses	EOW 54.3% ± 13.8 Weekly 58.2% ± 16.6	26.9% ± 14.3	0.0152 (vs. weekly)
							Mean % improvement from baseline: Draining fistulae	EOW 13.5% ± 25.3 Weekly 31.1% ± 26.3	-25.1% ± 30.4	0.166 (vs. weekly)
						Mean change from baseline ± SE	Modified Sartorius Score	EOW -32.0 ± 9.5 Weekly -40.2 ± 9.8	17.2 ± 9.8	0.097 (vs. weekly)
							DLQI	EOW -3.2 ± 0.8 Weekly -6.3 ± 0.9	-2.3 ± 0.9	0.001 (vs. weekly)
							TWPI	EOW -4.3 ± 3.2 Weekly -18.4% ± 4.1		<0.001 (vs. weekly)
							PHQ-9	EOW -1.3 ± 0.8 Weekly -3.7 ± 0.8	-0.9 ± 0.8	0.015 (vs. weekly)

Kimball et al. – 2 studies: (143)	2016	PIONEER I- 153	PIONEER I - 154	Adalimumab 160mg SC week 0, 80mg week 2, then 40mg weekly from week 4	12 weeks	1°:	Achieving positive HiSCR	**41.8%**	**26.0%**	0.003
						2°:	Total abscess and inflammatory nodule count of 0,1,2 %	28.9%	28.6%	0.96
							≥ 30% reduction and ≥1 unit reduction in skin pain	27.9%	24.8%	0.63
							Change in mean Modified Sartorius Score from baseline	-24.4	-15.7	0.12
		PIONEER II-163	PIONEER II - 163	Adalimumab 160mg SC week 0, 80mg week 2, 40mg weekly from week 4	12 weeks	1°:	Achieving positive HiSCR	**58.9%**	**27.6%**	<0.001
						2°:	Total abscess and inflammatory nodule count of 0,1,2 %	51.8%	32.2%	0.01
							≥ 30% reduction and ≥ 1 unit reduction in skin pain	45.7%	20.7%	<0.001
							Change in mean Modified Sartorius Score from baseline	-28.9	-9.5	<0.001
Tzanetakou et al.:(192)	2016	9	10	Anakinra (IL-1RA)	12 weeks	1°:	HiSCR	**78%**	**30%**	0.04
							Disease activity	**67%**	**20%**	0.04

				100mg SC daily			Sartorius score	**~0%**	**~0%**	
						2°:	Time to new exacerbation			0.01
Kanni et al.:(380)	2018	10	10	MABp-1 (anti- IL-1a) 7.5mg/kg IV every 14 days	12 weeks	1°:	Achieving positive HiSCR	**60%**	**10%**	0.035
						2°:	VAS for pain	70%	30%	
							Time to new exacerbation	11 weeks	7 weeks	0.159
							Decrease in at least 2 of: PGA, Disease activity, Modified Sartorius Score, VAS for pain, & DLQI)	80%	40%	0.054
							20% decrease of total lesion depth	22.2%	77.8%	0.027
Vossen et al.:(577)	2018	15	5	Apremilast PO 30mg twice daily	16 weeks	1°:	Achieving positive HiSCR	**53.3%**	**0%**	0.055
						2°:	Mean change AN count	-2.0 (-3.9 to -0.5)	2 (-0.8 to 4.8)	0.011
							Mean change DLQI	-2.3 (-5.9 to 1.3)	4.2 (-1.7 to 10.1)	0.230
							Mean change NRS for pain	-0.8 (-2.2 to 0.6)	2.2 (-0.1 to 4.5)	0.009
							Mean change NRS for itch	-1.1 (-2.5 to 0.3)	3.4 (0.1 to 4.7)	0.015

							Mean change NRS for disease burden	-1.0 (-2.3 to 0.3)	0.9 (-1.2 to 3)	0.049

AN: Abscess/Nodule; CRP: C-reactive Protein; DLQI: Dermatology Life Quality Index; EOW: every other week; ESR: Erythrocyte Sedimentation Rate; HiSCR: Hidradenitis Suppurativa Clinical Response; HSSI: Hidradenitis Suppurativa Severity Index; HS-PGA: Hidradenitis Suppurativa Physician's Global Assessment; IV: Intravenous; NRS: Numeric rating scale; PHQ-9: Patient Health Questionnaire-9; SC: Subcutaneous; TWPI: Total Work Productivity Index; VAS: Visual Analog Scale for pain

Table 2: Primary outcome measures in placebo-controlled trials in hidradenitis suppurativa

Outcome measure	**Studies**	**Assessment to determine efficacy**
Hidradenitis Suppurativa Severity Index (HSSI)	Grant et al.(21)	Composite score ranging from 0-19 - Assessing number of sites involved, percentage body surface involved, number of erythematous and painful lesions, number of dressing changes during working or leisure hours and pain on visual analog scale
Hurley Stage	Miller et al.(144)	Stage I = single or multiple abscesses Stage II = recurrent abscesses, sinus tract formation and scarring. Single or multiple lesions, widely separated Stage III = Diffuse involvement of entire area, multiple interconnected tracts and abscesses
Sartorius Score	Miller et al.(144)	Assessing anatomical regions involved, distance between lesions, and scoring individual lesions.
HS-Physicians Global Assessment (HS-PGA)	Kimball et al. (2012)(18)	Clear Minimal = presence of non-inflammatory nodules Mild = <5 inflammatory nodules or 1 abscess/fistula Moderate = >/= 5 inflammatory nodules 1 abscess or draining fistula and >/= 1 inflammatory nodule 2-5 abscesses or draining fistulas and <10 inflammatory nodules Severe = 2-5 abscesses or draining fistulas and >/= 10 inflammatory nodules Very severe = >5 abscesses or draining fistulas
HS Clinical Response (HiSCR)	Tzanetakou et al.(192) Kimball et al. (2016)(143) Kanni et al.(380) Vossen et al.(460)	Achieving at least a 50% reduction from baseline in abscess and inflammatory nodule count with no increase in abscess/fistula counts

Outcome measures used

Five different primary outcome measures were used in the studies. The Hidradenitis Suppurativa Severity Index (HSSI)(21), and Hurley score(16,144) were used in one study each. Sartorius scoring(17,144,192) and Physician's global assessment in hidradenitis suppurativa (HS-PGA) were used in two studies each(18,21). The hidradenitis suppurativa Clinical Response score (HiSCR)(20) was the most commonly used, in the five more recent studies on hidradenitis suppurativa(143,192,380,577).

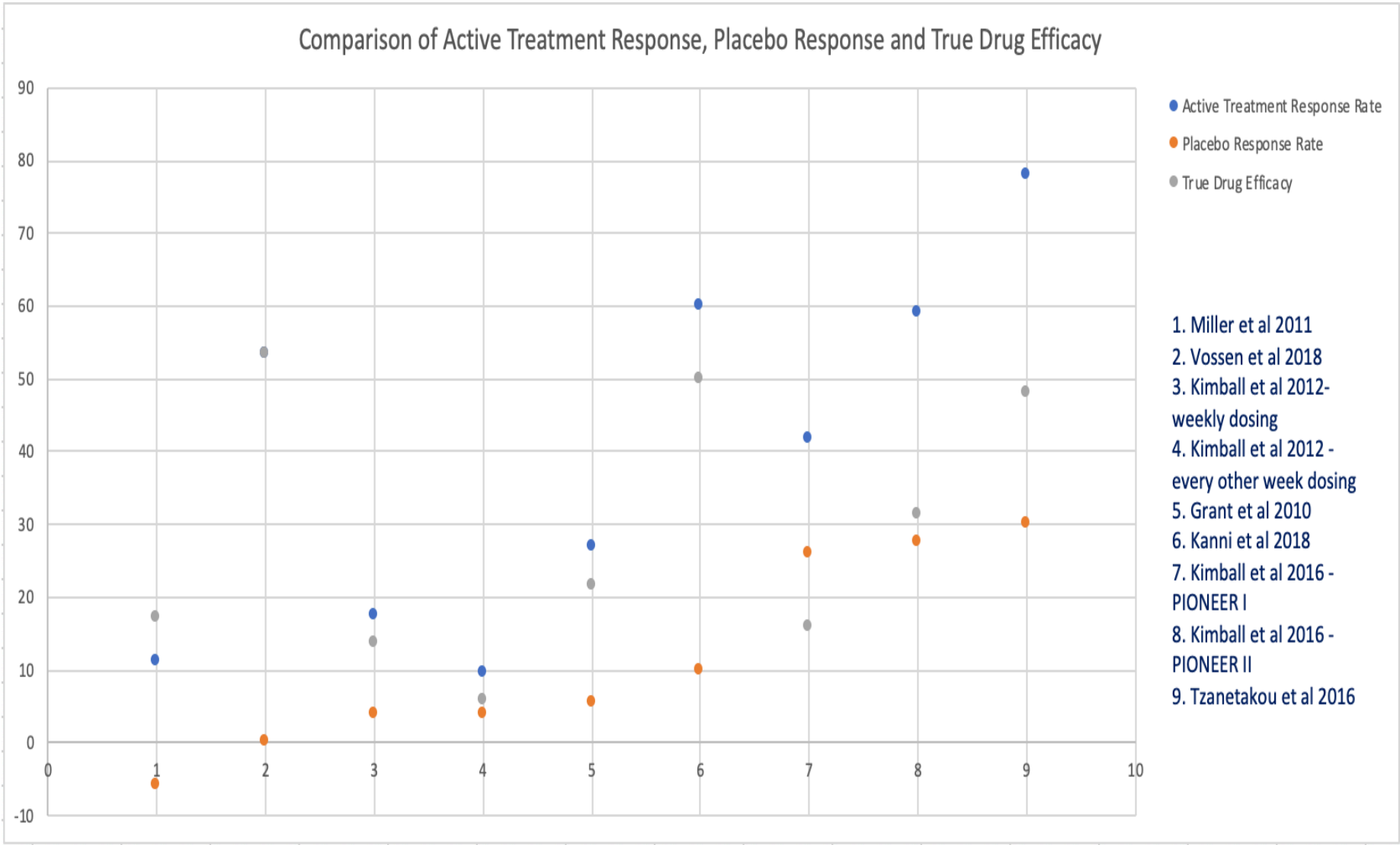
Interventions studied

Most of the interventions were biologics (6/7) with one systemic agent (1/7). Five studies compared the use of TNF-alpha inhibitors to placebo (18,21,143,144). Two agents targeted IL-1, one study comparing anakinra (anti IL-1)(192) to placebo and the other MABp1 (anti IL-1a)(380) to placebo. One study assessed response to the phosphodiesterase-4 inhibitor apremilast (577).

Placebo response rate

With significant heterogeneity among studies, the placebo rates across the studies varied from 0% to 30%. There was a significant trend for higher response rates to be associated with higher placebo rates (P-value < 0.05) when both sets of values from the Kimball et al. 2012 and the Kimball et al. 2016 studies were included (Figure 3).

Figure 3: Comparison of the active treatment response rate, placebo response rate and the true drug efficacy

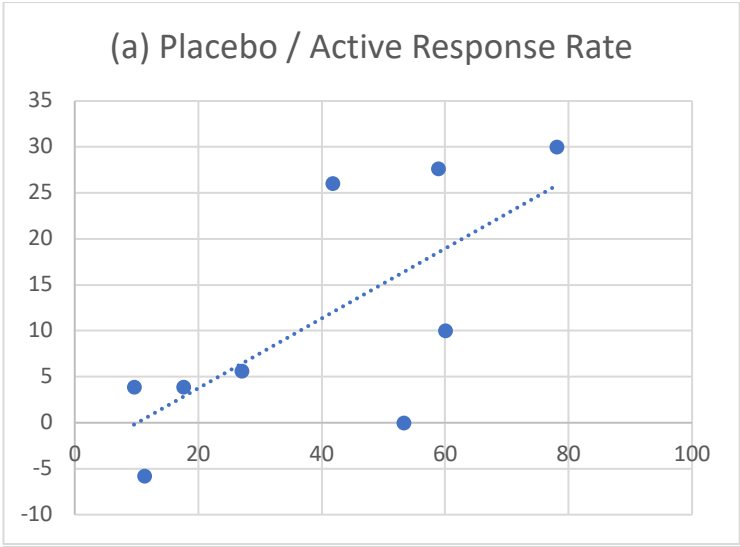


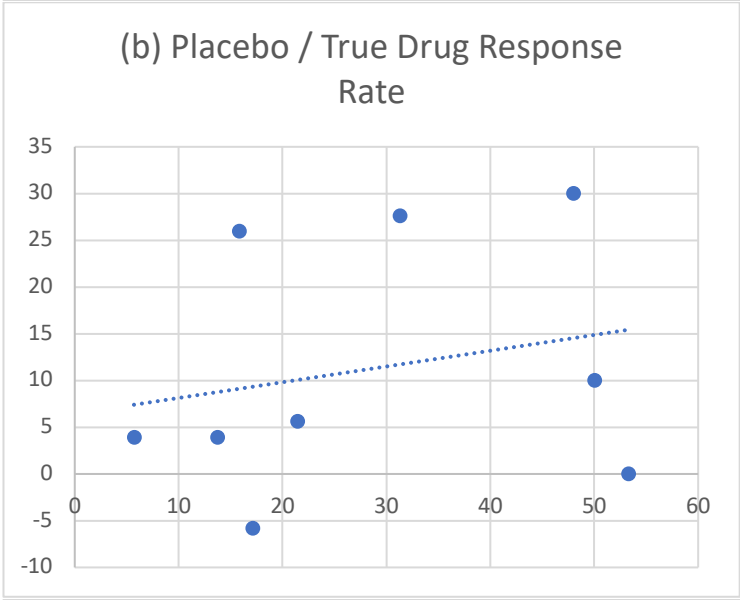
The average estimate for the 5 lowest placebo response rate studies was 1.5 (+ 4.6) with an active response rate of 23.7 (+17.9). This compares to a placebo response rate of 23.4 (+9.1) with an active response rate of 59.7 (+14.8).

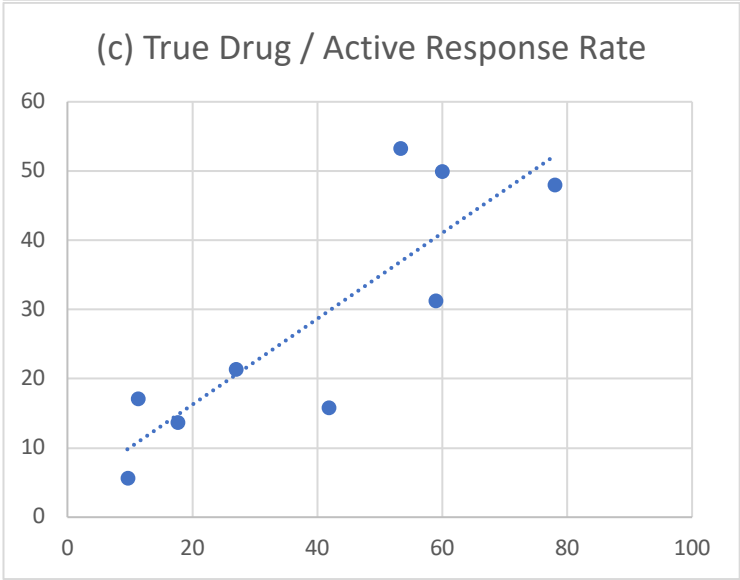
The true drug efficacy, as defined by the difference between the active and the placebo response, was calculated and investigated. There was no significant association between the placebo response rate and the true drug efficacy showing that that a smaller placebo rate is not associated with a greater true drug efficacy (Figure 4b).

However, there was a strong association between a greater true drug efficacy and the active response rate (P-value < 0.01), showing that an increase in the active response rate was important to increase the marginal response in these studies (Figure 4c). This was not statistically associated with study size, but it should be noted that the three studies with the highest true drug response rate are also three of the smaller studies.

Figure 4: (a) Association between placebo and active treatment response rate, (b) placebo response and true drug efficacy, and (c) the true drug efficacy and active drug response rate


(a) Placebo / Active Response Rate
35
30
25
20
15
10
5
0
-5
-10
0
20
40
60
80
100


(b) Placebo / True Drug Response Rate
35
30
25
20
15
10
5
0
-5
-10
0
10
20
30
40
50
60


(c) True Drug / Active Response Rate
60
50
40
30
20
10
0
0
20
40
60
80
100

2.4 Discussion

Double-blind placebo-controlled randomised controlled trials are the gold standard when assessing efficacy of new therapies. The inclusion of a placebo arm is particularly important in inflammatory conditions such as hidradenitis suppurativa, which are characterised by intermittent periods of acute exacerbation alternating with remission. Knowledge of placebo response is important to inform both pharmacological and non-pharmacological treatment of disease (578). In several of these studies of HS, marked clinical improvement was noted in the placebo arm. Factors that influence the placebo response rate in inflammatory disease include the study duration, the number of study visits, disease severity at entry, and the definition of response (570,571). A longer study duration can stabilise or lower the placebo response over time. Higher disease severity at study entry can lead to a higher placebo response rate due to the natural fluctuation of the disease course. Cognitive and behavioural factors also influence the placebo response, with patient expectations of a response leading to higher placebo response rates, and clinical improvement often seen in those assessed regularly in the setting of a clinical trial. Outcome measures used to determine disease response should also be chosen carefully. Pain and depression scores used as outcome measures can be more susceptible to placebo effect than other methods, and assessment of pain, in particular, forms an integral part of evaluating disease response in HS (579). Setting the primary outcome measure to assess clinical response and the follow up period is of paramount importance in these studies. The lack of a standardised definition of clinical response in hidradenitis suppurativa has resulted in significant heterogeneity between the primary and secondary outcome assessments used (18,21,143,144,192,380,460). Rates of placebo response in the randomised

controlled trials of hidradenitis suppurativa included in this review ranged from 0 to 30% (18,21,143,144,192,380,460). There was a significant trend for higher response rates to be associated with higher placebo rates (P-value < 0.05). There was no significant association between the placebo response rate and the true drug efficacy showing that that a smaller placebo rate is not associated with a greater true drug efficacy. Variable results were also seen in reviews of placebo response in the clinical trials of ulcerative colitis (0-67%) and Crohn's disease (0-46%), as well as atopic dermatitis (14-28%)(573–575). Both active treatment, and placebo response is strongly influenced by the measure of outcomes. Heterogeneity of the outcome measures used leads to difficulty interpreting results and comparing studies. The development of the Psoriasis Area Severity Index (PASI) standardised the assessment of primary outcomes in psoriasis, with clear meta-analysis available to compare efficacy of systemic treatments as well as the placebo response (580); however, the study design and follow up period can still result in variability. There is a need for more stringent definitions of objective outcomes and follow up in the clinical trial design of future studies in hidradenitis suppurativa. Work by the HISTORIC (HIdradenitis SuppuraTiva cORe outcomes set International Collaboration) group of IDEOM (International Dermatology Outcome Measures group) aims to create robust objective and consistent outcome measures in HS RCTs going forward (581). These will include pain, quality of life measures, physical signs, global assessments, and progression of disease over time. Eligibility criteria for inclusion into studies is also an important factor in assessing active treatment and placebo response rates. The tendency to increase severity scores to ensure inclusion into clinical trials is well described, leading to 'eligibility creep' and resulting perceived improvement in both the active treatment and placebo arms on initial

assessment of response (582). Thus stringent application of inclusion criteria will also form an important part of study design. Knowledge of these issues in the clinical trials of HS to date, which is highlighted by the variation in placebo response, will strengthen study design in future clinical trials via the introduction of agreed standardised outcome measures, follow-up periods, and inclusion criteria. This is of particular interest to us in informing the clinical trial design of future microbiota based interventions in HS.

2.5 Limitations

Statistical pooling was limited in this review due to heterogeneity among studies and small sample sizes. Publication bias may occur such that studies showing significant response to treatment may be more likely to be published than those showing no difference.

2.6 Conclusion

In conclusion, the placebo response rate in clinical trials of hidradenitis suppurativa varied across different studies and was dependent on the method of scoring disease activity as well as the active response rate.

3. Pain, Quality of Life, Adherence to treatment, and Exercise in Hidradenitis Suppurativa

3.1 Pain and Hidradenitis Suppurativa

Data published as part of SHIP study, Journal of European Academy of Dermatology and Venereology, 2017

Delany E, Gormley G, Hughes R, **McCarthy S**, Kirthi S, Markham T, Tobin AM, Murphy M, Kirby B. A cross-sectional epidemiological study of hidradenitis suppurativa in an Irish population (SHIP). Journal of the European Academy of Dermatology and Venereology. 2018 Mar;32(3):467-73.

Presentation at European Academy of Dermatology and Venereology, September 2017 and Irish Association of Dermatologists Autumn Meeting, October 2017

Abstract

Hidradenitis suppurativa (HS) is a chronic inflammatory disease that affects apocrine-gland bearing skin and has a substantial impact on quality of life. To date, few studies have described the pain experienced by patients with HS and the management of pain associated with HS.

Patients aged ≥18 years with a diagnosis of HS confirmed by a consultant dermatologist were recruited. The level of pain experienced by patients was measured using the visual analogue scale (VAS; where 0=no pain and 10=worst pain possible) and EQ-5D-5L questionnaires. Additional information was collected on the use of analgesics in this population.

Pain was widely reported in 134 responders to the visual analog scale questionnaire. 110 (82.1%) reported some level of pain (score ≥1) and 48 (35.8%) reported a score ≥5. In the EQ-5D-5L questionnaire, 118/145 (81.4%) responders indicated that they felt pain or discomfort, and 45/145 (31.0%) expressed “severe” or “extreme” pain/discomfort. The relationship between Hurley stage and EQ-5D-5L response on pain/discomfort was statistically significant ($p<0.001$). 61/150 (40.7%) patients reported taking analgesics. A total of 99 pain medications were reported, of which 61 (61.6%) were over-the-counter medications

Many patients with HS experience considerable pain, which has a substantial impact on their quality of life. In general, patients with more severe disease reported greater pain and discomfort. It is therefore crucial that physicians and researchers be aware of the pain experienced by patients with HS, and that pain be included as a key outcome in future clinical trials.

3.1.1 Introduction

HS may lead to painful eruptions and malodorous discharge with a significant negative impact on quality of life. Few studies to date have investigated the pain experienced by patients with HS, and how this pain is managed (583). The SHIP study was a cross-sectional, epidemiological study of HS in an Irish population (34). The primary objective was to estimate the prevalence of HS at selected dermatology clinics in a hospital setting in Ireland. Secondary objectives included assessment of disease characteristics and various aspects of disease burden, including pain.

3.1.2 Methods

Data were collected from four dermatology clinics over a six-month period in 2015. A total of 15,547 patients attended these sites during the recruitment period, of whom 221 (1.4%) had a diagnosis of HS, and 150 (1.0%) formed the full analysis set (FAS). The severity of pain experienced by patients in the FAS was measured using the Visual analogue scale (VAS; where 0 = no pain and 10 = worst pain possible) and Euro Quality of Life Health Outcome Measure (EQ-5D-5L). Information was also collected on the use of analgesics in this population. Statistics were performed using Excel (version 16.65) and R (version 4.3.1).

3.1.3 Results

150 patients were recruited over a six-month period in the four centres in 2015. The average age of the patients was 37 years and the majority were female (105, 70%). The point prevalence of HS in this particular Irish population was estimated to be 1.4%. The mean Body Mass Index (BMI) was 32 (females 33, males 30). In this

population, 56% were smokers, while 22% were former smokers. The average smoking pack years was 17.0. The average alcohol consumption was 4.4 units per week (SD 6.41). Of note the majority of the patients were employed, however this population took a mean of 15.9 sick days in the preceding 12 months.

Table 1: Patient Socio-Demographics

Parameter	Mean	SD	N
Age at consent (years)	36.5	11.28	150
Female	35.3		105
Male	39.2		45
Height (cm)	167.82	10.362	150
Weight (kg)	91.18	24.536	148
BMI (kg/m^2)	32.25	8.558	150
Female	33.07	9.168	105
Male	30.32	6.625	45
Gender			N (%)
Female			105 (70%)
Male			45 (30%)
Race			**N (%)**
White			143 (95.3%)
Black			1 (0.7%)
Asian			1 (0.7%)
Other			5 (3.5%)
Smoking and Alcohol			N (%)
Never smoked			33 (22.0%)
Smoker			84 (56.0%)
Former smoker			33 (22.0%)
Smoking pack years (for smokers and former smokers)	17	12.72	65

Alcohol consumption (units/week)	4.4	6.41	150
Work status			
Student			16 (10.7%)
Employed			76 (50.7%)
Unemployed			32 (21.3%)
Temporary Illness Disability			4 (2.7%)
Permanent Illness			10 (6.7%)
Other			12 (8.0%)
Sick Days in past 12 months	15.9	55.09	113

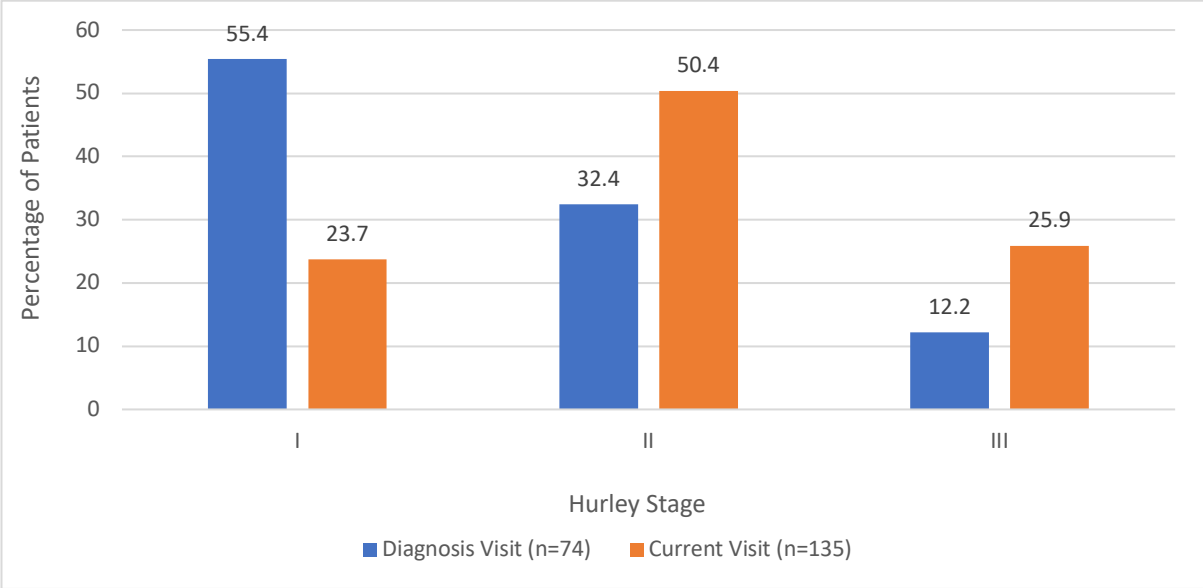
The mean age at diagnosis was 31.3 years and the mean duration of symptoms prior to diagnosis of HS was 8.49 years (SD 7.910). The average disease duration since diagnosis was 5.29 years (SD 7.246).

Table 2: Clinical profile of the study population

Parameter	Mean	SD	N	Missing
Age at time of diagnosis (years)	**31.3**	**10.13**	**146**	**4**
Female	29.6		104	1
Male	35.6		42	3
Duration of symptoms before diagnosis (years)	**8.49**	**7.910**	**146**	**4**
Female	8.67		102	3
Male	8.07		44	1
Duration of disease from diagnosis to study visit (years)	**5.29**	**7.246**	**145**	**5**
Female	5.66		103	2
Male	4.38		42	3

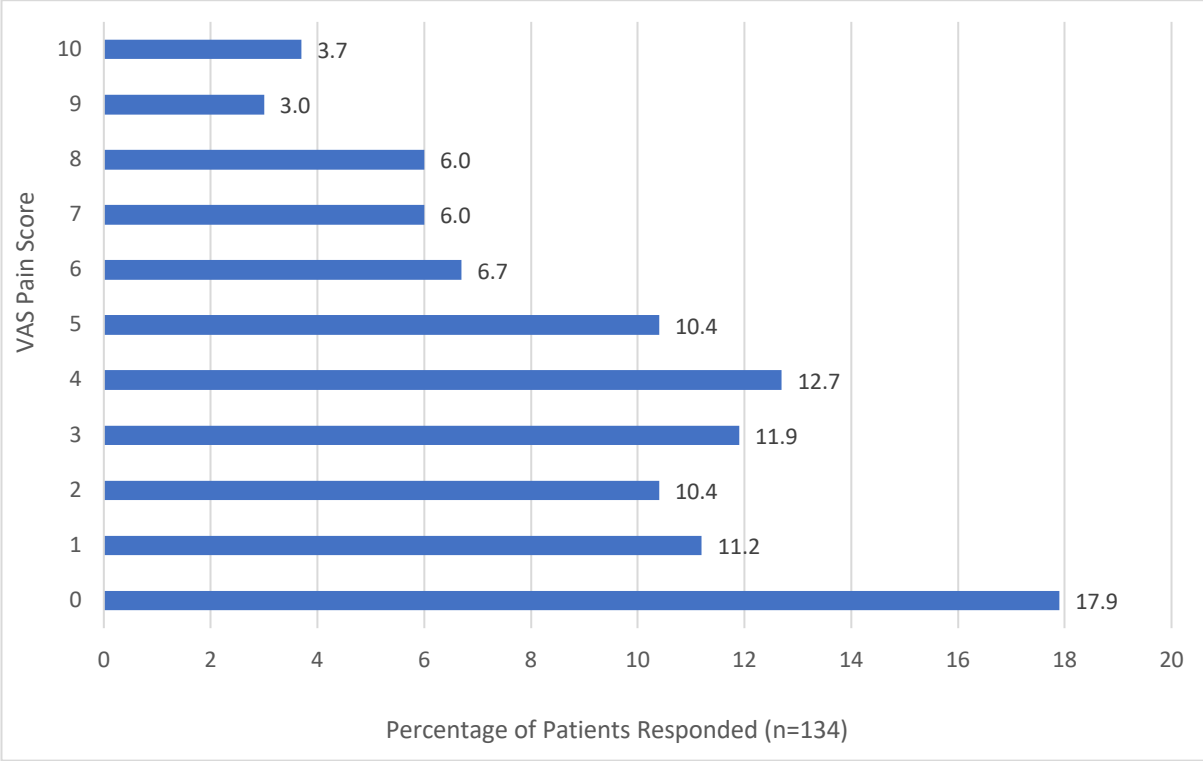
The majority of patients for whom data were available had Hurley stage I disease at the diagnosis visit (n=41; 55.4%). The majority had Hurley stage II disease at the study visit (n=68; 50.4%) (Figure 1).

Figure 1: Hurley Stage at diagnosis and at study visit



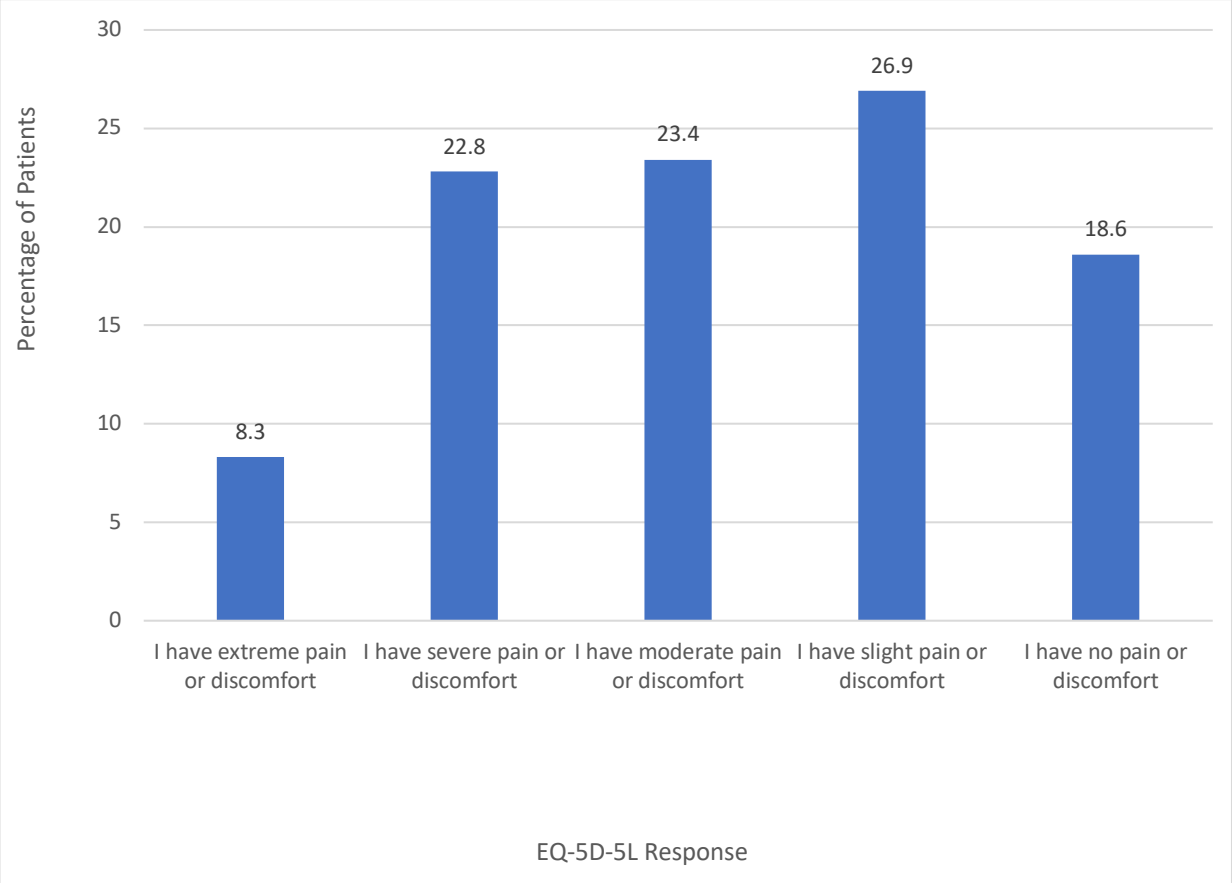
Pain was widely reported. Of 134 responders to the Visual Analog Scale, 82.1% (110) reported some degree of pain (score ≥1) and 35.8% (48) reported a score ≥5 (Figure 2).

Figure 2: Pain Intensity Scores at the Study Visit



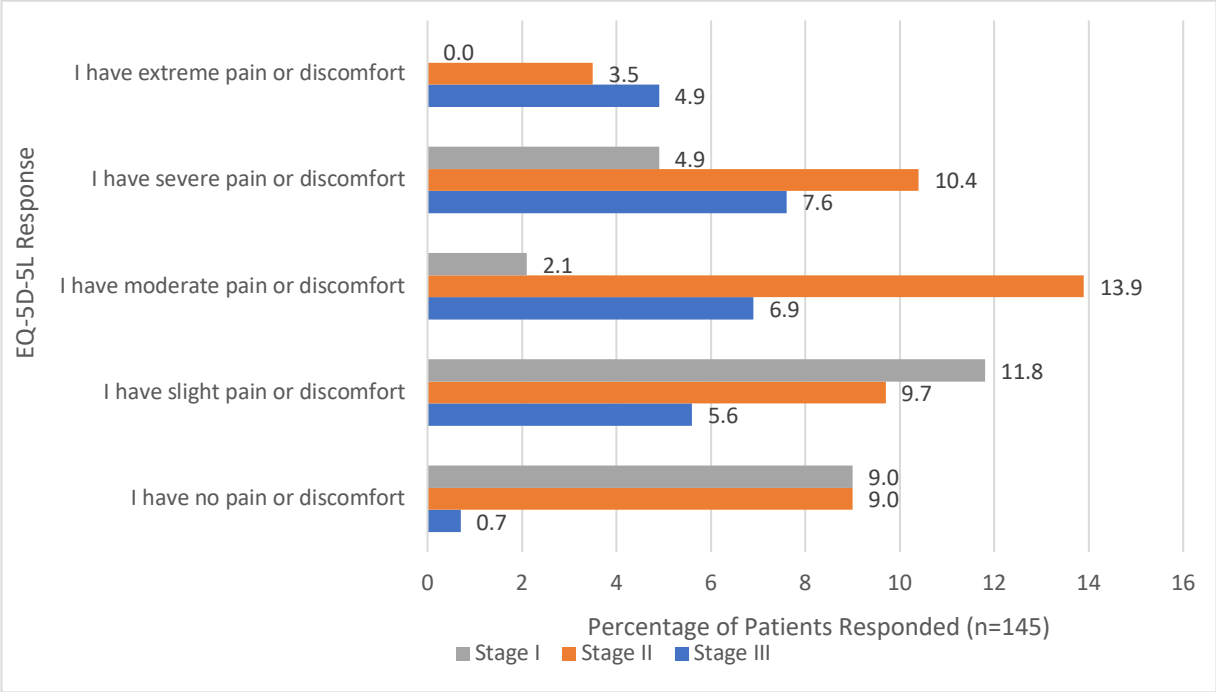
Patients also completed a Euro Quality of Life Health Outcome Measure questionnaire. The majority of patients reported pain associated with their HS, with just over 30 percent reporting severe to extreme pain (Figure 3).

Figure 3: EQ-5D-5L Responses



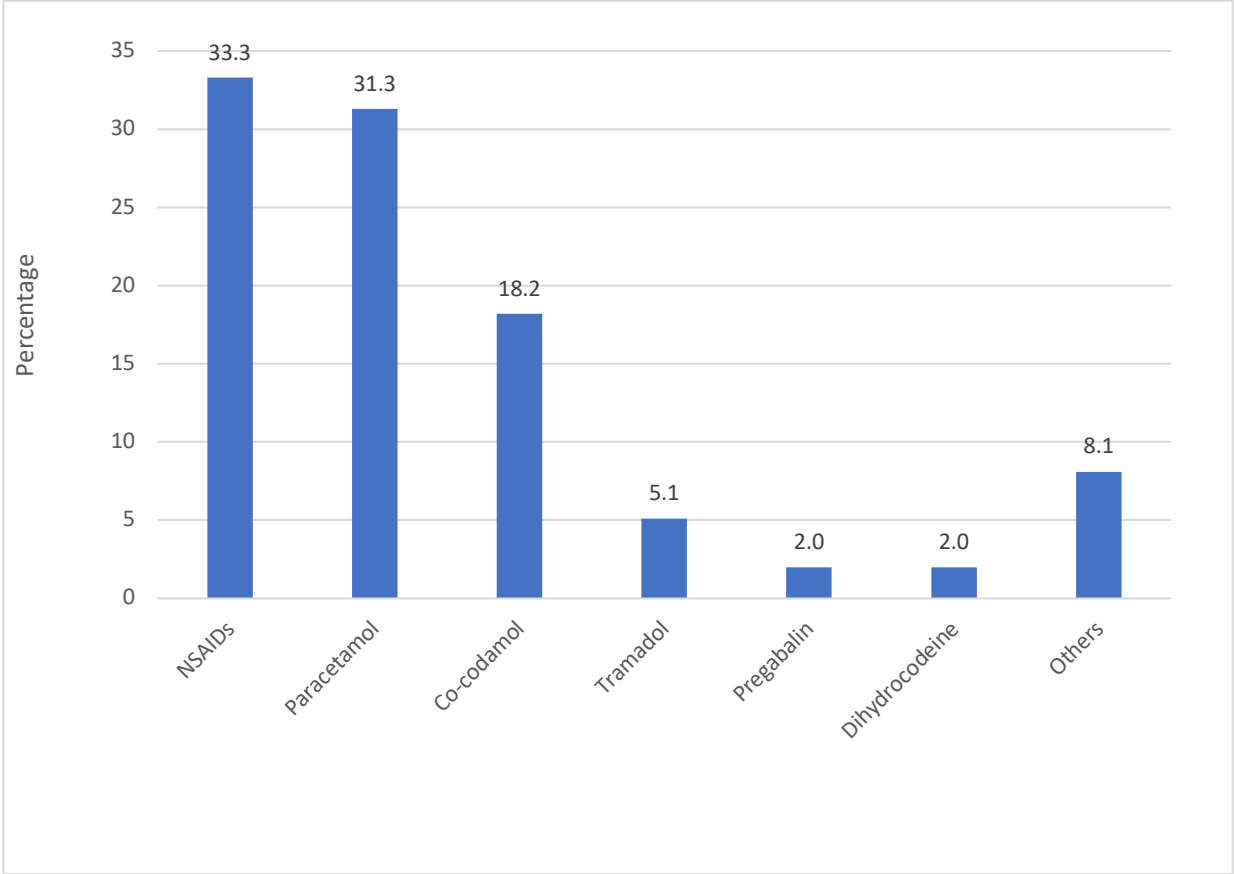
The relationship between Hurley Stage and this score was statistically significant with a p-value of <0.001 (Kruskal-Wallis). Patients who reported no pain or discomfort were predominantly Hurley stages I and II, while those reporting extreme pain or discomfort were exclusively stages II and III (Figure 4).

Figure 4: Association between Hurley stage and EQ5D-5L response



A significant proportion of patients (61/150, 40.7%) reported taking analgesics (Figure 5). A total of 99 analgesics were reported, the majority of which were over-the-counter medications accounting for 61.6% of analgesics taken. Weak negative correlation was seen between pain scores and the gut microbial diversity index chao1 (p=0.01), but this was not seen with other gut microbial diversity measures including Simpson and Shannon indices (p=0.05, p=0.12).

Figure 5: Reported use of analgesics in the study population



3.1.4 Discussion

Patients with HS often experience considerable pain, which has a meaningful impact on their quality of life. The characteristics of pain in HS have been described as hot, burning, pressure, stretching, cutting, sharp, taut, gnawing, throbbing, aching and splitting (584). Pain in HS correlated more highly with QoL impairment than even disease severity; however, more severe disease appears to be associated with greater pain and discomfort in the current study (24,585). The results align with a Danish study, in which patients reported a mean score of 3.9 (SD ±3.2) on a 10-point pain VAS (586). Another Danish study reported analgesic use in 65% of the study population highlighting the burden of disease (587). Regular analgesic use

addressing pain in HS in vital in improving QoL. However, there is little evidence in the literature to guide pharmacologic analgesia in HS, and dermatologists have limited training in complex pain management resulting in patient's self-management (588). Categorizing HS pain as either acute or chronic and predominantly nociceptive versus neuropathic aids the application of pain management practices in other conditions to HS management (589). HS pain is both nociceptive, with release of signalling molecules at sites of tissue injury, and neuropathic, with somatosensory nervous system dysfunction (590,591). Addressing both nociceptive and neuropathic pain is essential in managing pain in HS, balancing optimum dosage with side effects as well as addressing acute pain with strong analgesia and approaching chronic pain with a step-wise approach. There was weak negative correlation between pain scores and some markers of gut microbial diversity, suggesting a dysbiosis or reduction in gut microbial diversity may be associated with higher pain scores. This finding however was not reproducible for all alpha diversity markers and is thus likely not significant. Recently alterations in gut microbiota and their metabolites have been found to be associated with chronic pain, however the specific characteristics of this microbiome alteration remains inconsistent across the studies (592). Nevertheless, it appears that an altered host-microbe interaction contributes to the severity and duration of chronic pain and this should be further explored (592).

3.1.5 Conclusion

Collectively, these data highlight the need for greater awareness among physicians and researchers of the pain experienced by patients with HS, and suggest that pain should be included as a key outcome in future clinical trials.

3.2 Dermatology Life Quality Index and Hidradenitis Suppurativa

Abstract

Hidradenitis suppurativa (HS) is a recurrent, debilitating skin disorder presenting with painful inflammatory lesions of the apocrine-gland bearing skin. Pain, pruritus, malodour, and suppuration have a significant impact on quality of life (QoL) for HS patients (583).

Patients aged >18 with a diagnosis of hidradenitis suppurativa made by a consultant dermatologist were recruited from 2 dermatology centres in Ireland and completed the DLQI composed of 10 questions.

59 patients completed the standardised dermatology life quality index (DLQI). Mean DLQI was 12.15 (SD 7.67) with no differences noted in relation to age or sex. Mean DLQI for patients with Hurley stage I disease was 12 (SD 7.8), Hurley stage II disease 11.75 (SD 7.26) and Hurley stage III disease 12.1 (SD 8.27). Severity of HS did not correlate with higher total DLQI score. Although there was weak negative correlation between DLQI score and the gut microbiota alpha diversity measure chao1, no significant correlation was seen with the Simpson and Shannon indices (p 0.96, p 0.21). Six had a score of 0-1 (6/59;10.2%) showing no effect on their life, seven had a score of 2-5 (7/59;11.9%) showing a small effect on their life, and eleven had a score of 6-10 (11/59;18.6%) showing a moderate effect on their life. 24 scored 11-20 (24/59;40.7%) showing a very large effect on their life and 11 scored 21-30 (11/59;18.6%) showing an extremely large effect on their life.

HS has a significant impact on quality of life with DLQI scores in line with other severe dermatoses, as seen in our study (583,593–595). Highest DLQI scores were seen in relation to embarrassment or self-consciousness relating to HS and its impact on choice of clothing, as was reported previously, likely due to associated

suppuration and malodourous discharge. A high proportion of our cohort were unemployed and reported issues related to work and social activities. A high proportion also reported relationship difficulties and sexual dysfunction related to their diagnosis.

Understanding the overall burden of disease on QoL is important in providing holistic care in HS. Optimal treatment requires a multidisciplinary approach, addressing both the physical and psychosocial impacts of the disease, with the aim of improving clinical outcomes and QoL.

3.2.1 Introduction

Hidradenitis suppurativa (HS) is a recurrent, debilitating skin disorder presenting with painful inflammatory lesions of the apocrine-gland bearing skin. Pain, pruritus, malodour, and suppuration have a significant impact on quality of life (QoL) for HS patients (583). The tool most frequently used to assess patients QoL in patients attending dermatology clinics is the Dermatology Life Quality Index (DLQI)(596). Mean DLQI scores for HS range from 8.3-12.7 which is typical for severe dermatoses (594). The aim of the questionnaire is to measure how much the skin condition has affected the patient's life over the preceding week. The questions focus on physical sensations, embarrassment, interference with activities at home, clothing selection, impact on social activities, difficulty participating in a sport, preventing work or school attendance, causing relationship problems with close friends, relatives, or a partner, sexual difficulties, and impact of treatment on life, and lifestyle (596). Response options are "very much" scoring 3, "a lot" scoring 2, "a little" scoring 1, "not at all" scoring 0 and "not relevant" (596). The minimum score is 0 and maximum score is 30. A score of 0 to 1 shows no effect at all on patient's life, 2 to 5 a small effect on patient's life, 6 to 10 a moderate effect on patient's life, 11-20 very large effect on patient's life and 21-30 an extremely large effect on patient's life (596).

3.2.2 Methods

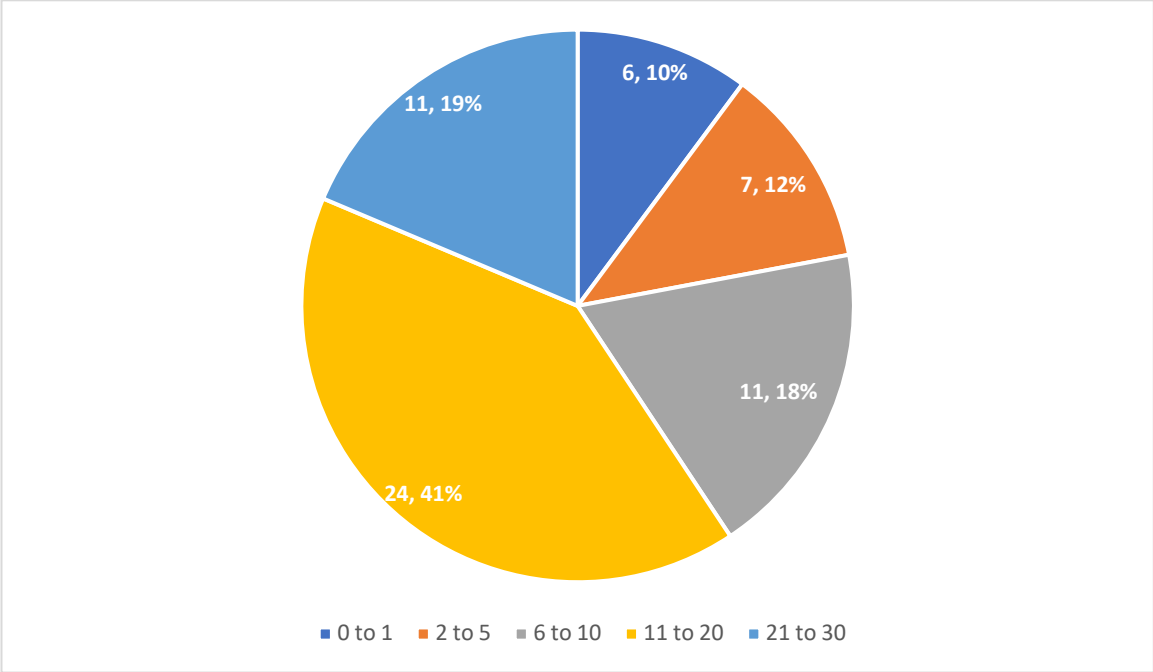
Patients with a diagnosis of hidradenitis suppurativa made by a consultant dermatologist were recruited from 2 dermatology centres in Ireland and completed the DLQI composed of 10 questions. Descriptive statistics were applied to report the questionnaire outcomes with continuous outcomes described as mean ± SD. To

calculate the differences between mean scores of two groups in normally distributed data, the independent Student's t-test was used. The Pearson correlation coefficient (r) and the Spearman correlation coefficient (r_S) were used to determine correlation. A $P < 0.05$ was considered statistically significant. Statistics were carried out using Excel (version 16.65) and R (version 4.3.1)

3.2.3 Results

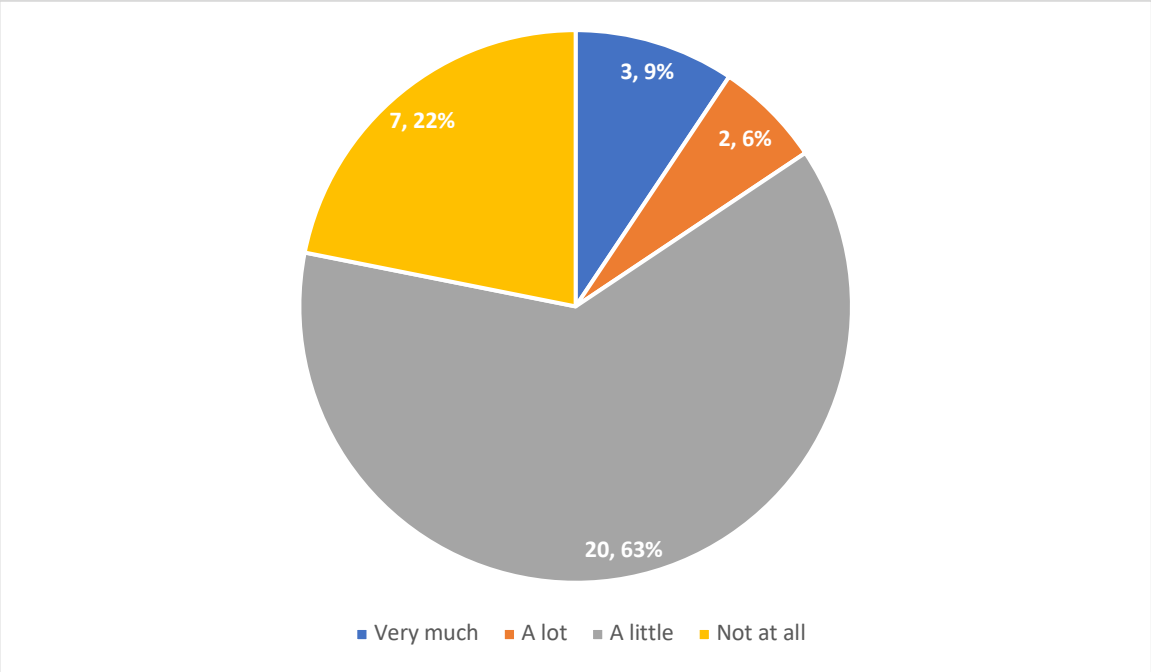
59 patients completed the standardised dermatology life quality index (DLQI). 45 were female and 14 were male. Mean age was 38.33 (SD 11.58). Mean age at diagnosis was 32.61 (SD 12.3). 17 (17/59; 29%) were Hurley stage I, 32 (32/59; 54%) were Hurley stage II, and 10 (10/59; 17%) were Hurley stage III. The majority (57/59;97%) were white and European, and 2 were of mixed ethnic origin (2/59; 3%). 57% (34/59) were current smokers and 32% (19/59) ex-smokers for an average of 16.5 (SD 12.19) pack years. Mean BMI was 31.13 (SD 7.18). Mean DLQI was 12.15 (SD 7.67) with no differences noted in relation to age or sex. Mean DLQI for patients with Hurley stage I disease was 12 (SD 7.8), Hurley stage II disease 11.75 (SD 7.26) and Hurley stage III disease 12.1 (SD 8.27). Severity of HS did not correlate with higher total DLQI score. Six had a score of 0-1 (6/59;10.2%) showing no effect on their life, seven had a score of 2-5 (7/59;11.9%) showing a small effect on their life, and eleven had a score of 6-10 (11/59;18.6%) showing a moderate effect on their life. 24 scored 11-20 (24/59;40.7%) showing a very large effect on their life and 11 scored 21-30 (11/59;18.6%) showing an extremely large effect on their life. (Figure 1) Although there was weak negative correlation between DLQI score and the gut microbial alpha diversity measure chao1, this was not seen got the Simpson and Shannon indices (p=0.96, p=0.21)

Figure 1: Total DLQI score



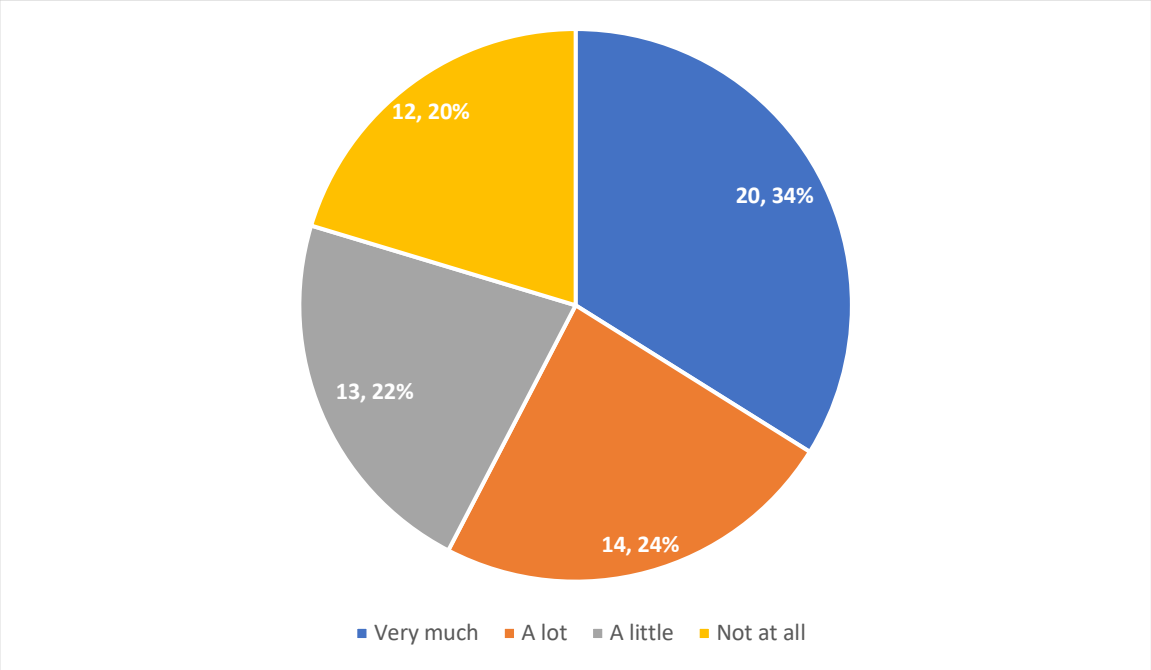
For the first question on the DLQI ‘Over the last week, how itchy, sore, painful or stinging has your skin been?’ 7 (22%) reported not at all, 20 (63%) a little, 2 (6%) a lot, and 3 (9%) very much. (Figure 2)

Figure 2: Question 1 - Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?



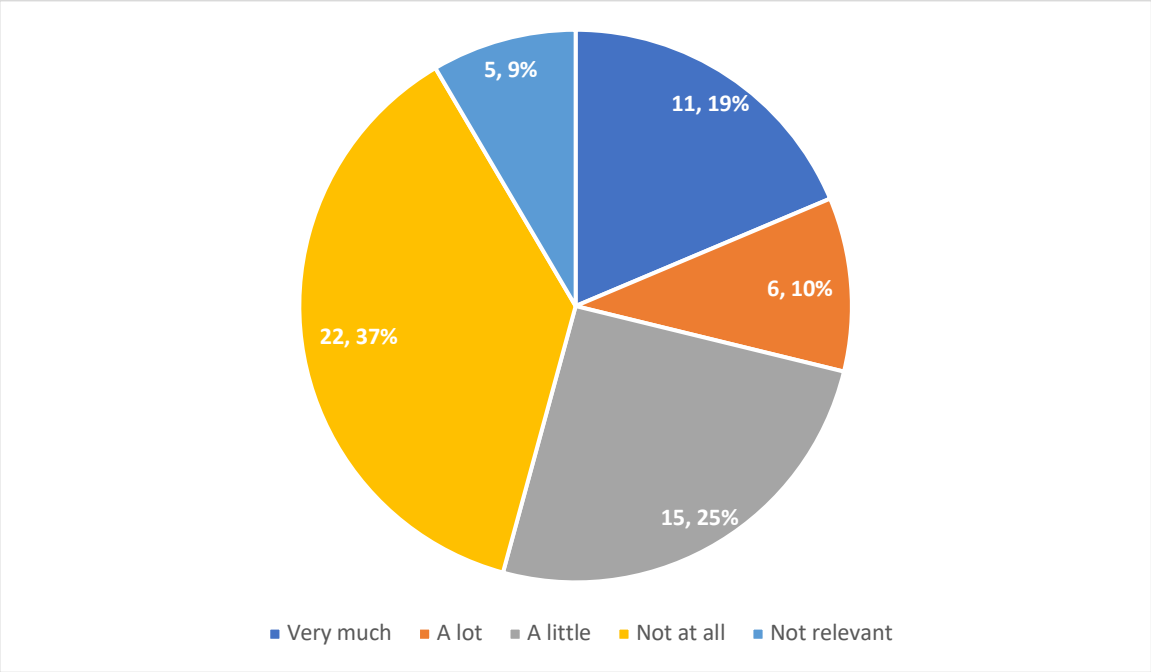
For the second question ‘Over the last week, how embarrassed or self-conscious have you been because of your skin?’ 12 (20%) reported not at all, 13 (22%) reported a little, 14 (24%) reported a lot, and 20 (34%) reported very much. (Figure 3)

Figure 3: Question 2 - Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?



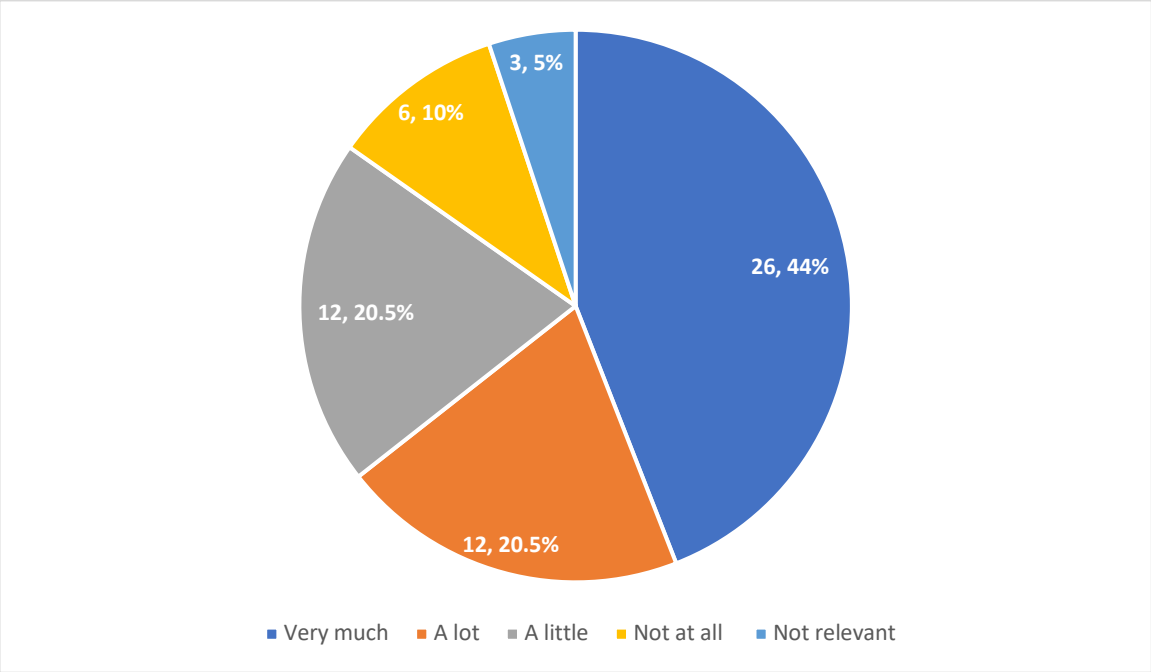
When asked ‘Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?’ 22 (37%) responded not at all, 15 (25%) a little, 6 (10%) a lot and 11 (19%) very much with 5 (9%) reporting that the question was not relevant. (Figure 4)

Figure 4: Question 3 - Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?



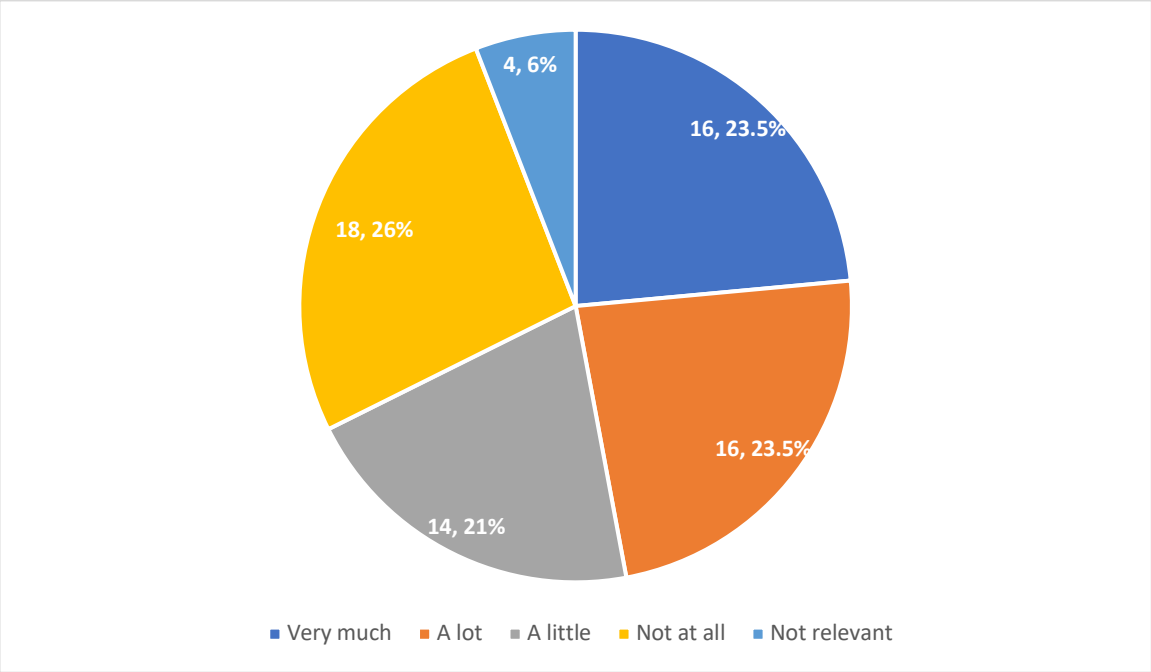
For the fourth question ‘Over the last week, how much has your skin influenced the clothes you wear?’ 6 (10%) reported not at all, 12 (20.5%) a little, 12 (20.5%) a lot, and 26 (44%) very much, with 3 (5%) reporting that the question was not relevant. (Figure 5)

Figure 5: Question 4 - Over the last week, how much has your skin influenced the **clothes** you wear?



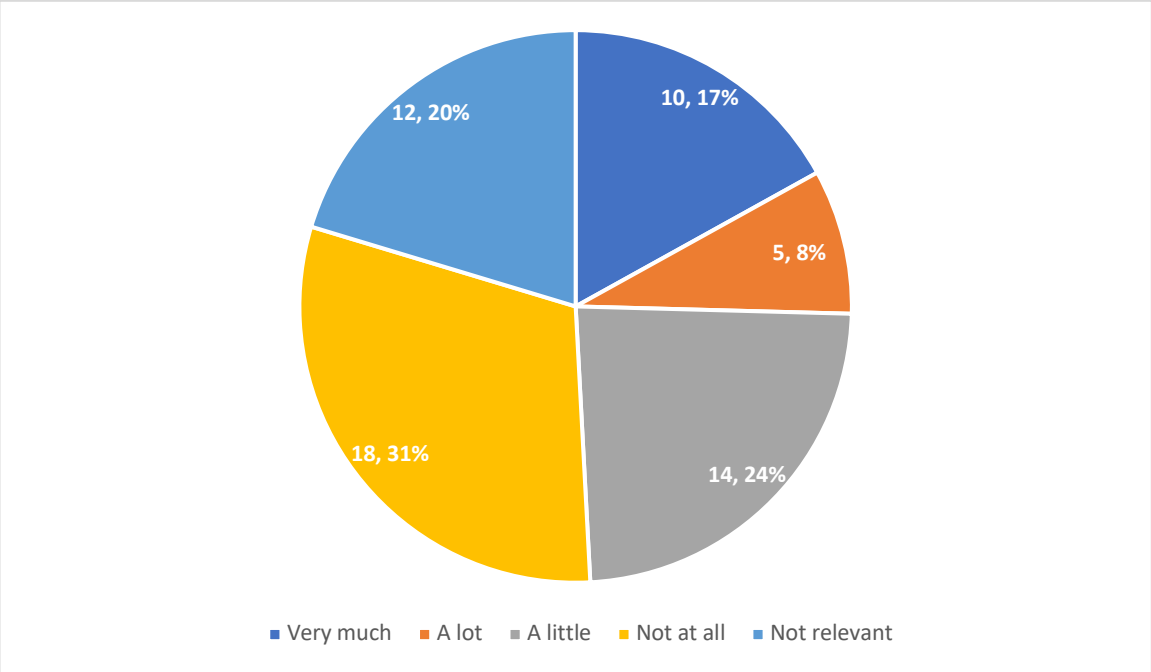
When asked ‘Over the last week, how much has your skin affected any social or leisure activities?’ 18 (26%) responded not at all, 14 (21%) a little, 16 (23.5%) a lot, and 16 (23.5%) very much, with 4 (6%) reporting that the question was not relevant. (Figure 6)

Figure 6: Question 5 - Over the last week, how much has your skin affected any **social** or **leisure** activities?



When asked ‘Over the last week, how much has your skin made it difficult for you to do any sport?’ 18 (31%) responded not at all, 14 (24%) a little, 5 (8%) a lot and 10 (17%) very much, with 12 (20%) reporting not engaging in sport. (Figure 7)

Figure 7: Question 6 - Over the last week, how much has your skin made it difficult for you to do any **sport**?



7 (12%) reported that their skin prevented them from working or studying in the previous week, with 23 (39%) not currently working or studying. (Figure 8) Of the 29 (49%) who did not report their skin preventing them from working or studying, 2 (7%) reported it was a little, and 16 (55%) a lot problematic. (Figure 9)

Figure 8: Question 7 - Over the last week, has your skin prevented you from **working** or **studying**?

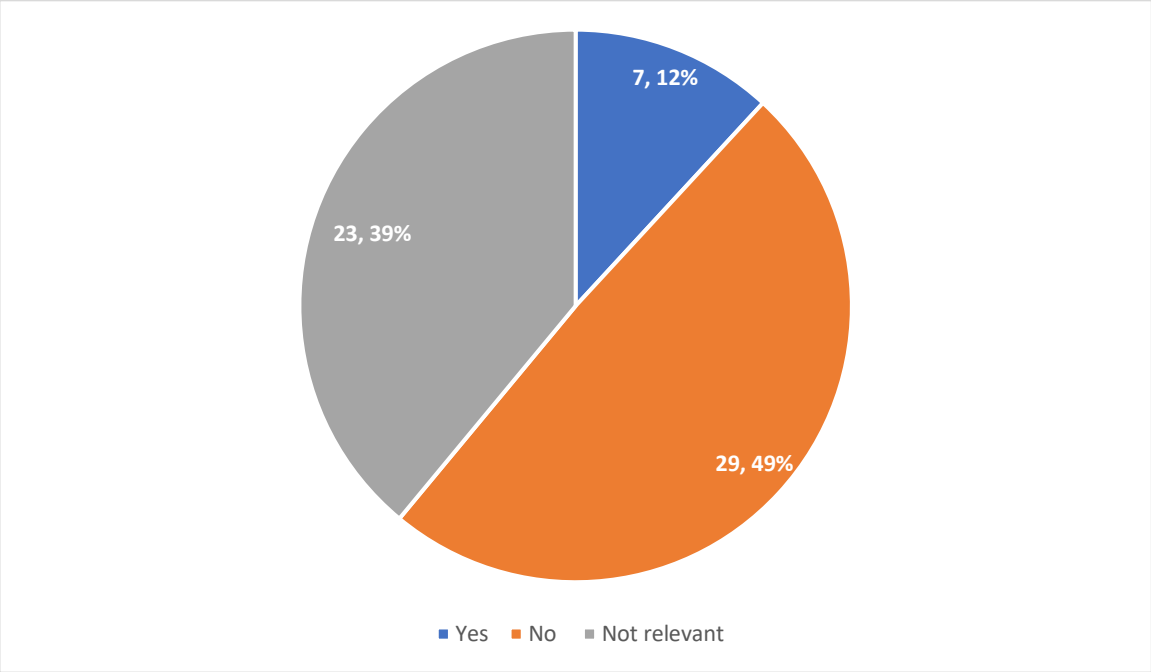
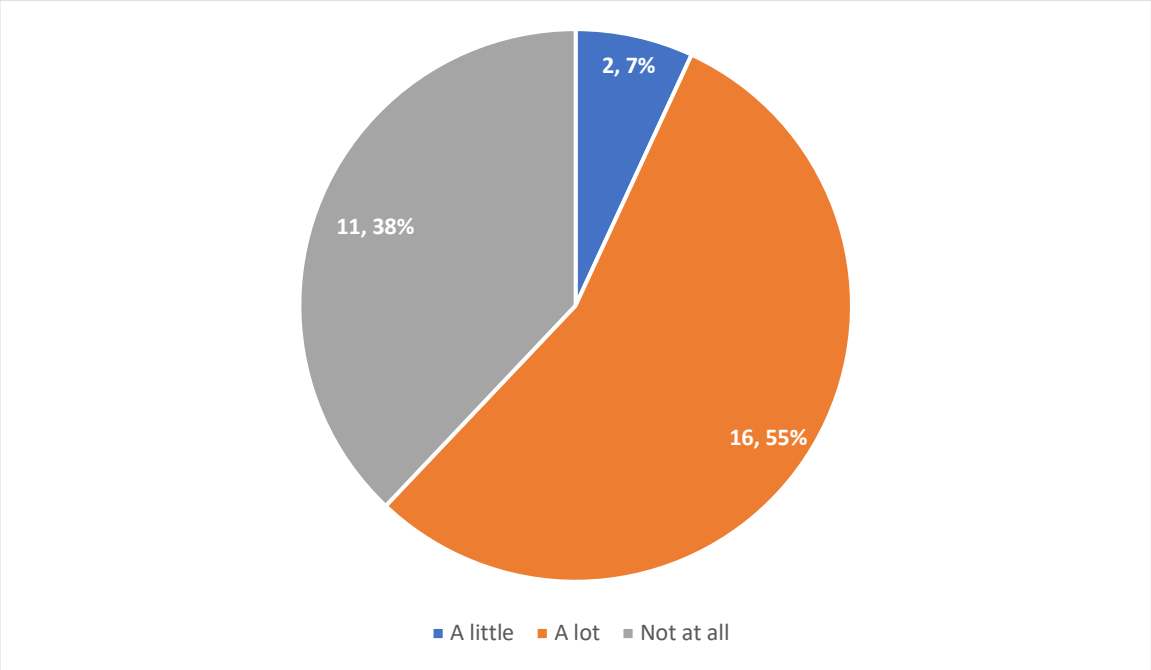
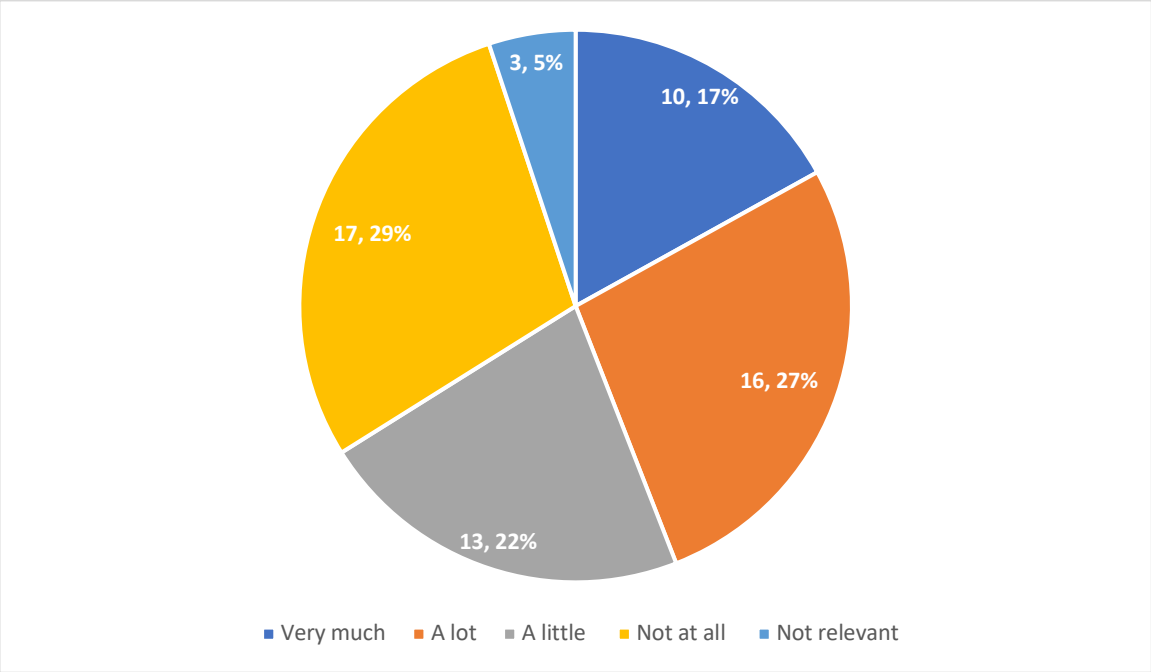


Figure 9: If "No", over the last week how much has your skin been a problem at work or studying?



When asked ‘Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?’ 17 (29%) reported not at all, 13 (22%) a little, 16 (27%) a lot, and 10 (17%) very much. 3 (5%) reported the question as irrelevant. (Figure 10)

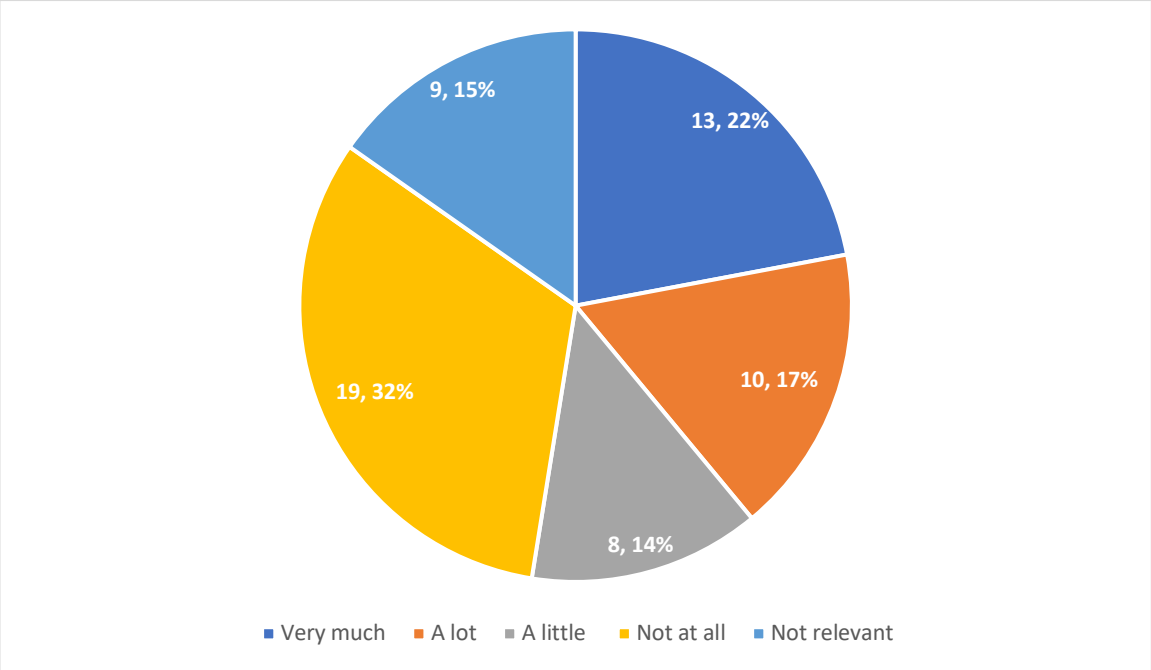
Figure 10: Question 8 - Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?



Of note 59% (35/59) of patients included in this study reported not being in a relationship.

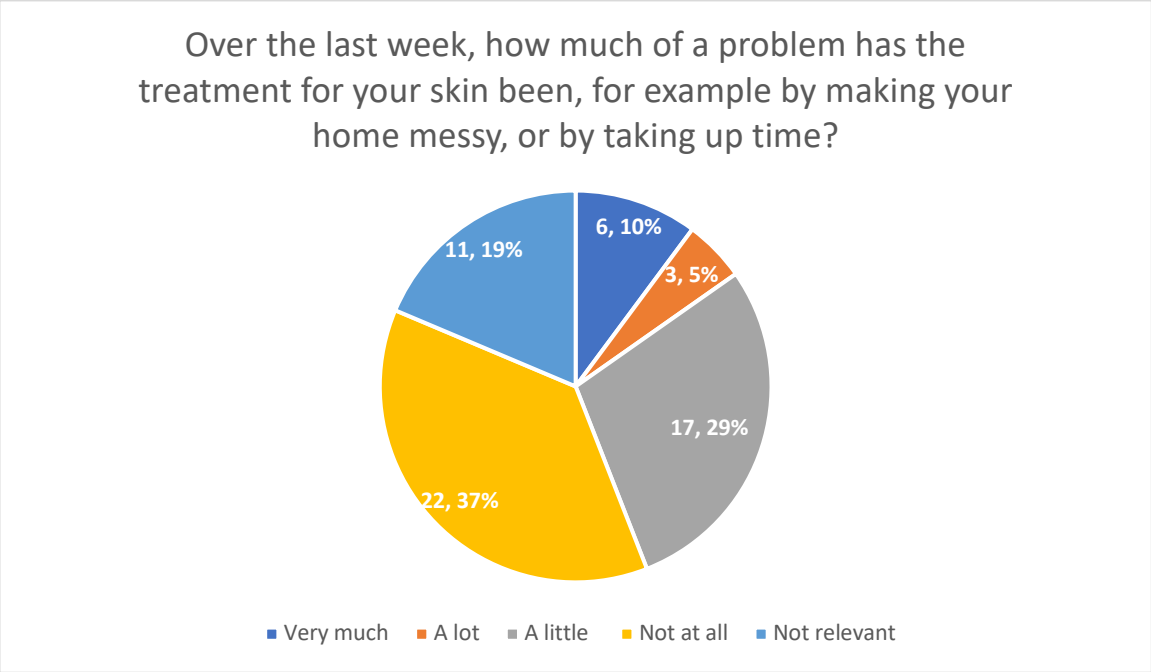
With regards how much has their skin has caused any sexual difficulties in the preceding week, 8 (14%) reported a little, 10 (17%) a lot, and 13 (22%) very much. 9 (15%) reported the question as irrelevant. (Figure 11)

Figure 11: Question 9 - Over the last week, how much has your skin caused any **sexual difficulties**?



17 (29%) reported that the treatment of their skin was a little bit problem, 3 (5%) a lot and 6 (10%) very much with 22 (37%) reporting no issues and 11 (19%) deeming the question irrelevant. (Figure 12)

Figure 12: Question 10 - Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?



3.2.4 Discussion

HS has a significant impact on quality of life with DLQI scores in line with other severe dermatoses, as seen in this study (583,593–595). However DLQI scores did not correlate with HS severity. This is contrary to prior studies which did show positive correlation of DLQI with HS severity as defined by Hurley staging (597–599). This may be due to the limitation of Hurley staging as a static measure that does not accurately account for flares of disease or subjective measures such as pain.

Gut microbial diversity also did not differ by DLQI score. Furthermore there was no correlation between DLQI score and the gut microbiota alpha diversity (a measure of species richness) metrics Shannon and Simpson indices suggesting that a severe impact on quality of life in HS does not correlate with alterations in gut microbiota. Highest DLQI scores were seen in relation to embarrassment or self-consciousness relating to HS and its impact on choice of clothing, as seen previously, likely due to associated suppuration and malodourous discharge. HS also has a significant impact on body image as previously described (600). Pain and itch once more appears to be a considerable issue in 15% of this cohort. Itch is an often underrecognized symptom which has been proven to have a significant negative impact on HS patients' psychosocial wellbeing (601).

Patients with HS also report issues in both their employment and leisure time. Previous studies have described frequent absences in work or education resulting in reduced productivity, and sometimes leading to unemployment (595,602). This was also noted in our study with 12% reporting absences in the previous week with a further 30% reporting that HS impacted a little or a lot on their work or studies. HS is also associated with higher risk of leaving the workforce, and this is reflected in our results with 39% of our cohort unemployed (602). Activities such as shopping, housework and work in the garden was a struggle for 29% of the patients with HS in this cohort highlighting the negative impact on activities of daily life.

Impact on social life and relationships is also a considerable issue for patients with HS. Social isolation and stigmatisation are seen in patients with HS with a major impact on QoL (594,595). 44% of our cohort reported issues with relationships related to their diagnosis. In our study 59% declared not to be in a relationship currently, and this is also reflected in the literature (603). A recent study showed the

negative impact on HS patients' partners' QoL, leading to discord in their relationships and this combined with low self-esteem in HS may account for the high proportion of this cohort not in a relationship (603). Sexual health is also impaired in HS and this is reflected in the study results, with 15% not sexually active and 22% reporting a high impact with sexual difficulties (604,605). In prior studies sexual dysfunction was higher in females, which was not found in this cohort; however there was a high ratio of females to males in this study (3:1) reflecting the higher incidence of HS in women (604,605).

Psychological stress in HS may also result in making or continuing negative lifestyle choices with a large proportion of our cohort current or ex-smokers and overweight or obese. HS can also limit physical activity due to painful lesions and in our cohort a quarter of patients reported issues with engaging with sport with a further 20% reporting they did not engage in sport at all. This lack of physical activity contributes to weight gain and poor cardiovascular health. Treatment of disease can also prove a significant burden to patients. In our cohort 15% reported that treatment of their HS was bothersome. Several studies report significant personal healthcare costs with regards to HS treatment, and along with its impact on employment, could lead to considerable financial strain (594,595,603).

3.2.5 Conclusion

Understanding the overall burden of disease on QoL is important in providing holistic care in HS. Optimal treatment requires a multidisciplinary approach, addressing both the physical and psychosocial impacts of the disease, with the aim of improving clinical outcomes and QoL.

3.3 Adherence to treatment in Hidradenitis Suppurativa

Abstract

Hidradenitis is a chronic relapsing remitting inflammatory disease of the apocrine gland bearing skin presenting. Treatment of hidradenitis suppurativa can be challenging with a limited range of evidence-based therapies and no current curative treatments (54). Adherence to medication is the extent to which patients use their prescribed treatments (606). Adherence to prescribed treatment is vital to ensure therapeutic success in chronic illnesses such as hidradenitis suppurativa. Little is known about patient adherence to treatment in hidradenitis suppurativa. We sought to determine levels of adherence to prescribed medications in a cohort of patients with hidradenitis suppurativa.

Patients aged >18 with a confirmed diagnosis of hidradenitis suppurativa by a consultant dermatologist were recruited to the study in two tertiary referral centres in Ireland. Patients were invited to complete the Morisky Medication Adherence Scale, a validated scale designed to estimate the risk of medication non-adherence (607).

In this study over 40% also reported some difficulty remembering to take their medications with 20% reporting that they forgot to take their medication in the previous 2 weeks. A further 25% of this cohort cut back on or stopped medications without discussing with their doctor.

Optimising the patient-doctor relationship, simplifying the regimen and careful explanation and education may improve adherence in chronic illness, and this approach should be used in the management of HS.

3.3.1 Introduction

Hidradenitis is a chronic relapsing remitting inflammatory disease of the apocrine gland bearing skin presenting with inflammatory nodules, abscesses, often progressing to sinus tract formation and scarring. Treatment of hidradenitis suppurativa can be challenging with a limited range of evidence-based therapies and no current curative treatments (54). Adherence to medication is the extent to which patients use their prescribed treatments (606). Adherence to prescribed treatment is vital to ensure therapeutic success in chronic illnesses such as hidradenitis suppurativa. Patients can be unintentionally non-adherent due to forgetfulness or misunderstanding, some however are intentionally non-adherent due to side effects or perceived ineffectiveness of treatments (606,608). In psoriasis it is estimated that up to 40% of patients do not use their medication as prescribed and the rate of non-adherence is particularly high for topical therapy (608,609). However, little is known about patient adherence to treatment in hidradenitis suppurativa. We sought to determine levels of adherence to prescribed medications in a cohort of patients with hidradenitis suppurativa.

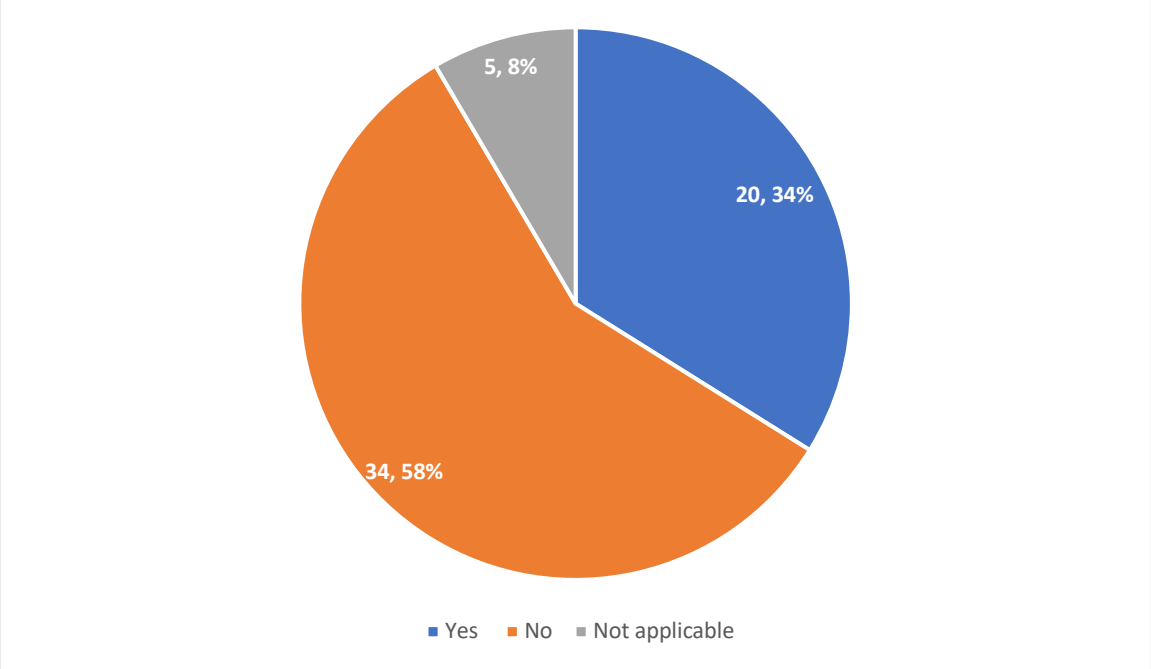
3.3.2 Methods

Patients aged >18 with a confirmed diagnosis of hidradenitis suppurativa by a consultant dermatologist were recruited to the study in two tertiary referral centres in Ireland. Patients were invited to complete the Morisky Medication Adherence Scale, a validated scale designed to estimate the risk of medication non-adherence (607). Data relating to age, sex, past medical history, and current and past medication history were collected. Statistics were performed using Excel (version 16.65).

3.3.3 Results

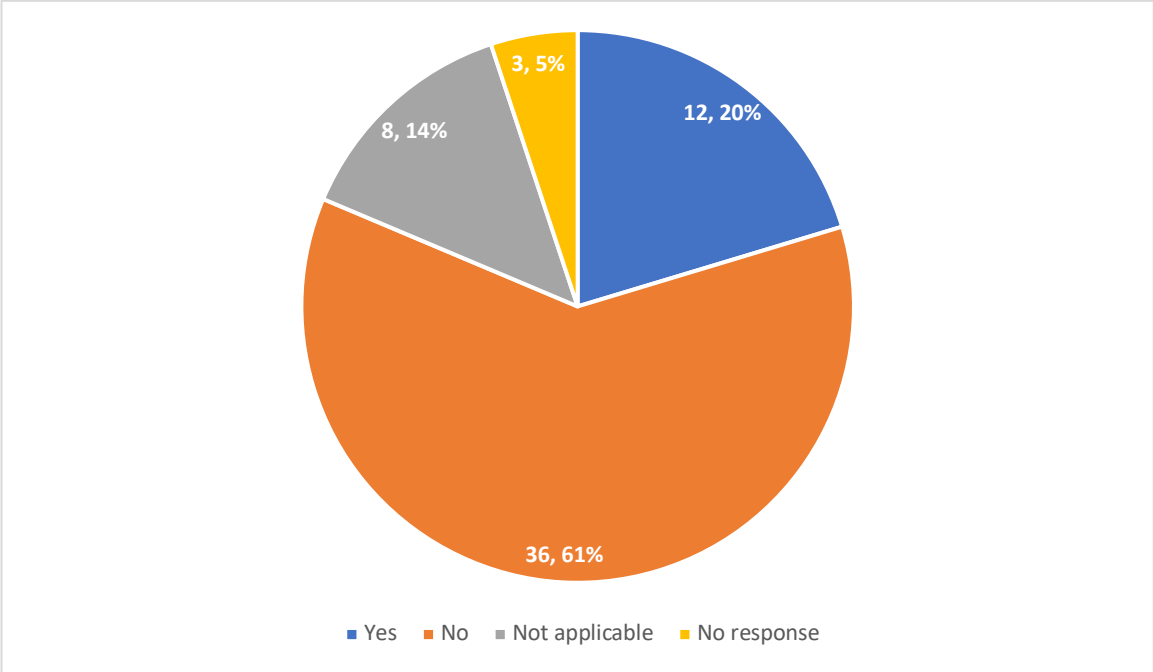
59 patients with a diagnosis of hidradenitis suppurativa completed the questionnaire, assessing adherence to all medications prescribed. Mean age was 38 (SD 12). 64.4% (38/59) were taking regular systemic medications, 2 were on topical or inhaled medications. Of the patients taking systemic medications, 10 (26%; 10/38) were prescribed subcutaneous or intravenous TNF-α inhibitors for HS and/or Crohn's disease. When asked if they sometimes forget to take their medications 33.9% (20/59) responded yes, with 57.6% (34/59) responded no. (Figure 1)

Figure 1: Do you forget to take medications sometimes?



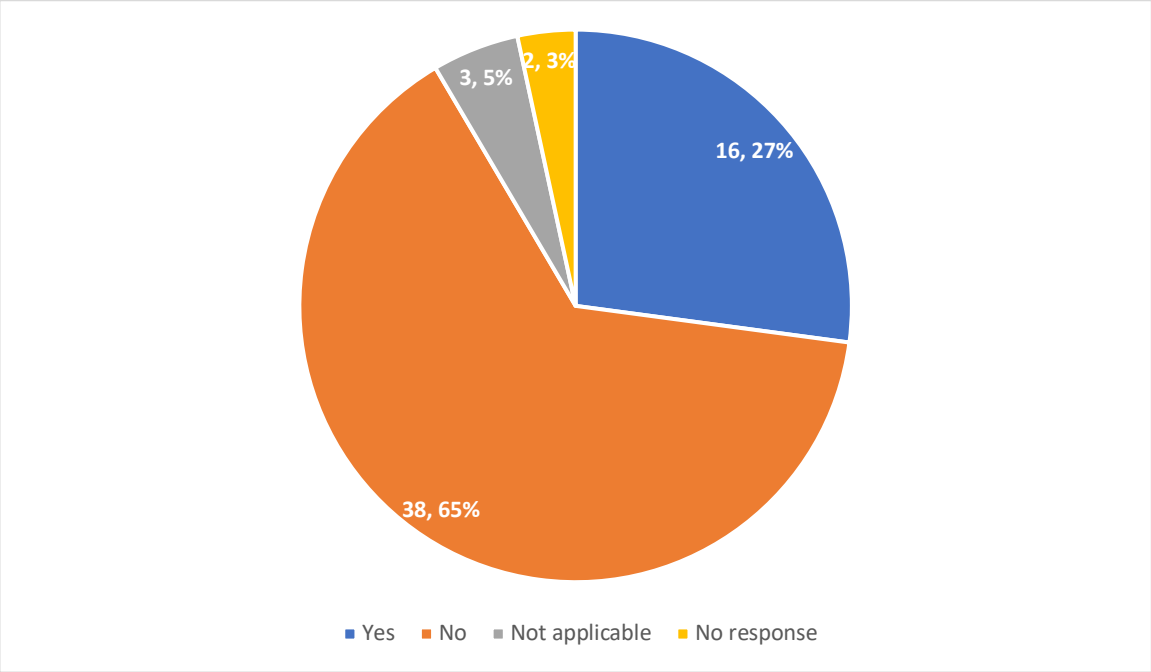
Patients were then asked if over the past two weeks were there any days when they did not take their medications. 20.3% (12/59) responded yes, and 61% (36/59) responded no. (Figure 2)

Figure 2: Thinking over the past two weeks, were there any days when you did not take your medications?



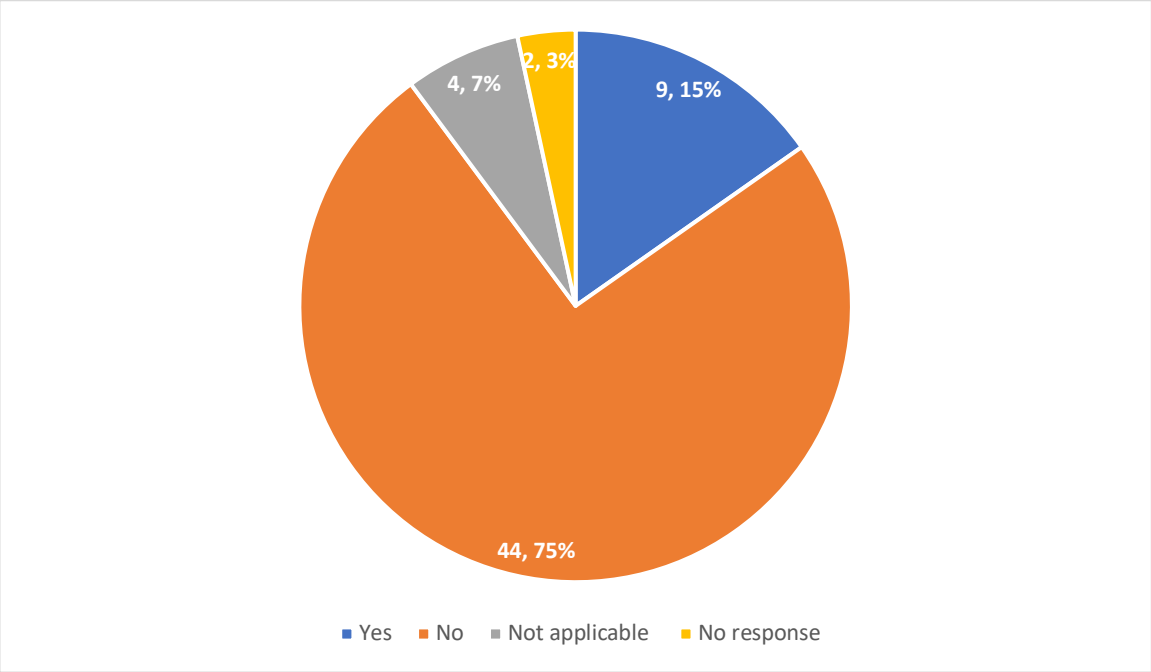
27.1% (16/59) reported cutting back or stopping medications without consulting their doctor because they felt worse when they took it. (Figure 3)

Figure 3: Have you ever cut back or stopped taking your medications without telling your doctor, because you felt worse when you took it?



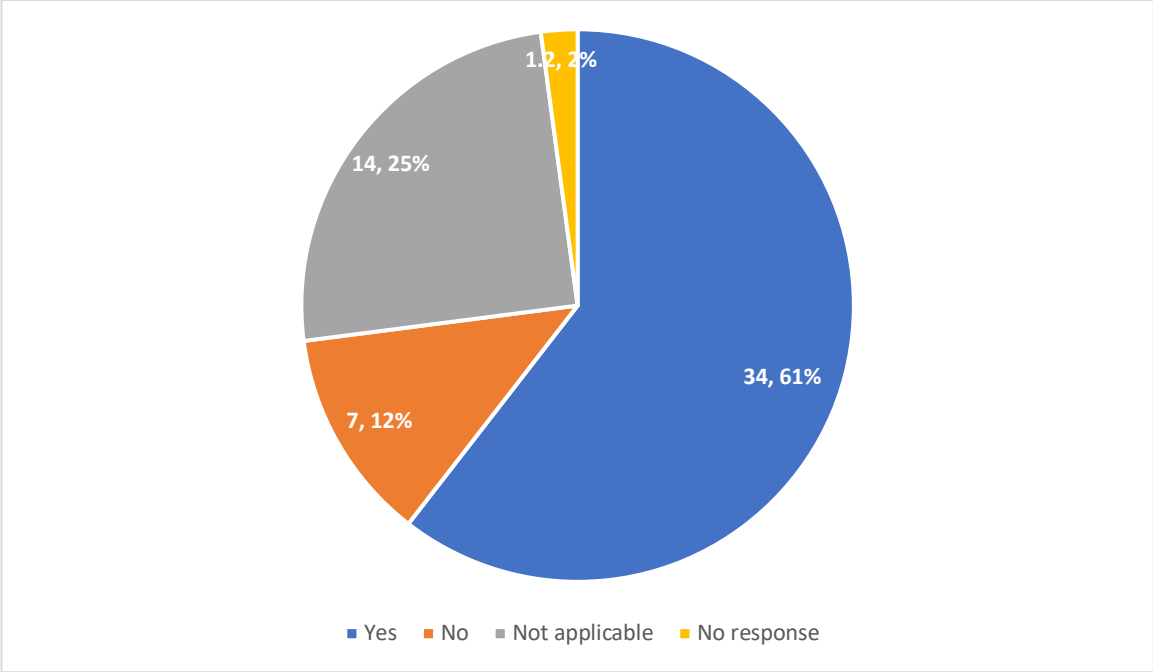
When travelling or leaving home most, 74.6% (44/59), remembered to bring their medications. (Figure 4)

Figure 4: When you travel or leave home, do you sometimes forget to bring along your medications?



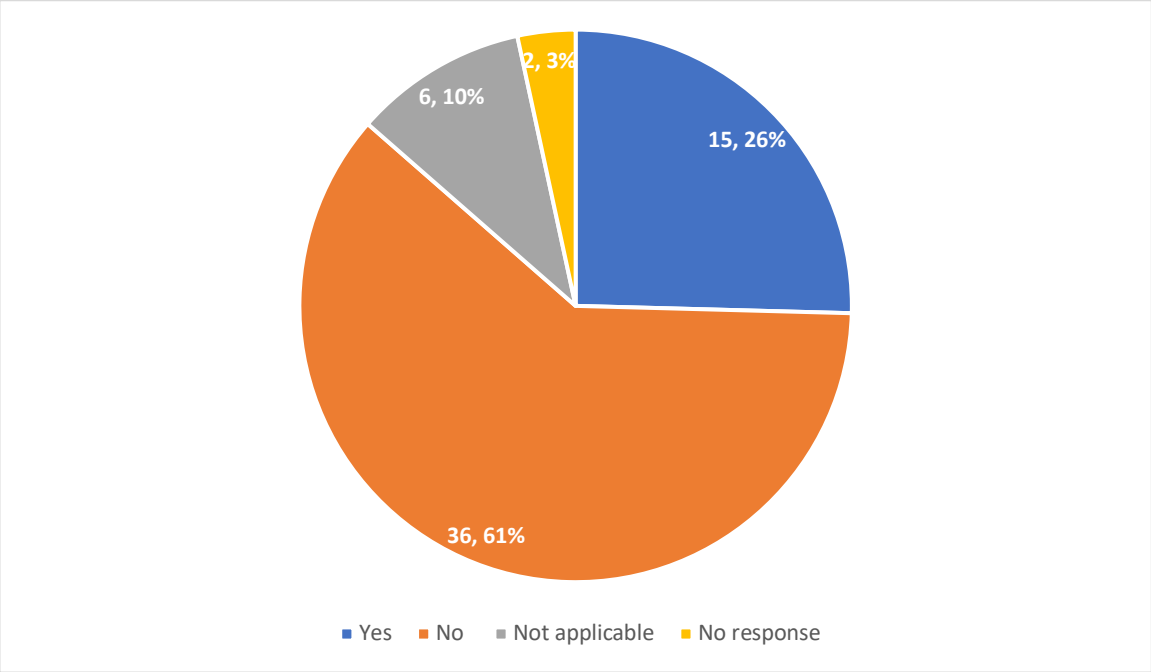
The majority reported remembering to take their medications yesterday, 57.6% (34/59). (Figure 5)

Figure 5: Did you take your medications yesterday?



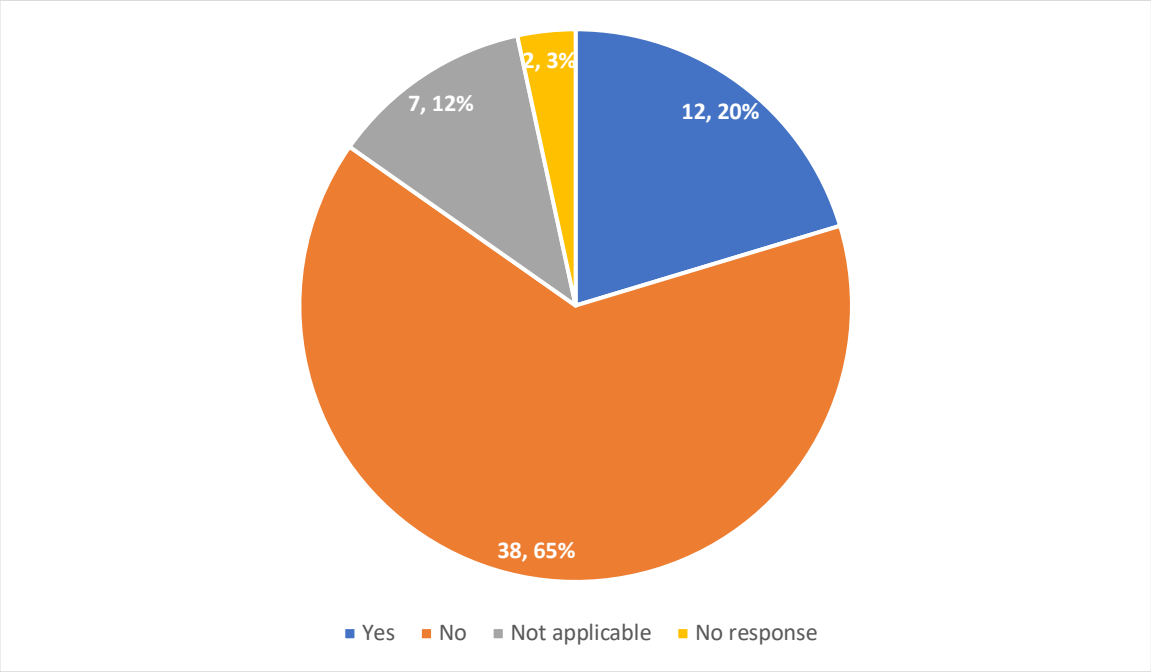
25.4% (15/59) report sometimes stopping their medication when they feel like their health condition is under control. (Figure 6)

Figure 6: When you feel like your health condition is under control, do you sometimes stop taking you medications?



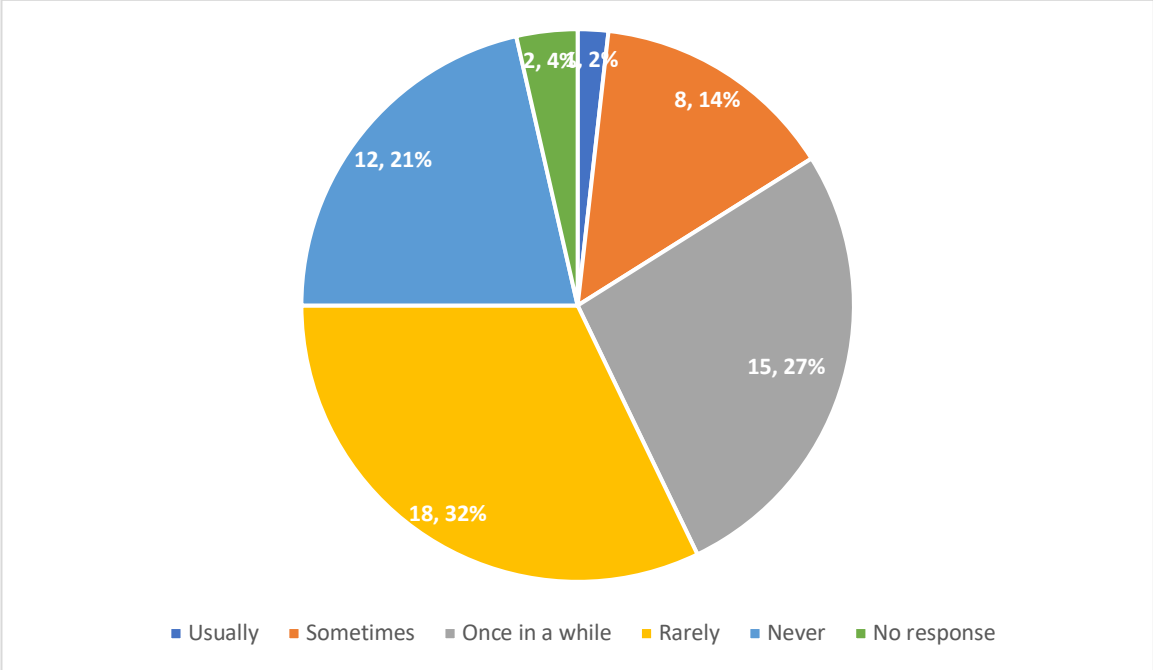
20% (12/59) reported feeling hassled sticking to their prescribed treatment plan. (Figure 7)

Figure 7: Do you ever feel hassled about sticking to your treatment plan?



40.7% (24/59) reported having some difficulty remembering to take their medications, while the majority, 50.8% reported this was rarely or never an issue. (Figure 8)

Figure 8: How often do you have difficulty remembering to take all your medications?



3.3.4 Discussion

In this study over 40% also reported some difficulty remembering to take their medications with 20% reporting that they forgot to take their medication in the previous 2 weeks. A further 25% of this cohort cut back on or stopped medications without discussing with their doctor. However, questionnaires measuring adherence to medications are believed to tend towards overestimating adherence which may affect our results (610). Little is published on adherence to medication in HS. One study reported low adherence to over the counter antimicrobial washes in HS (611). A tendency towards helplessness and passivity has also been described in patients

with HS which may lead to poor health maintenance, in the form of leaving appointments and non-adherence (612). It is accepted that optimising the patient-doctor relationship, simplifying the regimen and careful explanation and education may improve adherence in chronic illness, and this approach should be used in the management of HS (608). Biologic therapies are known to have high rates of adherence (613). As biologic therapy is the preferred treatment of moderate-to-severe HS which has failed standard therapy, adherence is likely to be higher in these patients.

3.3.5 Conclusion

This study suggests that non-adherence may be an issue in patients with HS, with over 40% reporting some difficulty remembering to take their medications and a quarter of patients stopping or cutting back on medications without discussing with a doctor. Further exploration is needed to determine the reasons for non-adherence in HS. Non-adherence should be explored in patients with HS, to ensure that that it is not a factor in non-response to therapies.

3.4 Physical Activity in Patients with Hidradenitis Suppurativa

Abstract

Physical activity has profound health benefits and has gained interest as an important modifiable environmental lifestyle factor in a variety of diseases, including cardiovascular disease, type II diabetes, and rheumatic disease (614–616). One study showed an inverse relationship between disease severity with intensity of physical activity in HS (170). In this study we sought to describe the physical activity of our cohort of patients with hidradenitis suppurativa.

Patients with a confirmed diagnosis of HS from two tertiary referral centres for dermatology were asked to complete the International Physical Activity Questionnaire (IPAQ) to determine their weekly physical activity scores (617).

61 patients with HS completed the questionnaire. 77% (47/61) were female and mean age was 38.33 years (SD 11.58). 18 (30%) patients had Hurley stage I disease, 33 (54%) patients had Hurley stage II disease, and 10 (16%) patients had Hurley stage III disease. 65% (40/61) reported high physical activity of >3000 MET-minutes per week. 25% (15/61) reported moderate physical activity of >600 MET-minutes per week. 10% (6/61) reported low physical activity of <600 MET-minutes per week. Median METs by Hurley score were high for Hurley stage I at 4492.5 METs per week (IQR 5722 METs), and Hurley stage II at 5964 METs per week (IQR 9375 METs), and a moderate 1917 METs per week (IQR 5040 METs) for Hurley stage III. No statistical difference was noted in physical activity scores by Hurley staging (p=0.108) and there was no correlation between physical activity and gut microbial diversity.

This cohort of patients with HS reported moderate to high levels of physical activity. Levels of physical activity in this study did not correlate with disease severity in

contrast to previous literature. Reporting physical activity is quite subjective relying on recall of the patient and it is therefore possible that our cohort have reported falsely elevated levels of physical activity reflecting the moderate to high levels of physical activity seen in this study.

3.4.1 Introduction

Physical activity has profound health benefits. The European guidelines for physical activity recommend a minimum of 30 minutes of daily moderate-intensity physical activity for adults including seniors (618). The World Health Organisation recommend at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or to do at least 75 minutes of vigorous-intensity activity throughout the week or an equivalent of moderate- and vigorous-intensity activity and that aerobic activity should be performed in bouts of at least 10 minutes duration (619). Physical activity has gained interest as an important modifiable environmental lifestyle factor in a variety of diseases, including cardiovascular disease, type II diabetes, and rheumatic disease (614–616). Some studies have also shown that physical activity may protect against the development of cancer, neurodegenerative and inflammatory disorders, and infections (620,621). Studies evaluating the association between physical activity and development of Crohn's disease have shown mixed results, however a meta-analysis suggests that physical activity has a protective effect (622). Few studies have described the physical activity of patients with HS, nor the impact of physical activity on the development of HS. A study by Lorite-Fuentes et al. showed an inverse relationship between disease severity with

intensity of physical activity (170). In this study we sought to describe the physical activity of a cohort of patients with hidradenitis suppurativa.

3.4.2 Methods

Patients with a confirmed diagnosis of HS from two tertiary referral centres for dermatology were asked to complete the International Physical Activity Questionnaire (IPAQ) to determine their weekly physical activity scores.(617) This questionnaire comprises of five parts; (1) Job-related physical activity, (2) Transportation physical activity, (3) Housework, house maintenance, and caring for family, (4) Recreation, sport, and leisure-time physical activity, and (5) Time spent sitting over the preceding 7 days. Activities were deemed vigorous if they make a person breathe much harder than normal, and moderate if they breathe somewhat harder than normal. Physical activity (PA) was categorised into three levels; Low/Inactive, Moderate, or High. Participants were deemed to be in the moderate category if their PA level was equivalent to 'half an hour of at least moderate-intensity PA on most days'. High category included those who engage in at least one hour per day of at least moderate-intensity activity above the basal level of PA (ie those that move at least 12,500 steps per day or the equivalent in moderate or vigorous activities). PA per week was calculated by determining metabolic equivalents or METs per week per participant. A MET is the ratio of your working metabolic rate relative to your resting metabolic rate. Metabolic rate is the rate of energy expended per unit of time. One MET is defined as the energy that you expend when resting or sitting still and an activity with a value of 2 METs expends double the energy than sitting still. Standard MET values are used in the IPAQ: Walking =

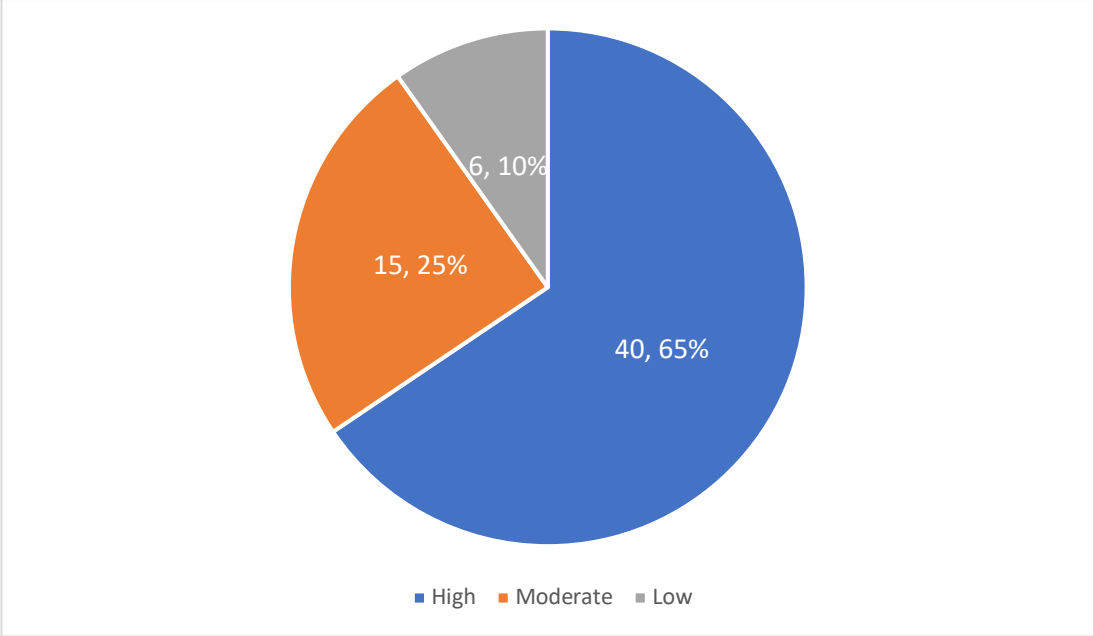
3.3 METs, Moderate PA = 4 METs and Vigorous PA = 8.0 METs. Statistics were performed using R (version 4.2.1).

3.4.3 Results

61 patients with HS completed the questionnaire. 77% (47/61) were female. Mean age was 38.33 years (SD 11.58). Mean weight was 87.7kg (SD 21.87) with a mean BMI of 31.37kg/m^2 (SD7.21). 18 (30%) patients had Hurley stage I disease, 33 (54%) patients had Hurley stage II disease, and 10 (16%) patients had Hurley stage III disease.

65% (40/61) reported high physical activity of >3000 MET-minutes per week. 25% (15/61) reported moderate physical activity of >600 MET-minutes per week. 10% (6/61) reported low physical activity of <600 MET-minutes per week. Median METs by Hurley score were high for Hurley stage I at 4492.5 METs per week (IQR 5722 METs), and Hurley stage II at 5964 METs per week (IQR 9375 METs), and a moderate 1917 METs per week (IQR 5040 METs) for Hurley stage III. No statistical difference was noted in physical activity scores by Hurley staging (p=0.108)(Kruskal-Wallis). There was no correlation seen between physical activity and the gut microbial diversity metrics chao1, Shannon and Simpson indices (p= 0.44, 0.29, 0.4)

Figure 1: Physical activity in patients with HS



The first domain of the IPAQ was occupation related physical activity. 48% (29/61) of patients were unemployed. Of those who were employed 56% (18/32) did no vigorous work. Of those that were employed 44% (14/32) patients engaged in vigorous activity (eg heavy lifting, digging, climbing stairs) at work for an average of 9 hours a week (IQR 29 hours) and 56% (18/32) patients engaged in moderate activity (eg carrying light loads) at work for a median of 9 hours (IQR 22.9 hours) a week. 50% (16/32) walked for at least 10 minutes as part of their work for a median of 17 hours a week (IQR 33 hours).

The second domain of the IPAQ was transportation related physical activity. 89% (54/61) travelled by motor vehicle for a median of 7 hours per week (IQR 10 hours). 3% (2/61) cycled in the past 7 days for a median of 1.25 hours (IQR 0.25 hours). 67% walked from place to place for a median of 3.25 hours per week (IQR 5 hours).

The third domain of the IPAQ was household activities. 18% (11/62) reported vigorous activity in the garden or yard (eg chopping wood or digging) for a median of 4 hours per week (IQR 4.3 hours) and 43% (26/61) reported moderate activities in

the garden or yard (eg washing windows, sweeping) for a median of 4 hours a week (IQR 4 hours). 80% (49/61) engaged in moderate activity in the home (eg sweeping, scrubbing floors) for a median of 4 hours (IQR 11 hours).

The final domain of the IPAQ was leisure related physical activity. 54% (33/61) walked for leisure for a median of 3.5 hours a week (IQR 4.4 hours). 8% (5/61) engaged in vigorous exercise (eg aerobics, running, fast cycling) for a median of 3 hours per week (IQR 3 hours). 11% (7/61) engaged in moderate exercise (eg gentle cycling, swimming at regular pace) for a median of 2 hours per week (IQR 1 hour). Patients reported sitting for a median of 5 hours per day during weekdays (IQR 4 hours) and 4 hours during weekends (IQR 3 hours).

3.4.4 Discussion

Our cohort of patients with HS reported moderate to high levels of physical activity. Levels of physical activity in this study did not correlate with disease severity. In contrast to this, a previous study by Lorite-Fuentes et al. found an inverse relationship between disease severity and the intensity of activity (170). This suggests a trend towards lower disease activity in those engaging in vigorous physical activity (170). Evidence from the literature suggests that weight loss can result in resolution of HS, especially at frictional locations (623,624). Physical activity in combination with a healthy diet can result in weight loss, thus explaining the inverse relationship seen in their study (170). Furthermore, exercise has been proven to alter the gut microbiota with resulting positive health effects (625). However, in this study levels of physical activity did not correlate with gut microbial diversity.

Although using metabolic equivalent of task (MET) is the gold standard in calculating physical activity, it is prone to error as patients can overestimate physical activity leading to distortion of the results and their impact on health outcomes (626,627). Reporting physical activity is quite subjective relying on recall of the patient and it is therefore possible that this cohort have reported falsely elevated levels of physical activity reflecting the moderate-to-high levels of physical activity seen in this study.

3.4.5 Conclusion

In conclusion moderate-to-high intensity physical activity was found in our cohort of patients with HS with no correlation with disease severity. It is possible that over-estimation of physical activity may have contributed to these findings.

4. The Skin Microbiota in Hidradenitis Suppurativa

Published in Journal of Investigative Dermatology

McCarthy S, Barrett M, Kirthi S, Pellanda P, Vlckova K, Tobin AM, Murphy M, Shanahan F, O'Toole PW. Altered Skin and Gut Microbiome in Hidradenitis Suppurativa. Journal of Investigative Dermatology. 2021 Aug 6.

Presented at European Academy of Dermatology and Venereology 30th Congress, September 2021

Abstract

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by the formation of nodules, abscesses, and fistula at intertriginous sites. The skin-gut axis is an area of emerging research in inflammatory skin disease and is a potential contributory factor to the pathogenesis of HS. 59 patients with HS provided nasal and skin swabs of affected sites for analysis. 20 healthy controls provided nasal and skin swabs. We performed bacterial 16S rRNA gene amplicon sequencing on total DNA derived from the samples. Microbiome alpha diversity was significantly lower in the skin and nasal samples of individuals with HS which may be secondary to disease biology or related to antibiotic usage. *Finegoldia magna* was over-abundant in HS skin samples relative to healthy controls. It is possible local inflammation is driven by *F. magna* through promoting the formation of neutrophil extracellular traps (NET). These alterations in the skin microbiome in HS warrant further exploration, and may inform future therapeutic strategies.

4.1 Introduction

Hidradenitis suppurativa (HS) is a chronic, debilitating, follicular skin disease presenting with deep-seated, painful, inflammatory nodules of the axillary, inframammary, inguinal, and anogenital regions (628). A population prevalence of up to 4% has been reported in the literature (229,628,629). There is a female predominance, with pubertal onset (628,630,631). Smoking, obesity are associated, and a genetic predisposition has been reported (630–632). Comorbidities have been identified in patients with HS including spondyloarthropathy, metabolic syndrome and inflammatory bowel disease (IBD), particularly Crohn's disease (61,633,634). As well as significant morbidity, HS is associated with increased mortality, in particular due to cardiovascular events, with increased cancer risk also recorded (635,636). Depression, anxiety and substance misuse are also common (637,638).

The cause of HS is incompletely understood, with follicular occlusion, dysregulated inflammatory response of cytokines such as tumour necrosis factor (TNF)-a, interleukin(IL)-1ß and IL-17, and an altered microbiota are thought to play a role (141,158,630,639–642).

In this study we tested for an association between microbiota alteration in the skin and nasal mucosa, and HS. The microbiota across the various niches was compared to that of healthy controls.

4.2 Material and Methods

4.2.1 Study Population

Adult patients with a confirmed clinical diagnosis of hidradenitis suppurativa made by a consultant dermatologist in two tertiary referral centres in Ireland were invited to participate in the study. Ethical approval (Cork Research Ethics Committee and Tallaght University Hospital Ethics Committee), and written informed consent from patients was obtained. Exclusion criteria included topical or oral antibiotic usage in the preceding four weeks. Data including age, gender, smoking status, weight, height, body mass index, presence of co-morbidities and severity of disease (Hurley Score)(16). Healthy adult controls were recruited from the general population, and were age and gender matched.

4.2.2 Sample collection

In patients with HS, skin swabs (DNA-free) were taken from affected sites (axilla, inframammary, inguinal and perineal/nates) using a buffer solution with firm swabbing for 30-60 seconds. Affected sites varied by number and location in HS patients. Participants did not bathe for at least 24-48 hours prior to taking swabs and were asked to not apply anti-perspirants or emollients on the skin in that time. Skin swabs were taken from corresponding sites in controls (axilla, inframammary, inguinal and perineal/nates) using the same technique. Nasal swabs were also taken from both groups.

4.2.3 Microbial DNA extraction

Nasal and skin swabs were extracted using QIAamp UCP Pathogen Mini Kit (Qiagen, Hilden, Germany) as per manufacturer's instructions. (See Supplementary Methods Chapter)

4.2.4 Library Preparation and 16S rRNA gene sequencing

Total community DNA extracted from clinical samples underwent 16S rRNA gene PCR. The 16S rRNA gene was amplified using primers for the V3-V4 region; forward, TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGCCTACGGGNGGCWGCAG-3′ and reverse, 5′-GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGGACTACHVGGGTATCTAATCC-3'[17](643).

Microbial genomic DNA extracted from skin swab samples was amplified using MTP Taq DNA Polymerase (Merck KGaA, Darmstadt, Germany) with the PCR thermocycler protocol as follows: Initiation step of 94°C for 1 min followed by 35 cycles of 94°C for 60 s, 55 °C for 45 s, and 72 °C for 30 s, and a final extension step of 72 °C for 5 min.

A subsequent indexing PCR was carried out to add unique sample-specific DNA barcodes to the generated amplicons in accordance with the Illumina 16S Metagenomic Sequencing Protocol (Illumina, California, USA)(644). Libraries DNA concentration was quantified using a Qubit fluorimeter (Invitrogen) using the 'High Sensitivity' assay and samples were pooled at a standardised concentration (644). The pooled library was sequenced on the Illumina MiSeq platform (Illumina, California, USA) utilising 2×300 bp chemistry.

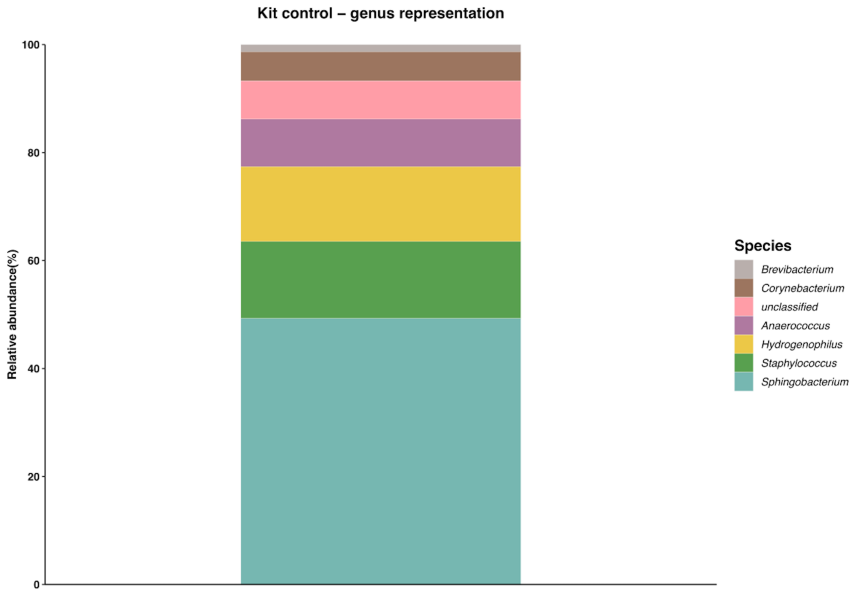
4.2.5 Bioinformatic and biostatistical analysis

The majority of the analysis was performed in R (v3.6.0). Paired reads were quality filtered, trimmed, merged and Amplicon Sequence Variants (ASV) inferred using the R package dada2 (v1.12.1)(645). Taxonomic classification was performed using the RDP Classifier within Mothur in conjugation with SPINGO, a species-level classifier (646). A confidence cut of 80% was used for taxonomic assignment. QIIME v1.9.1 and the R package vegan v2.5.6 were used to calculate β-diversity metrics (647). β-diversity was visualized via principal coordinates analysis (PCoA) plots whose coordinates were identified using with the Ape package v5.1. R-squared (R^2) and p-value were calculated using Permutational Multivariate Analysis of Variance (PERMANOVA) via the R package vegan (v2.4.2). Differential abundance analysis was carried out using DEseq2 (v1.22.2)(648). Random forest was performed in R using the package randomForest (v4.6.14). Genomic functionality was inferred using PICRUSt2 with the command picrust2_pipeline.py with default (649).

4.2.6 Identification of potential microbial DNA contamination

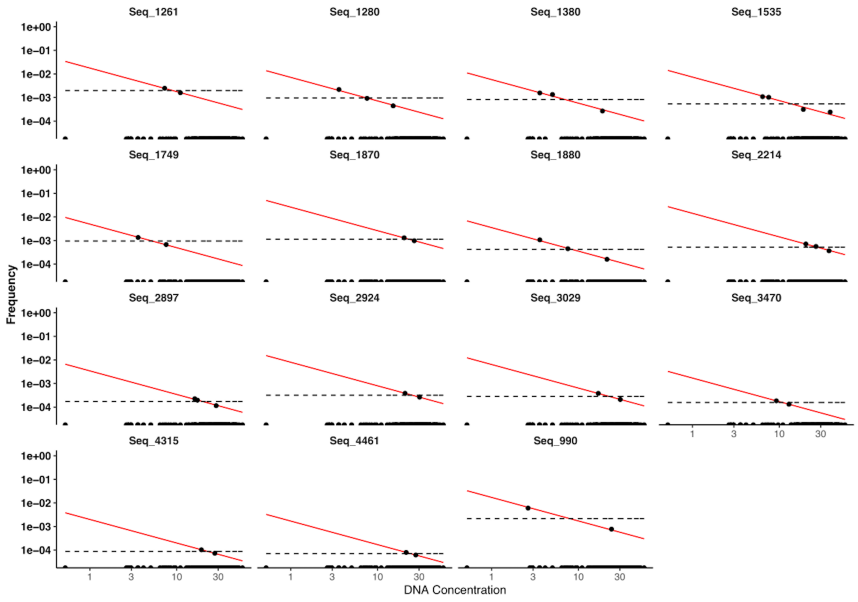
Because skin samples are considered low biomass with respect to bacterial load, we included protocols to mitigate the potential impact of contamination. Reagents used were selected based on their quality of being putatively microbial DNA free including the QIAamp Ultraclean production Pathogen Mini Kit (Qiagen, Hilden, Germany) and MTP Taq DNA Polymerase (Merck). However, these reagents can inadvertently contain contamination. Furthermore, contamination can come from a range of other sources including environmental and user-derived contamination. A negative control was run within the same sequencing batch to detect potential contamination from reagents. This negative control was dominated by taxa typical of contamination including *Sphingobacterium* and *Hydrogenophilus* (Figure 1)(650).

Figure 1: Taxonomic representation within mock extraction. Bar plots displaying the relative abundance of genera within the kit control.



Furthermore, the negative sample had atypically low DNA concentration (0.521ng/µl) relative to extracted clinical samples as measured by the qubit (Supplementary Table 1). Other non-contaminant taxa were found in the kit control but we posit that this is due to index swapping (651). We further utilized the R package decontam to detect contaminating ASVs (652). Using the 'frequency method' we identified 15 ASVs that reached the threshold (Supplementary Table 2). These ASVs contributed only modestly to the samples, median=0, mean=0.01881(Figure 2).

Figure 2: Decontam frequency graph. X-axis equals concentration of sample before normalisation. Y-axis equals frequency of ASV. Each dot represents a sample.



Filtering these ASVs from the ASV table had no effect on differential abundance analysis.

4.2.7 Storage of sequencing data

Datasets related to this article can be found at https://www.ebi.ac.uk/ena/browser/view/PRJEB43835, hosted at European Nucleotide Archive, accession number PRJEB43835 (653).

4.3 Results

4.3.1 Descriptive statistics of the study population

59 patients with HS were recruited providing skin swabs and nasal swabs (Table 1). 20 healthy controls provided skin and nasal swabs (Planned 3:1 ratio). Mean body mass index (BMI) in the HS group was 31.5, and 28.06 in the skin control group. Of the 59 patients with HS, 18 (30.5%) were Hurley Stage 1 (abscess formation without sinus tracts and cicatrisation), 32 (54.2%) were Hurley Stage 2 (recurrent abscesses with tract formation and scars) and 9 (15.3%) were Hurley Stage 3 (multiple interconnected tracts and abscesses throughout an entire area).

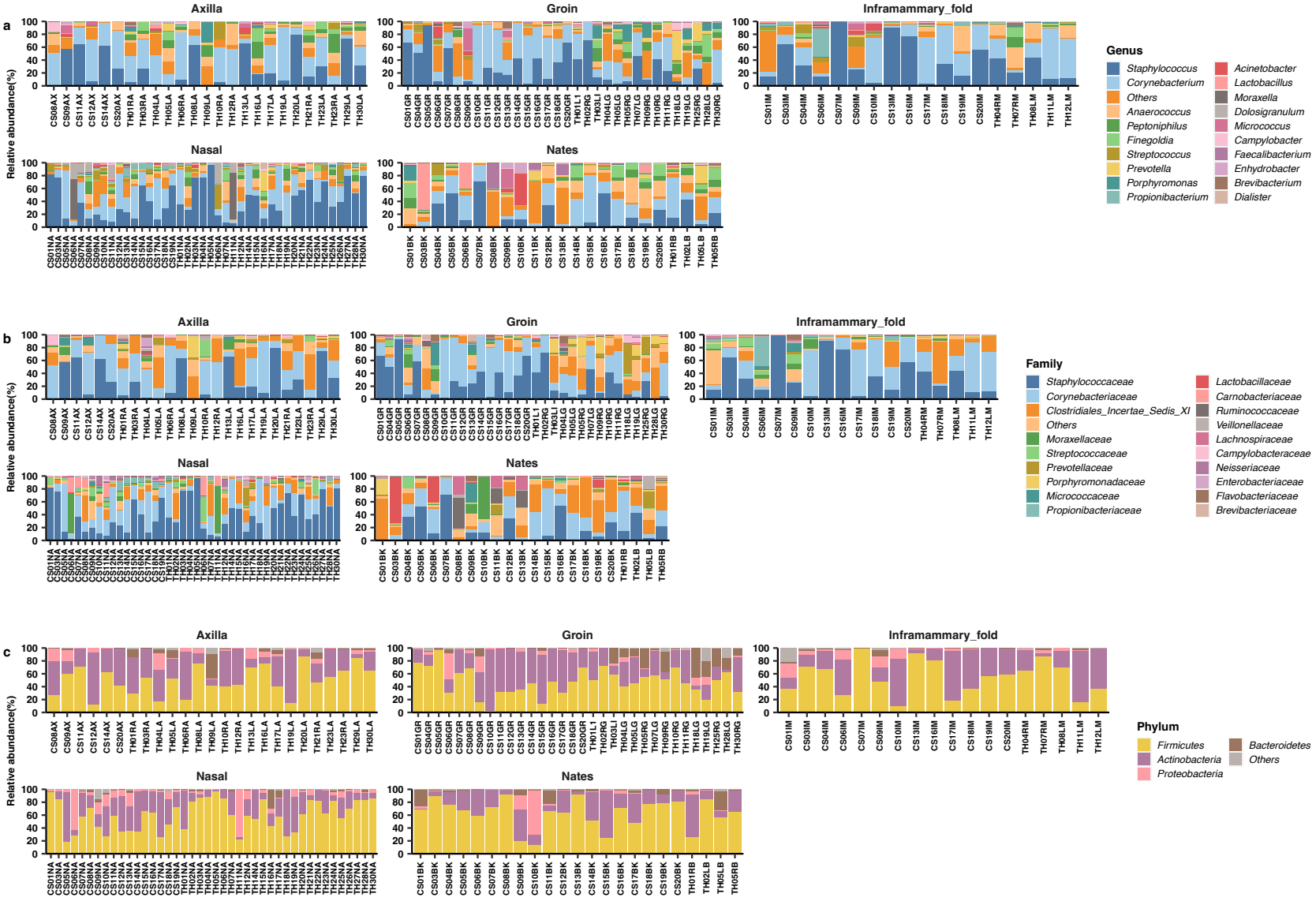
Table 1: Subject characteristics of HS subjects and healthy controls. Comparison of variables between HS cohort and healthy controls. Wilcoxon signed-rank test or $\chi 2$ statistic was used to determine significance.

	HS	**Controls**	**Significance**
N (patients)	59	20	n/a
Gender (Female/Male)	45/14	15/5	NS
Age (mean, range)	37, 21-62	41, 24-68	NS
BMI (mean, range)	31.5, 19.6-45.0	28.06, 20.3-40	0.023
Crohn's Disease (yes/no)	4/59	0/20	NS
TNF-α inhibitor therapy	9/59	0/20	
Nasal			
N (patients)	25	17	n/a
Gender (Female/Male)	22/3	12/5	NS
Age (mean, range)	41, 24-54	36, 24-68	NS
BMI (mean, range)	33, 20.4-45.0	29	NS
Axilla			
N (patients)	19	6	n/a
Gender (Female/Male)	16/3	2/4	NS
Age (mean, range)	39, 24-54	37, 29-52	NS
BMI (mean, range)	31, 19.6-45.0	29, 22.5-39.2	NS
Groin			
N (patients)	15	17	n/a
Gender (Female/Male)	12/3	12 /5	NS
Age (mean, range)	35, 24-52	40, 24-68	NS
BMI (mean, range)	30, 20.4-44.9	29, 20.9-40.0	NS
Breast			
N (patients)	5	13	n/a
Gender (Female/Male)	5/0	13/0	NS
Age (mean, range)	39, 25-52	39, 24-54	NS
BMI (mean, range)	30.5, 19.6-38.0	28.3, 23.6-40.0	NS
Nates			
N (patients)	4	19	n/a
Gender (Female/Male)	2/2	14/5	NS
Age (mean, range)	36, 28-39	40, 24-68	NS
BMI (mean, range)	31 30.0-31.6	28, 20.9-40.0	NS

4.3.2 Ecological structure is altered in nasal and skin microbiome

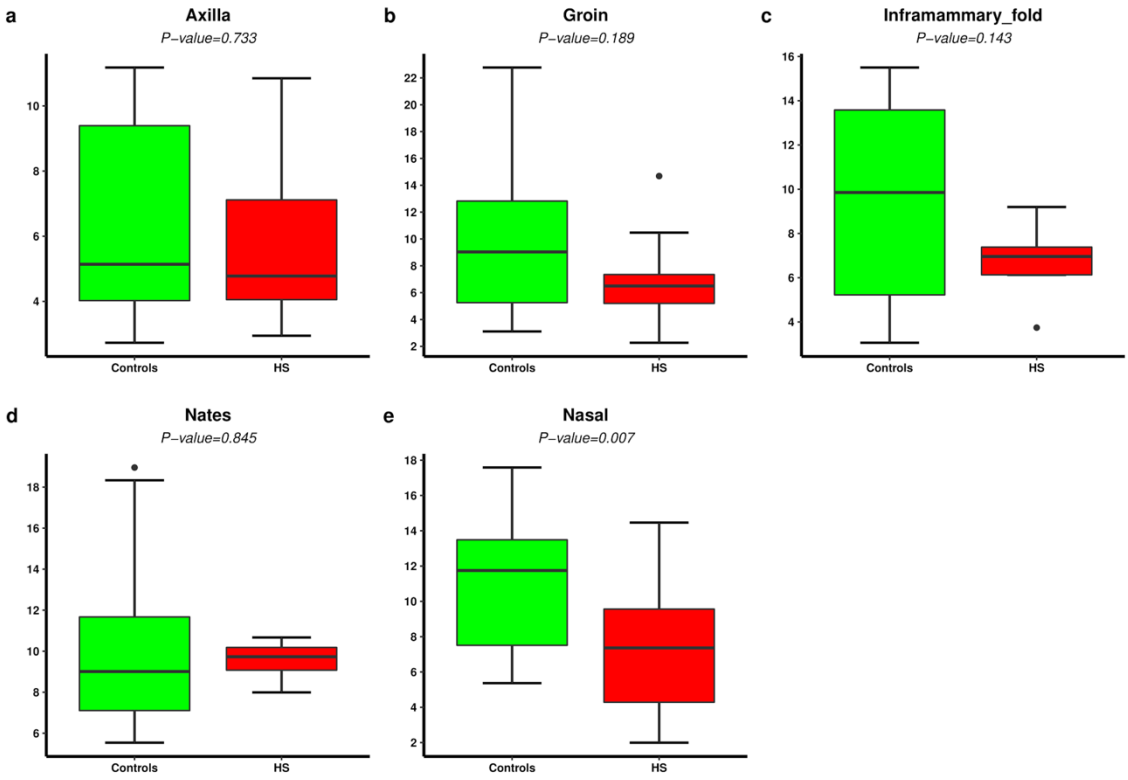
Microbial material derived from skin swabs is generally considered low biomass. In the current study, a high PCR cycle number was therefore used to maximise yield and the number of samples which produced usable amplicons. However, such a methodology is susceptible to contamination, that is, detection of microbial DNA not derived from the sample under study including reagent-derived microbial DNA. We employed a number of techniques to reduce and/or detect contaminant microbial DNA (See methods section). Although no overt level of contamination was detected, one cannot rule out all sources of contamination including environmental and user derived contamination. Skin and nasal samples with low PCR yield were excluded from the analysis resulting in differences in the final numbers of sites sampled per subject. The overall microbiome composition of nasal and skin samples studied was typical of what has been previously described, that is, mainly composed of the genera *Staphylococcus* and *Corynebacterium* (Figure 2).

Figure 2: Taxonomic representation of microbiome of nasal and skin specimens. (a) Bar plots displaying the relative abundance of genera within nasal and skin samples. Genera with a relative abundance of less than 0.5% across all samples grouped into ‘others’ with sequences not classified at the genus level. (b) Bar plots displaying the relative abundance of families within nasal and skin samples. Families with a relative abundance of less 0.5% across all samples grouped into ‘others’ with sequences not classified at the family level. (c) Bar plots displaying the relative abundance of phyla within nasal and skin samples. Families with a relative abundance of less 1% across all samples grouped into ‘others’ with sequences not classified at the phylum level.


a
Axilla
Groin
Inframammary_fold
Nasal
Nates
Relative abundance(%)
Genus
Staphylococcus
Corynebacterium
Others
Anaerococcus
Peptoniphilus
Finegoldia
Streptococcus
Prevotella
Porphyromonas
Propionibacterium
Acinetobacter
Lactobacillus
Moraxella
Dolosigranulum
Micrococcus
Campylobacter
Faecalibacterium
Enhydrobacter
Brevibacterium
Dialister
b
Axilla
Groin
Inframammary_fold
Nasal
Nates
Relative abundance(%)
Family
Staphylococcaceae
Corynebacteriaceae
Clostridiales_Incertae_Sedis_XI
Others
Moraxellaceae
Streptococcaceae
Prevotellaceae
Porphyromonadaceae
Micrococcaceae
Propionibacteriaceae
Lactobacillaceae
Carnobacteriaceae
Ruminococcaceae
Veillonellaceae
Lachnospiraceae
Campylobacteraceae
Neisseriaceae
Enterobacteriaceae
Flavobacteriaceae
Brevibacteriaceae
c
Axilla
Groin
Inframammary_fold
Nasal
Nates
Relative abundance(%)
Phylum
Firmicutes
Actinobacteria
Proteobacteria
Bacteroidetes
Others

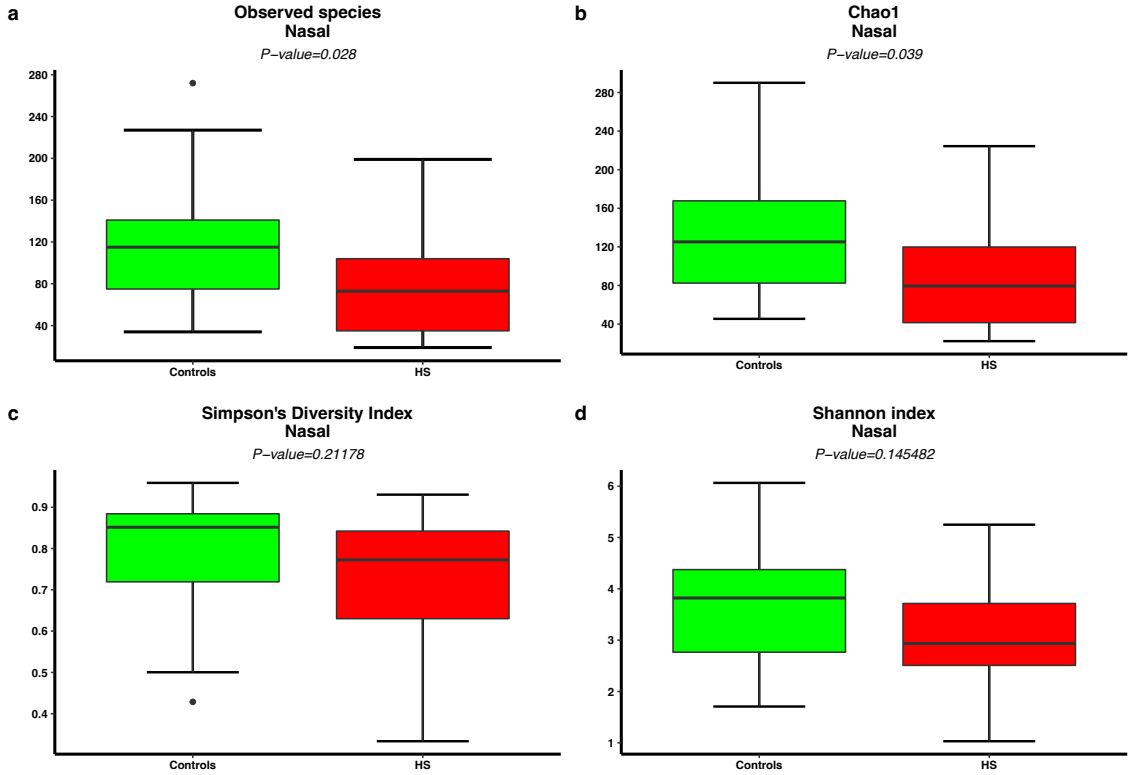
Both nasal and skins swabs showed a reduction in alpha-diversity in the HS cohort (Figure 3). However, only nasal swabs reached a statistically significant decrease.

Figure 3: Alpha-diversity comparisons across nasal and skin microbiome. Bar plots of alpha-diversity (Phylogenetic diversity) comparing healthy controls versus individuals with HS. Wilcoxon signed-rank test was used to calculate p-values.



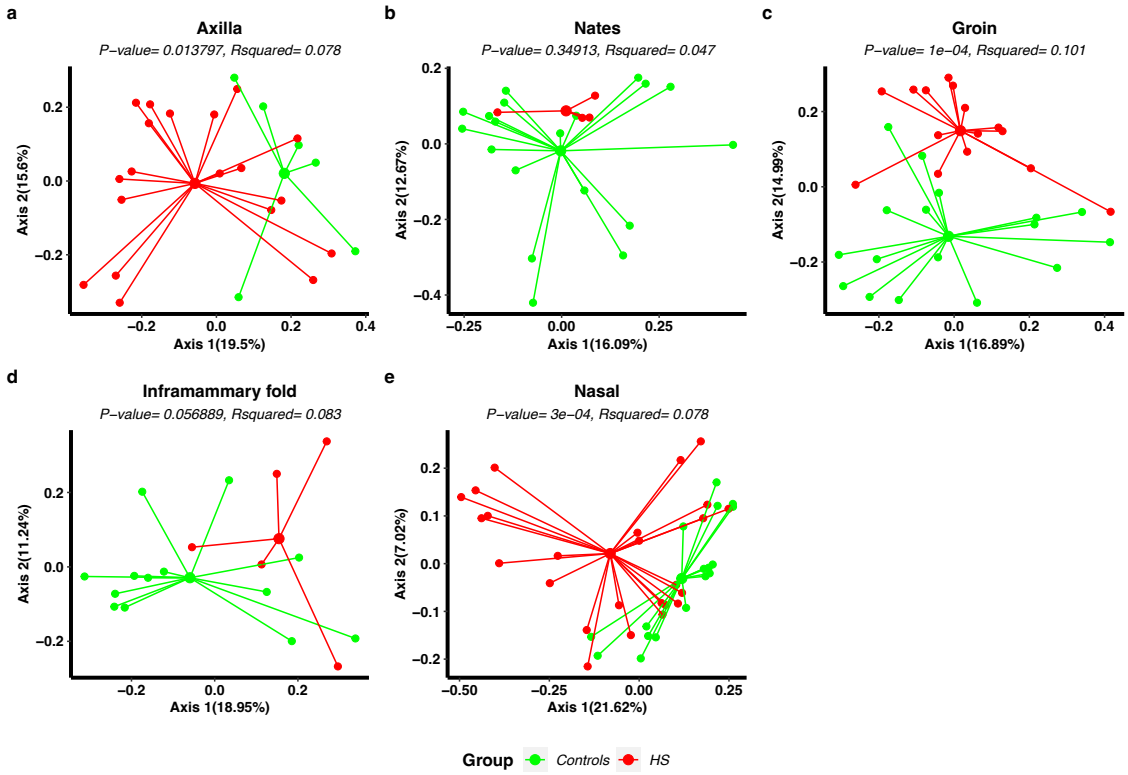
This was also true for other alpha-diversity metrics including Observed species and Chao1 but not for Simpson or Shannon indices (Figure 4).

Figure 4: Bar plots of alpha diversity metrics for nasal samples. (a) Phylogenetic diversity. (b) Chao1. (c) Simpson's Diversity Index. (d) Shannon index. Wilcoxon signed-rank test was used to calculate p-values.



The number of subjects that contributed samples to some sites was low, with a low control number, thus the statistical power was reduced and significance difficult to capture. There was a statistically significant separation in beta-diversity with respect to axilla, groin, and nasal microbiota datasets (Figure 5), showing that different microbiome communities are present at these body sites.

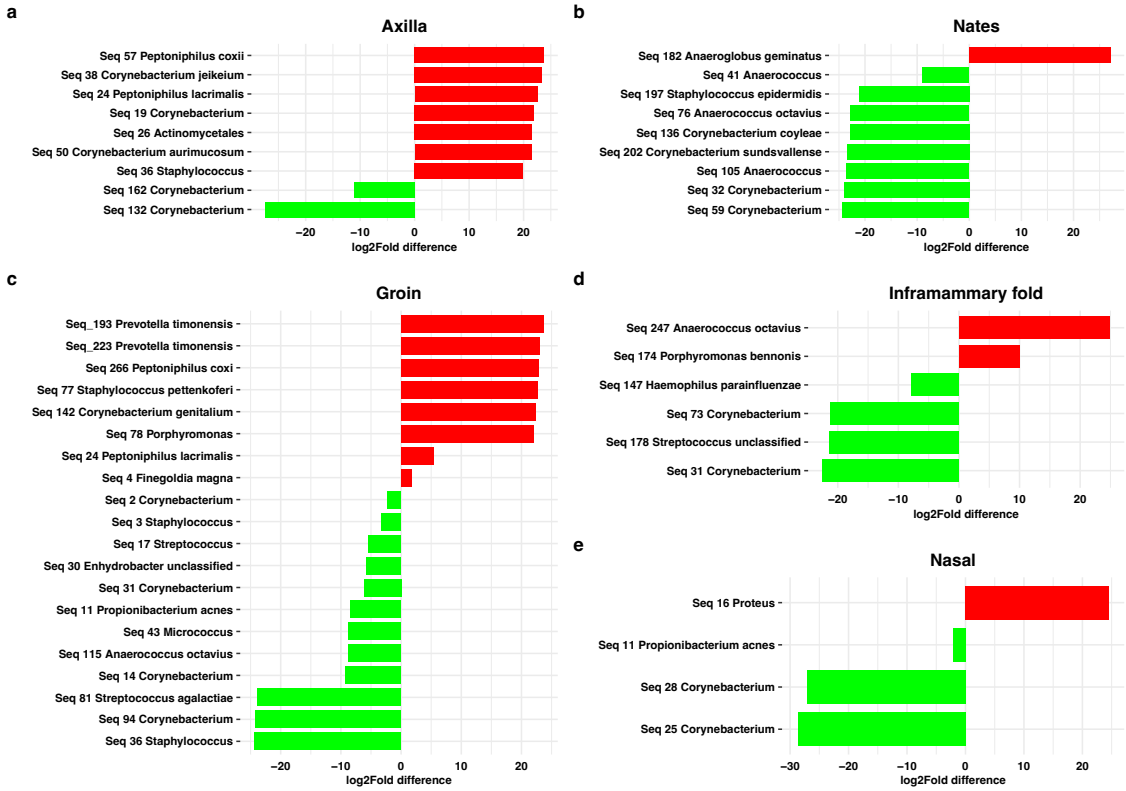
Figure 5: Beta-diversity comparisons of nasal and skin microbiome. Principal Coordinates Analysis representation of Beta diversity (Unweighted Unifrac) between individuals with HS versus healthy controls. Statistical testing was performed using Permutational Multivariate Analysis of Variance.



4.3.3 Differentially abundant ASVs and metabolic pathways in the nasal and skin microbiome of HS patients

We identified differentially abundant ASVs in the nasal microbiome and all skin sites studied (Figure 6). ASVs were collapsed to the species level and differential species abundance delineated (Figure 6).

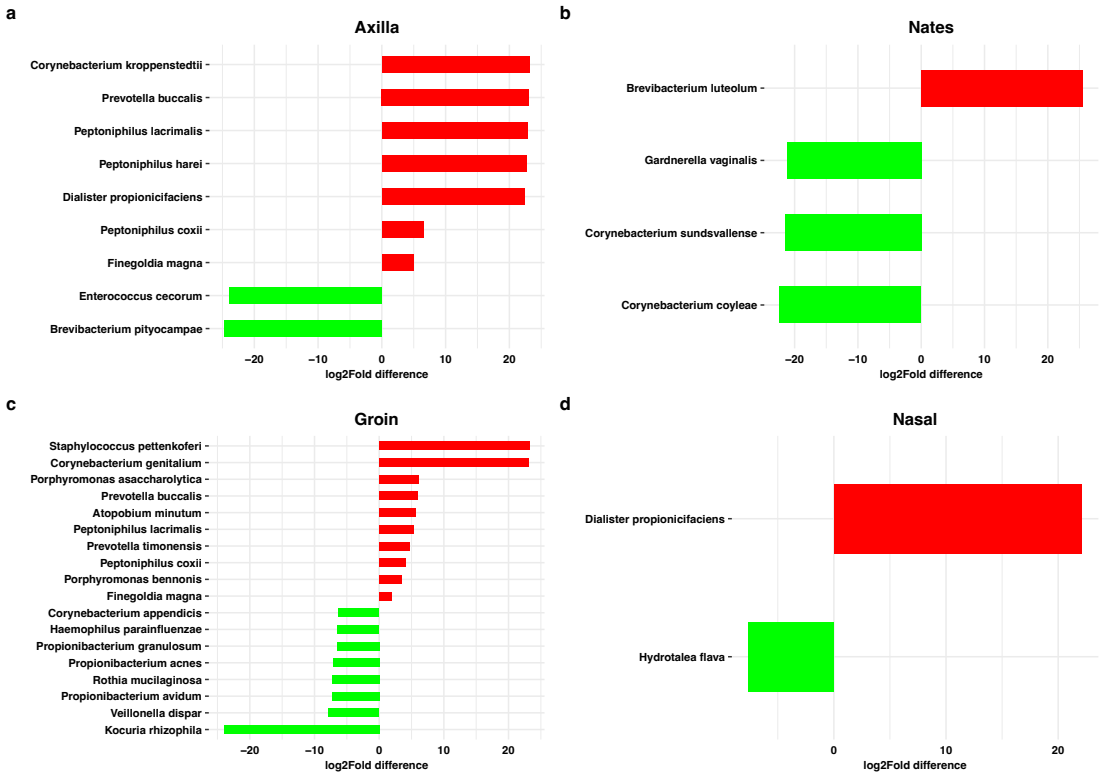
Figure 6: Bar plots of differentially abundant ASVs across nasal and skin swab samples. DESeq2 used to for statistical analysis. ASVs enriched in HS samples in red. ASVs enriched in control samples in green.



An ASV, Seq 4, assigned to *Finegoldia magna* had a significantly higher abundance at the groin site in individuals with HS relative to healthy controls. Furthermore, at

the species level, *F. magna* was more abundant in HS relative to healthy controls in groin and axilla samples (Figure 7).

Figure 7: Bar plots of differentially abundant species across nasal and skin sites. DESeq2 was used to for statistical analysis. Species enriched in HS samples in red. Species enriched in control samples in green.



HS is more common in women, resulting in an expected higher ratio of female to males in this study. To correct for this confounder, we performed differential abundance analysis, integrating gender in to the DESeq model, to identify differently abundant ASVs and species (Figure 8, Figure 9).

Figure 8: Bar plots of differentially abundant ASVs across nasal and skin swab samples. DESeq2 was used to for statistical analysis while controlling for gender as a confounder. ASVs enriched in HS samples in red. ASVs enriched in control samples in green.

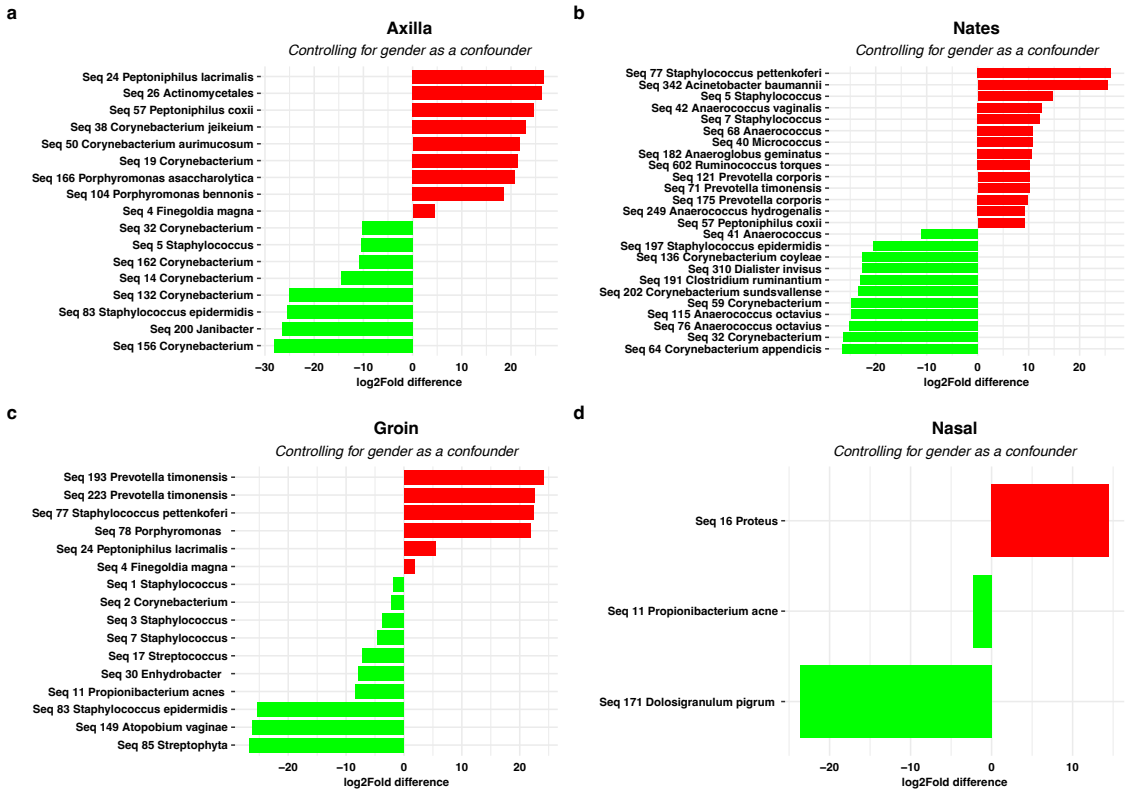
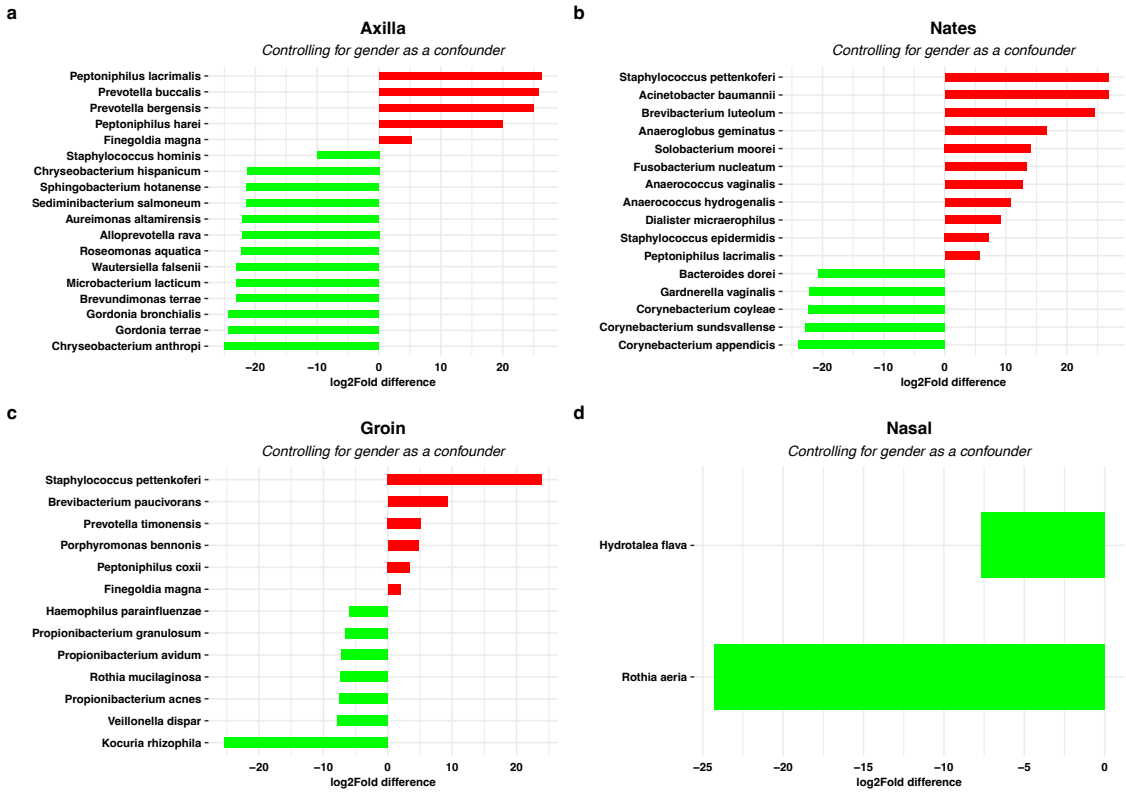


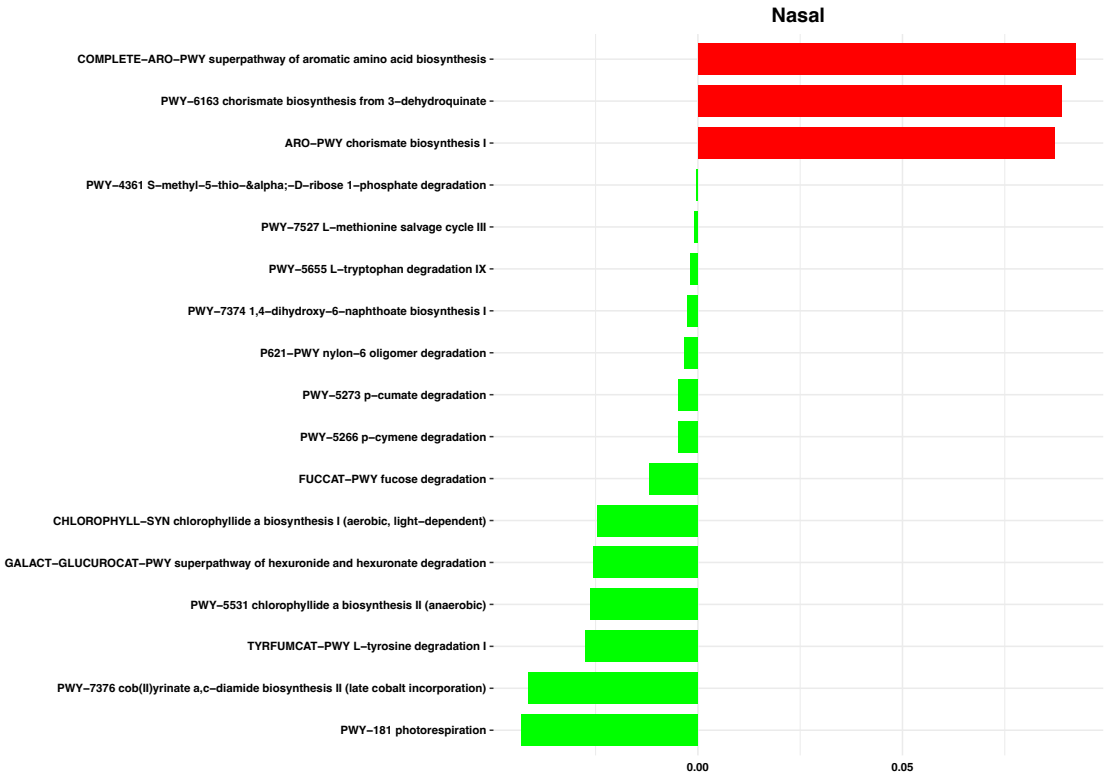
Figure 9: Bar plots of differentially abundant species across nasal and skin sites. DESeq2 was used to for statistical analysis while controlling for gender as a confounder. Species enriched in HS samples in red. Species enriched in control samples in green.



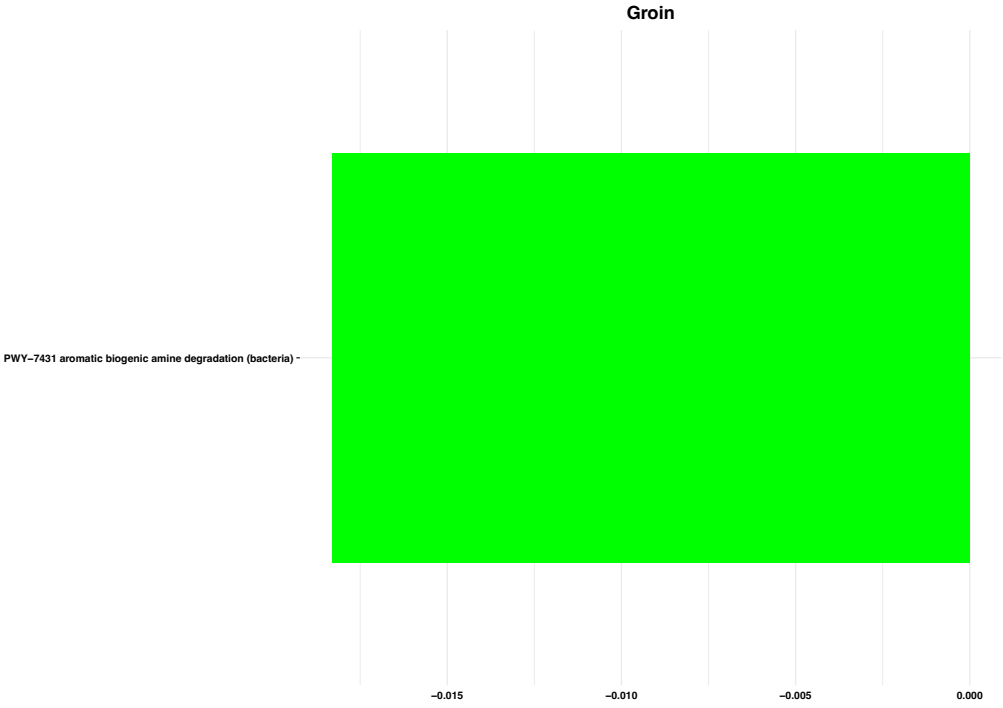
The *Finegoldia magna* assigned ASV Seq 4 was found at increased abundance in groin and axilla samples derived from individuals with HS relative to healthy controls. This was also reflected at the species level. Significantly differentially abundant pathways were found in relation to the nasal microbiome and one pathway in the groin microbiome (Figure 10).

Figure 10: Differential MetaCyc pathways across skin sites. (a) Nasal. (b) Groin. Wilcoxon signed-rank test was used to calculate p-values. MetaCyc pathways enriched in HS samples in red. MetaCyc pathways enriched in control samples in green.

(a)



(b)


Groin
PWY−7431 aromatic biogenic amine degradation (bacteria)
−0.015
−0.010
−0.005
0.000

4.4 Discussion

We identified a number of differences in microbiome configuration in faecal and swab samples from across a number of body sites in individuals with HS compared to healthy controls. Alpha diversity was lower in subjects with HS across most of these sites suggesting a reduction in the richness of the skin microbiota compared to controls. Decreases in alpha diversity in skin, and nasal microbiota have been reported in atopic dermatitis, with conflicting results for the gut microbiota (654–657). Alpha-diversity has been observed to be lower in skin samples from individuals with psoriasis, with even more variable results in the gut (658–660).

4.4.1 Skin Microbiome

Ring *et al* examined the difference in the skin microbiome between subjects with hidradenitis suppurativa and healthy controls using skin biopsies (159). Our analysis corroborates and extends the number of taxa found to differentially abundant. In particular there is agreement that *Peptoniphilus lacrimalis*, *Finegoldia magna*, *Peptoniphilus coxii, Anaerococcus murdochii, and Anaerococcus obesiensis* are more abundant in HS, with a higher abundance of *Cutibacterium acnes* in healthy controls (159). Colonisation and proliferation of certain strains of *C. acnes* may play a role in the pathogenesis of acne vulgaris (661,662). The depletion of *C. acnes* in individuals with HS suggests that it does not play a similar mechanistic role in HS as it does in acne. However, a decrease in *C. acnes* may alter the microbial ecological of skin and promote HS pathogenesis. Alpha diversity was reduced in nasal and groin samples. This is also found in atopic dermatitis; however, the corresponding increase in *Staphylococcus aureus* typically seen in atopic dermatitis was not detected in these patients with HS (663,664). Similarly, in psoriasis a reduction in alpha diversity is seen compared to healthy controls, featuring elevated

Streptococcus and reduction in *Propionibacterium* that was not seen in this cohort with HS (660). Higher numbers of bacteria with pathogenic capability namely *F. magna* was noted in the current study. *F. magna* has been shown to have immune modulating activities; in particular it can promote the formation of neutrophil extracellular traps (NET). These NETs feature prominently in HS lesions and their abundance is correlated with disease severity, as measured by Hurley staging (665). Thus *F. magna* may contribute to HS disease biology by stimulating NET formation. *F. magna* has also been shown to activate mast cells and basophils which in turn produce proinflammatory histamine and cytokines (666,667). In a recent study *F. magna* was demonstrated to activate proinflammatory neutrophils mediated by virulence factors protein L and FAF (*F. magna* adhesion factor)(668).

4.4.2 Potential impact

There is a lack of high-quality evidence for treatment options in HS (226,628,669). A multidisciplinary approach with a combination of medical and surgical treatment is often needed, combined with lifestyle measures: smoking cessation and weight loss (226,628,669). Antibiotics remain the initial treatment for most patients, with TNF-alpha inhibitors in those who fail to respond (226,628,669). The use of antibiotics in HS, for their anti-inflammatory rather than anti-microbial effect, may play a role in the reduction in alpha-diversity seen in this study; however, we detected no significant difference in ASVs in those who received antibiotics in the preceding year compared to those who did not. Microbiota based therapies may have potential benefits in HS, in particular targeted microbial supplementation to increase diversity and richness. The selective depletion of certain microbes such as *F. magna* and *R. gnavus*, which may play a pathogenic role, could provide therapeutic targets.

4.5 Conclusion

We have characterised the skin microbiota in patients with HS compared to healthy controls. The identification of particular taxa that may contribute to HS pathogenesis, such as *F. magna,* could inform future microbiota-based therapeutic strategies.

Supplementary Table 1: DNA concentration of samples as measured by the qubit.

Sample name	Patient	disease_state	qubit_values	skin_site	sample_type
Blank	Blank	blank	0.521	blank	blank
CS01BK	CS01	control	29.6	Buttock	swab
CS01GR	CS01	control	30.4	Groin	swab
CS01IM	CS01	control	2.63	Inframammary_fold	swab
CS01NA	CS01	control	30.7	Nasal	swab
CS03BK	CS03	control	35.1	Buttock	swab
CS03IM	CS03	control	7.25	Inframammary_fold	swab
CS03NA	CS03	control	31.7	Nasal	swab
CS04BK	CS04	control	28.6	Buttock	swab
CS04GR	CS04	control	24.9	Groin	swab
CS04IM	CS04	control	26.3	Inframammary_fold	swab
CS05BK	CS05	control	15.1	Buttock	swab
CS05GR	CS05	control	22.4	Groin	swab
CS05NA	CS05	control	8.53	Nasal	swab
CS06BK	CS06	control	28	Buttock	swab
CS06GR	CS06	control	7.55	Groin	swab
CS06IM	CS06	control	3.59	Inframammary_fold	swab
CS06NA	CS06	control	23.8	Nasal	swab
CS07BK	CS07	control	17.3	Buttock	swab
CS07GR	CS07	control	16.6	Groin	swab
CS07IM	CS07	control	16.1	Inframammary_fold	swab
CS07NA	CS07	control	40.2	Nasal	swab
CS08AX	CS08	control	18.6	Axilla	swab
CS08BK	CS08	control	25.3	Buttock	swab
CS08GR	CS08	control	24.3	Groin	swab
CS08NA	CS08	control	27.5	Nasal	swab
CS09AX	CS09	control	25.1	Axilla	swab
CS09BK	CS09	control	30.6	Buttock	swab
CS09GR	CS09	control	37.3	Groin	swab
CS09IM	CS09	control	26.4	Inframammary_fold	swab
CS09NA	CS09	control	20.2	Nasal	swab
CS10BK	CS10	control	3.55	Buttock	swab
CS10GR	CS10	control	23	Groin	swab
CS10IM	CS10	control	23.9	Inframammary_fold	swab
CS10NA	CS10	control	15.9	Nasal	swab
CS11AX	CS11	control	11	Axilla	swab
CS11BK	CS11	control	24	Buttock	swab
CS11GR	CS11	control	16.3	Groin	swab
CS11NA	CS11	control	19.6	Nasal	swab
CS12AX	CS12	control	15.9	Axilla	swab
CS12BK	CS12	control	24.5	Buttock	swab
CS12GR	CS12	control	24	Groin	swab

CS12NA	CS12	control	30.3	Nasal	swab
CS13BK	CS13	control	18.5	Buttock	swab
CS13GR	CS13	control	14.8	Groin	swab
CS13IM	CS13	control	23.8	Inframammary_fold	swab
CS13NA	CS13	control	18.9	Nasal	swab
CS14AX	CS14	control	2.98	Axilla	swab
CS14BK	CS14	control	18.2	Buttock	swab
CS14GR	CS14	control	32.7	Groin	swab
CS14NA	CS14	control	16.9	Nasal	swab
CS15BK	CS15	control	24.2	Buttock	swab
CS15GR	CS15	control	28.4	Groin	swab
CS15NA	CS15	control	19.2	Nasal	swab
CS16BK	CS16	control	5.02	Buttock	swab
CS16GR	CS16	control	13.9	Groin	swab
CS16IM	CS16	control	8.03	Inframammary_fold	swab
CS16NA	CS16	control	31.6	Nasal	swab
CS17BK	CS17	control	15.3	Buttock	swab
CS17GR	CS17	control	16.2	Groin	swab
CS17IM	CS17	control	19.2	Inframammary_fold	swab
CS17NA	CS17	control	13.6	Nasal	swab
CS18BK	CS18	control	16.2	Buttock	swab
CS18GR	CS18	control	9.69	Groin	swab
CS18IM	CS18	control	9.25	Inframammary_fold	swab
CS18NA	CS18	control	6.42	Nasal	swab
CS19BK	CS19	control	24	Buttock	swab
CS19IM	CS19	control	21.4	Inframammary_fold	swab
CS19NA	CS19	control	19.8	Nasal	swab
CS20AX	CS20	control	20.6	Axilla	swab
CS20BK	CS20	control	32	Buttock	swab
CS20GR	CS20	control	32.2	Groin	swab
CS20IM	CS20	control	27.1	Inframammary_fold	swab
TH01L1	TH01	HS	20.6	Groin	swab
TH01NA	TH01	HS	35.9	Nasal	swab
TH01RA	TH01	HS	32.5	Axilla	swab
TH01RB	TH01	HS	32.8	Buttock	swab
TH02LB	TH02	HS	20.7	Buttock	swab
TH02NA	TH02	HS	38.5	Nasal	swab
TH02RG	TH02	HS	36.2	Groin	swab
TH03LI	TH03	HS	30.7	Groin	swab
TH03NA	TH03	HS	2.76	Nasal	swab
TH03RA	TH03	HS	48	Axilla	swab
TH04LA	TH04	HS	2.95	Axilla	swab
TH04LG	TH04	HS	23.9	Groin	swab
TH04NA	TH04	HS	25.6	Nasal	swab
TH04RM	TH04	HS	20.1	Inframammary_fold	swab

TH05LA	TH05	HS	21.8	Axilla	swab
TH05LB	TH05	HS	36.5	Buttock	swab
TH05LG	TH05	HS	18.1	Groin	swab
TH05NA	TH05	HS	22.1	Nasal	swab
TH05RB	TH05	HS	29.2	Buttock	swab
TH05RG	TH05	HS	44.8	Groin	swab
TH06NA	TH06	HS	30.8	Nasal	swab
TH06RA	TH06	HS	32	Axilla	swab
TH07LG	TH07	HS	43.1	Groin	swab
TH07NA	TH07	HS	45.8	Nasal	swab
TH07RM	TH07	HS	33.5	Inframammary_fold	swab
TH08LA	TH08	HS	39.7	Axilla	swab
TH08LM	TH08	HS	44.9	Inframammary_fold	swab
TH08SP	TH08	HS	28.7	Suprapubic	swab
TH09LA	TH09	HS	31	Axilla	swab
TH09RG	TH09	HS	24.6	Groin	swab
TH10RA	TH10	HS	28	Axilla	swab
TH10RG	TH10	HS	33.7	Groin	swab
TH11LM	TH11	HS	47.8	Inframammary_fold	swab
TH11NA	TH11	HS	37.1	Nasal	swab
TH11RG	TH11	HS	18.8	Groin	swab
TH12LM	TH12	HS	33.1	Inframammary_fold	swab
TH12NA	TH12	HS	28.6	Nasal	swab
TH12RA	TH12	HS	52	Axilla	swab
TH13LA	TH13	HS	29.9	Axilla	swab
TH14NA	TH14	HS	57	Nasal	swab
TH15NA	TH15	HS	27.4	Nasal	swab
TH16LA	TH16	HS	27.9	Axilla	swab
TH16NA	TH16	HS	31.8	Nasal	swab
TH16RAB	TH16	HS	35.6	Abdomen	swab
TH17LA	TH17	HS	2.78	Axilla	swab
TH17NA	TH17	HS	44.9	Nasal	swab
TH18LG	TH18	HS	28.6	Groin	swab
TH18NA	TH18	HS	40.3	Nasal	swab
TH19LA	TH19	HS	19.7	Axilla	swab
TH19LG	TH19	HS	40.2	Groin	swab
TH19NA	TH19	HS	23.3	Nasal	swab
TH20LA	TH20	HS	37.9	Axilla	swab
TH20NA	TH20	HS	47.3	Nasal	swab
TH21NA	TH21	HS	22.9	Nasal	swab
TH21RA	TH21	HS	4.14	Axilla	swab
TH22NA	TH22	HS	32.1	Nasal	swab
TH22SP	TH22	HS	30.4	Suprapubic	swab
TH23LA	TH23	HS	38.9	Axilla	swab
TH23NA	TH23	HS	26.5	Nasal	swab

TH23RA	TH23	HS	34.7	Axilla	swab
TH24LSP	TH24	HS	27.5	Suprapubic	swab
TH24NA	TH24	HS	12.9	Nasal	swab
TH25NA	TH25	HS	31.1	Nasal	swab
TH25RG	TH25	HS	45.6	Groin	swab
TH26AB	TH26	HS	43.2	Abdomen	swab
TH26NA	TH26	HS	49.5	Nasal	swab
TH27NA	TH27	HS	31.1	Nasal	swab
TH28LG	TH28	HS	6.89	Groin	swab
TH28NA	TH28	HS	27.9	Nasal	swab
TH29LA	TH29	HS	21.3	Axilla	swab
TH29LSP	TH29	HS	40.7	Suprapubic	swab
TH30LA	TH30	HS	34.7	Axilla	swab
TH30NA	TH30	HS	34.1	Nasal	swab
TH30RG	TH30	HS	30.3	Groin	swab

Supplementary Table 2: 15 ASVs that reached the threshold using the 'frequency method'

	Kingdom	Phylum	Class	Order	Family	Genus	Species
Seq 990	Bacteria	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	Blautia	Blautia luti
Seq 1261	Bacteria	Cyanobacteria/Chloroplast	Chloroplast	Chloroplast	Streptophyta	unclassified	unclassified
Seq 1280	Bacteria	Actinobacteria	Actinobacteria	Actinomycetales	Micrococcaceae	Kocuria	unclassified
Seq 1380	Bacteria	Proteobacteria	Alphaproteobacteria	Sphingomonadales	Sphingomonadaceae	Sphingomonas	unclassified
Seq 1535	Bacteria	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	Lactobacillus	Lactobacillus delbrueckii
Seq 1749	Bacteria	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Pseudomonadaceae	Pseudomonas	Pseudomonas rhizosphaerae
Seq 1870	Bacteria	Bacteroidetes	Flavobacteriia	Flavobacteriales	Flavobacteriaceae	Wautersiella	Wautersiella falsenii
Seq 1880	Bacteria	Proteobacteria	Alphaproteobacteria	Rhizobiales	Xanthobacteraceae	Xanthobacter	unclassified
Seq 2214	Bacteria	Candidatus Saccharibacteria	unclassified	unclassified	unclassified	unclassified	unclassified
Seq 2897	Bacteria	Proteobacteria	Alphaproteobacteria	Rhizobiales	Methylobacteriaceae	Methylobacterium	Methylobacterium aquaticum
Seq 2924	Bacteria	Firmicutes	Erysipelotrichia	Erysipelotrichales	Erysipelotrichaceae	unclassified	unclassified
Seq 3029	Bacteria	Firmicutes	Bacilli	Bacillales	Bacillaceae 1	Bacillus	unclassified
Seq 3470	Bacteria	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	Tannerella	Tannerella forsythia
Seq 4315	Bacteria	Acidobacteria	Acidobacteria Gp4	Blastocatella	unclassified	unclassified	unclassified
Seq 4461	Bacteria	Proteobacteria	Epsilonproteobacteria	Campylobacterales	Campylobacteraceae	Campylobacter	Campylobacter ureolyticus

5. The Gut Microbiota in Hidradenitis Suppurativa

Published in Journal of Investigative Dermatology

McCarthy S, Barrett M, Kirthi S, Pellanda P, Vlckova K, Tobin AM, Murphy M, Shanahan F, O'Toole PW. Altered Skin and Gut Microbiome in Hidradenitis Suppurativa. Journal of Investigative Dermatology. 2021 Aug 6.

Presented at European Academy of Dermatology and Venereology 30th Congress, September 2021

Abstract

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by the formation of nodules, abscesses, and fistula at intertriginous sites. The skin-gut axis is an area of emerging research in inflammatory skin disease and is a potential contributory factor to the pathogenesis of HS. 59 patients with HS provided faecal samples for analysis. 30 healthy controls provided faecal samples. We performed bacterial 16S rRNA gene amplicon sequencing on total DNA derived from the samples. Microbiome alpha diversity was significantly lower in the faecal samples of individuals with HS which may be secondary to disease biology or related to antibiotic usage. *Ruminococcus gnavus* was more abundant in the faecal microbiome of individuals with HS, which is also reported in Crohn's disease (CD), suggesting comorbidity due to shared gut microbiota alterations. These alterations in gut microbiome in HS warrant further exploration, and therapeutic strategies including faecal microbiota transplant (FMT) or bacteriotherapy could be of benefit.

5.1 Introduction

Hidradenitis suppurativa (HS) is a chronic, debilitating, follicular skin disease presenting with deep-seated, painful, inflammatory nodules of the axillary, inframammary, inguinal, and anogenital regions (628). A population prevalence of up to 4% has been reported in the literature (229,628,629). There is a female predominance, with pubertal onset (628,630,631). Smoking, obesity are associated, and a genetic predisposition has been reported (630–632). Comorbidities have been identified in patients with HS including spondyloarthropathy, metabolic syndrome and inflammatory bowel disease (IBD), particularly Crohn's disease (61,633,634). As well as significant morbidity, HS is associated with increased mortality, in particular due to cardiovascular events, with increased cancer risk also recorded (635,636). Depression, anxiety and substance misuse are also common (637,638).

The cause of HS is incompletely understood, with follicular occlusion, dysregulated inflammatory response of cytokines such as tumour necrosis factor (TNF)-a, interleukin(IL)-1ß and IL-17, and an altered microbiota are thought to play a role (141,158,630,639–642).

HS and IBD share common manifestations of sterile abscesses, and sinus tract formation (670). Similar pathways are activated in Crohn's disease and HS, with elevated production of the innate immune mediators IL-1, IL-6, IL-17, IL-23 and TNF-α (671–673). Smoking and obesity are common associations, and HS and IBD respond to TNF-a inhibitor therapy (630,674–676). Research supports the role of the gut microbiota in IBD and other inflammatory conditions including rheumatoid arthritis, and psoriasis (677–683). Although the skin microbiota in HS is an area of expanding research, the gut microbiota or the 'gut-skin axis' in HS deserves greater

consideration (236,639,684). One study investigated *Faecalibacterium prausnitzii* and *Escherichia coli* levels in patients with psoriasis, concomitant psoriasis and IBD, HS, and concomitant HS and IBD (684). Increased levels of *E. coli* and decreased levels of *F. prausnitzii* was noted in patients with psoriasis. A significant difference in abundance of *E. coli* or *F. prausnitzii* was not noted in patients with HS (684). As an altered gut microbiota has been associated with various pathophysiologies involving immune dysregulation, it may play a role in the development of HS.
In this study we tested for an association between microbiota alteration in faeces and HS.

5.2 Material and Methods

5.2.1 Study Population

Adult patients with a confirmed clinical diagnosis of hidradenitis suppurativa made by a consultant dermatologist in two tertiary referral centres in Ireland were invited to participate in the study. Ethical approval (Cork Research Ethics Committee and Tallaght University Hospital Ethics Committee), and written informed consent from patients was obtained. Exclusion criteria included topical or oral antibiotic usage in the preceding four weeks. Data including age, gender, smoking status, weight, height, body mass index, presence of co-morbidities and severity of disease (Hurley Score)(16) were recorded. Healthy adult controls were recruited from the general population, and were age and gender matched.

5.2.2 Sample collection

Fresh (<24 hours) faecal samples were provided by patients and controls and stored at -80°C prior to microbial DNA extraction.

5.2.3 Microbial DNA extraction

Microbial DNA was extracted from stool samples using the repeated bead beating method, with some modifications (685). (See Supplementary Methods chapter)

5.2.4 Library Preparation and 16S rRNA gene sequencing

Total community DNA extracted from clinical samples underwent 16S rRNA gene PCR. The 16S rRNA gene was amplified using primers for the V3-V4 region; forward, TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGCCTACGGGNGGCWGCAG-3′ and reverse, 5′-GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGGACTACHVGGGTATCTAATCC-3'[17].(643)

Faecal microbial genomic DNA was amplified using Phusion High-Fidelity DNA Polymerase (Thermo Scientific, Massachusetts, USA) with the PCR thermocycler protocol as follows: Initiation step of 98 °C for 3 min followed by 25 cycles of 98 °C for 30 s, 55 °C for 60 s, and 72 °C for 20 s, and a final extension step of 72 °C for 5 min.

A subsequent indexing PCR was carried out to add unique sample-specific DNA barcodes to the generated amplicons in accordance with the Illumina 16S Metagenomic Sequencing Protocol (Illumina, California, USA)(644). Libraries DNA concentration was quantified using a Qubit fluorimeter (Invitrogen) using the 'High Sensitivity' assay and samples were pooled at a standardised concentration (644). The pooled library was sequenced on the Illumina MiSeq platform (Illumina, California, USA) utilising 2×300 bp chemistry.

5.2.5 Microbiome profiling

The microbiome composition of samples was profiled by standard 16S rRNA gene sequencing protocols as previously published by our laboratory (685). (See Supplementary Methods chapter)

5.2.6 Bioinformatic and biostatistical analysis

The majority of the analysis was performed in R (v3.6.0). Paired reads were quality filtered, trimmed, merged and Amplicon Sequence Variants (ASV) inferred using the R package dada2 (v1.12.1)(645). Taxonomic classification was performed using the RDP Classifier within Mothur in conjugation with SPINGO, a species-level classifier (646). A confidence cut of 80% was used for taxonomic assignment. QIIME v1.9.1 and the R package vegan v2.5.6 were used to calculate β-diversity metrics (647). β-diversity was visualized via principal coordinates analysis (PCoA) plots whose coordinates were identified using with the Ape package v5.1. R-squared (R^2) and p-value were calculated using Permutational Multivariate Analysis of Variance (PERMANOVA) via the R package vegan (v2.4.2). Differential abundance analysis was carried out using DEseq2 (v1.22.2)(648). Random forest was performed in R using the package randomForest (v4.6.14) Genomic functionality was inferred using PICRUSt2 with the command picrust2_pipeline.py with default (649).

5.2.7 Storage of sequencing data

Datasets related to this article can be found at https://www.ebi.ac.uk/ena/browser/view/PRJEB43835, hosted at European Nucleotide Archive, accession number PRJEB43835 (653).

5.3 Results

5.3.1 Descriptive statistics of the study population

59 patients with HS were recruited providing faecal samples. 30 healthy controls provided faecal samples (Planned 2:1 ratio) (Table 1). Mean body mass index (BMI) in the HS group was 31.5, and 28.2 in the faecal control group. 4 (6.8%) patients in the HS group had a history of Crohn's disease. Of the 59 patients with HS, 18 (30.5%) were Hurley Stage 1 (abscess formation without sinus tracts and cicatrisation), 32 (54.2%) were Hurley Stage 2 (recurrent abscesses with tract formation and scars) and 9 (15.3%) were Hurley Stage 3 (multiple interconnected tracts and abscesses throughout an entire area).

Table 1: Subject characteristics of HS subjects and healthy controls

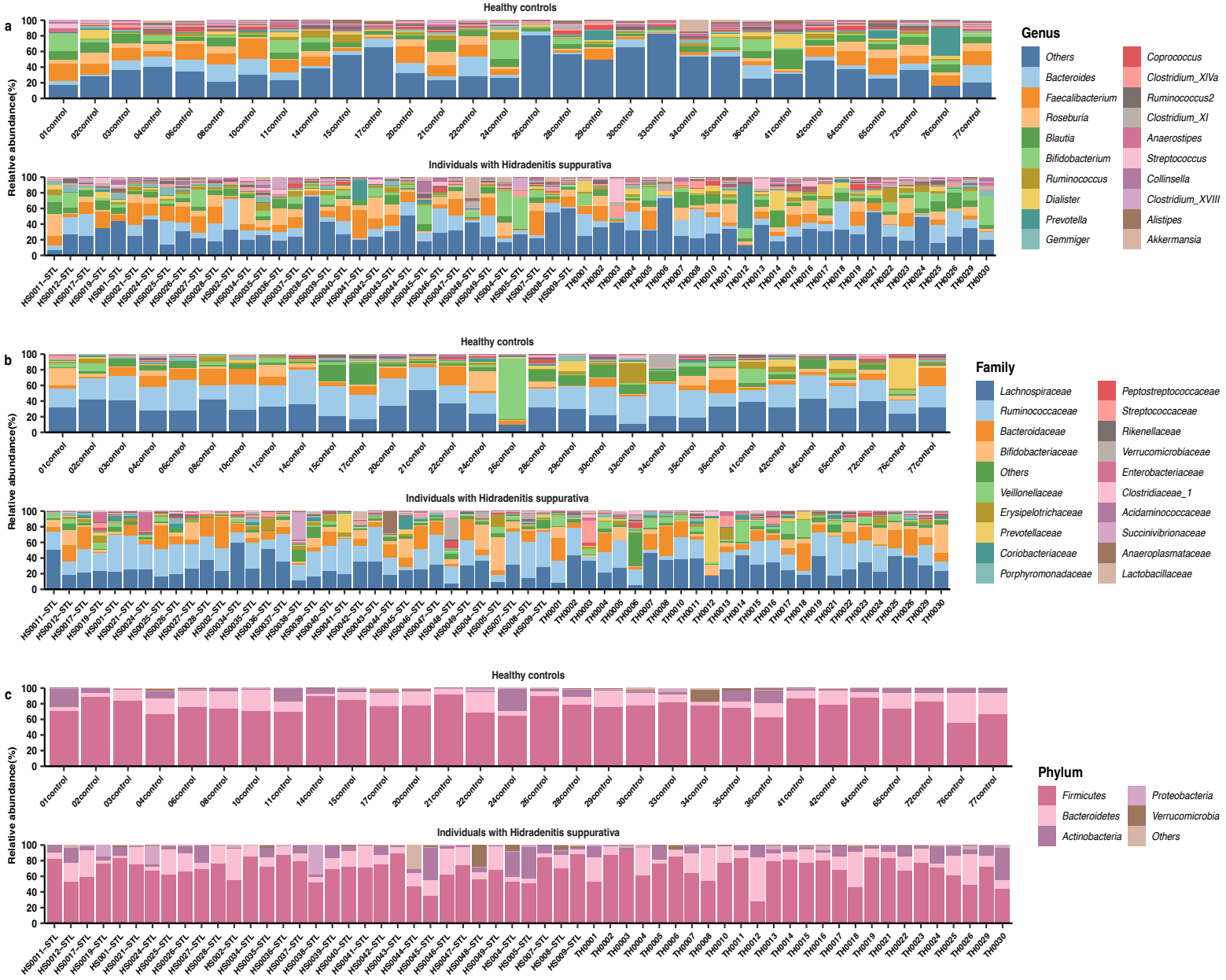
Comparison of variables between HS cohort and healthy controls. Wilcoxon signed-rank test or $\chi 2$ statistic was used to determine significance.

	HS	**Controls**	**Significance**
N (patients)	59	30	n/a
Gender (Female/Male)	45/14	20/10	NS
Age (mean, range)	37, 21-62	38, 19-62	NS
BMI (mean, range)	31.5, 19.6-45.0	28.2, 18.7-46.3	0.023
Crohn's Disease (yes/no)	4/59	0/30	NS
TNF-α inhibitor therapy	9/59	0/30	

5.3.2 Overall structure of the faecal microbiota is altered in HS

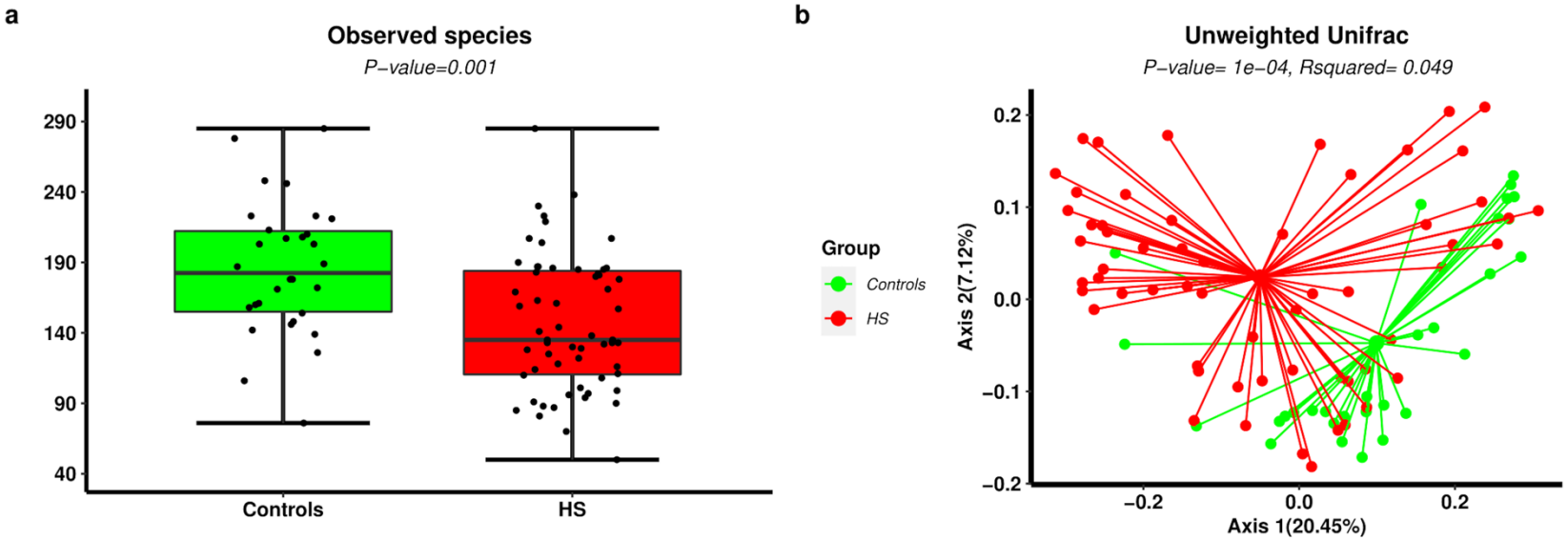
We examined the microbiome composition of 59 and 30 faecal specimens from individuals with HS and healthy controls respectively (Figure 1).

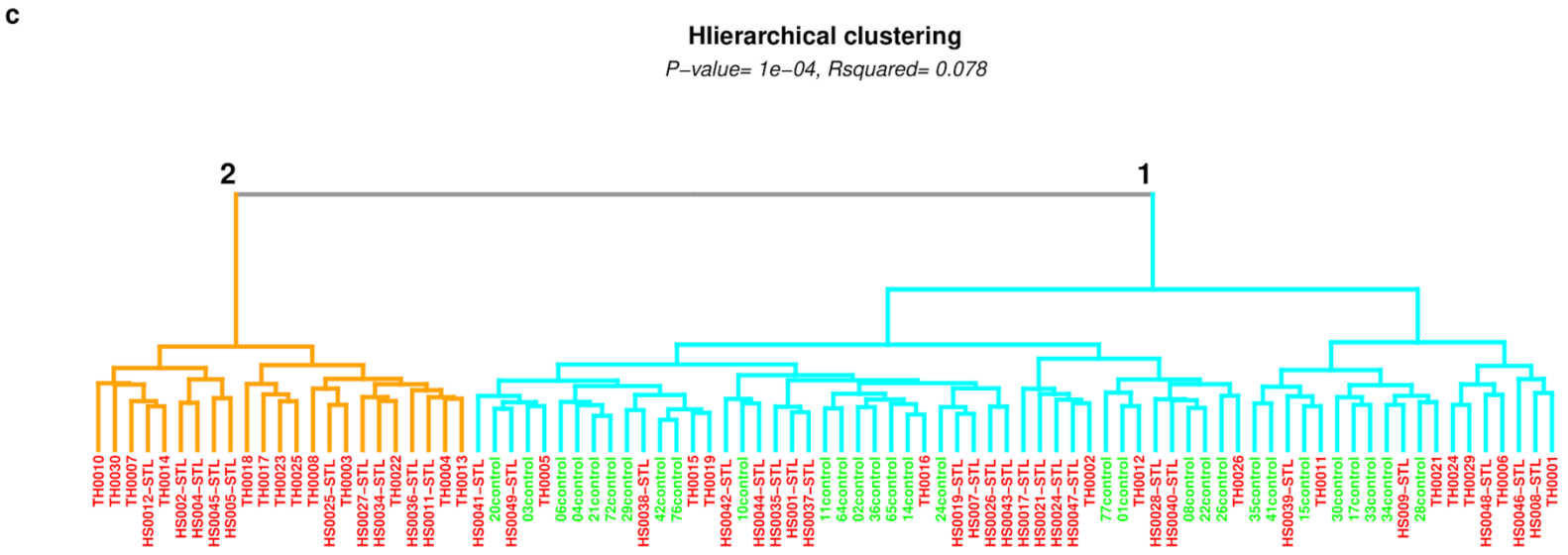
Figure 1: Taxonomic representation of microbiome in faecal specimens. (a) Bar plots displaying the relative abundance of genera in faecal samples. Genera with a relative abundance of less than 1% across all samples were grouped into ‘others’ i.e. with sequences not classified at the genus level. (b) Bar plots displaying the relative abundance of families in faecal samples. Families with a relative abundance of less than 0.5% across all samples were grouped into ‘others’ i.e. with sequences not classified at the family level. (c) Bar plots displaying the relative abundance of phyla in faecal samples. Families with a relative abundance of less 0.5% across all samples were grouped into ‘others’ i.e. with sequences not classified at the phylum level.


a
Healthy controls
Individuals with Hidradenitis suppurativa
Relative abundance(%)
Genus
Others
Bacteroides
Faecalibacterium
Roseburia
Blautia
Bifidobacterium
Ruminococcus
Dialister
Prevotella
Gemmiger
Coprococcus
Clostridium_XlVa
Ruminococcus2
Clostridium_Xl
Anaerostipes
Streptococcus
Collinsella
Clostridium_XVIII
Alistipes
Akkermansia
b
Family
Lachnospiraceae
Ruminococcaceae
Bacteroidaceae
Bifidobacteriaceae
Others
Veillonellaceae
Erysipelotrichaceae
Prevotellaceae
Coriobacteriaceae
Porphyromonadaceae
Peptostreptococcaceae
Streptococcaceae
Rikenellaceae
Verrucomicrobiaceae
Enterobacteriaceae
Clostridiaceae_1
Acidaminococcaceae
Succinivibrionaceae
Anaeroplasmataceae
Lactobacillaceae
c
Phylum
Firmicutes
Bacteroidetes
Actinobacteria
Proteobacteria
Verrucomicrobia
Others

Ecological metrics showed a difference between the microbiome of individuals with HS and healthy controls (Figure 2). Alpha-diversity, a marker of microbial species richness or variation within a sample, was significantly lower in individuals with HS (Figure 2a).

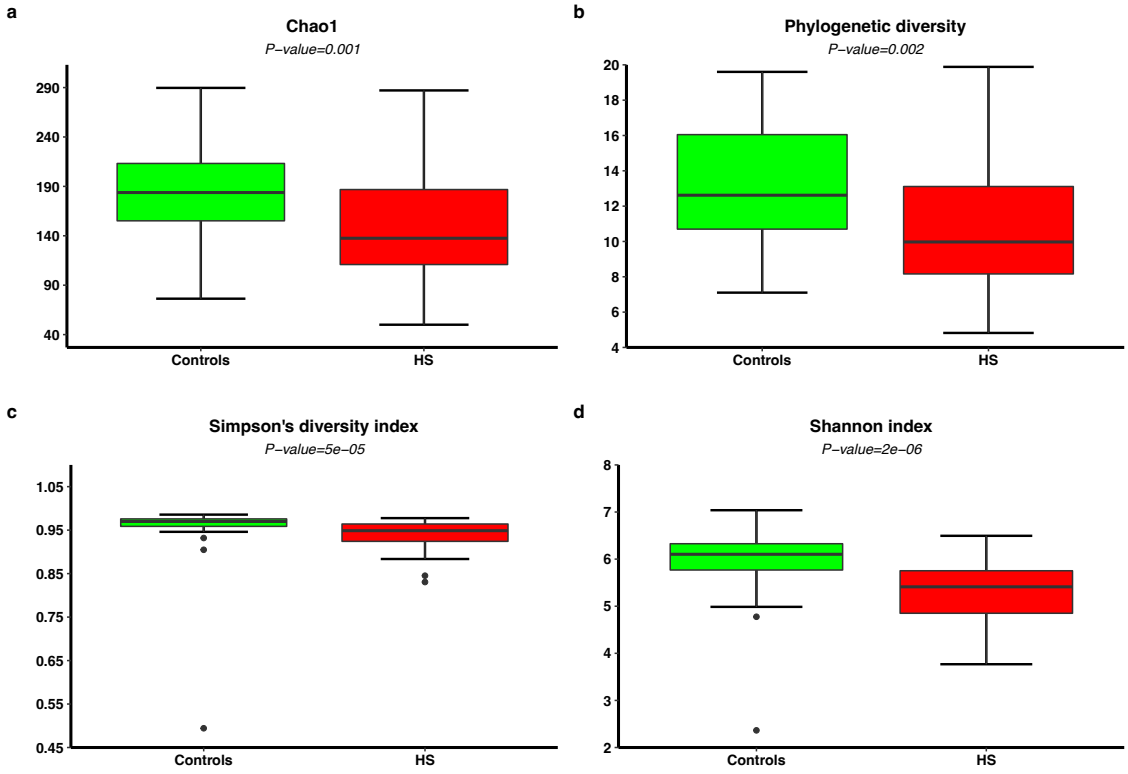
Figure 2: Ecological overview of faecal microbiome data. (a) Alpha-diversity. Boxplot comparing alpha diversity (observed species index) between individuals with HS versus healthy controls. Wilcoxon signed-rank test was used to calculate p-values **(b) Beta diversity**. Respective distance between samples based on their microbiome composition was calculated using unweighted Unifrac. Principal Coordinates Analysis (PCoA) was performed to obtain the coordinates of the first two PCoA axes which were plotted. Statistical testing was performed using Permutational Multivariate Analysis of Variance (PERMANOVA). **(c) Hierarchical clustering.** The relatedness between samples based on their microbiome composition was calculated using Spearman's rank correlation coefficient. Hierarchical clustering was performed using the Ward2 method and the results plotted as a dendrogram. Statistical testing was performed using Permutational Multivariate Analysis of Variance (PERMANOVA).


a
Observed species
P−value=0.001
290
240
190
140
90
40
Controls
HS
b
Unweighted Unifrac
P−value= 1e−04, Rsquared= 0.049
Group
Controls
HS
0.2
0.1
0.0
−0.1
−0.2
Axis 2(7.12%)
−0.2
0.0
0.2
Axis 1(20.45%)


c
Hlierarchical clustering
P−value= 1e−04, Rsquared= 0.078
2
1
TH0010
TH0030
TH0007
HS0012−STL
TH0014
HS002−STL
HS0004−STL
HS0045−STL
HS005−STL
TH0018
TH0017
TH0023
TH0025
TH0008
HS0025−STL
TH0003
HS0027−STL
HS0034−STL
TH0022
HS0036−STL
HS0011−STL
TH0004
TH0013
HS0041−STL
20control
HS0049−STL
03control
TH0005
06control
04control
21control
72control
29control
HS0038−STL
42control
76control
TH0015
TH0019
HS0042−STL
10control
HS0044−STL
HS0035−STL
HS001−STL
HS0037−STL
11control
64control
02control
36control
65control
14control
TH0016
24control
HS0019−STL
HS007−STL
HS0026−STL
HS0043−STL
HS0017−STL
HS0021−STL
HS0024−STL
HS0047−STL
TH0002
77control
01control
TH0012
HS0028−STL
HS0040−STL
08control
22control
26control
TH0026
35control
41control
HS0039−STL
15control
TH0011
30control
17control
33control
34control
HS009−STL
28control
TH0021
TH0024
TH0029
HS0048−STL
TH0006
HS0046−STL
HS008−STL
TH0001

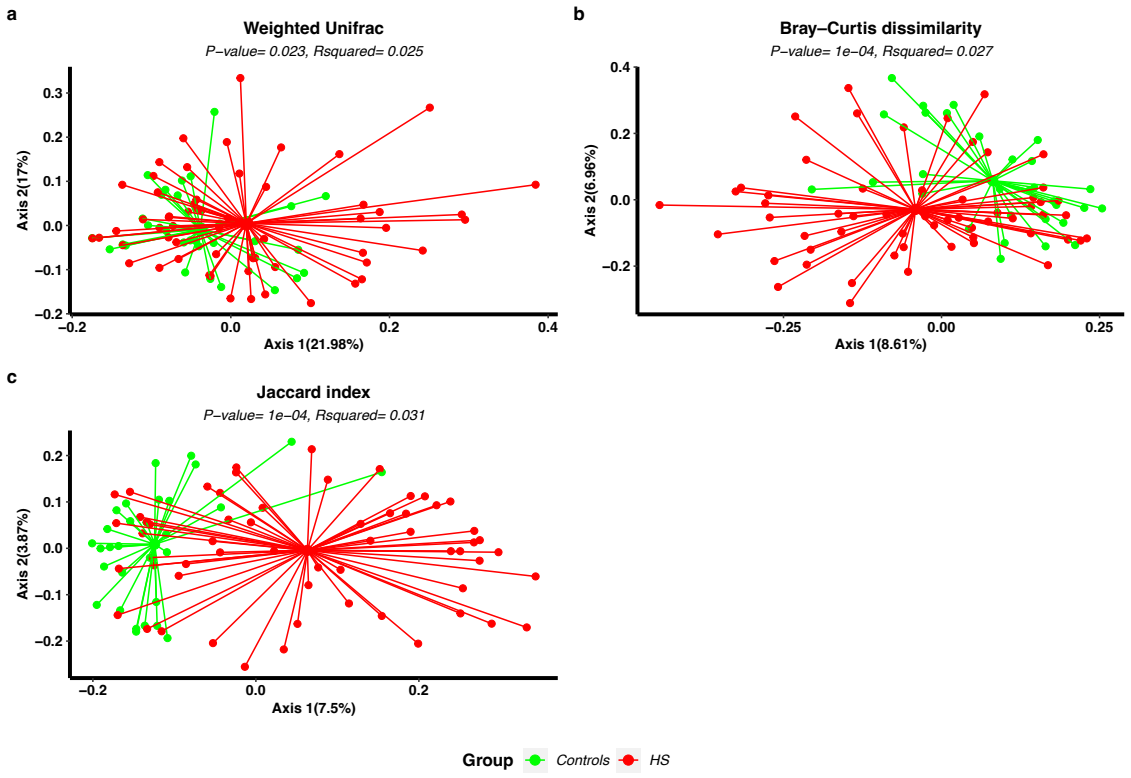
This reduction was also observed for four other metrics of alpha-diversity including Shannon and phylogenetic diversity (Figure 3).

Figure 3: Bar plots of alpha diversity metrics for faecal samples. (a) Chao1. (b) Phylogenetic diversity. (c) Simpson's Diversity Index. (d) Shannon index. Wilcoxon signed-rank test was used to calculate p-values.



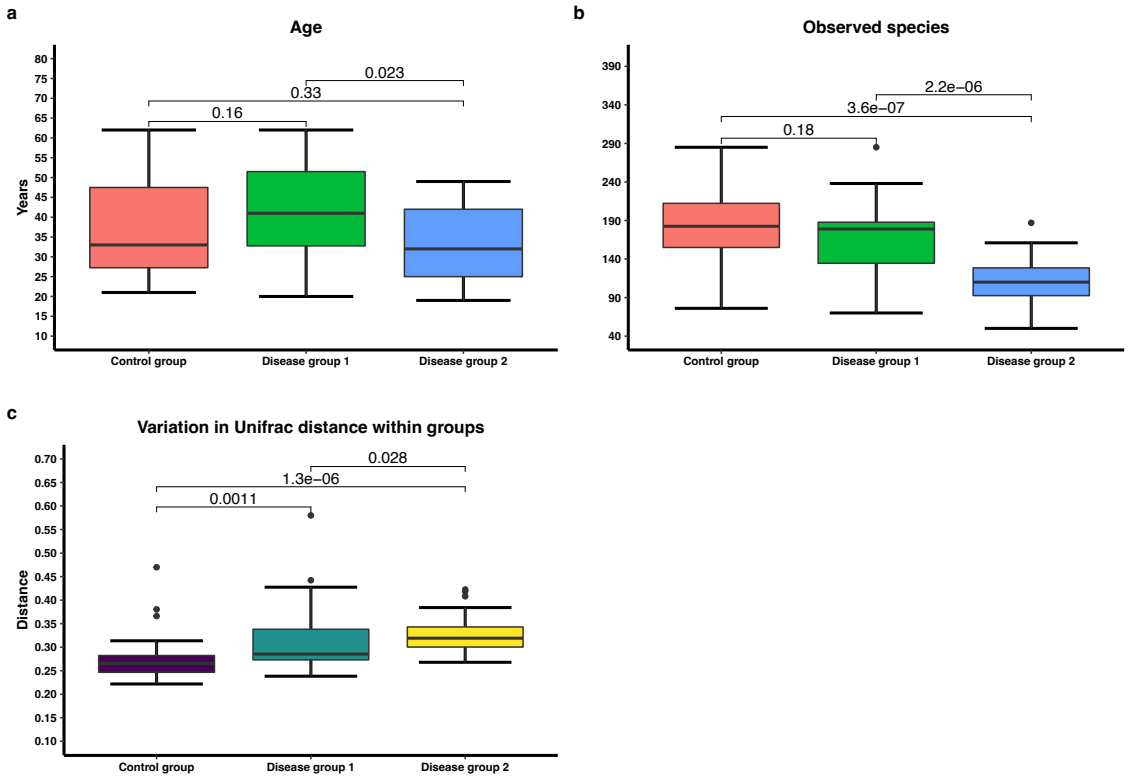
A microbiome separation in beta-diversity, (a comparison of global microbial composition in all the samples), between the HS and healthy controls was observed across all metrics tested (Figure 2b) (Figure 4), noting also less clustering within the HS samples. Hierarchical clustering replicated and reinforced this separation as seen by the presence of a cluster composed exclusively of patients with HS (Figure 4c).

Figure 4: PCoA representing Beta diversity metrics for faecal samples. (a) Weighted Unifrac. (b) Bray–Curtis Dissimilarity. (c) Jaccard index. Statistical testing was performed using Permutational Multivariate Analysis of Variance (PERMANOVA).



We further investigated this cohort by grouping the individuals informed by the hierarchical clustering that is, control group (control samples, cyan branch, branch No.1), disease group 1 (cyan branch, branch No.1) and disease group 2 (orange branch, branch No.2). We found that disease group 2 was composed of significantly younger subjects than disease group 1 but not the controls (Figure 5a). Alpha diversity was lower in disease group 2 compared to the disease group 1 and the control group (Figure 5b). There was greater within-group microbiome variation, evidenced by higher levels of Unifrac distance between samples, within disease group 2 compared to the other two groups (Figure 5c).

Figure 5: Difference in groups informed by clustering. (a) Bar plot of age differences. (b) Bar plots of observed species. (c) Differences in the Variation in Unifrac distance within groups. Wilcoxon signed-rank test was used to calculate p-values.



We found no statistical difference with respect to gender between these groups. Menopause has been previously reported to be associated with compositional changes in the microbiota.(686) Although we did not have direct information on menopausal status, we classified individuals as possibly being menopausal if over age 50 (average of menopause age in western populations being 51) and of the female sex (Table 2).(687–689)

Table 2: Menopausal status of females with HS studied

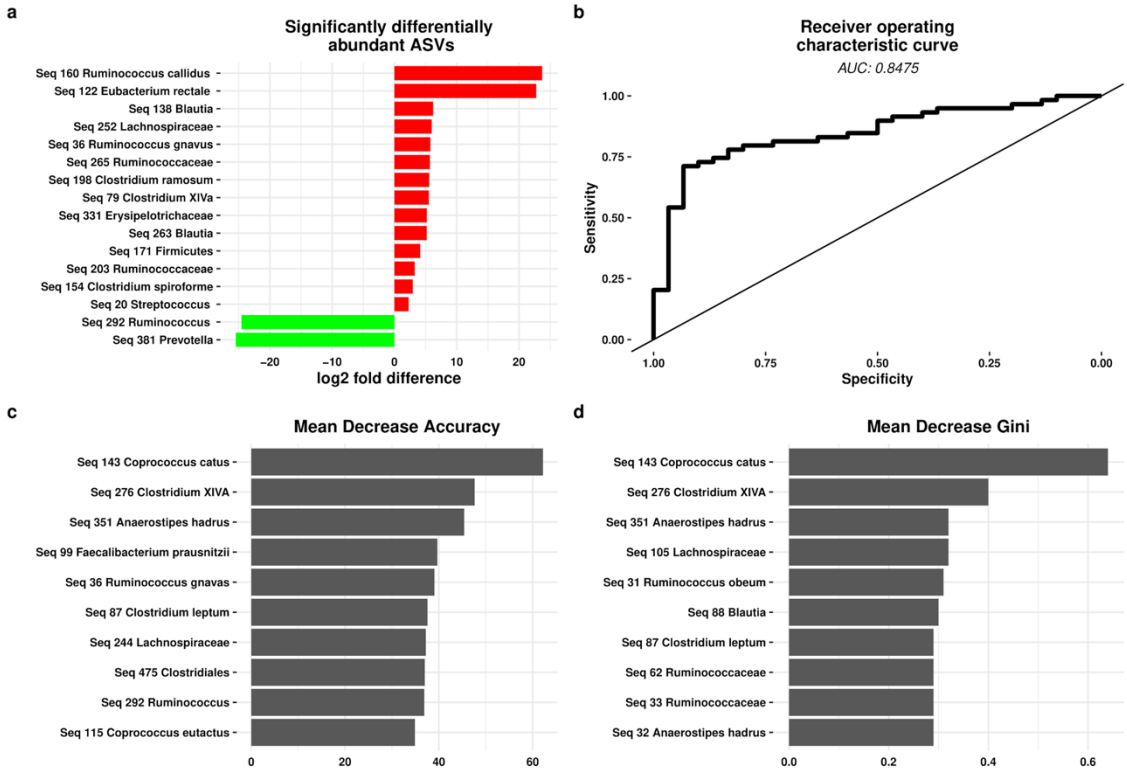
	Menopausal*	**Non-menopausal***
Control group	5	25
Disease group 1	4	32
Disease group 2	0	23

Using this as a proxy for menopausal state, we did not find a statically significant difference between the three groups (chi-squared test). Furthermore microbiome alpha diversity did not show any correlation with known Crohn's disease or calprotectin level (Pearson correlation).

5.3.3 Differentially abundant ASVs in the faecal microbiome

Microbial amplicon sequencing data can be rationalised in terms of amplicon sequence variants (ASVs) which allows the data to be resolved down to single-nucleotide difference (690). A number of ASVs were found to be differentially abundant between the faecal microbiome of patients with HS and healthy controls (Figure 6a).

Figure 6: Differentially abundant ASVs and machine learning classification. (a) Bar plot of differential abundant ASVs expressed as log fold difference. Negative values indicate those overrepresented in controls. Positive values indicate overrepresented in individuals with HS. **(b)** Receiver operating characteristic curves (ROC). **(c,d)** Top discriminatory ASVs with regard to discriminating the HS subjects from healthy controls. **(c)** Mean Decrease Accuracy. **(d)** Mean Decrease Gini.

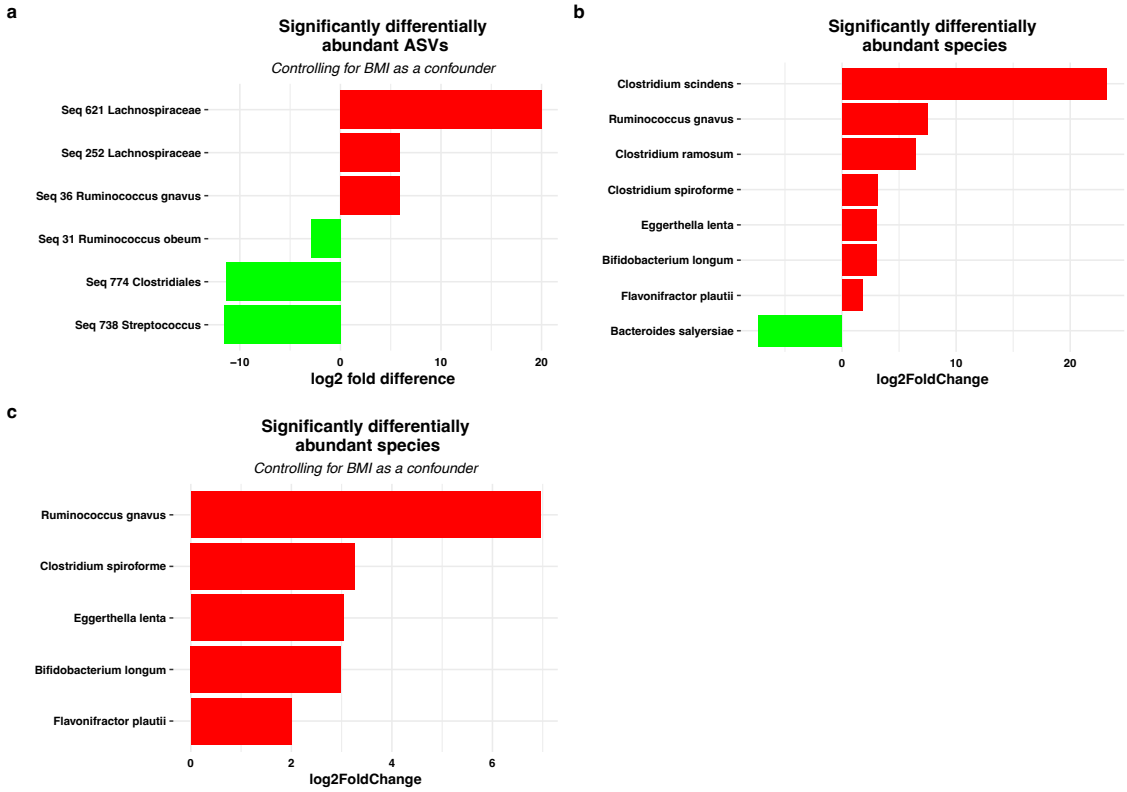


With regard to log2 fold differences, the ASVs assigned to the taxa *Ruminococcus callidus* and *Eubacterium rectale* were the most enriched in individuals with HS relative to healthy controls. However, with respect to proportional abundance, the greatest difference was detected in ASVs assigned to the taxa *Streptococcus* spp. (an

average relative abundance of 0.19% in the control cohort versus 0.95% in the HS cohort) and *Ruminococcus gnavus* (average relative abundance values of 0.01% in the control cohort versus 0.7% in the HS cohort).

As BMI was significantly different between the groups, the DESeq2 model was re-run to adjust for BMI (Figure 7). The differential over-abundance of *Ruminococcus gnavus* remained statistically significant in the HS cohort. However, an ASV assigned to *Ruminococcus obeum* was revealed to be depleted in individuals with HS. ASVs were also collapsed to the species level and differential abundance of species determined with and without BMI as a confounder (Figure 7). *R. gnavus* was retained as being significantly over-abundant in the HS cohort in both analyses.

Figure 7: Bar plots of differential abundant ASVs and species in faecal samples. (a) Significantly differentially abundant ASVs with BMI integrated into the model. (b) Significantly differentially abundant species. (c) Significantly differentially abundant species with BMI integrated into the model. DESeq2 used to for statistical analysis. ASVs/species enriched in HS samples in red. ASVs/species enriched in control samples in green.



Antibiotic usage for the previous year was recorded in the HS cohort. There were no significant ASVs that were differently abundant between those who had received antibiotic therapy in the last year and those who did not.

5.3.4 Machine learning identification of HS-related microbiota members

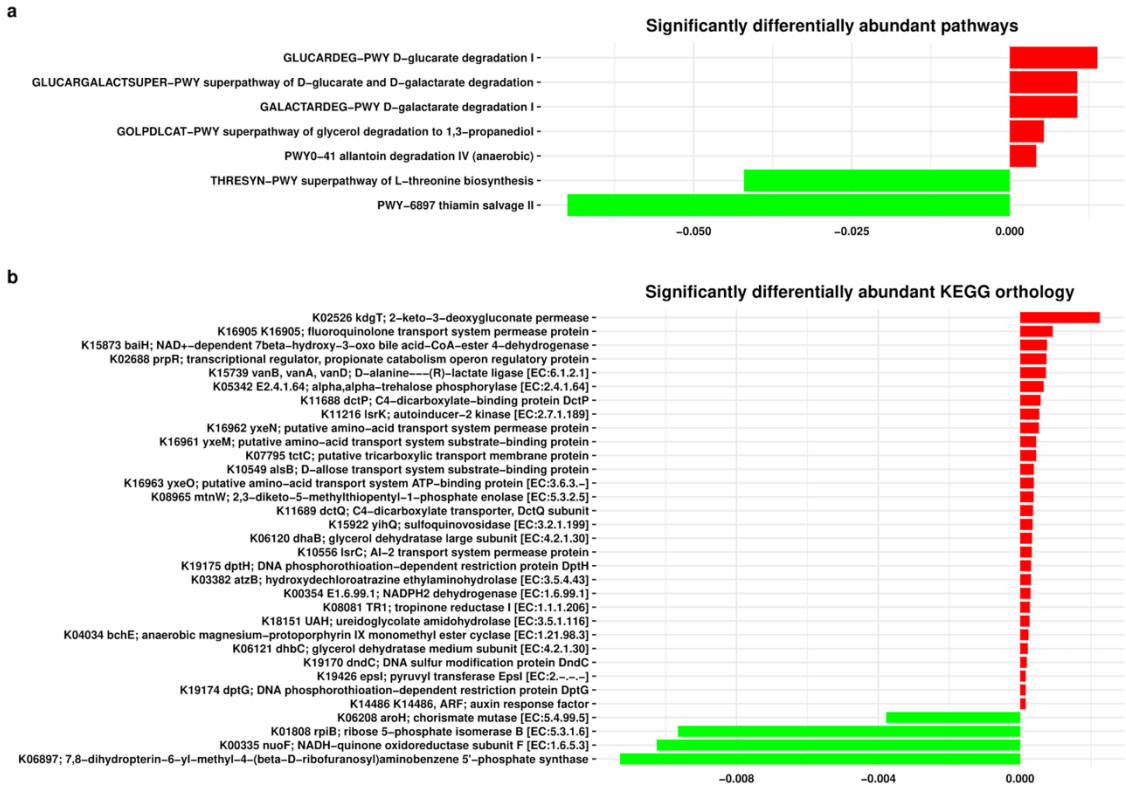
The machine learning classifier random forest (RF) was employed to test if ASVs could discriminate the HS patients from the healthy control cohort. The RF classifier performed reasonably with an area under the curve (AUC) of 0.848 (Figure 6b). A number of ASVs identified as discriminatory (i.e. as contributing to the RF model) were taxonomically assignable to butyrate-producing bacterial species including *Faecalibacterium prausnitzii*, *Coprococcus eutactus*, *Coprococcus catus* and *Anaerostipes hadrus* (Figure 6c). A number of ASVs that we had identified using the DESeq2 model as being differentially abundant were also identified including *Ruminococcus gnavus* and *Ruminococcus obeum*.

5.3.5 Changes in predicted metabolic function of the faecal microbiota

Metagenomic functionality was inferred using the algorithm PICRUSt2, which is based on the metabolic pathways of reference microbiota data to which a test-set of 16S data is compared. Several metabolic pathways were thus predicted to be differentially abundant between HS and control metagenomes (Figure 7a). Metabolic pathways for D-glucarate degradation and D-galactarate degradation, which are associated with a poor prognosis in CD, were overrepresented in individuals with HS relative to healthy controls (691).

Figure 7: Differentially abundant metabolic pathways and KEGG orthologs.

(a) Bar plot of differential abundant MetaCyc as expressed by difference in mean proportional abundance. MetaCyc pathways enriched in HS samples in red. MetaCyc pathways enriched in control samples in green. **(b)** Bar plot of differential abundant KOs as expressed by difference in mean proportional abundance. KOs enriched in HS samples in red. KOs enriched in control samples in green. Wilcoxon signed-rank test was used to calculate p-values.



5.4 Discussion

We identified a number of differences in microbiome configuration in faecal samples in individuals with HS compared to healthy controls. Alpha diversity was lower in subjects with HS suggesting a reduction in the richness of the gut microbiota compared to controls. Decreases in alpha diversity in skin, and nasal microbiota have been reported in atopic dermatitis, with conflicting results for the gut microbiota (654–657). Alpha-diversity has been observed to be lower in skin samples from individuals with psoriasis, with even more variable results in the gut (658–660).

5.4.1 Gut Microbiome in HS

Elevated levels of *Ruminococcus gnavus* and *Clostridium ramosum* were among the greatest differences in relative abundance between patients with HS and healthy control microbiomes in this study. *R. gnavus* has been consistently found to be overrepresented in subjects with Crohn's Disease and is associated with spondyloarthritis, and irritable bowel syndrome (679,692–697). *R. gnavus* is linked to development of eczema and other allergic diseases in infants, possibly due to its effect on the host immune system development (696,698). A mechanistic role of *R. gnavus* in Crohn's disease has been experimentally supported by the production of a potent proinflammatory polysaccharide which induces the production TNF-α via interacting with the toll-like receptor 4 (TLR4) of innate immune cells, such as dendritic cells (699). The production of this polysaccharide may contribute to the pathogenesis of HS. It is possible that the diseases that are comorbid with HS have a common aetiology, due, in part, to the activity of *R. gnavus. C. ramosum* has also been reported to be increased in Crohn's disease and obesity (680,700). In a previous

study, *R. obeum* was strongly enriched in controls relative to individuals with IBD as seen in our study (701).

We found pathways related to galactarate and glucarate degradation were more abundant in the faecal microbiome from individuals with HS. These metabolic pathways have also been implicated in Crohn's disease clinical outcome and may link to systemic inflammation. In a paired whole exome shotgun metagenomics study comparing individuals with IBD and healthy controls, immune-related gene CABIN1 was associated with an increase of D-glucarate degradation (702). Both D-glucarate degradation and D-galactarate degradation were overrepresented in individuals with Crohn's Disease with a poor prognosis (691). Antibiotics are known to induce a host-mediated elevation in levels of galactarate and glucarate in the gut and increased expression of microbial genes responsible for galactarate and glucarate degradation may be a response to this (703). Mouse model studies demonstrated that antibiotic treatment increases galactarate and glucarate through increased expression of inducible nitric oxide synthase (iNOS)(704).

5.4.2 Potential impact

There is a lack of high-quality evidence for treatment options in HS (226,628,669). A multidisciplinary approach with a combination of medical and surgical treatment is often needed, combined with lifestyle measures; smoking cessation and weight loss (226,628,669). Antibiotics remain the initial treatment for most patients, with TNF-alpha inhibitors in those who fail to respond (226,628,669). The use of antibiotics in HS, for their anti-inflammatory rather than anti-microbial effect, may play a role in the reduction in alpha-diversity seen in this study;

however, we detected no significant difference in ASVs in those who received antibiotics in the preceding year compared to those who did not. Microbiota based therapies may have potential benefits in HS, in particular targeted microbial supplementation to increase diversity and richness. The selective depletion of certain microbes such as *R. gnavus*, which may play a pathogenic role, could provide therapeutic targets.

5.5 Conclusion

We have characterised the gut microbiota in patients with HS compared to healthy controls. We have provided evidence for a possible microbial link between IBD and HS, with *R. gnavus* abundant in both conditions. The identification of particular taxa that may contribute to HS pathogenesis, such as *R. gnavus,* could inform future microbiota-based therapeutic strategies.

6. Faecal Calprotectin and Serum C5a levels in Hidradenitis Suppurativa

6.1 Faecal Calprotectin Levels in Hidradenitis Suppurativa

Abstract

Introduction

Hidradenitis suppurativa (HS) is a chronic, painful skin disease, presenting with recurrent inflammatory nodules and abscesses in intertriginous areas, often healing with scar formation (225). HS shares common clinical manifestations, genetic susceptibility, and immunologic features with Crohn's disease (705). Faecal calprotectin is a cytosolic protein released during neutrophil activation and is a marker of gastrointestinal inflammation (706). It is a metric of disease activity, therapeutic response, and prognosis in inflammatory bowel disease (707). We sought to determine if faecal calprotectin levels were elevated in patients with HS.

Adult patients with HS were recruited and provided fresh stool samples. Calprotectin was determined by enzyme-linked immunoassay (CALPROLAB™ Calprotectin ELISA (HRP).

Fifty-nine patients with hidradenitis suppurativa were recruited. Sixteen patients (27.1%) had a raised faecal calprotectin level of >50mg/kg. 11 (18.6%) had levels of 50mg-150mg/kg. Of these eleven patients, one had a history of Crohn's disease (9%). Five patients (8.5%) had a faecal calprotectin level of >150mg/kg. Of these five patients one had a diagnosis of Crohn's disease, on no systemic treatment.

The results show that over a quarter of patients with HS have evidence of occult gastrointestinal inflammation. Elevated faecal calprotectin levels were found in patients with HS, without concurrent Crohn's disease. Given the potential for misdiagnosis and the possibility of co-morbidity, we recommend this simple test for

all patients with HS with due consideration of further investigations in patients with an elevated faecal level of calprotectin.

6.1.1 Introduction

Hidradenitis suppurativa (HS) is a chronic, painful skin disease, presenting with recurrent inflammatory nodules and abscesses in intertriginous areas, often healing with scar formation (225). The cause of HS is unclear, with follicular occlusion, dysregulated inflammatory response of cytokines and altered microbiota thought to be contributory (705). HS shares common clinical manifestations, genetic susceptibility, and immunologic features with Crohn's disease and the two conditions are often associated (705). Due to this association, it is suggested that HS patients be screened for symptoms of IBD and symptomatic patients referred for further investigations (708). HS and Crohn's disease are also both associated with spondyloarthropathy, and common risk factors include a genetic predisposition, smoking and obesity (705). Both HS and Crohn's disease respond well to tumor necrosis factor inhibitors (705). Furthermore, an altered gut microbiome has been described in inflammatory bowel disease and in HS (709,710).

Inflammatory markers are an important adjunct in assessing disease severity and response to treatment. Calprotectin, a member of the S100 protein family, is a calcium-binding heterodimeric cytosolic protein expressed in a wide variety of cell types, including neutrophils and monocytes (711). Calprotectin has a regulatory function in inflammatory processes and elevated levels are seen in acute phase inflammatory reactions(711). Serum calprotectin has been found to be elevated in many inflammatory conditions including HS (712). Faecal calprotectin is released during neutrophil activation in the gut and is a marker of gastrointestinal

inflammation used by gastroenterologists (706). It is a metric of disease activity, therapeutic response, and prognosis in inflammatory bowel disease (707). Elevated faecal calprotectin levels have also been found in spondyloarthritis, psoriatic arthritis, and colorectal cancer (706,713,714).

Thus we sought to determine if faecal calprotectin levels were elevated in patients with HS and to compare these calprotectin levels to the altered faecal microbiome discussed in Chapter 5 (710).

6.1.2 Methods

Adult patients with a confirmed clinical diagnosis of hidradenitis suppurativa in two tertiary referral centres in Ireland were invited to participate in the study. Demographics including age, gender, Hurley stage, body mass index (BMI), medication history, and the presence of co-morbidities were recorded. Fresh (<24 hours) stool samples were collected by the patient and were stored at -80°C prior to extraction and testing. Microbial DNA was extracted and library preparation and 16S rRNA gene sequencing was carried out (as previously discussed in Chapter 5) (710). Calprotectin was determined by an enzyme-linked immunoassay (CALPROLAB™ Calprotectin ELISA (HRP)).(See Supplementary Methods) Levels were normal if 5-50mg/kg, and elevated if >50mg/kg.(706) Results of 50-150mg/kg were deemed mildly elevated, warranting repeat testing, with levels >150mg/kg suggestive of active bowel inflammation. Statistical analysis was performed using R (v3.6.0).

6.1.3 Results

59 patients with hidradenitis suppurativa were recruited. The mean age was 38.6 years (SD 11.5); 45 were female (76.3%) and four had a history of Crohn's disease

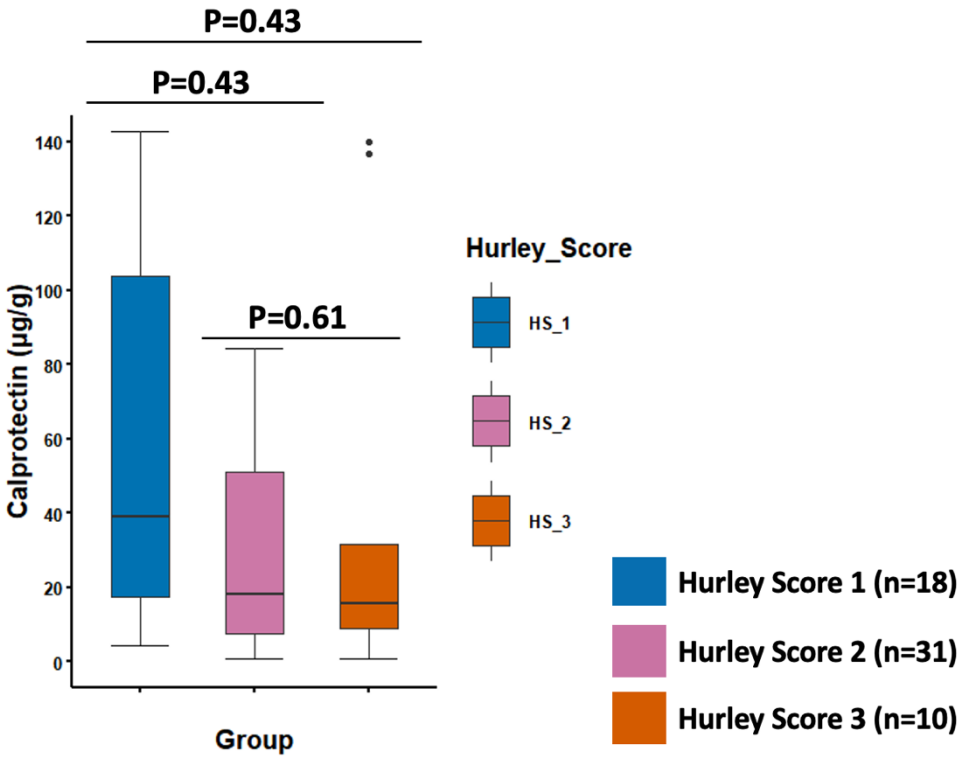
(6.8%). 18 were Hurley Stage I, 32 were Hurley Stage II, and 9 were Hurley Stage III.(Table 1).

Table 1: Patient demographics and results

		All Patients
Gender N (%)		Female 45 (76.3) Male 14 (23.7)
Mean age (SD)		38.6 years (11.5)
Mean body mass index (mg/m^2) (SD)		31.9kg/m^2
Hurley Stage (N)	**I** **II** **III**	18 32 9
Positive history of Crohn's Disease N(%)		4 (6.8)
Systemic therapy: **TNF- α N (%)**		9 (15.3)
Calprotectin 50mg-150mg/kg N (%)		11 (18.6)
Calprotectin >150mg/kg N (%)		5 (8.5%)

Sixteen patients (27.1%) had a raised faecal calprotectin level of >50mg/kg. 11 (18.6%) had levels of 50mg-150mg/kg. Of these eleven patients, one had a history of Crohn's disease (9%). Five patients (8.5%) had a faecal calprotectin level of >150mg/kg. Of these five patients one had a diagnosis of Crohn's disease, on no systemic treatment. Faecal calprotectin levels did not differ by Hurley stage in those studied (p=0.43)(Figure 1).

Figure 1: Calprotectin levels as per Hurley staging



Hierarchal clustering identified two distinct microbiome groups (710)(Figure 2). No significant difference in faecal calprotectin was noted between these two groups (p=0.88)(Figure 3).

Figure 2: Two distinct faecal microbiome groups seen in patients with HS

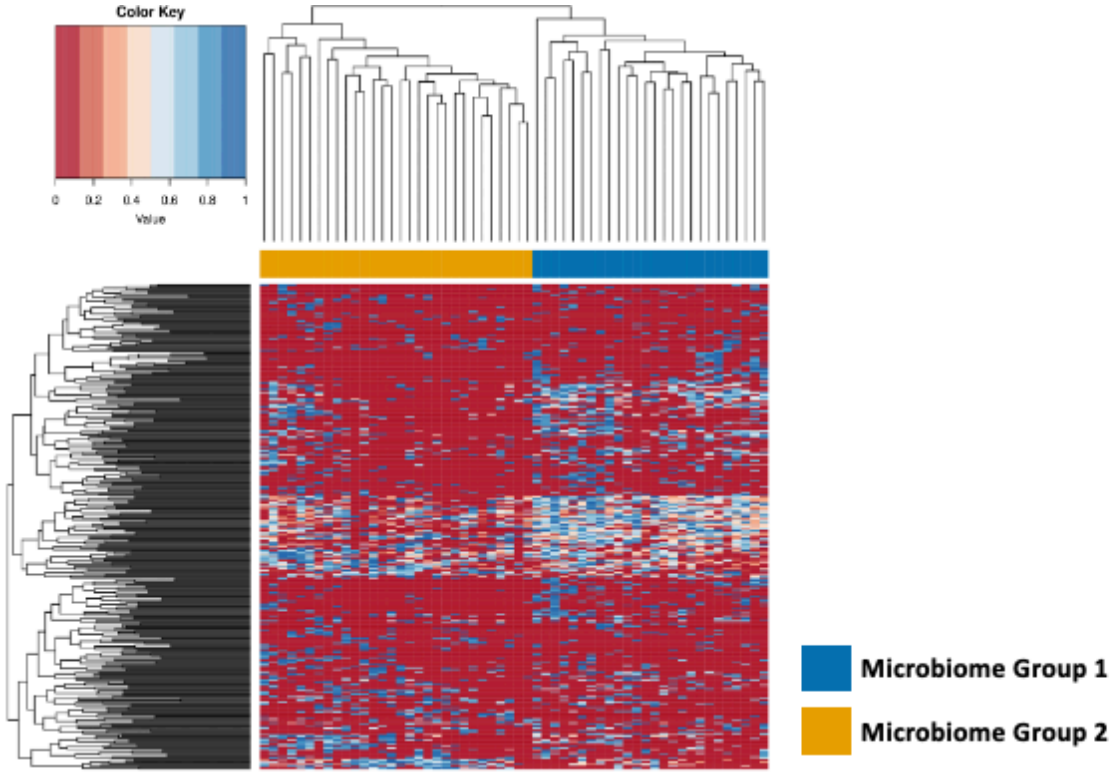
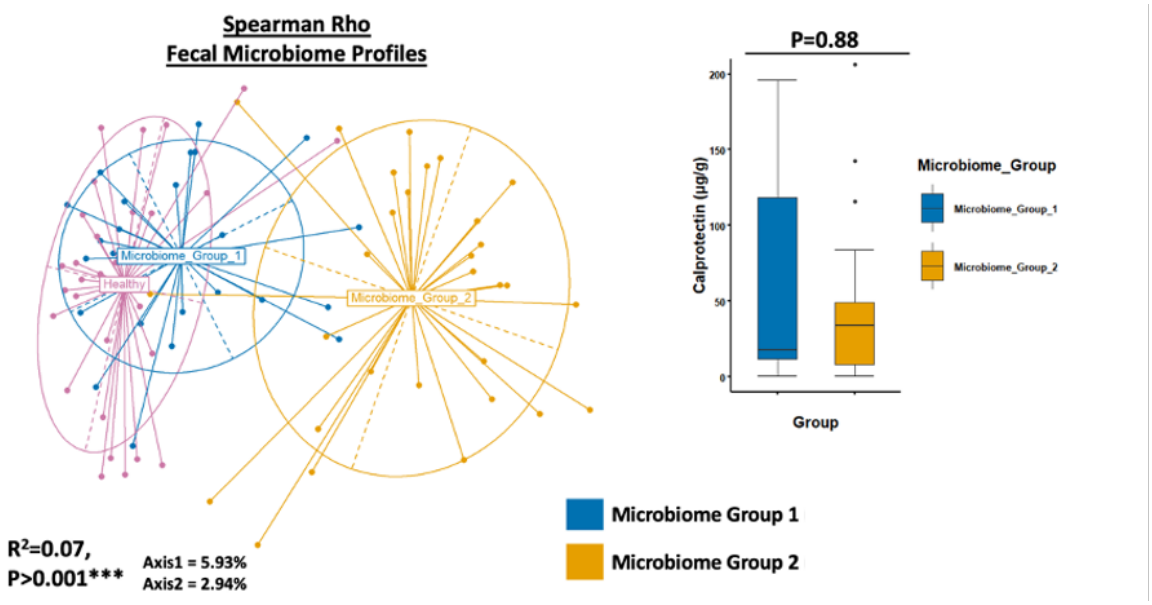


Figure 3: No significant difference in faecal calprotectin was noted between the two distinct microbiome groups noted in HS patients



Of those with no history of Crohn's disease and elevated faecal calprotectin levels, 2 (14%) were taking prophylactic aspirin, and 1 (7%) was taking a non-steroidal anti-inflammatory drugs (NSAIDs). Nine patients (15.3%) in this study were receiving treatment with a tumour necrosis factor (TNF-α) inhibitor, 2 (22%) of whom had elevated levels of calprotectin. We did not find any significant association between levels of calprotectin and TNF-α inhibitor therapy with regard to both current and previous use (Wilcoxon rank-sum test).

6.1.4 Discussion

Serum calprotectin has been used as a marker of disease activity in rheumatoid arthritis, spondyloarthritis and psoriatic arthritis, as well as sepsis and cancer and is not specific to gastrointestinal inflammation (715). Elevated serum levels of calprotectin in HS has previously been described with no correlation with Hurley disease stage, as seen in our study (712). Its use as a biomarker in HS has yet to be proven(712). Other S100 proteins, S100A4 and S100A15 have recently been found to be elevated in HS, and may play a role in HS pathogenesis by promoting inflammation and fibrosis (716).

Faecal calprotectin levels in inflammatory conditions, including HS, has become a recent area of research interest. Elevated faecal calprotectin levels have also been described in spondyloarthritis, psoriasis and psoriatic arthritis (706,714). Interestingly in psoriatic arthritis, it appears gut inflammation perpetuates joint inflammation (714). Furthermore in spondyloarthritis, chronic gut inflammation was deemed an independent risk factor for the development of inflammatory bowel disease (717).

Faecal calprotectin levels were elevated in 16 (27.1%) of patients in this study. Of those with no history of Crohn's disease and elevated faecal calprotectin levels, 2 were taking prophylactic aspirin, which may raise calprotectin levels (718). The consistent use of non-steroidal anti-inflammatory drugs has been associated with an increase in calprotectin levels, with one patient taking an NSAIDs in this study with an elevated calprotectin level (719). Nine patients (15.3%) in this study were receiving treatment with a tumour necrosis factor (TNF-α) inhibitor, two (22%) of whom had elevated levels of calprotectin. TNF-α inhibitors are used to control inflammation in both inflammatory bowel disease and HS and thus may result in low levels of calprotectin in these patients. However, we did not find any significant association between levels of calprotectin and TNF-α inhibitor therapy with regard to both current and previous use. Studies in inflammatory bowel disease proved that a reduction in faecal calprotectin level indicated mucosal improvement in patients commenced on TNF-α inhibitor treatment (720).

Our results are consistent with other studies on faecal calprotectin levels in HS, which suggest faecal calprotectin could be used as a marker of disease activity (721,722). Faecal calprotectin does not appear to correlate with disease stage as defined by Hurley Staging, however this is a static assessment that does not evaluate disease activity (19,721). This elevated faecal calprotectin in HS suggests subclinical gut inflammation which may be related to their disease, however we cannot outrule concurrent inflammatory bowel disease, with Crohn's disease a common association (705).

Faecal calprotectin is an easy, non-invasive test which may play an role in determining risk of developing inflammatory bowel disease as suggested by a recent study on prevalence of inflammatory bowel disease in paediatric HS (723). However

the significance of subclinical gut inflammation in HS is unknown, and further study is required to determine if this inflammation is simply a marker of disease activity, if it contributes to HS flares or if it signifies a risk of developing inflammatory bowel disease in future. Furthermore, we have demonstrated an altered gut microbiota in HS (710). It is possible that this subclinical gut inflammation, as indicated by the elevated faecal calprotectin levels in this cohort, may be as a result of alterations in the gut microbiota; however, levels of calprotectin did not differ between the two distinct microbiome groups described in this study(710).

6.1.5 Conclusion

Elevated faecal calprotectin levels were found in patients with HS, without concurrent Crohn's disease. Faecal and serum calprotectin may be a marker of disease activity in HS, however its utility in assessing response to treatment is yet unknown. It is also unknown if elevated faecal calprotectin may signify a risk of developing inflammatory bowel disease in future. Given the potential for misdiagnosis and the possibility of co-morbidity, we recommend this simple test be considered in patients with HS with due consideration of further investigations in patients with an elevated faecal level of calprotectin.

6.2 Serum Complement C5a Levels in Hidradenitis Suppurativa

Abstract

The complement system plays a key role in innate immunity, enhancing the ability of antibodies and phagocytic cells to defend against pathogens. C5a is an anaphylatoxin, a product of the complement cascade, which plays a role in supporting inflammation by the recruitment of immune cells to the site of activation, and the release of granule based enzymes (724). Increased circulating levels of C5a and C5b-9 anaphylotoxins have been described in one study, with resultant high levels of TNF-α production (138). We sought to determine the serum concentration of anaphylatoxin C5a in our cohort of patients with HS.

Patients with a confirmed diagnosis of HS by a consultant dermatologist from two tertiary referral centres were invited to participate in the study. Complement C5a levels were assessed using enzyme-linked immunosorbent assay (Abcam ab193695 Complement C5a Human ELISA Kit).

54 patients with HS provided serum samples for analysis. Median complement C5a level was elevated at 47 ng/ml (IQR 30.55 ng/ml). Complement C5a levels did not correlate with disease severity as defined by Hurley staging.

The study findings are in keeping with the prior study by Kanni et al. which described levels of C5a >28 ng/ml in patients with HS, however negative correlation of C5a with HS severity was found in their study and no correlation was found by disease severity in ours (138). C5a may provide a therapeutic target in patients with HS and serum C5a may act a biomarker of the disease.

6.2.1 Introduction

Hidradenitis Suppurativa is a chronic inflammatory skin disease of primarily intertriginous sites presenting with recurrent painful nodules, abscesses and often progressing to scarring and sinus tract formation. The pathogenesis of HS is incompletely understood but genetic, endocrine, environmental, immunological and microbial factors play a role (40,725,726). The primary event is thought to be follicular hyperkeratosis and dilatation, followed by follicular rupture (725,726). This induces an exaggerated response in the innate immune system resulting in recruitment of inflammatory cells and mediators to the dermis, with resultant abscess formation and chronic inflammation (725). The complement system plays a key role in innate immunity, enhancing the ability of antibodies and phagocytic cells to defend against pathogens. C5a is an anaphylatoxin, a proinflammatory polypeptide product of the complement cascade, which plays a role in supporting inflammation by the recruitment of immune cells to the site of activation including neutrophils, eosinophils, monocytes, and T lymphocytes, the activation of phagocytic cells, and the release of granule based enzymes (724). Little research has looked at the role of the complement cascade in HS however it is thought that anaphylatoxins recruit neutrophils to the affected skin resulting in suppuration (138). Increased circulating levels of C5a and C5b-9 have been described in one study, with resultant high levels of TNF-α production (138). In this study levels of C5a exceeding 28 ng/ml were associated with a specificity of >90% with occurrence of HS (138). The addition of IFX-1, a C5a blocker, in this study led to a reduction in TNF-α suggesting a therapeutic target in HS (138). However, a further study by Prens et al. failed to show elevated serum levels of C5a in HS (727). We sought to determine the serum concentration of anaphylatoxin C5a in a cohort of patients with HS.

6.2.2 Methods

Patients with a confirmed diagnosis of HS by a consultant dermatologist from two tertiary referral centres were invited to participate in the study. Demographics including age, gender, Hurley stage, body mass index (BMI), medication history, and the presence of co-morbidities were recorded. Serum samples were obtained and stored at -80°C prior to testing. Complement C5a levels were assessed using enzyme-linked immunosorbent assay (Abcam ab193695 Complement C5a Human ELISA Kit). Statistical analysis was performed using R (version 4.1.3)

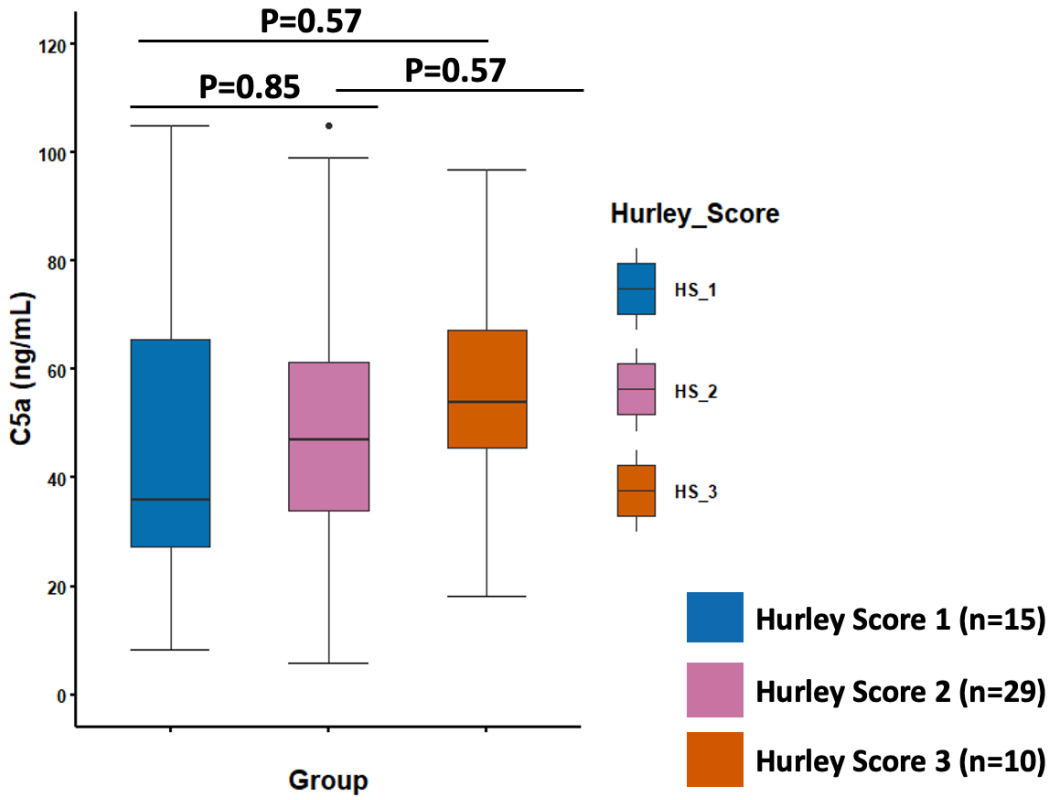
6.2.3 Results

54 patients with HS provided serum samples for analysis. Mean age was 37.1 years (SD 11.23). 43 (80%) were female and 11 (20%) were male. 15 (28%) were Hurley stage I, 29 (54%) were Hurley stage II, and 10 (18%) were Hurley stage III. 9 patients were currently prescribed adalimumab and 1 patient was prescribed infliximab, both TNF-α inhibitors, for their HS. 4 patients had inflammatory bowel disease (3 Crohn's, 1 ulcerative colitis), 4 had psoriasis, 3 had eczema, 1 had cutaneous lupus, and 1 patient had psoriatic arthritis. Median complement C5a level was 47 ng/ml (IQR 30.55 ng/ml). Complement C5a levels did not correlate with disease severity as defined by Hurley staging (Krukall-wallis with Dunns post-hoc test)(Figure 1). Patients with Hurley stage I had a median complement C5a level of 35.8 ng/ml (IQR 38.13), Hurley stage II 47 ng/ml (IQR 27.34) and Hurley stage III 54 ng/ml (IQR 21.58).

Table 1: Patient demographics

	All Patients
Gender N (%)	Female 43 (80%) Male 11 (20%)
Mean age (SD)	37.1 years (11.23)
Mean body mass index	
Hurley Stage (N) **I** **II** **III**	15 29 10
History of **Inflammatory bowel disease** **Psoriasis** **Eczema** **Psoriatic arthritis** **Cutaneous lupus**	 4 4 3 1 1
Systemic therapy: **TNF- α N (%)**	 10 (19%)

Figure 1: The inflammatory marker C5a is not significantly different by disease severity. All p values are FDR (False discovery rate) corrected.



6.2.4 Discussion

C5a is an activation product of the complement cascade and may result in neutrophil activation and infiltration of the skin in HS lesions (138). Complement C5a levels were elevated in patients with HS in this study, however this did not correlate with disease severity. This is in keeping with the prior study by Kanni et al. which described levels of C5a >28 ng/ml in patients with HS, however they noted negative correlation of C5a with HS severity which may suggest complement activation occurs in the early stages before progression to stage II, and III (138). Our study supports further the role of systemic complement activation in HS and C5a levels may be used as a biomarker in future. The addition of IFX-1, a C5a blocker, in the study by Kanni et al. led to a reduction in TNF-α suggesting a therapeutic target in HS (138). In an open-label single-arm trial by Giamarellos-Bourboulis et al. twelve patients with HS received 800mg of IFX-1 on days 1, 4, 8, 15, 22, 29, 36, 43, and 50 and 75% achieved the primary endpoint of positive Hidradentitis Suppurativa Clinical Response score (HiSCR) on day 50, and 83.3% on day 134 (139). This further supports the role of C5a in HS and the use of C5a blockade as therapy. There is also a randomised, double-blind, placebo-controlled phase II trial ongoing targeting C5a in patients with HS, the results of which are awaited (728).

6.2.5 Conclusion

In conclusion we found elevated levels of C5a in our cohort of patients with hidradenitis suppurativa. C5a may provide a therapeutic target in patients with HS and serum C5a may act a biomarker of the disease.

7. Diet and Hidradenitis Suppurativa

Abstract

The gut-skin axis is an expanding area of research, and several skin conditions including HS, have gut comorbidities (164–166). An abnormal gut microbiota, or dysbiosis, has been linked to the development of skin disease and diet has a significant impact on the gut microbiota composition (166,167). The aim of this study was to describe the diet of a cohort of patients with HS and to determine if diet had an interaction with the gut and skin microbiome, inflammatory markers, and disease severity.

Adult patients with a confirmed clinical diagnosis of hidradenitis suppurativa made by a consultant dermatologist in two tertiary referral centres in Ireland were invited to participate in the study. Patients with HS were asked to complete a Food Frequency Questionnaire which examined their diet over the past year. Comparative analysis to 102 patients with Crohn's Disease (CD) and 95 controls was carried out. Fresh faecal samples were provided by patients and controls. Microbial DNA was extracted and library preparation and 16S rRNA gene sequencing was carried out (as previously described in Chapter 5) (710). Calprotectin was evaluated by an enzyme-linked immunosorbent assay (CALPROLAB™ Calprotectin ELISA (HRP)) and complement C5a levels were evaluated by enzyme-linked immunosorbent assay (Abcam ab193695 Complement C5a Human ELISA Kit).

No significant difference in faecal microbiota composition or overall habitual diet was seen in the patients with HS. Diet was not associated with disease severity and faecal microbiota composition did not differ by Hurley stage. Two distinct microbiome groups were noted and there was no significant difference in overall

habitual diet between the microbiome groups. Two distinct dietary groups were noted by hierarchal clustering and microbiome groups did differ by dietary group. Dietary group 1, whose members had lower calprotectin levels, had higher consumption of several dietary ingredients associated with Western diet. C5a levels were not significantly different between dietary groups. The habitual diet of patients with HS differed from healthy controls, and was similar to those with CD.

In conclusion, we described the diet of a cohort of patients with HS and explored the relationships between the gut and skin microbiome, inflammatory markers, and disease severity. Modification of the gut microbiota via interventional diets may have a potential role to play in HS treatment in future.

7.1 Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory dermatosis presenting with painful nodules, abscesses, and sinus tracts in intertriginous sites. The gut-skin axis is an expanding area of research, and several skin conditions including HS, have gut comorbidities (164–166). An abnormal gut microbiota, or dysbiosis, has been linked to the development of skin disease (166). Diet has a significant impact on the gut microbiota composition (166,167). Study on the role of dietary factors in the development of HS is lacking (168). It has been suggested that a dairy-free diet and avoidance of high glycaemic load foods can result in improvement in HS (168,169). It is postulated that dairy products and high glycaemic foods can act through hormonal mechanisms by triggering androgen-driven obstruction of follicles (169). Other studies suggested avoiding nightshades (Solanaceae) and foods and drinks containing brewer's yeast such as bread and beer (168). Adherence to a Mediterranean diet in HS demonstrated lower disease activity and severity in another study (170). These studies, however, provide little information on the effect of diet on the microbiota as a potential aetiological factor. The current aim was therefore to describe the diet of a cohort of patients with HS and to determine if diet had an interaction with the gut and skin microbiome, inflammatory markers, and disease severity. We also compared the habitual diet of patients with HS, to controls and to patients with Crohn's disease (CD).

7.2 Methods

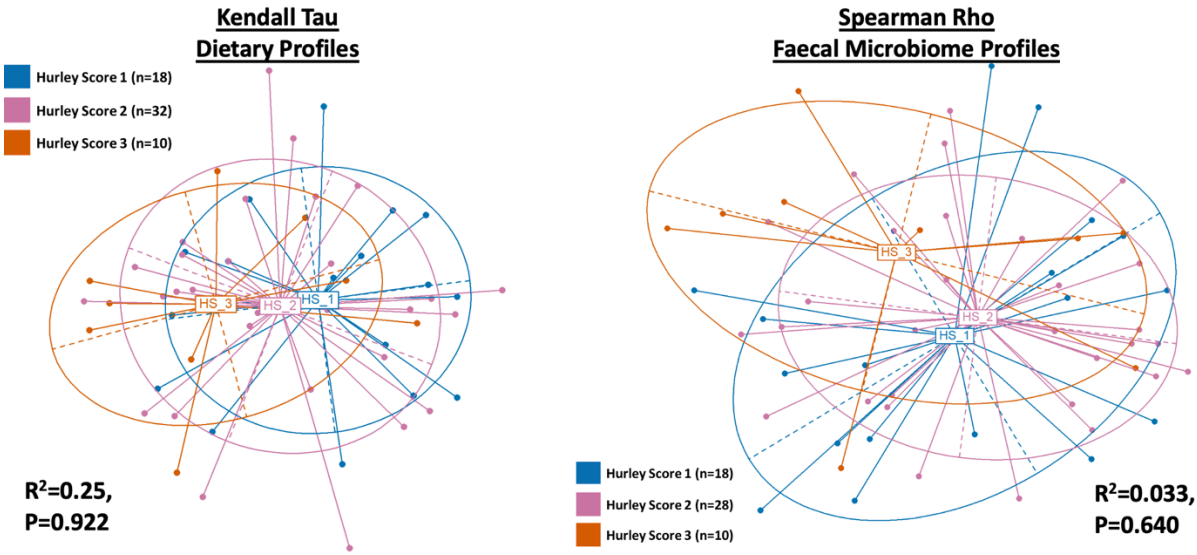
Adult patients with a confirmed clinical diagnosis of hidradenitis suppurativa made by a consultant dermatologist in two tertiary referral centres in Ireland were invited to participate in the study. Ethical approval (Cork Research Ethics Committee and

Tallaght University Hospital Ethics Committee) and written informed consent from patients was obtained. Exclusion criteria included topical or oral antibiotic usage in the preceding four weeks. Data including age, gender, smoking status, weight, height, body mass index, presence of co-morbidities and severity of disease (Hurley Score) were recorded (16). Healthy adult controls were recruited from the general population, and were age and gender matched. For comparative analysis we included data for 102 patients with Crohn's disease and 95 controls obtained from a previously published dataset (559). Patients with HS were asked to complete a Food Frequency Questionnaire which examined their diet over the past year (See Supplementary Methods). Patients were asked to estimate their average intake of specified foods, including meat, fish and poultry, bread and biscuits, cereals, potatoes, rice and pasta, dairy products, fruit, vegetables, sweets and snacks, and drinks. Intake of functional foods such as probiotics was also examined, as well as vitamin supplements, and any special diets. Fresh (<24 hours) faecal samples were provided by patients and controls and stored at -80°C prior to microbial DNA extraction. Microbial DNA was extracted and library preparation and 16S rRNA gene sequencing was carried out (as previously described in Chapter 5) (710). Calprotectin was evaluated by an enzyme-linked immunosorbent assay (CALPROLAB™ Calprotectin ELISA (HRP)) and complement C5a levels were evaluated by enzyme-linked immunosorbent assay (Abcam ab193695 Complement C5a Human ELISA Kit). (See Supplementary Methods) Statistical analysis was performed using R (version 4.2.1).

7.3 Results

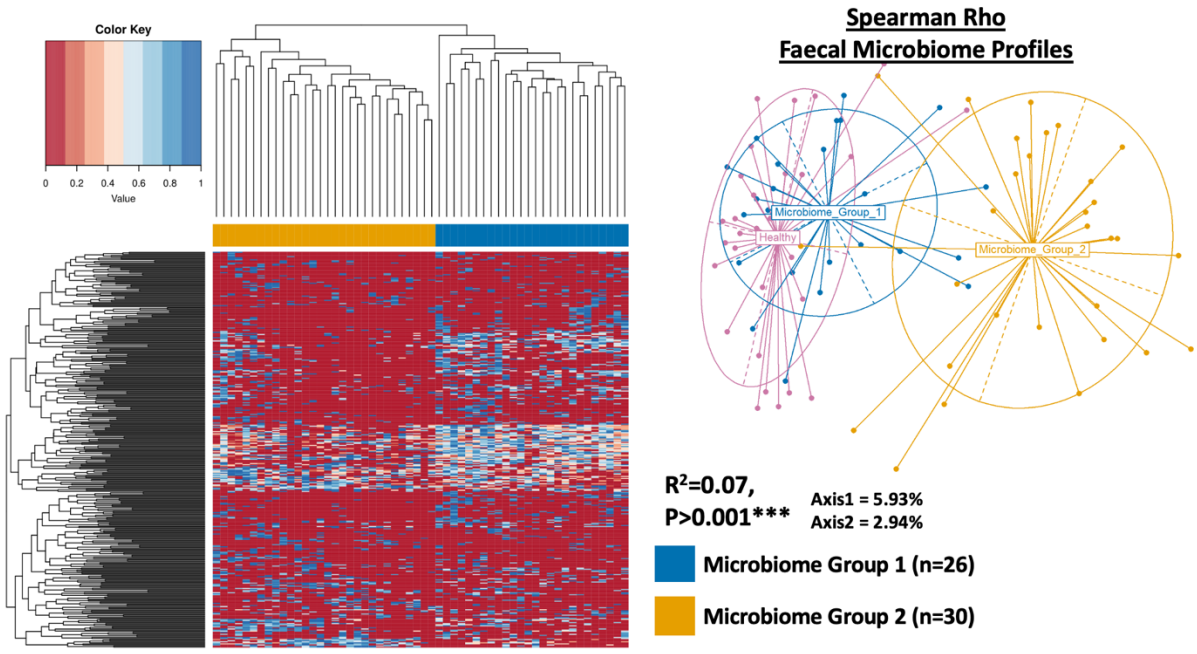
56 patients with HS and 30 healthy controls provided faecal samples for analysis and completed food frequency questionnaires. 18 had Hurley stage I disease, 28 Hurley stage II disease and 10 Hurley stage III disease. No significant difference in faecal microbiota composition or overall habitual diet was seen in the patients with HS (Figure 1). Diet was not associated with disease severity and faecal microbiota composition did not differ by Hurley stage (p=0.640; Figure 1).

Figure 1: Faecal microbiota composition and dietary profiles by Hurley stage



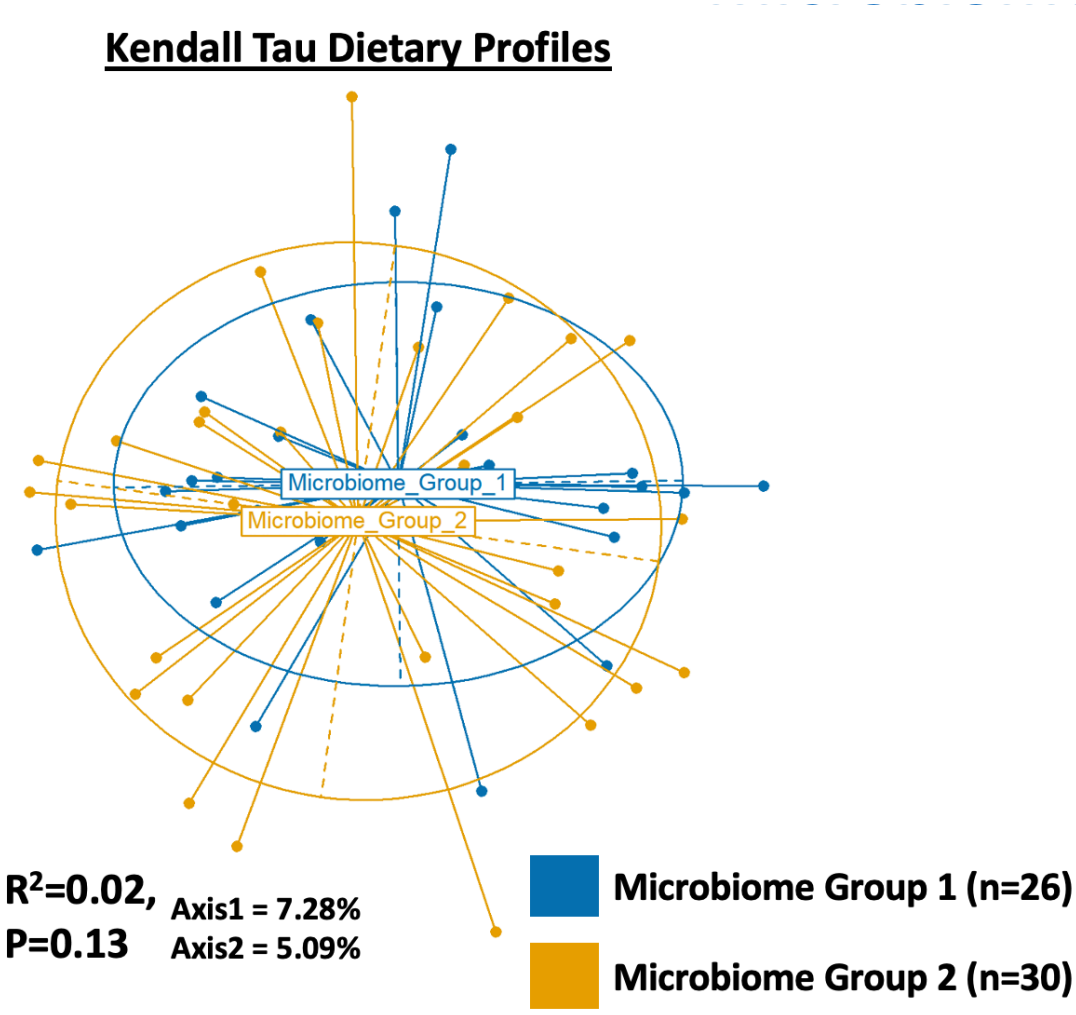
Hierarchal clustering revealed two distinct microbiome groups (as previously discussed in Chapter 5)(710)(Figure 2).

Figure 2: Hierarchal clustering of microbiome groups



Differences in individual dietary ingredients were also examined. Cohens d test was used to remove food items with small effect size and logistic regression was used to control for age, age at diagnosis, previous antibiotic use, gender, Hurley stage and body mass index (BMI). There was no significant difference in overall habitual diet between the microbiome groups (p=0.13)(Figure 3).

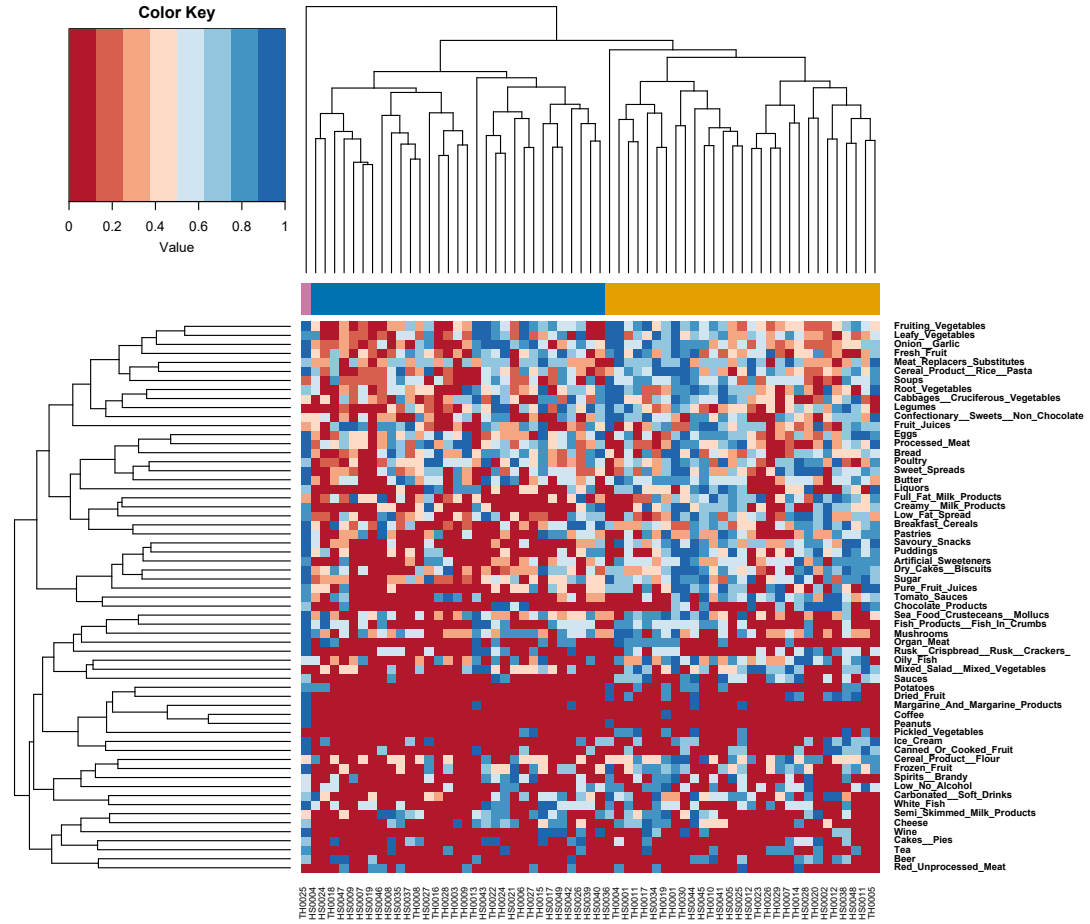
Figure 3: Dietary profiles of two distinct HS microbiome groups



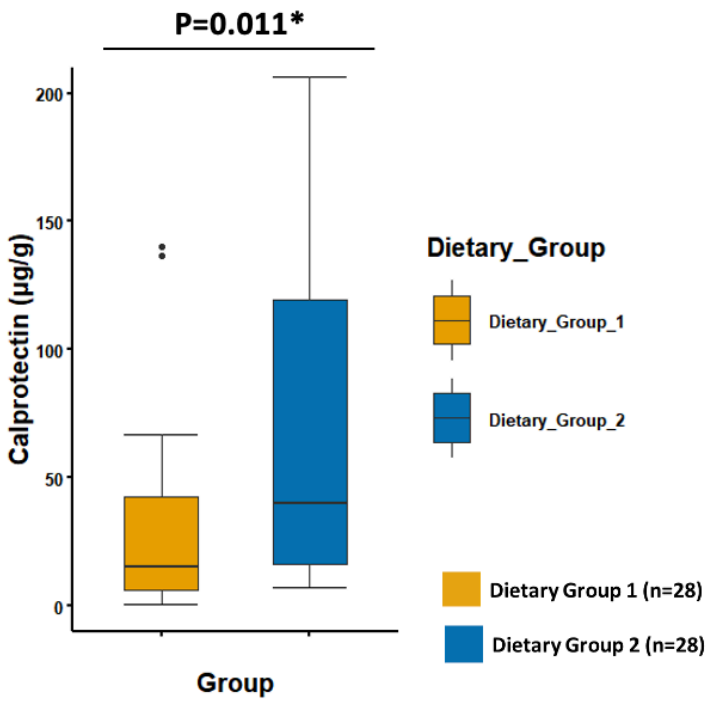
However, hierarchal clustering revealed two distinct habitual dietary patterns among HS patients with higher levels of calprotectin in dietary group 2 (p=0.011)(Figure 4). Dietary group 1, whose members had lower calprotectin levels, had higher consumption of several dietary ingredients associated with Western diet.

Figure 4: (a) Hierarchal clustering of habitual dietary patterns among HS patients, (b) with higher calprotectin levels in dietary group 2

(a)

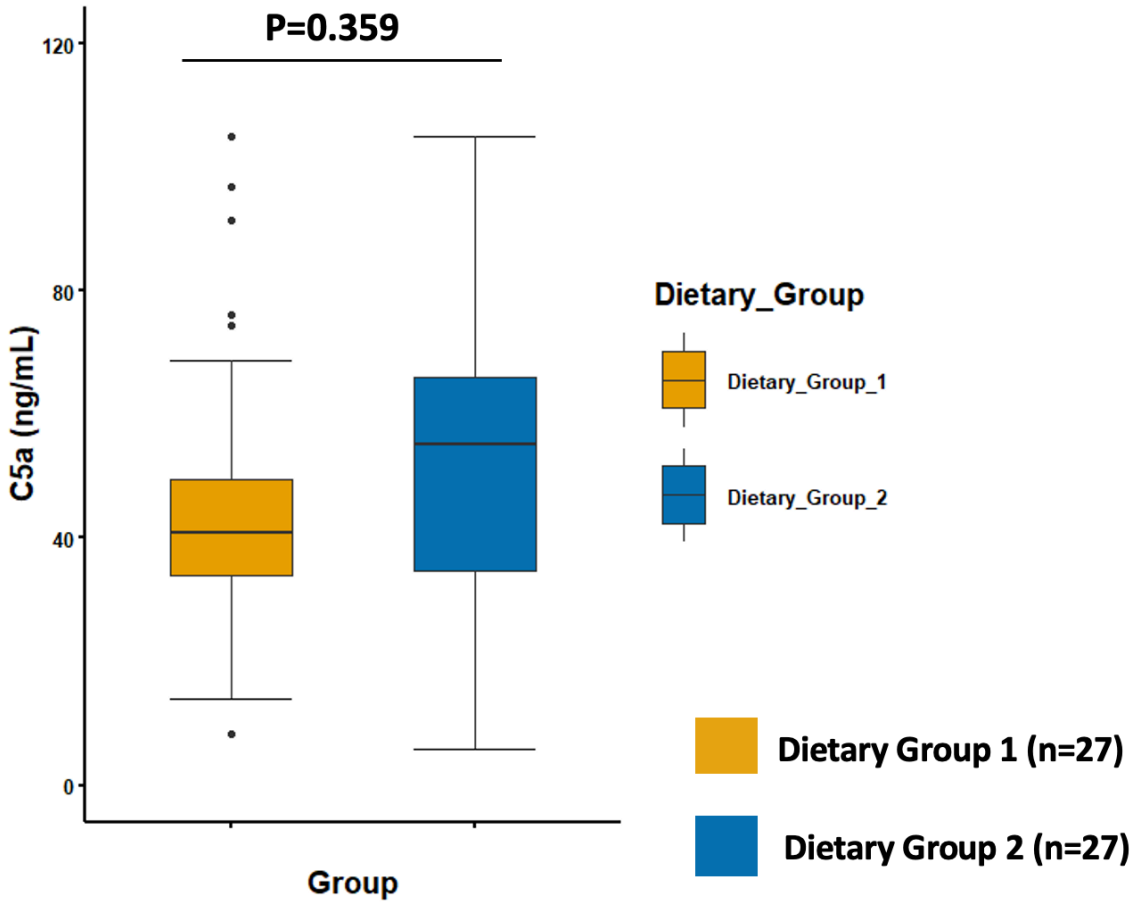


(b)



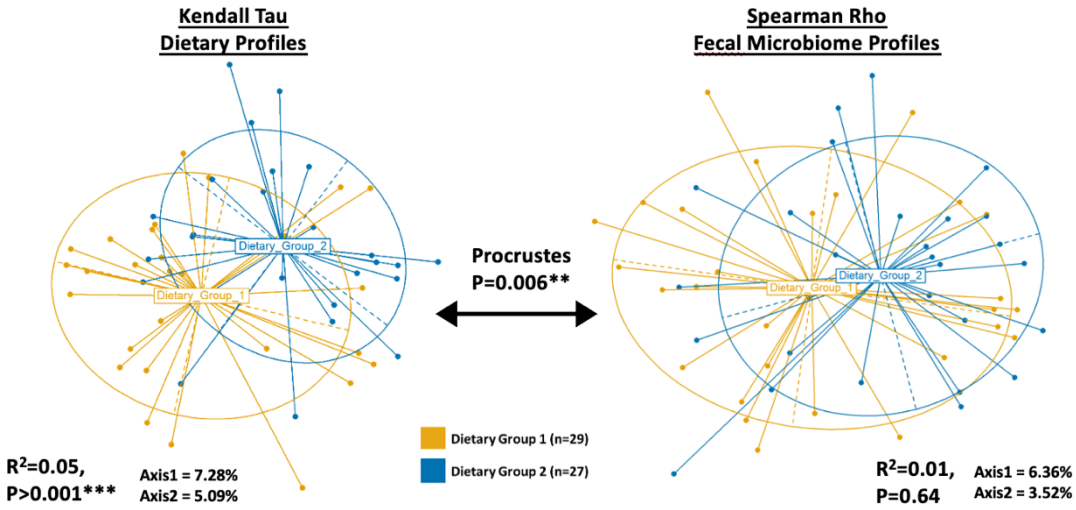
C5a levels were not significantly different between dietary groups (p=0.359)(Figure 5).

Figure 5: C5a levels by dietary group



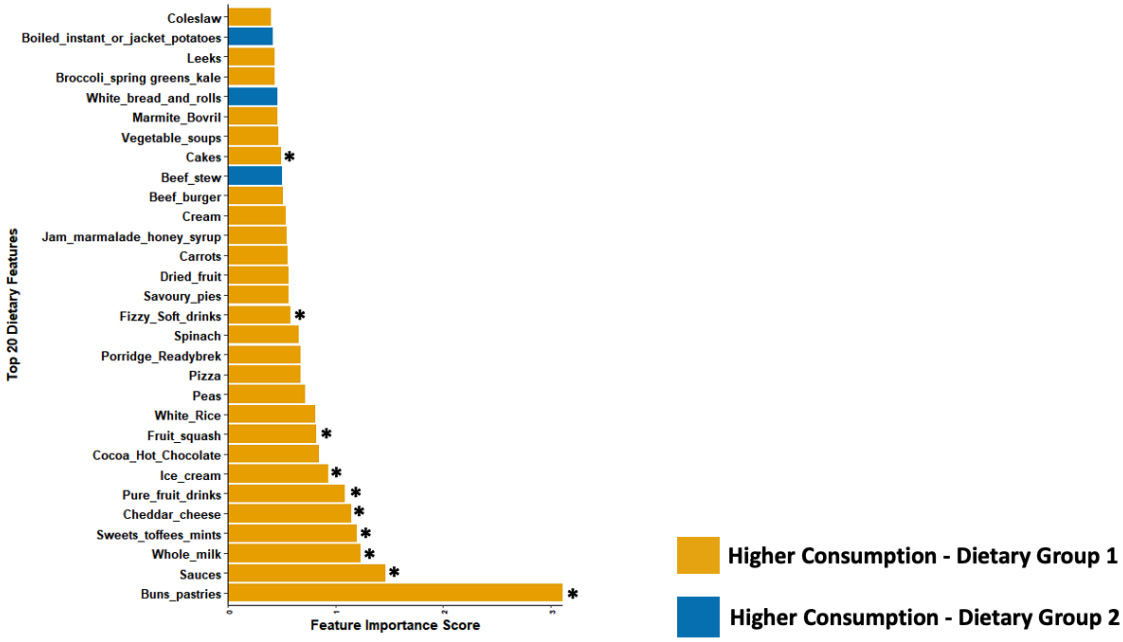
A significant association was seen between habitual diet and faecal microbiota composition (Figure 6).

Figure 6: Association between habitual diet and faecal microbiota composition



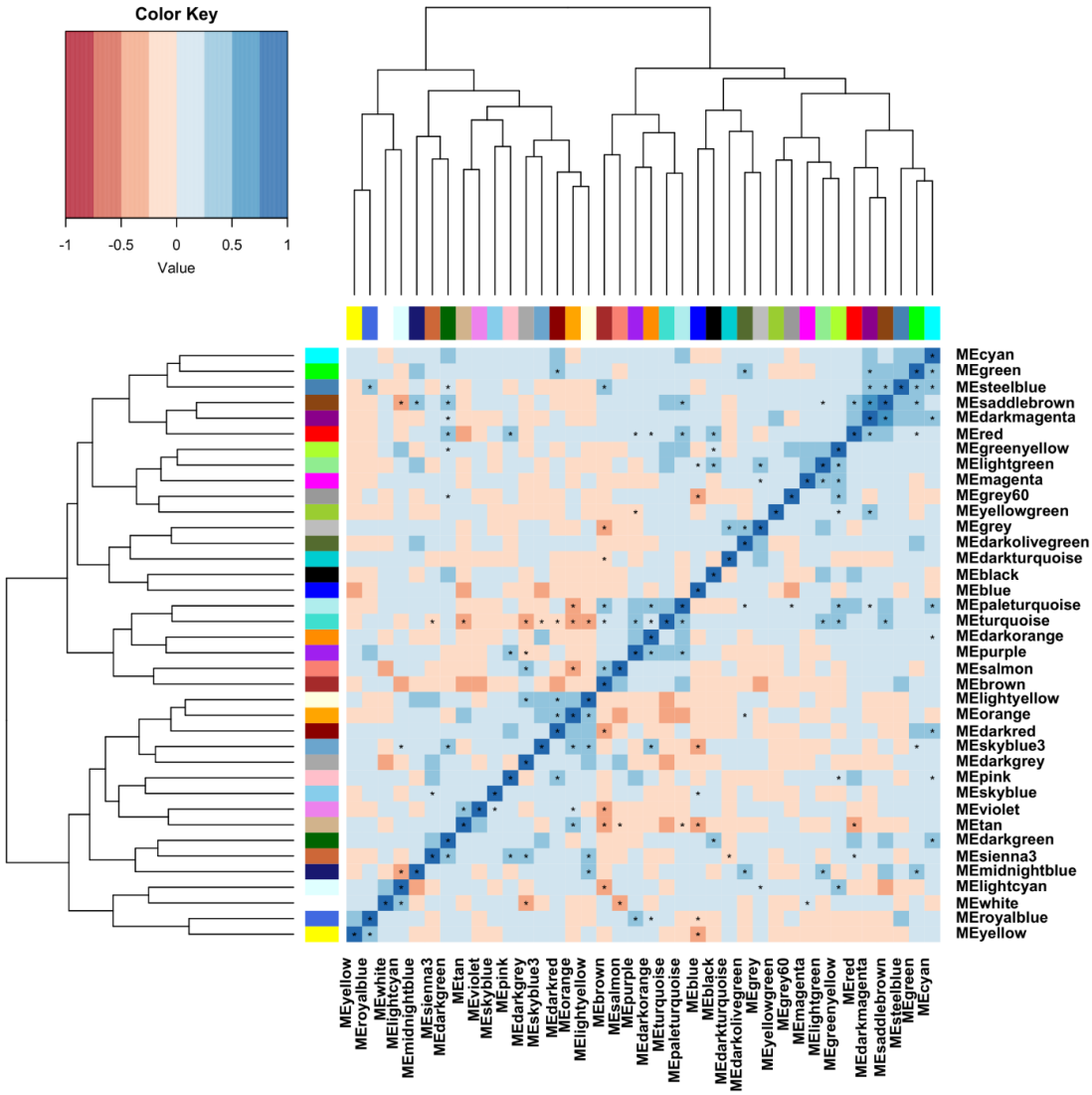
Random Forest classification was used to determine the top 30 dietary features in HS (Figure 7). Dietary group 1 had higher consumption of several dietary ingredients associated with Western diet (Cakes, buns, pastries, soft drinks, sweets, and dairy products).

Figure 7: Random Forest classification with an accuracy of 90% demonstrating top 30 dietary features (with accuracy of 90%). * denotes dietary ingredient significantly different through logistic regression



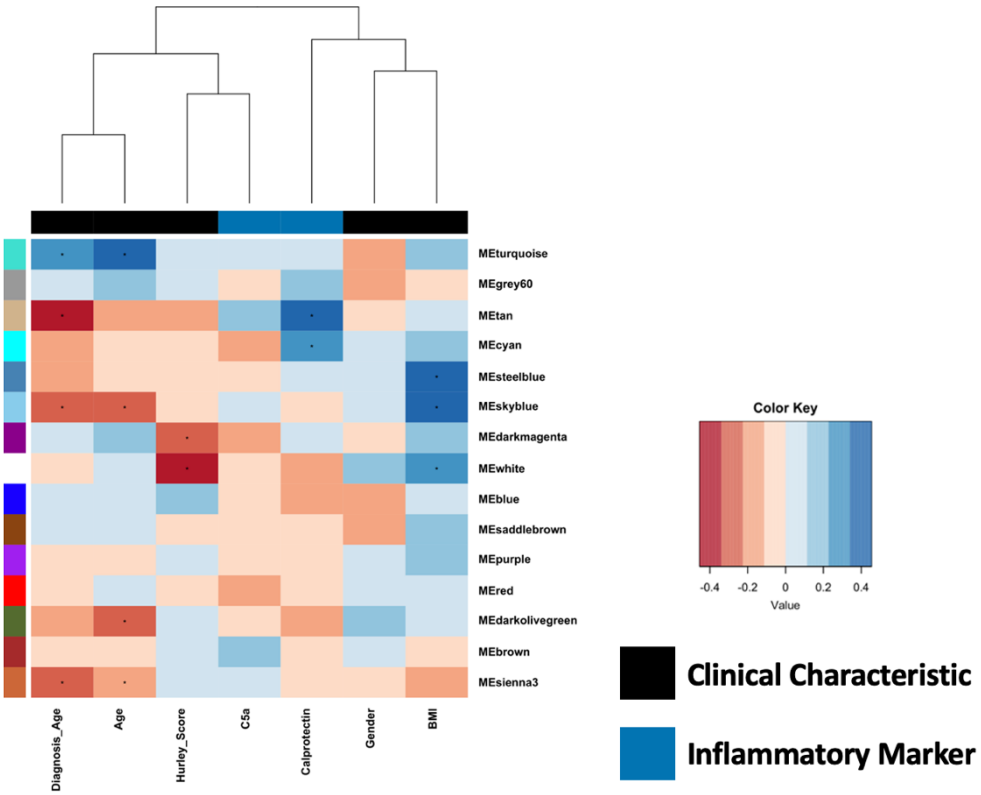
Exploration of the relationships between different gene sets (modules) via weighted gene co-expression network analysis (WGCNA) identified 38 modules of interest. WGCNA constructs co-expression networks based on correlations between the quantitative measurements of each taxon (729). Spearman correlations show associations between different modules (Figure 8). This heatmap shows correlations of the food frequency questionnaire and clinical metadata to the faecal microbiome. The modules included common gut taxa such as Lactobacilli, Ruminococcaceae, Clostridiales, and Firmicutes. The full list of module taxon content for the faecal microbiome is available in Appendix 1.

Figure 8: Spearman correlation between different modules



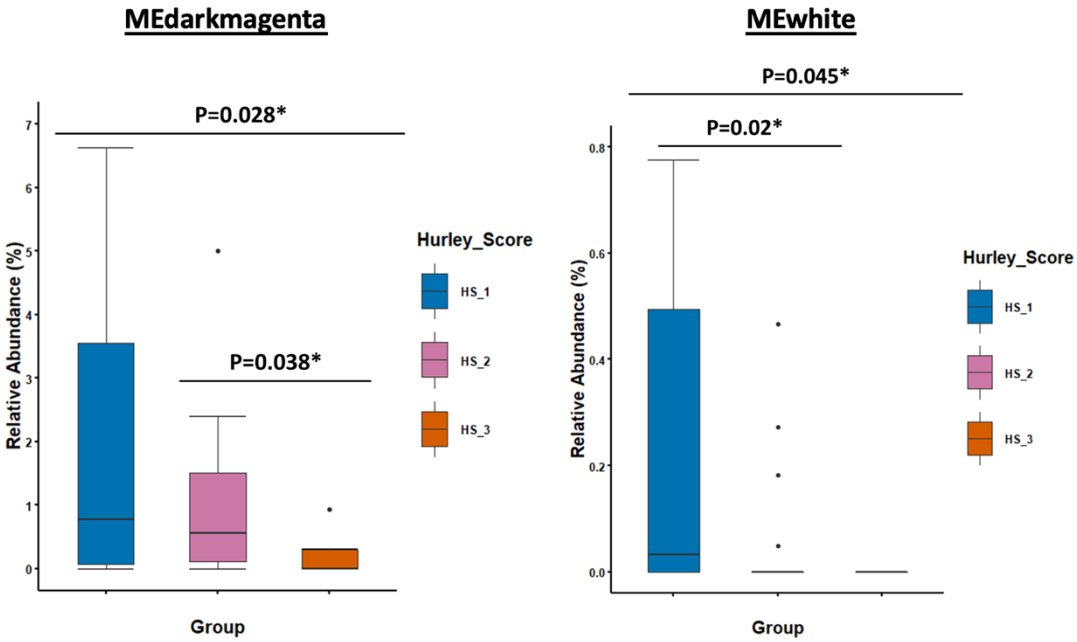
We conducted spearman correlation analysis between clinical characteristics and inflammatory markers with the top 15 most important features (WGCNA modules) in distinguishing between the HS and healthy microbiota from a random forest classifier (Figure 9).

Figure 9: Spearman correlation between modules, clinical characteristics, and inflammatory markers for faecal microbiome



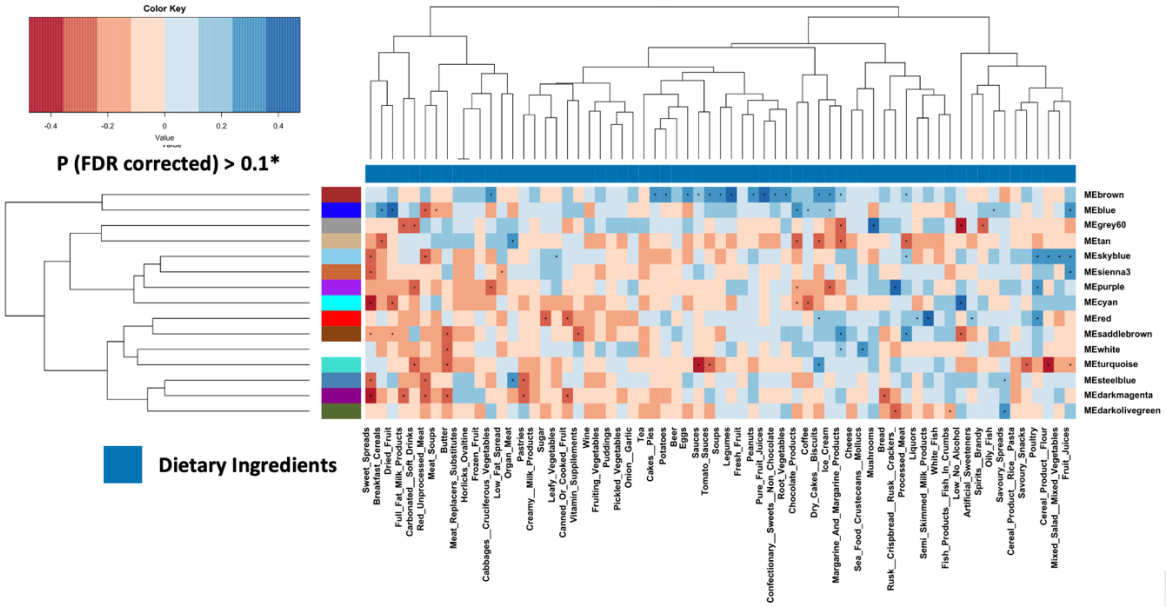
Calprotectin levels had strong positive correlation with taxa in the tan and cyan modules. The tan module included *Ruminococcus gnavus*, which was overabundant in HS as previously discussed, and the cyan module included taxa such as Ruminococcaceae, Clostridiales, and *Faecalibacterium prausnitzii.* Loss of taxa was a feature of two WGCNA modules, darkmagenta and white. Depletion of these taxa was associated with disease severity in HS (Figure 10). The darkmagenta and the white modules included Firmicutes and Lactobacilli which are beneficial bacteria.

Figure 10: Loss of taxa in two WGCNA modules (darkmagenta and white) associated with disease severity in HS patients



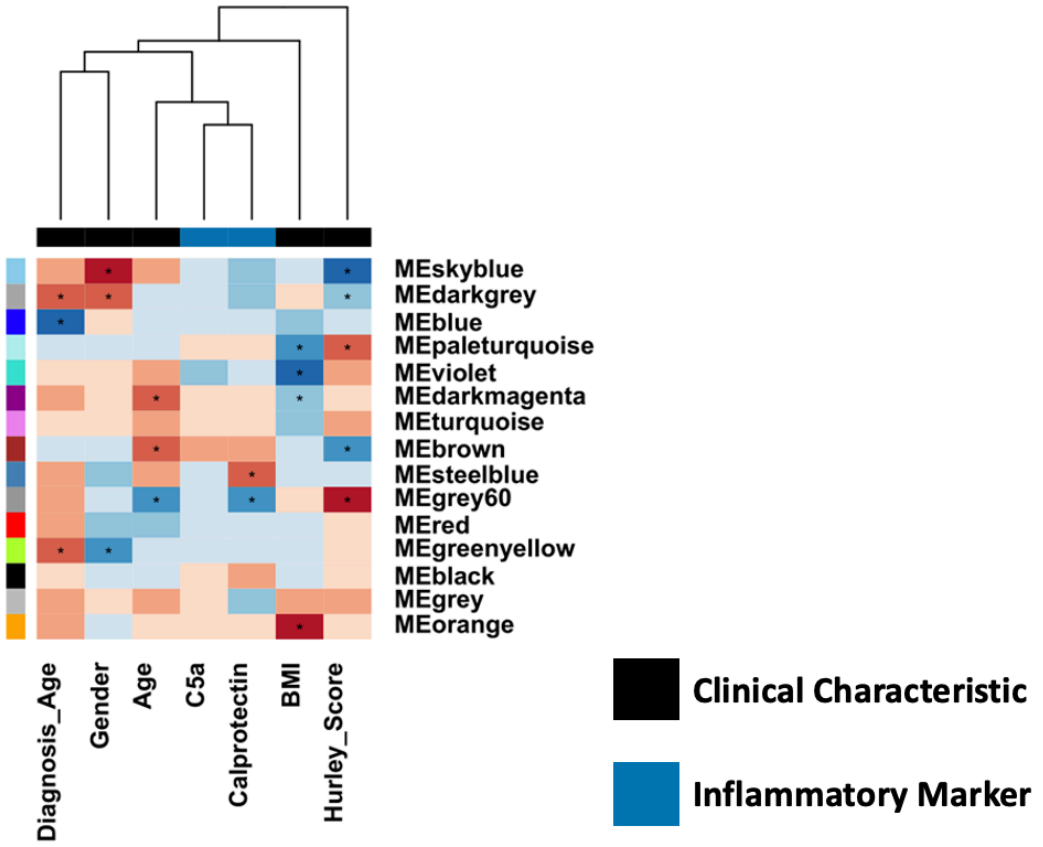
Correlation between modules and dietary ingredients for faecal microbiome was investigated using Spearman correlation analysis. (Figure 11) Positive correlation between processed carbohydrates, dairy products, and red meat were seen with several modules. These modules included the taxa Ruminococcaceae, and Clostridiales.

Figure 11: Spearman correlation between modules and dietary ingredients for faecal microbiome



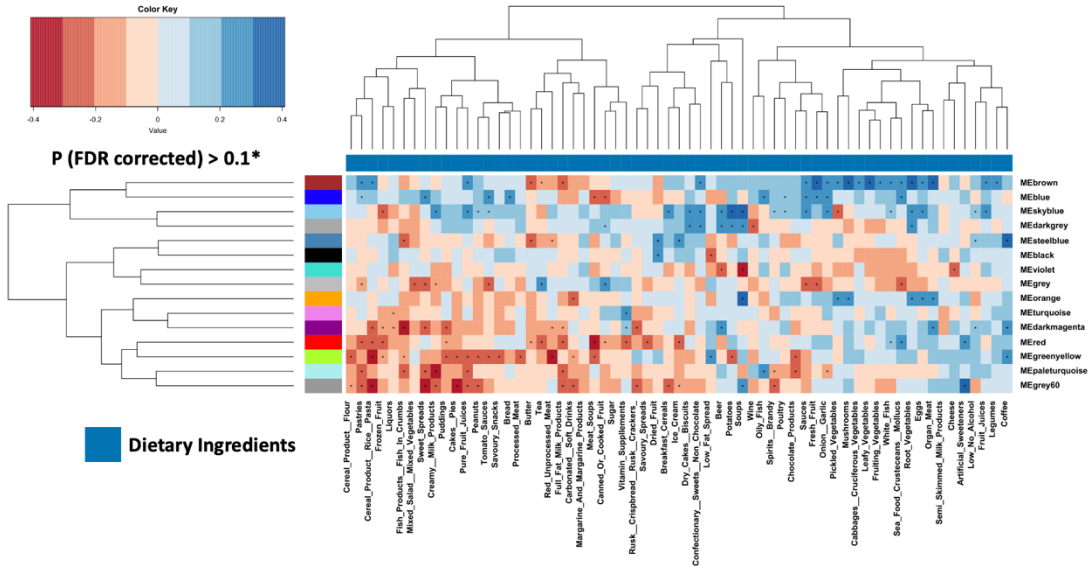
WGCNA of the skin microbiota identified 35 modules of interest. Spearman correlation was computed to assess the relationship between the 15 most important features (WGCNA modules), clinical characteristics and inflammatory markers for the skin microbiome (Figure 13). Calprotectin levels, BMI and Hurley staging all showed positive correlation with modules depleted in healthy controls, and these modules consisted of taxa including Corynebacterium, *Staphylococcus epidermidis*, Streptococci and anaerobes. The full list of module taxon content for the skin microbiome is available in Appendix 2.

Figure 12: Spearman correlation between modules, clinical characteristics, and inflammatory markers for the skin microbiome



Spearman correlation was conducted between the modules and dietary ingredients for the skin microbiome showing association between processed carbohydrates, dairy products and processed meats and the taxa Corynebacterium, *Staphylococcus epidermidis*, Streptococci and anaerobes (Figure 13).

Figure 13: Spearman correlation between modules and dietary ingredients for skin microbiome

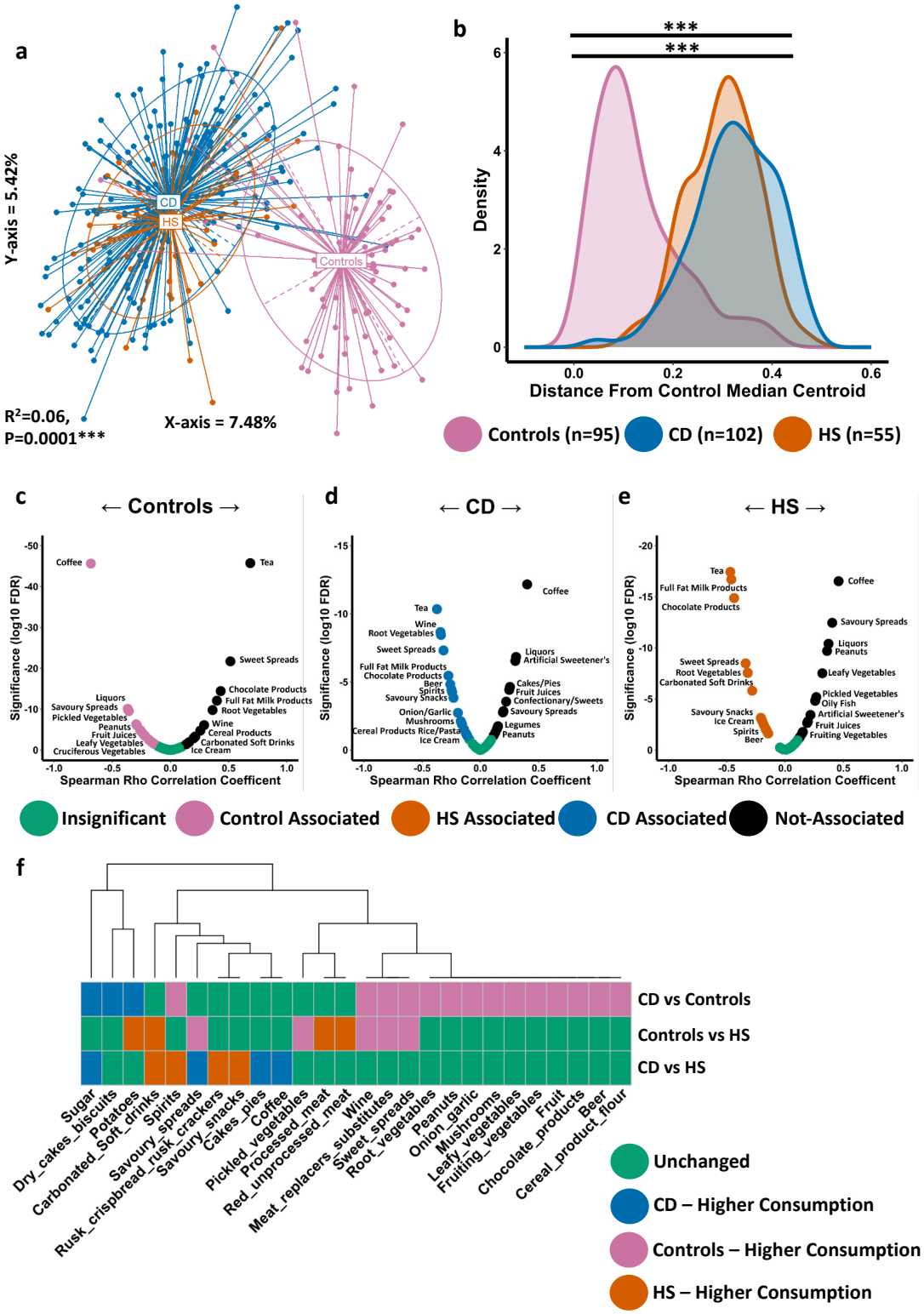


We conducted principal component analysis using the Kendall tau distance measure to investigate differences in habitual diet of patients with HS, patients with Crohn's disease (CD) and healthy controls (Figure 14a). We observed a statistically significant separation between the groups (PERMANOVA FDR-corrected $P < 0.0001$: $R2 = 0.06$). Habitual diet in patients with HS was significantly different to controls (Figure 12a). Interestingly, the HS habitual diet was not significantly different to diet of those with CD (Figure 14a and 14b). Given the large difference in habitual diet between patients with HS and controls, we wanted to establish what specific dietary ingredients were most or least associated with the median dietary pattern of each group. We conducted Spearman correlation analysis between the consumption levels of each dietary ingredient with the distance from the median centroid of each study group respectively, as calculated from Figure 14a (Figure 14c-14e). As expected, the control group was observed to have a strong negative correlation with the distance from the

control median centroid for a number of food items considered to be health promoting and high in dietary fibre (Figure 14c). This list included a variety of vegetables (cruciferous, leafy, and pickled) as well as fish (Figure 14c). Dietary ingredients which were least associated (positive correlation) with controls using this approach included chocolate products, ice-cream and carbonated soft drinks, all of which are elements of the Western diet. Using this approach, an opposing trend was identified for CD (Figure 14d) and HS (Figure 14e). A number of food items whose consumption is typical for the Western diet were found to negatively correlate with the distance from the HS median centroid (Figure 14e), including processed meat, sugar, carbonated soft drinks, ice-cream and chocolate. Several alcoholic beverages were also found to be associated with the HS diet including beer, wine and spirits. Dietary ingredients which were least associated with the HS diet (positive correlation) included fish, a variety of vegetables (pickled, leafy and fruiting) as well as fruit (Figure 14e).

Figure 14: Habitual diet of patients with HS resembles the Western diet similar to patients with CD. (a) Principal Component Analysis (PCoA) of habitual dietary profiles (Kendall tau distance) based on daily frequency of consumption. The P Value (0.0001) obtained using a PERMONOVA shows there is statistically significant separation between the groups. The eigen values are also reported which show the variation reported in the X-axis (7.48%) and Y-axis (5.24%) of the PCoA. (b) Using the PCoA coordinates from (a) the median control centroid was calculated and the distance of all samples from those coordinates was subsequently determined and displayed here as a density plot. Density is displayed on the Y-axis while the actual reported distance from the control median centroid is displayed on the X-axis. Kruskal-Wallis with Dunn's post hoc test was used to determine significant

differences between the groups for this distance measure. The annotations used for P values are $P < 0.05$ *; $P < 0.01$ **; $P < 0.001$***. All displayed P values are FDR corrected. (c-d) Volcano plot showing spearman correlations between the consumption of dietary ingredients and (c) the median control centroid, (d) the CD median centroid and (e) the HS median centroid. A significant negative correlation indicates that a specific dietary ingredient is associated with the median pattern of that patient group as its consumption increase the shorter the distance to the median centroid. Significant positive correlations indicate that a specific food item is not associated with the median dietary of that patient group as it consumption increases the larger the distance from the median centroid. (f) Wilcoxon test was conducted to determine what food items were differentially consumed between each pairwise comparison and shown in a colour coded heatmap. Each colour signifies whether that specific genera was unchanged (green), higher in controls (purple), higher in patients with CD (blue) or higher in patients with HS (orange).


a
Y-axis = 5.42%
X-axis = 7.48%
R²=0.06,
P=0.0001***
CD
HS
Controls
b
***
***
Density
Distance From Control Median Centroid
Controls (n=95)
CD (n=102)
HS (n=55)
c
← Controls →
d
← CD →
e
← HS →
Significance (log10 FDR)
Spearman Rho Correlation Coefficent
Insignificant
Control Associated
HS Associated
CD Associated
Not-Associated
f
CD vs Controls
Controls vs HS
CD vs HS
Unchanged
CD – Higher Consumption
Controls – Higher Consumption
HS – Higher Consumption

7.4 Discussion

This study found no significant difference in faecal microbiota composition or overall habitual diet in the patients with HS. Diet was not associated with disease severity and faecal microbiota composition did not differ by Hurley stage. Furthermore, there was no significant difference in overall habitual diet between the two distinct microbiome groups previously described. Interestingly a more western diet was associated with lower faecal calprotectin levels, the reason for which is unexplained..

Explorations of the relationships between diet, the skin and faecal microbiome, inflammatory markers, and clinical characteristics was also performed. Modules associated with the taxa Ruminococcaceae and Clostridiales positively correlated with calprotectin levels in faecal microbiome analysis. These taxa were also associated with a diet rich in processed carbohydrates, dairy products, and red meat. An abundance of *Ruminococcus gnavus* has previously been described in the faecal microbiome of patients with HS (710). Loss of beneficial taxa, including Firmicutes and Lactobacilli, in two modules correlated with disease severity in HS (730). Regarding the skin microbiome, calprotectin levels, BMI, and Hurley staging all showed positive correlation with modules including the taxa Corynebacterium, *Staphylococcus epidermidis*, streptococci and anaerobes which are found to be pathogenic in HS (531). Furthermore, these skin taxa were found to correlate with a diet rich in processed carbohydrates, dairy products, and processed meat.

The dietary pattern in patients with HS resembled that of the Western diet, differed from controls, and was similar to that of Crohn's Disease. Dietary ingredients found

to positively associate with HS were high in sugar and saturated fat. In addition, food items least associated with HS included vegetables and fruit which are high in dietary fibre and health promoting. These findings highlight the need for greater nutritional support for patients with HS. Structured dietary advice and/or dietary intervention represents a promising avenue to alleviate disease burden

Diet can have a profound effect on the gut microbiome and gut microbes in turn influence the absorption, metabolism, and storage of nutrients (731). Current research shows that dietary fibres promote the growth of beneficial bacteria and suppress the growth of pathogenic species (730). The quantity and type of fat and protein also modulates both beneficial and potentially pathogenic microbes (730). Diets low in fibre and high in processed carbohydrates and fats can result in lower gut microbial diversity (731). Lower gut microbial diversity has been linked to the development of several inflammatory conditions, including inflammatory bowel disease (732–734). The response of the gut microbiota to diet may provide a valuable tool to exploit, with potential to develop interventional diets to treat diseases associated with gut dysbiosis. Such interventional diets have been trialled in inflammatory bowel disease with reported success (735). A diet rich in fibre-rich plant foods, and low in processed carbohydrates and red meat could prove to have an anti-inflammatory effect in HS, reducing disease severity and flares. Such a diet may also prevent development of HS in those who are predisposed.

7.5 Conclusion

In conclusion, we described the diet of a cohort of patients with HS and explored the relationships between the gut and skin microbiome, inflammatory markers, and

disease severity. Modification of the gut microbiota via interventional diets may have a potential role to play in HS treatment in future.

8. Conclusions and Future Perspectives

HS is a chronic, debilitating disease, the pathogenesis of which is still not completely understood. HS can prove challenging to treat as discussed in the introductory chapter, and the lack of randomised placebo-controlled trials in HS has resulted in little evidence in the literature for effective treatments for HS. Furthermore, the lack of a standardised outcome measure has made comparison of the different treatments difficult. **Chapter 2** examined the placebo-controlled trials in the literature, commenting on the placebo response rates and estimating the true drug efficacy, as well as commenting on the heterogeneity of the outcome measures used which limits a systematic approach to comparison. Knowledge of placebo response is of interest to inform design of future microbiota based intervention trials in future.

HS is a debilitating painful disorder with a significant impact on patients' quality of life. **Chapter 3** described the impact of HS on the quality of life of the cohort of patients studied here. Our findings were in keeping with the published literature, highlighting the challenges faced in patients with HS, with 59% reporting a large or extremely large effect of the disease on their life. Highest scores were recorded for levels of embarrassment and self-consciousness relating to the disease and choice of clothing. This adds to the growing literature on the impact on body image noted in patients with HS. Furthermore, a negative impact on employment and leisure time was observed, and this needs to be tackled to ensure patients can continue work and social commitments. Social isolation was also a feature of patients with HS and supports should be made available to these patients to ensure psychological stresses are addressed in addition to the physical aspects of the disease. This chapter also

studied pain in a cohort of patients with HS and emphasises the need for guidelines on the appropriate treatment of pain in HS, which is often overlooked by GPs, dermatologists and surgeons in their assessment and treatment of this cohort. Finally, some subjects reported that the treatment of their HS was bothersome. This chapter also assessed adherence to prescribed treatment in a cohort with HS. Adherence has been noted as poor in patients with HS in the literature, and this was mirrored in our results with a significant proportion reporting their difficulty remembering to take their medication and a further proportion cutting back or stopping medications without medical input. Ensuring adherence to prescribed treatment through enhanced supports tackling the perceived barriers to compliance would be of benefit in patients with HS. It is important to appreciate that non-adherence is not solely 'the fault' of patients but several healthcare factors including poor access and poor communication can have an impact; thus these issues should be further explored in HS. I used validated questionnaires in this study which gives important quantitative results. However, such questionnaires lack depth of information with standardised responses, and thus a mixed methods approach with more qualitative data from focus groups or interviews exploring themes surrounding pain, impact on quality of life, and adherence to prescribed treatment in HS would have added more insight into their thoughts, feelings, and experiences. I also sought to describe the physical activity undertaken by a cohort of patients with HS. In this study it appears that patients with HS had moderate to high levels of activity; however, overestimation of physical activity is a trend observed in many studies assessing exercise levels. The use of a questionnaire to assess physical activity appears to be prone to bias, and therefore the use of individual interviews to clarify responses, and objective

measurement of pedometer or smartphone-based activity would have given more robust findings.

The skin microbiome is an area of expanding research in HS, with more robust data coming to light about the bacteria found in lesions of HS, and their possible role in the pathogenesis of the disease, since the introduction of next generation sequencing in recent years. **Chapter 4** described the skin microbiome composition in a cohort of patients with HS compared to healthy controls. A dysbiosis with lower alpha diversity, a marker of species richness, and elevated levels of *Finegoldia magna* was noted in patients with HS. This is in agreement with the prior literature.

There is a paucity of data on the gut microbiome in HS in the literature to date. **Chapter 5** described the gut microbiome in a cohort of patients with HS compared to healthy controls. This is the first large study on the gut microbiome in HS showing an altered gut microbiome with low alpha diversity and an abundance of *Ruminococcus gnavus*.

As with any microbiome study, we were limited by the lack of a good definition of a 'healthy microbiome'. A strength of this study in this respect is the inclusion of a control group which was lacking in many of the prior microbiome studies in HS. Furthermore, with next generation sequencing the results can be biased due to incomplete reference databases, and varying PCR amplification frequencies used; and the clinical significance of the identified dysbiosis is unknown. Skin samples in particular prove challenging for amplicon-based sequencing as they are low biomass. The number of subjects that contributed swab samples to some sites was low, with a

low control number. Attempts to optimise sample collection were made including no cleansing of the skin for at least 24 hours before sample collection, the use of a scraping and firm swabbing method to increase yield, and the use of a buffer skin solution. Reagents and swabs were selected as reported to be DNA-free and a negative control was run within the same sequencing batch to detect contamination. A further limitation of the study is the lack of swabs from unaffected skin which has been proven to show an altered microbiome in a study by Ring et al (546). I did however attempt to sequence the microbiome of affected and unaffected skin biopsies from 9 patients. Unfortunately limited bacterial DNA concentrations were extracted, with high levels of off-target amplification of human DNA, an issue which has been encountered in other studies (736–738). This is a general feature of microbiome analysis of low biomass samples (739). Therefore, standardisation of analysis of microbial DNA in skin biopsies is required to reduce human DNA by unbiased whole genome amplification (736). From this study, it appears primer selection in sample processing and sequencing may have resulted in this contamination (737,738). Optimising DNA extraction from skin biopsies is an aim for future studies in HS and other skin conditions I plan to explore.

This research adds to the expanding knowledge of the microbiome in HS, describing an altered skin and gut microbiome. However, despite this growing knowledge of the microbiome in HS, it remains unclear whether dysbiosis is cause or effect; that is whether the skin inflammation is because of the dysbiosis or whether the dysbiosis is caused by the skin inflammation. Therefore, the true role of the gut and skin microbiome in the pathogenesis of HS needs to be further elucidated. The way forward for this should be further large cohort studies with a control group, and

standardisation of methodology to ensure the homogeneity across studies for direct comparison. Assessing the gut and skin microbiome over time in the same patients may also be of benefit, as would describing the microbiome present during flares and remissions, as well determining the role that it may play in the relapsing and remitting nature of the condition. Other areas of research, which have thus far been neglected in the literature, are the oral and genital microbiome which should be included in future microbiome studies in HS. With new technology, further research on the skin microbiome in HS, such as a prospective cohort study assessing the transient microbiota present during flares and the core microbiota present during remissions, as well as the skin microbiota present pre and post therapy, with next generation sequencing of the skin microbiome from skin swabs and biopsies of affected and unaffected areas, would add to the current knowledge. This might be challenging as the distinction between stable and transient microbiota, which may be in low abundance, can be difficult to decipher (736). Identifying these microbiota present during remissions and flares may inform future manipulation of the skin microbiota via intervention studies such as skin probiotics.

A further prospective cohort study on the gut microbiome in HS, characterising the gut microbiome during flares and remissions of the disease, and pre and post therapy would add to the growing literature and provide potential targets for HS treatment.. Other areas of further research on the gut microbiome include the impact of long-term antibiotics on the microbiome in HS. Our study evaluated patients off antibiotics for at least 4 weeks and did not note any difference between groups with no antibiotic therapy versus those who had antibiotic therapy in the preceding year. A cohort study to evaluate the gut and skin microbiome pre-antibiotic therapy for HS

and on treatment could determine the impact of the antibiotics used in HS on the gut and skin microbiome. Describing the skin and gut microbiome in HS further may also allow us to develop more targeted or narrower-spectrum antibiotics for the treatment of HS in future. This is one way to tackle the emerging issue of anti-microbial resistance, which is of concern with the current long-term use of broad-spectrum antibiotics in HS. It may also provide a way to better target the deep-seated lesions of HS which often poorly respond to antibiotic therapy due to biofilm creation, and may, too, reduce HS patients' risk of developing the antibiotic associated infection *C. difficile*.

The impact of the biologics on the skin and gut microbiome should also be further evaluated. It has been shown in studies on inflammatory bowel disease that adalimumab alters the gut microbiome towards eubiosis (740). If this is also true of anti-TNF-α therapy in HS, the implications of this are worth exploring. Studies have also described how the gut microbiome can affect patient responses to cancer immunotherapy (741). It is therefore possible that certain microbiome patterns may indicate better response to certain treatments also in HS.

High species diversity is positively correlated with resistance to pathogens in both the skin and gut microbiome. Further targeting the gut microbiome may be achieved through faecal microbiota transplantation (FMT), transferring live microorganisms from healthy donors to affected patients. FMT has proven beneficial in the management of *C. difficile*, and inflammatory bowel disease, and its use is also being explored in other areas including cancer immunotherapy (742,743). A clinical trial has also been registered assessing the safety and efficacy of FMT in patients with

chronic inflammatory diseases including several rheumatological conditions, psoriasis, and HS (FRONT) (744). Similarly in the area of treating skin disease, cutaneous microbiota transplants have been trialled in atopic dermatitis and should be explored in HS. Supplementation with pre-biotics and probiotics may also be explored via a randomised controlled trial with the aim of restoring healthy high species diversity, with possible impact on both the skin and gut microbiota. Prebiotics are non-digestible ingredients that selectively stimulate the growth of health-related bacteria such as Bifidobacterium and Lactobacilli, whereas probiotics are living microorganisms that confer a health benefit on the host. To date, no evidence exists for the benefits of prebiotics and probiotics in HS with varied results in atopic dermatitis, acne, and psoriasis (745). Restoring commensal microbial homeostasis replacing pathogenic species, using probiotic strains in HS, may be the way forward in modulating the inflammatory cascade. This is true for both the cutaneous and gut microbiomes. A randomised controlled trial assessing supplementation with beneficial bacteria such as *Ruminococcus obeum*, which was depleted in patients with HS and enriched in healthy controls, would be of interest with the aim of reducing pathogenic bacteria such as *Ruminococcus gnavus* and *Clostridium ramosum* identified in this study, increasing alpha diversity, and restoring eubiosis in the treatment group compared to controls. A randomised controlled trial of a topical probiotic in HS would also be of interest, and targets such as restoring *Propionibacterium acnes* and depleting pathogenic bacteria such as *Finegoldia magna* should be explored.

As gut microbiome research moves on to address the mechanisms influencing host health the crosstalk between the immune system, the gut, and the cutaneous

microbiome, and the role of this pathway in the development of skin disease in HS should be elucidated. A way of evaluating this may be the development of a mouse model of HS. An adequate mouse model of HS does not currently exist and development of such will be important to understand HS pathogenesis better. The first murine models focused on γ-secretase associated polymorphisms which have been described in cases of familial HS(746). Although these mouse models showed some cyst formation they failed to develop the clinical characteristics of inflammation, abscess formation, fistulation and scarring (746). Similarly NCSTN knockout mice showed inflammation of hair follicles but failed to develop abscesses. As human and murine skin differs greatly, xenograft models may be a be a better approach to study HS pathogenesis further and attempts are underway to complete this. The potential impact of the skin and gut microbiome on the development of HS and the utility of manipulation of the microbiome could be further elucidated via these mouse models.

Ex vivo studies of lesional human skin in HS may also be give further insights into the pathogenesis of HS and response to therapy. A study by Vossen et al. of punch biopsy transwell culture demonstrated the contribution of IL-1 in driving inflammation in HS and the inhibitory effect of anti-inflammatory drugs on proinflammatory cytokines and anti-microbial peptides (AMPs)(747). Ex vivo studies are promising and optimisation of such models should be a further area of research to explore.

Calprotectin is a protein biomarker present in the serum and faeces. Gut inflammation and elevated levels may indicate undiagnosed inflammatory bowel

disease. Complement C5a is a potent anaphylatoxin which mediates inflammation and is a chemoattractant for neutrophils. **Chapter 6** described the faecal calprotectin and serum C5a levels in a cohort of patients with HS. Both calprotectin and C5a levels were raised in this study. Elevated faecal calprotectin may indicate sub-clinical inflammation of the bowel mucosa in HS and supports the close monitoring of patients in HS at risk of developing inflammatory bowel disease. Complement C5a may in future be used as a biomarker of disease activity in HS if further studies confirm such an elevation. Furthermore, clinical trials are ongoing to assess the success of targeting C5a in treating HS (728).

Diet is known to be a significant modulator of the gut microbiota (730). Diets high in fat and highly processed carbohydrates, and low in fibre content predispose to gut dysbiosis, with potential implications on health (730). **Chapter 7** described the diet of the cohort of patients with HS and its correlation with the microbial composition, clinical characteristics, serum C5a, and faecal calprotectin levels. We also compared habitual diet of those with HS to healthy controls and patients with Crohn's disease. A western diet was described in patients with HS compared to controls, and similar to those with Crohn's disease. To date little research has shown the impact of diet on development or exacerbation of HS with small sample sizes and no placebo group in the published literature. Diets high in fibre rich plant foods, and low in red meats and processed foods could reduce disease severity and flares, and enhance response to therapy in those with HS, and lower risk of HS developing in those predisposed. Dietary fibre exerts a protective effect on gut microbiota composition and is fermented to produce short chain fatty acids which exert an anti-inflammatory effect on T cells and macrophages (748,749). The next step to assess the impact of diet on

HS would be a randomised controlled trial of dietary intervention with dietary fibre to determine its effect on the altered microbiota described, comparing the gut and skin microbiota pre and post intervention, and to further explore further the role diet plays in HS.

The pathogenesis of HS is likely a result of several different factors including immune dysregulation and an altered microbiome, and so multimodal treatments are likely to be the way forward in future. I look forward to future studies exploring the microbiome further in HS. This is a young and exciting area of research with great potential, impacting on our understanding of the pathogenesis of HS, and informing the development of future treatments.

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10. Supplementary Methods and Appendices

Patient Recruitment

Inclusion Criteria

To be considered eligible for enrolment into the study, subjects must;

1. Be able to give written informed consent.
2. Be between 18 and 65 years of age.
3. Study group will compromise those with a diagnosis of hidradenitis suppurativa.
4. Control group will include healthy individuals with no chronic medical conditions.

Exclusion criteria

Subjects will be excluded from the study if they meet any of the below criteria;

1. Are less than 18 and greater than 65 years of age.
2. Have a significant acute or chronic coexisting illness (cardiovascular, gastrointestinal, immunological, metabolic or any condition which contraindicates, in the investigators judgement, entry to the study).
3. Have a condition or taking a medication that the investigator believes would interfere with the objectives of the study, pose a safety risk, or confound the interpretation of the study results.
4. Subjects may not be receiving treatment involving experimental drugs.
5. If the subject has been in a recent experimental trial, these must have been completed not less than 30 days prior to this study.

Extraction of Microbial DNA from Nasal and Skin Swabs using Qiagen UCP kit

1. Pre-treatment of Microbial DNA from Nasal, and Skin Swabs

    1. Equilibrate samples to room temperature (15–25°C).
    2. If a precipitate has formed in Buffer ATL or Buffer APL2, dissolve byincubating at 56°C.
    3. Heat a thermoshaker to 56°C.
    4. Heat a water bath or heating block to 70°C.
    5. Equilibrate Buffer AVE to room temperature.
    6. Cut the tip off a swab and place it in a 2ml microcentrifuge tube.
    7. Add 500 µl Buffer ATL.
    8. Place the tube on a thermoshaker and incubate for 10 min at 56°C with continuous shaking at 600 rpm.
    9. Open the 2 ml tube and carefully transfer all the liquid into a fresh 2ml tube.

2. Purification of Microbial DNA from pre-treated samples

    1. Add 40 µl Proteinase K and mix the sample by vortexing for 10 s.
    2. Incubate the sample at 56°C for 10 min.
    3. Add 200 µl of Buffer APL2 to the sample. Close the cap and mix by pulse-vortexing for 30 s.
    4. Incubate at 70°C for 10 min.
    5. Briefly spin the tube to remove drops from the inside of the lid.
    6. Add 300 µl ethanol to the lysate. Close the cap, and mix

thoroughly by pulse-vortexing for 15–30 s.

7. Carefully apply 600 µl of the mixture from step 6 to the QIAamp UCP Mini spin column (in a 2ml collection tube) without wetting the rim.Close the cap, and centrifuge at 6000 x g (8000 rpm) for 1 min. Place the QIAamp Mini spin column in a clean 2 ml collection tube (provided), and discard the tube containing the filtrate.

8. Repeat step 7 by applying the remaining mixture from step 6 to the QIAamp UCP Mini spin column.

9. Carefully open the QIAamp UCP Mini spin column and add 600 µl Buffer APW1 without wetting the rim. Close the cap and centrifuge at6000 x g (8000 rpm) for 1 min. Place the QIAamp UCP Mini spin column in a clean 2 ml collection tube (not provided), and discard the collection tube containing the filtrate.

10. Carefully open the QIAamp UCP Mini spin column and add 750 µl Buffer APW2 without wetting the rim. Close the cap and centrifuge atfull speed (20,000 x g; 14,000 rpm) for 3 min.

11. Place the QIAamp UCP Mini spin column in a new 2ml collection tube and discard the old collectiontube with the filtrate. Centrifuge at full speed for 1 min. Place the QIAamp UCP Mini column into a new 2 ml collection tube.Open the lid and incubate the assembly at 56°C for 3 min to dry themembrane completely.

12. Place the QIAamp UCP Mini column in a clean 1.5 ml elution tube and discard the collection tube. Carefully apply 20–100 µl of BufferAVE to the center of the QIAamp UCP Mini membrane. Close the lidand incubate at room temperature for 1 min.

    Important: Ensure that the elution buffer is equilibrated to room temperature. If elution is done in small volumes (<50 µl) the elution buffer has to be dispensed onto the center of the membrane for complete elution of bound DNA. Elution volume is flexible and can be adapted according tothe requirements of downstream applications. The recovered eluate volumewill up to 5 µl less than the elution volume applied onto the column.

13. Centrifuge at full speed (20,000 x g; 14,000 rpm) for 1 min to elute the DNA.

14. Repeat steps 13 and 14.

DNA Extraction Procedure for Human Faeces

1. Cell Lysis

1. Transfer 0.25g of sample into a fresh 2ml screw cap tube. Add 1ml of lysis buffer and 0.4g of sterile zirconia beads.
2. Homogenize for 60 seconds at a maximum speed on a Mini-Bead Beater.
3. Place on ice for 30-60 to allow the tube to cool. Repeat steps 2 and 3 twice more.
4. Incubate at 70°C for 15 min, with gentle shaking by hand every 5 min.
5. Centrifuge at 4°C for 5 min at full speed. Transfer the supernatant to a fresh 2ml Eppendorf tube.
6. Add 300ul of fresh lysis buffer to the lysis tube and repeat the steps 2-5, and then pool the supernatant.

2. Precipitation of nucleic acids

7. Add 347ul of 7.5M (260ul of 10M) ammonium acetate to each lysate tube, mix well and incubate on ice for 5mins.
8. Centrifuge at 4°C for 10 min at full speed.
9. Transfer the supernatant to two 1.5ml Eppendorf tubes, add one volume of isopropanol (650ul) and mix well, and incubate on ice for 30 min.
10. Centrifuge at 4°C for 15 min at full speed, remove the supernatant using aspiration(decanting), wash the nucleic acids pellet with 300ul 70% ethanol, and dry the pellet for ~30mins, or until completely dry.
11. Dissolve the nucleic acid pellet in 100ul of TE (Tris-EDTA) buffer and pool the two aliquots.

3. Removal of RNA, protein and purification

    12. Add 2ul of DNase-free RNase (10mg/ml) and incubate at 37°C for 15min.
    13. Add 15ul of Proteinase K and 200ul of Buffer AL (from the QIAamp DNA Stool Mini Kit), mix well, and incubate at 70°C for 10 min.
    14. Add 200ul of ethanol and mix well. Transfer to a QIAamp column and centrifuge at full speed for 1 min.
    15. Discard the flow through, place column in new collecting tube. Add 500ul of Buffer AW1 (Qiagen) and centrifuge for 1 min at room temperature.
    16. Discard the flow through, replace the collecting tube, Add 500ul of Buffer AW2 (Qiagen) and centrifuge for 1 min at room temperature.
    17. Discard the flow through and dry the column by centrifugation at room temperature for 1 min.
    18. Place column in Eppendorf tube. Add 200ul of Buffer AE (Qiagen) and incubate at room temperature for 2 min.
    19. Centrifuge at room temperature for 1 min to elute the DNA.
    20. Discard the column and store the labelled tube at -20°C.
    21. Can check quality of DNA by running on 0.8% gel.

Table 1:

Item	Supplier
NU-AGE Faecal DNA	N/A
16S Amplicon PCR Forward Primer	
16S Amplicon PCR Reverse Primer	
Nuclease-Free Water (10 x 50 ml)	Qiagen
Phusion Taq High-Fidelity Buffer (10 x 1.5 ml)	Fisher
PCR microplate Thermo-Fast 96 well natural semi-skirted Thermo Scientific ABgene	Fisher
Microtube PCR DNase and RNase free polypropylene with flat lid 0. 2ml clear MBP	Fisher
Microcentrifuge tube 2 ml	Sarstedt
Microcentrifuge tube 0.5 ml	Fisher
Gilson Pipetman P1000, P200 and P20 pipettes	Fisher
Fisherbrand SureOne pipette tips 1000 µl, 200 µl, 20 µl	Fisher
Pipetting reservoir sterile polystyrene 50 ml	Fisher
PCR cap flat cap polypropylene natural cap-strip for 96-well plates	Fisher
Veriti Applied Biosystems 96-well Thermal Cycler	Fisher
Microcentrifuge	N/A
Biosafety Cabinet	N/A
Plate centrifuge	N/A

Prepare PCR Reaction:

1. Turn the safety cabinet on and place a red waste bag in the bag support.
2. Place tips, pipettes, PCR and other tubes, PCR plate, strip caps, pipetting reservoirs, tube racks, permanent markers, nuclease-free water and any other materials needed inside the cabinet and UV them for 20 min.
3. Thaw primers, 2x Phusion Taq High-Fidelity Mix and samples.
4. After thawed flick each sample to homogenise them.
5. After the 20 min, prepare the 16S Amplicon PCR Master Mix (use reaction template 16S for calculation).

Table 2: 16S Amplicon PCR Master Mix

16S Amplicon PCR Mix	Sequence (5'-3')	stock conc.	volume / well	final conc.
NU-AGE Faecal DNA		7.5 ng/ µl	2.0 µl	15 ng/ 30 µl
Nuclease-Free Water		-	10.6 µl	-
16S Amplicon PCR Forward Primer	TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGCCTACGGGNGGCWGCAG	5 µM	1.2 µl	0.2 µM
16S Amplicon PCR Reverse Primer	GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGGACTACHVGGGTATCTAATCC	5 µM	1.2 µl	0.2 µM
2x Phusion Taq High-Fidelity Mix		2x	15 µl	1x
Total			30 µl	

6. Distribute 28 µl per well in all the wells of one a PCR microplate.
7. Add 2.0 µl of each of the diluted DNA samples and 2.0 µl of H2O (negative control) into the corresponding well
8. Mix well by pipetting up and down.
9. Cover wells of plate with PCR cap flat strips (or adhesive film).
10. Centrifuge plate, 1000 rpm for 1 min.
11. Place plate in the preheated 96-well Thermal Cycler and run the program as below.

Table 3: 16S Amplicon PCR Cycling Conditions

Temperature	Time	Repeats	Step
98°C	30"	none	Initialisation
98°C	10"	X 25 cycles	Denaturation
55°C	15"		Annealing
72°C	20"		Extension
72°C	5'	none	Elongation

Relevant Literature:

16S Metagenomic Sequencing Library Preparation. Preparing 16S Ribosomal RNA Gene Amplicons for the Illumina MiSeq System. Part# 15044223Rev.B. Illumina.

Klindworth A, Pruesse E, Schweer T, Peplles J, Quast C, et al. (2013) Evaluation of general 16S ribosomal RNA gene PCR primers for classical and next-generation sequencing-based diversity studies. Nucleic Acids Res 41(1).The gene-specific sequences used in this protocol target the 16S V3 and V4 region. They are selected from the Klindworth et al. 2013. Illumina adapter overhang nucleotide sequences are added to the gene-specific sequences. The full length primer sequences, using standard IUPAC nucleotide nomenclature, to follow the protocol targeting this region are: 16S Amplicon PCR Forward Primer (S-D-Bact-0341-b-S-17) = 5' TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGCCTACGGGNGGCWGCAG

16S Amplicon PCR Reverse Primer (S-D-Bact-0785-a-A-21) = 5' GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGGACTACHVGGGTATCTAATCC. The amplicon size is of 531 bp.

DERMATOLOGY LIFE QUALITY INDEX

Hospital No: Date:

Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much ☐ A lot ☐ A little ☐ Not at all ☐
2.	Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?	Very much ☐ A lot ☐ A little ☐ Not at all ☐
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes ☐ No ☐ Not relevant ☐

	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot □ A little □ Not at all □
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much □ A lot □ A little □ Not at all □ Not relevant □
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much □ A lot □ A little □ Not at all □ Not relevant □
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much □ A lot □ A little □ Not at all □ Not relevant □

Please check you have answered EVERY question. Thank you.

AY Finlay, GK Khan, April 1992 www.dermatology.org.uk, used with the permission of the authors.

Morisky 8 item medication adherence questionnaire

- Do you sometimes forget to take your medication?
  - Yes ☐
  - No ☐
- People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your medicine?
  - Yes ☐
  - No ☐
- Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?
  - Yes ☐
  - No ☐
- When you travel or leave home, do you sometimes forget to bring along your medicine?
  - Yes ☐
  - No ☐
- Did you take all your medicines yesterday?
  - Yes ☐
  - No ☐
- When you feel like your symptoms are under control, do you sometimes stop taking your medicine?
  - Yes ☐
  - No ☐
- Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan
  - Yes ☐
  - No ☐
- How often do you have difficulty remembering to take all your medicine?
  - Never/rarely ☐
  - Once in a while ☐
  - Sometimes ☐
  - Usually ☐
  - All of the time ☐

Score

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (October 2002)

LONG LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ

The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ

Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation

Translation from English is encouraged to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ

International collaboration on IPAQ is on-going and an ***International Physical Activity Prevalence Study*** is in progress. For further information see the IPAQ website.

More Information

More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective.* Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** and **moderate** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

☐ Yes

☐ No → Skip to PART 2: TRANSPORTATION

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include traveling to and from work.

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**? Think about only those physical activities that you did for at least 10 minutes at a time.

_____ days per week

☐ No vigorous job-related physical activity → ***Skip to question 4***

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

_____ hours per day
_____ minutes per day

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

_____ days per week

☐ No moderate job-related physical activity → ***Skip to question 6***

5. How much time did you usually spend on one of those days doing **moderate**

physical activities as part of your work?

_____ hours per day
_____ minutes per day

6. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.

_____ days per week

☐ No job-related walking → ***Skip to PART 2: TRANSPORTATION***

7. How much time did you usually spend on one of those days **walking** as part of your work?

_____ hours per day
_____ minutes per day

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the **last 7 days**, on how many days did you **travel in a motor vehicle** like a train, bus, car, or tram?

_____ days per week

☐ No traveling in a motor vehicle → ***Skip to question 10***

9. How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?

_____ hours per day
_____ minutes per day

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you **bicycle** for at least 10 minutes at a time to go **from place to place**?

_____ days per week

☐ No bicycling from place to place → ***Skip to question 12***

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

_____ hours per day
_____ minutes per day

12. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go **from place to place**?

_____ days per week

☐ No walking from place to place → ***Skip to PART 3: HOUSEWORK***

13. How much time did you usually spend on one of those days **walking** from place to place?

_____ hours per day
_____ minutes per day

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the **last 7 days** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

_____ days per week

☐ No vigorous activity in garden or yard → ***Skip to question 16***

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

_____ hours per day
_____ minutes per day

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____ days per week

☐ No moderate activity in garden or yard → ***Skip to question 18***

17. How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

_____ hours per day
_____ minutes per day

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

_____ days per week

☐ No moderate activity inside home → ***Skip to PART 4:RECREATION,***

19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

_____ hours per day
_____ minutes per day

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the **last 7 days** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?

_____ days per week

☐ No walking in leisure time → ***Skip to question 22***

21. How much time did you usually spend on one of those days **walking** in your leisure time?

_____ hours per day
_____ minutes per day

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

_____ days per week

☐ No vigorous activity in leisure time → ***Skip to question 24***

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ hours per day
_____ minutes per day

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

_____ days per week

☐ No moderate activity in leisure time → ***Skip to PART 5: SITTING***

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?

_____ hours per day
_____ minutes per day

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

_____ hours per day
_____ minutes per day

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?

_____ hours per day
_____ minutes per day

This is the end of the questionnaire, thank you for participating.

1. Extraction using the weighing method (without extraction device)

1. Weigh (tare) an empty screw cap tube with an inoculation loop.
2. Take out approx. 100 mg (between 40 and 120 mg) faeces by means of the inoculation loop and place it intothe screw cap tube. Avoid taking out solid, undigested material like fibres and seeds.
3. Weigh tube and loop with faeces which will give the net faeces weight.
4. Break or cut off the top half of the loop handle and leave the bottom part inside the tube.
5. Add extraction buffer to a weight: volume ratio 1:50, for instance 4.9 ml buffer to 100 mg faeces. Close the tube.
6. Mix vigorously for 30 seconds by means of a vortex mixer.
7. Continue the mixing on a shaker (at approx. 1000 rpm) for 30±5 minutes with the loop inside the tube as an agitator.
8. Allow a couple of minutes on the bench for particles to settle and pipette carefully from the top of the tube. No centrifugation is necessary, but a short centrifugation can be performed if a particle-free solution is required.
9. The extract, which represents a 1:50 dilution (weight:volume) of the stool sample, is now ready for dilution and testing.
10. For storage, transfer about 0.5 ml to a new tube. Extracts can be stored at 2 - 8°C for at least five days or frozen below -20°C for up to 2 years

2. ELISA Procedure

1. Dilute faeces extract samples 1:100 (e.g. 10 µI sample + 990 µI Sample Dilution Buffer) and mix well by vortexing.
2. Add 100 µI of each standard, control and diluted sample in duplicate wells.
3. Cover the plate with a sealing foil and incubate at room temperature for 40±5 min on a horizontal plate shaker (approximately 500 -700 rpm).
4. At the end of the incubation time, remove the liquid and wash the wells by adding 300 µl Washing Solution to each well. Remove as much liquid as possible and repeat until a total of three washings have been performed. If a plate washer is used, check that all aspirating and filling probes are unblocked to ensure efficient washing of all wells. After the final wash, invert the plate and tap the well openings thoroughly on absorbent tissue to remove any remaining Washing Solution.
5. Mix the content of the Enzyme Conjugate vial gently prior to use (do not shake). Add 100 µI of conjugate to each well, preferably using a repetitive or multichannel pipette.
6. Cover the plate with sealing foil and incubate at room temperature for 40±5 min on a horizontal plate shaker.
7. Repeat the washing steps as described above, three times with 300 µL Washing Solution per well.
8. Add 100 µI Enzyme Substrate Solution to each well, preferably using a repetitive or multichannel pipette.
9. Incubate the plate at room temperature (without shaking) for 20 - 30

minutes, protected from light.

10. Add 100 µL 0.2 M sulphuric acid stop solution to each well if a fixed incubation period is required.
11. Read the optical density (OD) values at 450 nm using an ELISA reader. If the plate reader has this option, shake the plate briefly (2-3 seconds} before reading.

3. Calculation of Calprotectin concentration in patient faecal samples:

1. Calculate the mean OD values of all duplicate wells (standards and samples).
2. Plot the value of each standard concentration (ng/ml) on the x axis against its mean OD value on the y-axis to obtain a standard curve. A 4-parameter curve fit function is recommended (see Figure 1 below). If a logarithmic x axis is required, a value of 0.001 ng/ml must be used for standard A (0 ng/ml).
3. Use the calibration curve to determine the Calprotectin concentration in the diluted samples (ng/ml) based on their OD values

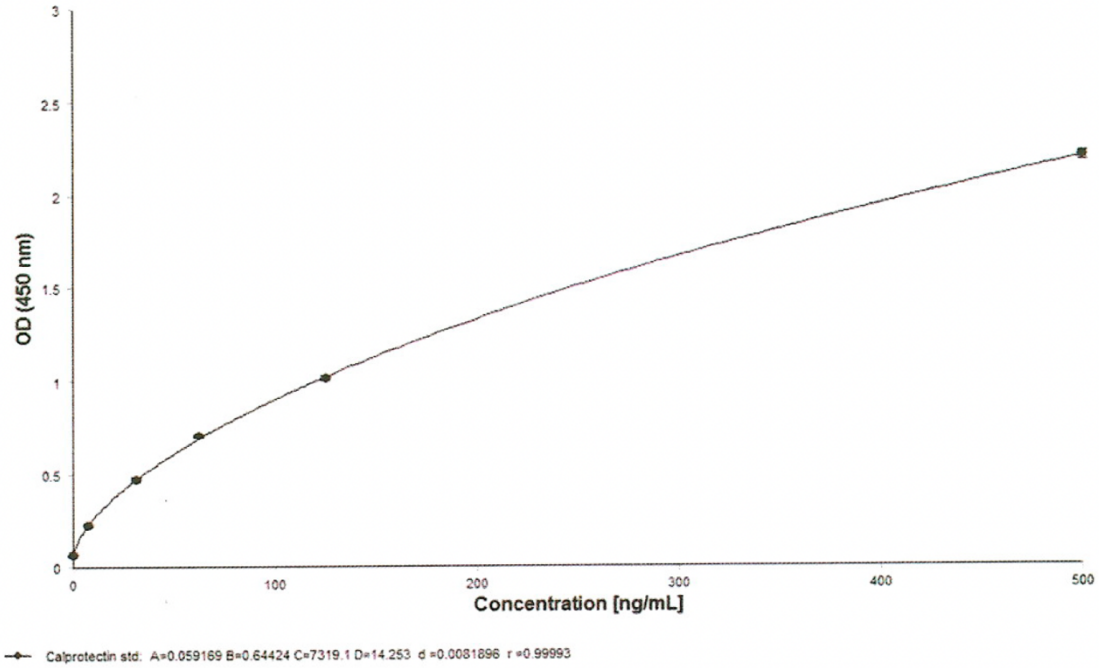


Figure 1: A representative standard curve using 4-parameter curve fit.

1. Standard Preparation

Equilibrate all reagents to room temperature (18-25°C) prior to use.

1. Briefly centrifuge the vial of Human C5a Standard and then add 400 µL Assay Diluent A (for serum/plasma samples) or 1X Assay
2. Diluent B (for cell culture supernatants) into the Human C5a Standard vial to prepare a 50 ng/mL Stock Standard. Mix thoroughly but gently.
3. Label tubes #1-8.
4. Prepare the 2000 pg/mL Standard #1 by adding 40 µL Stock Standard into tube #1 along with 960 µL Assay Diluent A or 1x Assay Diluent B. Mix thoroughly but gently.
5. Add 300 µL Assay Diluent A or 1x Assay Diluent B into tubes 2-8.
6. Prepare Standard #2 by adding 300 µL Standard #1 to tube #2. Mix thoroughly but gently.
7. Prepare Standard #3 by adding 300 µL from Standard #2 to tube #3. Mix thoroughly but gently.
8. Using the table below as a guide, prepare further serial dilutions.
9. Standard #8 contains no protein and is the Blank control.

2. Sample Preparation

1. Add 100 µL of each standard and sample into appropriate wells. Cover plate and incubate for 2.5 hours at room temperature or overnight at 4°C with gentle shaking.
2. Discard the solution and wash 4 times with 1X Wash Buffer. Wash by filling each well with 300 µL 1X Wash Buffer using a multichannel pipette or

automatic plate washer. Complete removal of liquid at each step is essential to good performance. After the

last wash, remove any remaining Wash Buffer by aspirating or decanting. Invert the plate and blot it by tapping gently against clean paper towels.

3. Add 100 µL of the prepared biotinylated Human C5a Detection Antibody to each well. Incubate for 1 hour at room temperature with gentle shaking.
4. Discard the solution. Repeat the wash as in step 2.
5. Add 100 µL of prepared 1X HRP-Streptavidin solution to each well. Incubate for 45 minutes at room temperature with gentle shaking
6. Discard the solution. Repeat the wash as in step 2.
7. Add 100 µL of TMB One-Step Substrate Reagent to each well. Incubate for 30 minutes at room temperature in the dark with gentle shaking.
8. Add 50 µL of Stop Solution to each well. Read at 450 nm immediately.

3. Calculations

1. Calculate the mean absorbance for each set of duplicate standards, controls and samples, and subtract the average zero standard optical density.
2. Plot the standard curve on log-log graph paper, with standard concentration on the x-axis and absorbance on the y-axis.
3. Draw the best-fit straight line through the standard points

Name:

YOUR DIET OVER THE PAST YEAR

For each food there is an amount shown, of what we think is a "medium serving" or a common household unit such as a slice or teaspoon. Please put a tick in the box to indicate how often, **on average**, you have eaten the specified amount of each food, to the nearest whole number **during the past year.**

Please estimate your average food use as best you can. Please answer every question, do not leave ANY lines blank.

EXAMPLES:

The following are examples on how to estimate how often and how much bread and potatoes you ate over the past year. Please estimate your food intake for all foodstuffs in the same way.

Potatoes: If you ate a medium serving of potatoes 3 times per week over the past year put a tick in the box "2-4 per week". If you think you usually ate more or less than a medium serving please try to estimate which box suits best.

	AVERAGE USE LAST YEAR								
BREAD AND SAVOURY BISCUITS (One slice or one biscuit)	Never or less than once	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
White bread and rolls (including ciabatta and pannini bread)								√	

	AVERAGE USE LAST YEAR								
Potatoes, Rice and Pasta (medium serving)	Never or less than once	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day

Boiled, instant or jacket potatoes				√					

For white bread a medium serving is one medium sized slice. Therefore if you usually ate 1 medium slice 4 or 5 times per day, you should put a tick in the column headed “4-5 per day”. If you ate 2 medium slices 4 or 5 times per day, then you should put a tick in the column “6+ per day”.

Please check that you put a tick (√) on every line

	AVERAGE USE LAST YEAR								
A. MEAT, FISH AND POULTRY (Medium serving – the size of a deck of cards)	Never or less than once	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
1. Beef roast									
2. Beef: steak									
3. Beef: mince									
4. Beef: stew									
5. Beef burger (1 burger)									
6. Pork: roast									
7. Pork: chops									
8. Pork: slices/escalopes									
9. Lamb: roast									
10. Lamb: chops									
11. Lamb: stew									
12. Chicken portion or other poultry e.g.									
13. Breaded chicken, chicken nuggets,									
14. Bacon									
15. Ham									
16. Corned beef, Spam, Luncheon									
17. Sausages, Frankfurters (1 sausage)									
18. Savoury pies (e.g. meat pie, pork pie, steak & kidney pie, sausage									
19. Liver, heart, kidney									
20. Liver paté									
21. Fish fried in batter, as in fish and chips									
22. Fish fried in breadcrumbs									
23. Oven baked/grilled fish (in breadcrumbs or									
24. Fish fingers/fish cakes									
25. Other white fish, fresh or frozen (e.g. cod, haddock, plaice, sole,									
26. Oily fish, fresh or canned (e.g. mackerel, kippers, tuna, salmon, sardines, herring)									
27. Shellfish (e.g. crab, prawns,									

	AVERAGE USE LAST YEAR								
B. BREAD AND SAVOURY BISCUITS (One slice or one biscuit)	Never or less than once	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
1. White bread and rolls (including ciabatta and pannini									
2. Brown bread and rolls									
3. Wholemeal bread and rolls									
4. Cream crackers, cheese biscuits									
5. Crisp bread, e.g. Ryvita									
6. Pancakes, muffins, oatcakes									

	AVERAGE USE LAST YEAR								
C. CEREALS (One medium sized bowl)	Never or less than once	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
1. Porridge, Readybrek									
2. All Bran, Weetabix,									
3. Branflakes, Bran Buds									
4. Cornflakes, Rice Krispies									
5. Muesli (e.g. Country Store, Alpen, sugar									
6. Sugar Coated Cereals (e.g. Frosties, Crunchy Nut Cornflakes, Crunchy Sugar Coated Muesli)									

	AVERAGE USE LAST YEAR								
D. POTATOES, RICE AND PASTA (Medium serving – about a cupful)	Never or less than once	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
1. Boiled, instant or jacket potatoes									
2. Mashed potatoes									
3. Chips									
4. Roast potatoes									
5. Potato Salad									
6. White Rice									
7. Brown Rice									
8. White/yellow or green pastas (e.g. spaghetti, macaroni, noodles)									
9. Wholemeal pasta									
10. Lasagne (meat based)									
11. Lasagne (vegetarian)									
12. Moussaka									
13. Pizza									
14. Macaroni Cheese									

	AVERAGE USE LAST YEAR								
E. DAIRY PRODUCTS AND FATS	Never or less than once	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
1. Cream (tablespoon)									
2. Full-fat yoghurt or Greek- style Yoghurt (125g									
3. Dairy desserts (125g carton)									
4. Cheddar cheese (medium serving)									
5. Low-fat cheddar cheese (medium									
6. Eggs as boiled, fried, scrambled, poached									
7. Quiche (medium serving)									
8. Light salad cream or light mayonnaise									
9. Salad cream, mayonnaise									
10. French dressing									
11. Other salad dressing									
12. The following on bread or vegetables									
13. Butter (teaspoon)									
14. Lite Butter e.g. Dawn Lite, Connacht Gold									
15. Sunflower margarine e.g. Flora (teaspoon)									
16. Low-fat margarine (e.g. low- low)									
17. Cholesterol Lowering Spreads e.g. Flora Pro Active, Dairy Gold Heart (teaspoon)									
18. Cream & Vegetable Oil spread e.g. Golden Pasture, Kerrymaid, Dairy Gold – teaspoon									

19. Olive oil spread e.g. Golden Olive (teaspoon)									

	AVERAGE USE LAST YEAR								
F. FRUIT (1 Fruit or medium serving)	Never or less than once	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
1. Apples									
2. Pears									
3. Oranges, satsumas, mandarins									
4. Grapefruit									
5. Bananas									
6. Grapes									
7. Melon									
8. Peaches, plums									
9. Apricots									
10. Strawberries, raspberries, kiwi fruit									
11. Tinned fruit									
12. Dried fruit e.g. raisins									
13. Frozen fruit									

	AVERAGE USE LAST YEAR								
G. VEGETABLES Fresh, frozen or tinned (Medium Serving – 2 tablespoons)	Never or less than once	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
1. Carrots									
2. Spinach									
3. Broccoli, spring greens, kale									
4. Brussel sprouts									
5. Cabbage									
6. Peas									
7. Green beans, broad beans, runner beans									
8. Courgettes									
9. Cauliflower									
10. Parsnips, turnips									
11. Leeks									
12. Onions									
13. Garlic									
14. Mushrooms									
15. Sweet peppers									
16. Beansprouts									
17. Green salad, lettuce									

18. Cucumber, celery									
19. Tomatoes									
20. Sweetcorn									
21. Beetroot									
22. Coleslaw									
23. Baked beans									
24. Dried lentils, beans, peas									
25. Tofu, soya meat, TVP									

	AVERAGE USE LAST YEAR								
H. SWEETS AND SNACKS (Medium serving)	Never or less than once	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
1. Chocolate coated sweet biscuits e.g. digestive									
2. Plain sweet biscuits e.g. Marietta, digestives, rich tea (one)									
3. Cakes e.g. fruit, sponge									
4. Buns, pastries e.g. croissants,									
5. Fruit pies, tarts, crumbles									
6. Sponge puddings									
7. Milk puddings e.g. rice, custard, trifle									
8. Ice cream, choc ices, Frozen									
9. Chocolates, singles or squares									
10. Sweets, toffees, mints									
11. Sugar added to tea coffee, cereal									
12. Sugar substitute e.g. canderel added to tea coffee, cereal (teaspoon)									
13. Crisps or other packet snacks									
14. Peanuts or other nuts									

	AVERAGE USE LAST YEAR								
I. SOUPS, SAUCES AND SPREADS	Never or less than once	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
1. Vegetable soups: homemade/fresh (1									
2. Vegetable soups: tinned/ packet (1 bowl)									
3. Meat soups: homemade/fresh (1									
4. Meat soups: tinned/ packet (1 bowl)									
5. Sauces e.g. white sauce, cheese sauce, gravy (tablespoon)									
6. Tomato based sauces e.g. pasta sauces									
7. Curry-type sauces									
8. Pickles, chutney (tablespoon)									
9. Marmite, Bovril (tablespoon)									
10. Jam, marmalade, honey, syrup (teaspoon)									
11. Peanut butter (teaspoon)									

	AVERAGE USE LAST YEAR								
J. DRINKS	Never or less than once	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
1. Tea (cup)									
2. Coffee instant (cup)									
3. Coffee ground (cup)									
4. Coffee, decaffeinated (cup)									
5. Coffee whitener e.g. coffee-mate									
6. Cocoa, Hot Chocolate (cup)									
7. Horlicks, Ovaltine (cup)									
8. Wine (glass)									
9. Beer, Larger or Cider (half pint)									
10. Alcopops e.g. Bacardi Breezer									

11. Whole milk (cup) – cow or goat (including milk used in tea, cereal etc)									
12. Semi-skimmed milk (cup) (including milk used in tea, cereal etc)									
13. Port, Sherry, Vermouth, liqueurs									
14. Spirits e.g. Gin, Whiskey (single									
15. Low calorie or diet soft fizzy (glass)									
16. Fizzy Soft drinks e.g. Cocoa Cola									
17. Pure fruit drinks e.g. orange juice (small									
18. Fruit squash (small glass)									

	AVERAGE USE LAST YEAR								
K. Functional Foods	Never or less than once	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
1. Probiotic drinks/yoghurt e.g. Actimel, Yakult ***Please specify brand name:***									

	AVERAGE USE LAST YEAR								
K. Functional Foods	Never or less than once	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
2. Vitamin supplements									

Please mention if you have been on any particular diets during the last 12 months, and if so, how many months/weeks ago and for how long were you on the diet:

Diet name and description	Months ago commenced diet	Months ago ceased diet (if diet ongoing say ongoing)

Appendix 1: Faecal module taxa list

Taxa	Colours
Seq_1_Eubacterium_rectale	black
Seq_25_Megamonas	black
Seq_112_Veillonella_ratti	black
Seq_134_Lactobacillus	black
Seq_172_Clostridiales	black
Seq_177_Ruminococcaceae	black
Seq_193_Bacteroides_plebeius	black
Seq_383_Eubacterium_eligens	black
Seq_501_Bacteroides_xylanisolvens	black
Seq_507_Streptococcus	black
Seq_531_Eubacterium_eligens	black
Seq_567_Bacteroides_plebeius	black
Seq_586_Roseburia_faecis	black
Seq_592_Roseburia	black
Seq_652_Haemophilus_parainfluenzae	black
Seq_710_Faecalibacterium_prausnitzii	black
Seq_758_Lachnospiraceae	black
Seq_789_Ruminococcus_obeum	black
Seq_807_Firmicutes	black
Seq_833_Bacteroides_massiliensis	black
Seq_859_Ruminococcaceae	black
Seq_896_Haemophilus	black
Seq_1029_Ruminococcus_bromii	black
Seq_1032_Ruminococcus_obeum	black
Seq_1054_Lachnospiraceae	black
Seq_1090_Veillonella_rogosae	black
Seq_1129_Faecalibacterium_prausnitzii	black
Seq_1148_Veillonella_atypica	black
Seq_1155_Actinomyces_odontolyticus	black
Seq_1197_Streptococcus_parasanguinis	black
Seq_1203_Lachnospiraceae	black
Seq_1204_Bacteroides_ovatus	black
Seq_1213_Eubacterium_ruminantium	black
Seq_1237_Veillonella_dispar	black
Seq_1301_Streptococcus	black
Seq_1307_Roseburia_inulinivorans	black
Seq_1339_Parabacteroides_merdae	black
Seq_1490_Lachnospiraceae	black
Seq_1570_Faecalibacterium_prausnitzii	black
Seq_1625_Clostridium_aldenense	black
Seq_1724_Eubacterium_eligens	black
Seq_1730_Enterococcus	black

Seq_1763_Ruminococcus_albus	black
Seq_1768_Streptococcus	black
Seq_1783_Barnesiella_intestinihominis	black
Seq_1791_Streptococcus_parasanguinis	black
Seq_1864_Clostridiales	black
Seq_1888_Dorea	black
Seq_1891_Streptococcus	black
Seq_1938_Blautia_faecis	black
Seq_1940_Olsenella	black
Seq_1988_Prevotella_copri	black
Seq_2016_Ruminococcaceae	black
Seq_2044_Enterobacteriaceae	black
Seq_2045_Alloscardovia_omnicolens	black
Seq_2073_Lactobacillus_oris	black
Seq_2090_Granulicatella	black
Seq_2187_Collinsella_aerofaciens	black
Seq_2218_Ruminococcaceae	black
Seq_2321_Collinsella_aerofaciens	black
Seq_2322_Rothia_mucilaginosa	black
Seq_2412_Allisonella_histaminiformans	black
Seq_2520_Proteus	black
Seq_2563_Streptophyta	black
Seq_2574_Streptococcus	black
Seq_2575_Streptococcus_sobrinus	black
Seq_2627_Lactobacillus_delbrueckii	black
Seq_2737_Porphyromonadaceae	black
Seq_2881_Pseudoflavonifractor	black
Seq_2882_Atopobium_parvulum	black
Seq_2915_Ruminococcaceae	black
Seq_2998_Clostridiales	black
Seq_2999_Gemella_morbillorum	black
Seq_3040_Actinomyces_graevenitzii	black
Seq_3169_Ruminococcaceae	black
Seq_3526_Clostridiales	black
Seq_3529_Lachnospiraceae	black
Seq_3_Blautia	blue
Seq_32_Anaerostipes_hadrus	blue
Seq_61_Asteroleplasma_anaerobium	blue
Seq_63_Catenibacterium_mitsuokai	blue
Seq_68_Prevotella_copri	blue
Seq_81_Succinivibridextrinosolvens	blue
Seq_82_Clostridiales	blue
Seq_99_Faecalibacterium_prausnitzii	blue
Seq_119_Firmicutes	blue
Seq_120_Clostridiales	blue

Seq_121_Erysipelotrichaceae	blue
Seq_129_Succinivibridextrinosolvens	blue
Seq_146_Firmicutes	blue
Seq_155_Ruminococcaceae	blue
Seq_157_Eubacterium_eligens	blue
Seq_166_Ruminococcus_bromii	blue
Seq_197_Paraprevotella_clara	blue
Seq_205_Bacteroides_massiliensis	blue
Seq_212_Ruminococcus	blue
Seq_227_Bacteroides_coprocola	blue
Seq_235_Clostridium_disporicum	blue
Seq_244_Lachnospiraceae	blue
Seq_255_Ruminococcaceae	blue
Seq_260_Coprococcus_eutactus	blue
Seq_266_Ruminococcaceae	blue
Seq_273_Ruminococcaceae	blue
Seq_333_Lachnospiraceae	blue
Seq_337_Ruminococcaceae	blue
Seq_357_Clostridiales	blue
Seq_375_Clostridiales	blue
Seq_394_Lachnospiraceae	blue
Seq_408_Clostridium_XlVa	blue
Seq_425_Bacteroides_massiliensis	blue
Seq_451_Ruminococcaceae	blue
Seq_457_Lachnospiraceae	blue
Seq_505_Prevotella	blue
Seq_520_Firmicutes	blue
Seq_527_Clostridium_sensu_stricto	blue
Seq_545_Clostridiales	blue
Seq_553_Bacteroidetes	blue
Seq_599_Clostridium_sensu_stricto	blue
Seq_600_Lachnospiraceae	blue
Seq_641_Ruminococcaceae	blue
Seq_668_Phascolarctobacterium_succinatutens	blue
Seq_781_Collinsella_aerofaciens	blue
Seq_823_Ruminococcaceae	blue
Seq_830_Bacteroidales	blue
Seq_838_Clostridiales	blue
Seq_863_Ruminococcaceae	blue
Seq_869_Bacteroides_massiliensis	blue
Seq_878_Oscillibacter	blue
Seq_932_Clostridium_XlVa	blue
Seq_940_Clostridia	blue
Seq_941_Ruminococcaceae	blue
Seq_970_Bacteroidetes	blue

Seq_1015_Clostridiales	blue
Seq_1165_Prevotellaceae	blue
Seq_1193_Streptococcus	blue
Seq_1195_Mitsuokella_jalaludinii	blue
Seq_1215_Firmicutes	blue
Seq_1227_Prevotella	blue
Seq_1249_Olsenella	blue
Seq_1266_Prevotella	blue
Seq_1292_Bacteroides_eggerthii	blue
Seq_1324_Clostridiales	blue
Seq_1344_Coriobacteriaceae	blue
Seq_1345_Ruminococcaceae	blue
Seq_1356_Ruminococcaceae	blue
Seq_1366_Mogibacterium	blue
Seq_1415_Coriobacteriaceae	blue
Seq_1436_Flavonifractor_plautii	blue
Seq_1459_Bifidobacterium	blue
Seq_1477_Mitsuokella_jalaludinii	blue
Seq_1491_Bacteroidetes	blue
Seq_1515_Phascolarctobacterium_succinatutens	blue
Seq_1582_Ruminococcus_callidus	blue
Seq_1617_Bacteria	blue
Seq_1626_Prevotella_copri	blue
Seq_1672_Ruminococcaceae	blue
Seq_1761_Lachnospiraceae	blue
Seq_1795_Ruminococcaceae	blue
Seq_1843_Ruminococcaceae	blue
Seq_1868_Bacteria	blue
Seq_1889_Bacteria	blue
Seq_1916_Bacteria	blue
Seq_2060_Clostridia	blue
Seq_2095_Clostridiales	blue
Seq_2126_Clostridiales	blue
Seq_2185_Ruminococcaceae	blue
Seq_2186_Ruminococcus_bromii	blue
Seq_2216_Clostridiales	blue
Seq_2268_Clostridiales	blue
Seq_2311_Bacteria	blue
Seq_2312_Clostridiales	blue
Seq_2319_Bacteroides_eggerthii	blue
Seq_2442_Butyricimonas_virosa	blue
Seq_2453_Bacteria	blue
Seq_2504_Oscillibacter	blue
Seq_2566_Bacteroides_finegoldii	blue
Seq_2692_Barnesiella_intestinihominis	blue

Seq_2693_Coriobacteriaceae	blue
Seq_2695_Firmicutes	blue
Seq_2783_Clostridiales	blue
Seq_2883_Methanosphaera_stadtmanae	blue
Seq_3001_Bacteroidetes	blue
Seq_3004_Butyricimonas	blue
Seq_3158_Bacteria	blue
Seq_3161_Coriobacteriaceae	blue
Seq_3163_Ruminococcaceae	blue
Seq_3409_Catenibacterium_mitsuokai	blue
Seq_3410_Streptophyta	blue
Seq_3414_Succinivibridextrinosolvens	blue
Seq_3417_Faecalibacterium_prausnitzii	blue
Seq_3420_Clostridiales	blue
Seq_3421_Bacteria	blue
Seq_18_Clostridium_XVIII	brown
Seq_23_Ruminococcaceae	brown
Seq_45_Alistipes_putredinis	brown
Seq_62_Ruminococcaceae	brown
Seq_90_Eubacterium_siraeum	brown
Seq_92_Prevotella_copri	brown
Seq_111_Clostridiales	brown
Seq_125_Bacteroides_caccae	brown
Seq_147_Blautia_luti	brown
Seq_156_Ruminococcaceae	brown
Seq_167_Lactobacillus_ruminis	brown
Seq_208_Bacteroides_vulgatus	brown
Seq_213_Collinsella	brown
Seq_229_Oscillibacter_valericigenes	brown
Seq_264_Clostridium_XlVb	brown
Seq_274_Bacteroides_uniformis	brown
Seq_291_Desulfovibripiger	brown
Seq_293_Dialister_succinatiphilus	brown
Seq_306_Ruminococcaceae	brown
Seq_310_Bacteroides	brown
Seq_332_Slackia_isoflavoniconvertens	brown
Seq_349_Clostridiales	brown
Seq_350_Gemmiger_formicilis	brown
Seq_358_Clostridiales	brown
Seq_377_Sutterella_wadsworthensis	brown
Seq_392_Asaccharobacter	brown
Seq_435_Bacteroides_fragilis	brown
Seq_477_Bacteroidetes	brown
Seq_497_Odoribacter_splanchnicus	brown
Seq_524_Ruminococcaceae	brown

Seq_534_Clostridiales	brown
Seq_566_Ruminococcaceae	brown
Seq_606_Coriobacteriaceae	brown
Seq_620_Clostridiales	brown
Seq_625_Flavonifractor_plautii	brown
Seq_716_Ruminococcaceae	brown
Seq_719_Erysipelotrichaceae	brown
Seq_728_Erysipelotrichaceae	brown
Seq_855_Ruminococcus_bromii	brown
Seq_862_Lactobacillus_ruminis	brown
Seq_868_Firmicutes	brown
Seq_911_Clostridium_XlVb	brown
Seq_917_Clostridiales	brown
Seq_933_Clostridium_XlVa	brown
Seq_987_Clostridium_IV	brown
Seq_989_Clostridiales	brown
Seq_993_Lachnospiraceae	brown
Seq_1008_Parabacteroides_distasonis	brown
Seq_1042_Prevotella_copri	brown
Seq_1051_Enterorhabdus	brown
Seq_1077_Clostridium_IV	brown
Seq_1158_Eubacterium_siraeum	brown
Seq_1229_Firmicutes	brown
Seq_1244_Barnesiella_intestinihominis	brown
Seq_1253_Alphaproteobacteria	brown
Seq_1283_Paraprevotella_clara	brown
Seq_1294_Lachnospiraceae	brown
Seq_1323_Ruminococcaceae	brown
Seq_1355_Clostridiales	brown
Seq_1363_Prevotellaceae	brown
Seq_1434_Porphyromonadaceae	brown
Seq_1460_Clostridium_leptum	brown
Seq_1487_Coriobacteriaceae	brown
Seq_1527_Lachnospiraceae	brown
Seq_1560_Bacteroides	brown
Seq_1583_Collinsella_tanakaei	brown
Seq_1591_Firmicutes	brown
Seq_1638_Butyricimonas_virosa	brown
Seq_1641_Gordonibacter	brown
Seq_1682_Bacteria	brown
Seq_1713_Anaerofilum_pentosovorans	brown
Seq_1738_Ruminococcaceae	brown
Seq_1780_Clostridiales	brown
Seq_1834_Sutterella_stercoricanis	brown
Seq_1855_Firmicutes	brown

Seq_1862_Clostridiales	brown
Seq_1869_Firmicutes	brown
Seq_1890_Peptococcus_niger	brown
Seq_2009_Clostridium_leptum	brown
Seq_2014_Ruminococcaceae	brown
Seq_2035_Clostridium_leptum	brown
Seq_2036_Eubacteriaceae	brown
Seq_2107_Ruminococcaceae	brown
Seq_2127_Barnesiella_intestinihominis	brown
Seq_2128_Enterorhabdus	brown
Seq_2156_Howardella_ureilytica	brown
Seq_2157_Clostridiales	brown
Seq_2158_Ruminococcaceae	brown
Seq_2200_Ruminococcaceae	brown
Seq_2369_Desulfovibrionales	brown
Seq_2410_Paraprevotella_clara	brown
Seq_2411_Erysipelotrichaceae	brown
Seq_2457_Ruminococcaceae	brown
Seq_2505_Oscillibacter	brown
Seq_2506_Ruminococcaceae	brown
Seq_2568_Adlercreutzia_equolifaciens	brown
Seq_2569_Erysipelotrichaceae	brown
Seq_2570_Parabacteroides_distasonis	brown
Seq_2571_Butyricimonas_virosa	brown
Seq_2625_Porphyromonadaceae	brown
Seq_2626_Clostridiales	brown
Seq_2696_Anaerotruncus_colihominis	brown
Seq_2884_Ruminococcaceae	brown
Seq_2885_Coriobacteriaceae	brown
Seq_2886_Ruminococcaceae	brown
Seq_2887_Ruminococcaceae	brown
Seq_2889_Lachnospiraceae	brown
Seq_3007_Butyricimonas_virosa	brown
Seq_3008_Prevotella_copri	brown
Seq_3164_Clostridiales	brown
Seq_3165_Clostridium_leptum	brown
Seq_3431_Clostridiales	brown
Seq_59_Bifidobacterium	cyan
Seq_97_Phascolarctobacterium_faecium	cyan
Seq_102_Ruminococcus_albus	cyan
Seq_116_Alistipes	cyan
Seq_176_Eubacterium_desmolans	cyan
Seq_188_Bilophila_wadsworthia	cyan
Seq_230_Bacteroides_ovatus	cyan
Seq_303_Flavonifractor_plautii	cyan

Seq_338_Clostridium_ruminantium	cyan
Seq_511_Asaccharobacter	cyan
Seq_540_Phascolarctobacterium_faecium	cyan
Seq_558_Bifidobacterium_longum	cyan
Seq_570_Lachnospiraceae	cyan
Seq_610_Ruminococcaceae	cyan
Seq_638_Lachnospiraceae	cyan
Seq_678_Bacteroides_xylanisolvens	cyan
Seq_733_Coriobacteriaceae	cyan
Seq_741_Ruminococcus_albus	cyan
Seq_754_Blautia	cyan
Seq_812_Lachnospiraceae	cyan
Seq_900_Firmicutes	cyan
Seq_925_Lachnospiraceae	cyan
Seq_1036_Clostridiales	cyan
Seq_1192_Ruminococcaceae	cyan
Seq_1387_Lachnospiraceae	cyan
Seq_1429_Lachnospiraceae	cyan
Seq_1463_Ruminococcaceae	cyan
Seq_1553_Roseburia_intestinalis	cyan
Seq_1595_Firmicutes	cyan
Seq_1636_Lachnospiraceae	cyan
Seq_1686_Parabacteroides_distasonis	cyan
Seq_1732_Blautia_faecis	cyan
Seq_1766_Ruminococcus_torques	cyan
Seq_1767_Faecalibacterium_prausnitzii	cyan
Seq_1782_Lachnospiraceae	cyan
Seq_1970_Actinomyces_odontolyticus	cyan
Seq_2001_Flavonifractor_plautii	cyan
Seq_2046_Eubacterium_tenue	cyan
Seq_2076_Cloacibacillus_evryensis	cyan
Seq_2301_Parabacteroides_distasonis	cyan
Seq_2409_Clostridiales	cyan
Seq_2499_Candidatus_Saccharibacteria	cyan
Seq_2526_Clostridiales	cyan
Seq_2527_Clostridium_XlVa	cyan
Seq_2731_Ruminococcaceae	cyan
Seq_2733_Desulfovibrionaceae	cyan
Seq_2734_Ruminococcaceae	cyan
Seq_2735_Ruminococcaceae	cyan
Seq_2925_Erysipelotrichaceae	cyan
Seq_3046_Ruminococcaceae	cyan
Seq_3210_Eubacteriaceae	cyan
Seq_3211_Clostridiales	cyan
Seq_3549_Clostridiales	cyan

Seq_3550_Bacteria	cyan
Seq_3553_Ruminococcaceae	cyan
Seq_3554_Lachnospiraceae	cyan
Seq_10_Gemmiger_formicilis	darkgreen
Seq_51_Ruminococcus_bromii	darkgreen
Seq_75_Ruminococcaceae	darkgreen
Seq_101_Streptococcus	darkgreen
Seq_135_Eubacterium_rectale	darkgreen
Seq_202_Porphyromonadaceae	darkgreen
Seq_353_Eubacterium_rectale	darkgreen
Seq_398_Paraprevotella_clara	darkgreen
Seq_454_Lachnospiraceae	darkgreen
Seq_462_Clostridium_XlVa	darkgreen
Seq_466_Bacteroides	darkgreen
Seq_585_Bacteroides_ovatus	darkgreen
Seq_681_Barnesiella_intestinihominis	darkgreen
Seq_712_Firmicutes	darkgreen
Seq_769_Faecalibacterium_prausnitzii	darkgreen
Seq_809_Ruminococcus_callidus	darkgreen
Seq_834_Adlercreutzia_equolifaciens	darkgreen
Seq_949_Blautia_faecis	darkgreen
Seq_1001_Bacteroidetes	darkgreen
Seq_1183_Flavonifractor_plautii	darkgreen
Seq_1306_Ruminococcaceae	darkgreen
Seq_1489_Coriobacteriaceae	darkgreen
Seq_1530_Clostridium_leptum	darkgreen
Seq_1616_Parabacteroides_distasonis	darkgreen
Seq_1624_Bacteroidetes	darkgreen
Seq_1714_Clostridiales	darkgreen
Seq_1722_Phascolarctobacterium_succinatutens	darkgreen
Seq_1803_Ruminococcus_lactaris	darkgreen
Seq_1804_Bacteroidetes	darkgreen
Seq_1859_Coriobacteriaceae	darkgreen
Seq_1987_Clostridium_hathewayi	darkgreen
Seq_2013_Bacteroidetes	darkgreen
Seq_2155_Eubacterium_infirmum	darkgreen
Seq_2255_Barnesiella_intestinihominis	darkgreen
Seq_2366_Ruminococcaceae	darkgreen
Seq_2392_Prevotella_bivia	darkgreen
Seq_2690_Firmicutes	darkgreen
Seq_2691_Lachnospiraceae	darkgreen
Seq_2780_Ruminococcaceae	darkgreen
Seq_2879_Solobacterium_moorei	darkgreen
Seq_2880_Prevotella_corporis	darkgreen
Seq_2995_Bacteroidales	darkgreen

Seq_2996_Porphyromonas_uenonis	darkgreen
Seq_2997_Prevotella_buccalis	darkgreen
Seq_3404_Clostridiales	darkgreen
Seq_7_Bifidobacterium_longum	darkgrey
Seq_55_Bifidobacterium_bifidum	darkgrey
Seq_171_Firmicutes	darkgrey
Seq_298_Bifidobacterium_breve	darkgrey
Seq_322_Veillonella_parvula	darkgrey
Seq_422_Lachnospiraceae	darkgrey
Seq_496_Clostridium_XVIII	darkgrey
Seq_542_Bacteria	darkgrey
Seq_577_Ruminococcaceae	darkgrey
Seq_605_Eggerthella_lenta	darkgrey
Seq_621_Lachnospiraceae	darkgrey
Seq_665_Ruminococcaceae	darkgrey
Seq_715_Flavonifractor_plautii	darkgrey
Seq_914_Ruminococcaceae	darkgrey
Seq_998_Blautia	darkgrey
Seq_1069_Clostridium_IV	darkgrey
Seq_1100_Ruminococcaceae	darkgrey
Seq_1161_Eubacterium_fissicatena	darkgrey
Seq_1303_Allisonella_histaminiformans	darkgrey
Seq_1456_Escherichia/Shigella	darkgrey
Seq_1513_Ruminococcaceae	darkgrey
Seq_1518_Erysipelotrichaceae	darkgrey
Seq_1676_Clostridium_ruminantium	darkgrey
Seq_1787_Ruminococcaceae	darkgrey
Seq_1871_Ruminococcaceae	darkgrey
Seq_1920_Clostridium_IV	darkgrey
Seq_1962_Clostridium_ruminantium	darkgrey
Seq_1986_Lactonifactor_longoviformis	darkgrey
Seq_2018_Ruminococcaceae	darkgrey
Seq_2068_Allisonella_histaminiformans	darkgrey
Seq_2165_Prevotella_copri	darkgrey
Seq_2192_Enterococcus	darkgrey
Seq_2212_Lactobacillus_vaginalis	darkgrey
Seq_2406_Butyricicoccus	darkgrey
Seq_2510_Actinomyces_odontolyticus	darkgrey
Seq_2511_Prevotella_bivia	darkgrey
Seq_2581_Clostridium_XlVb	darkgrey
Seq_2620_Fusobacterium_nucleatum	darkgrey
Seq_3023_Enterobacter	darkgrey
Seq_3024_Streptococcus_agalactiae	darkgrey
Seq_3183_Atopobium_minutum	darkgrey
Seq_31_Ruminococcus_obeum	darkmagenta

Seq_50_Erysipelotrichaceae	darkmagenta
Seq_122_Eubacterium_rectale	darkmagenta
Seq_195_Gemmiger_formicilis	darkmagenta
Seq_328_Ruminococcaceae	darkmagenta
Seq_355_Alistipes_finegoldii	darkmagenta
Seq_452_Parabacteroides_distasonis	darkmagenta
Seq_568_Bacteroides_clarus	darkmagenta
Seq_587_Dialister_invisus	darkmagenta
Seq_593_Dialister_invisus	darkmagenta
Seq_618_Clostridium_XlVa	darkmagenta
Seq_805_Dorea_longicatena	darkmagenta
Seq_861_Clostridiales	darkmagenta
Seq_880_Eubacterium_rectale	darkmagenta
Seq_902_Firmicutes	darkmagenta
Seq_934_Alistipes_indistinctus	darkmagenta
Seq_1058_Allisonella_histaminiformans	darkmagenta
Seq_1214_Lachnospiraceae	darkmagenta
Seq_1262_Eubacterium_rectale	darkmagenta
Seq_1313_Lachnospiraceae	darkmagenta
Seq_1444_Gemmiger_formicilis	darkmagenta
Seq_1470_Desulfovibrilegallii	darkmagenta
Seq_1587_Lachnospiraceae	darkmagenta
Seq_1746_Bilophila_wadsworthia	darkmagenta
Seq_1808_Clostridiales	darkmagenta
Seq_1965_Oscillibacter_valericigenes	darkmagenta
Seq_1992_Porphyromonadaceae	darkmagenta
Seq_2064_Parabacteroides_distasonis	darkmagenta
Seq_2135_Ruminococcaceae	darkmagenta
Seq_2225_Ruminococcaceae	darkmagenta
Seq_2639_Clostridium_butyricum	darkmagenta
Seq_2651_Ruminococcaceae	darkmagenta
Seq_2721_Oxalobacteraceae	darkmagenta
Seq_2807_Lactobacillus	darkmagenta
Seq_2910_Bacteroidales	darkmagenta
Seq_3200_Bacteria	darkmagenta
Seq_3506_Streptophyta	darkmagenta
Seq_127_Catenibacterium_mitsuokai	darkolivegreen
Seq_164_Catenibacterium_mitsuokai	darkolivegreen
Seq_335_Bacteroides_vulgatus	darkolivegreen
Seq_509_Bacteroides_vulgatus	darkolivegreen
Seq_522_Faecalibacterium_prausnitzii	darkolivegreen
Seq_543_Blautia_luti	darkolivegreen
Seq_794_Coriobacteriaceae	darkolivegreen
Seq_839_Eubacterium_desmolans	darkolivegreen
Seq_956_Erysipelotrichaceae	darkolivegreen

Seq_1002_Ruminococcus_bromii	darkolivegreen
Seq_1055_Phascolarctobacterium_succinatutens	darkolivegreen
Seq_1088_Roseburia_faecis	darkolivegreen
Seq_1147_Anaerostipes_hadrus	darkolivegreen
Seq_1154_Dorea	darkolivegreen
Seq_1208_Sutterella_stercoricanis	darkolivegreen
Seq_1418_Lachnospiraceae	darkolivegreen
Seq_1442_Blautia_luti	darkolivegreen
Seq_1473_Clostridium_IV	darkolivegreen
Seq_1486_Eubacterium_desmolans	darkolivegreen
Seq_1551_Eubacterium_desmolans	darkolivegreen
Seq_1631_Anaerotruncus	darkolivegreen
Seq_1635_Lachnospiraceae	darkolivegreen
Seq_1807_Slackia_piriformis	darkolivegreen
Seq_2096_Lachnospiraceae	darkolivegreen
Seq_2257_Ruminococcaceae	darkolivegreen
Seq_2288_Ruminococcaceae	darkolivegreen
Seq_2328_Erysipelotrichaceae	darkolivegreen
Seq_2372_Firmicutes	darkolivegreen
Seq_2591_Blautia	darkolivegreen
Seq_2698_Clostridiales	darkolivegreen
Seq_2699_Clostridium_leptum	darkolivegreen
Seq_2700_Clostridium_XI	darkolivegreen
Seq_2718_Enterobacteriaceae	darkolivegreen
Seq_2787_Butyricimonas_virosa	darkolivegreen
Seq_2819_Bacteroides_clarus	darkolivegreen
Seq_2909_Parasutterella_excrementihominis	darkolivegreen
Seq_3167_Clostridium_leptum	darkolivegreen
Seq_3437_Clostridiales	darkolivegreen
Seq_5_Ruminococcaceae	darkorange
Seq_206_Bacteroides_eggerthii	darkorange
Seq_219_Ruminococcaceae	darkorange
Seq_326_Faecalibacterium_prausnitzii	darkorange
Seq_363_Dorea_longicatena	darkorange
Seq_554_Ruminococcaceae	darkorange
Seq_688_Ruminococcaceae	darkorange
Seq_760_Clostridiales	darkorange
Seq_866_Clostridium_XlVa	darkorange
Seq_908_Coprococcus_eutactus	darkorange
Seq_928_Lachnospiraceae	darkorange
Seq_1065_Eubacterium	darkorange
Seq_1199_Ruminococcaceae	darkorange
Seq_1256_Eubacterium_desmolans	darkorange
Seq_1275_Lachnospiraceae	darkorange
Seq_1287_Oscillibacter_valericigenes	darkorange

Seq_1364_Clostridiales	darkorange
Seq_1457_Clostridiales	darkorange
Seq_1605_Ruminococcaceae	darkorange
Seq_1831_Flavonifractor_plautii	darkorange
Seq_2131_Parabacteroides_distasonis	darkorange
Seq_2166_Holdemania_filiformis	darkorange
Seq_2167_Lachnospiraceae	darkorange
Seq_2206_Clostridium_XlVa	darkorange
Seq_2233_Ruminococcaceae	darkorange
Seq_2259_Bacteroides_thetaiotaomicron	darkorange
Seq_2260_Pseudoflavonifractor	darkorange
Seq_2492_Firmicutes	darkorange
Seq_2512_Coprobacillus_cateniformis	darkorange
Seq_2582_Ruminococcaceae	darkorange
Seq_2614_Ruminococcaceae	darkorange
Seq_2631_Ruminococcaceae	darkorange
Seq_2708_Prevotella_corporis	darkorange
Seq_2797_Actinomyces_turicensis	darkorange
Seq_3026_Ruminococcaceae	darkorange
Seq_3187_Bacteria	darkorange
Seq_3473_Gordonibacter_pamelaeae	darkorange
Seq_3476_Erysipelotrichaceae	darkorange
Seq_3477_Porphyromonas	darkorange
Seq_3478_Clostridiales	darkorange
Seq_89_Bacteroides_ovatus	darkred
Seq_106_Ruminococcus2	darkred
Seq_272_Ruminococcaceae	darkred
Seq_289_Ruminococcus_bromii	darkred
Seq_331_Erysipelotrichaceae	darkred
Seq_345_Blautia	darkred
Seq_365_Dialister_invisus	darkred
Seq_584_Erysipelotrichaceae	darkred
Seq_632_Flavonifractor_plautii	darkred
Seq_635_Ruminococcus	darkred
Seq_636_Bacteroides_coprophilus	darkred
Seq_742_Ruminococcus_flavefaciens	darkred
Seq_792_Lachnospiraceae	darkred
Seq_831_Blautia	darkred
Seq_915_Paraprevotella_clara	darkred
Seq_921_Bacteroides_coprophilus	darkred
Seq_938_Holdemania_filiformis	darkred
Seq_1064_Sarcina_ventriculi	darkred
Seq_1130_Lachnospiraceae	darkred
Seq_1259_Lachnospiraceae	darkred
Seq_1267_Clostridium_XlVa	darkred

Seq_1290_Ruminococcaceae	darkred
Seq_1479_Lachnospiraceae	darkred
Seq_1540_Eubacterium_desmolans	darkred
Seq_1586_Clostridium_sensu_stricto	darkred
Seq_1710_Ruminococcaceae	darkred
Seq_1897_Ruminococcus_lactaris	darkred
Seq_1922_Clostridium_XlVa	darkred
Seq_1964_Paraprevotella_clara	darkred
Seq_2019_Ruminococcaceae	darkred
Seq_2124_Erysipelotrichaceae	darkred
Seq_2151_Ruminococcaceae	darkred
Seq_2224_Ruminococcaceae	darkred
Seq_2295_Firmicutes	darkred
Seq_2373_Bacteroides	darkred
Seq_2419_Coriobacteriaceae	darkred
Seq_2449_Ruminococcaceae	darkred
Seq_2519_Erysipelotrichaceae	darkred
Seq_2592_Bacteroides	darkred
Seq_2636_Ruminococcaceae	darkred
Seq_2637_Lachnospiraceae	darkred
Seq_2638_Lachnospiraceae	darkred
Seq_2720_Paraprevotella_clara	darkred
Seq_3035_Ruminococcaceae	darkred
Seq_3504_Lachnospiraceae	darkred
Seq_3505_Clostridiales	darkred
Seq_186_Megasphaera_elsdenii	darkturquoise
Seq_220_Blautia	darkturquoise
Seq_224_Hallella	darkturquoise
Seq_389_Megasphaera_elsdenii	darkturquoise
Seq_406_Prevotella_buccae	darkturquoise
Seq_426_Prevotella_stercorea	darkturquoise
Seq_445_Megasphaera_elsdenii	darkturquoise
Seq_458_Megasphaera_elsdenii	darkturquoise
Seq_494_Megasphaera_elsdenii	darkturquoise
Seq_700_Fusobacterium	darkturquoise
Seq_722_Prevotella_buccae	darkturquoise
Seq_748_Veillonellaceae	darkturquoise
Seq_764_Prevotella_buccae	darkturquoise
Seq_796_Roseburia_faecis	darkturquoise
Seq_889_Anaeroglobus_geminatus	darkturquoise
Seq_916_Fusobacterium_nucleatum	darkturquoise
Seq_1003_Prevotella_stercorea	darkturquoise
Seq_1011_Clostridium_sensu_stricto	darkturquoise
Seq_1028_Clostridium_disporicum	darkturquoise
Seq_1252_Megasphaera_micronuciformis	darkturquoise

Seq_1288_Veillonellaceae	darkturquoise
Seq_1310_Anaeroglobus	darkturquoise
Seq_1361_Dialister	darkturquoise
Seq_1405_Veillonellaceae	darkturquoise
Seq_1417_Fusobacterium	darkturquoise
Seq_1480_Collinsella_aerofaciens	darkturquoise
Seq_1764_Campylobacter_concisus	darkturquoise
Seq_1790_Dorea_longicatena	darkturquoise
Seq_1857_Blautia_luti	darkturquoise
Seq_1968_Pediococcus	darkturquoise
Seq_2006_Bacteria	darkturquoise
Seq_2020_Selenomonas_flueggei	darkturquoise
Seq_2072_Megasphaera_micronuciformis	darkturquoise
Seq_2137_Megasphaera_micronuciformis	darkturquoise
Seq_2160_Ruminococcaceae	darkturquoise
Seq_2188_Enterobacteriaceae	darkturquoise
Seq_2195_Coriobacteriaceae	darkturquoise
Seq_2289_Ruminococcaceae	darkturquoise
Seq_2331_Veillonellaceae	darkturquoise
Seq_2469_Campylobacter	darkturquoise
Seq_2470_Succiniclasticum_ruminis	darkturquoise
Seq_2643_Dialister_pneumosintes	darkturquoise
Seq_2722_Prevotella_stercorea	darkturquoise
Seq_3170_Ruminococcaceae	darkturquoise
Seq_16_Blautia_luti	green
Seq_142_Ruminococcus_albus	green
Seq_152_Parabacteroides_distasonis	green
Seq_153_Bacteroides_cellulosilyticus	green
Seq_242_Clostridium_leptum	green
Seq_268_Alistipes	green
Seq_301_Clostridium_scindens	green
Seq_318_Parasutterella_excrementihominis	green
Seq_324_Ruminococcaceae	green
Seq_364_Parabacteroides_distasonis	green
Seq_384_Prevotellaceae	green
Seq_419_Prevotellaceae	green
Seq_440_Ruminococcaceae	green
Seq_448_Clostridiales	green
Seq_456_Clostridium_XlVa	green
Seq_467_Eubacterium_rectale	green
Seq_472_Lachnospiraceae	green
Seq_502_Coriobacteriaceae	green
Seq_574_Ruminococcaceae	green
Seq_611_Firmicutes	green
Seq_619_Faecalibacterium_prausnitzii	green

Seq_657_Bacteroides_fragilis	green
Seq_671_Oscillibacter	green
Seq_676_Blautia	green
Seq_684_Faecalibacterium_prausnitzii	green
Seq_708_Alistipes_indistinctus	green
Seq_744_Ruminococcaceae	green
Seq_751_Deltaproteobacteria	green
Seq_763_Prevotellaceae	green
Seq_782_Clostridium_lactatifermentans	green
Seq_786_Ruminococcaceae	green
Seq_811_Ruminococcaceae	green
Seq_856_Olsenella	green
Seq_857_Ruminococcus_albus	green
Seq_872_Barnesiella_intestinihominis	green
Seq_887_Bacteroides_vulgatus	green
Seq_955_Oscillibacter	green
Seq_957_Ruminococcaceae	green
Seq_976_Eubacterium_desmolans	green
Seq_984_Lachnospiraceae	green
Seq_1021_Lachnospiraceae	green
Seq_1093_Clostridiales	green
Seq_1101_Clostridium_XlVa	green
Seq_1118_Prevotella_stercorea	green
Seq_1176_Anaerofustis_stercorihominis	green
Seq_1184_Ruminococcaceae	green
Seq_1201_Coriobacteriaceae	green
Seq_1238_Butyricimonas_virosa	green
Seq_1360_Erysipelotrichaceae	green
Seq_1416_Clostridium_leptum	green
Seq_1556_Ruminococcaceae	green
Seq_1610_Ruminococcaceae	green
Seq_1611_Lachnospiraceae	green
Seq_1652_Clostridium_XlVb	green
Seq_1745_Coriobacteriaceae	green
Seq_1792_Subdoligranulum_variabile	green
Seq_1877_Desulfovibrionaceae	green
Seq_1923_Ruminococcus_gnavus	green
Seq_1967_Eubacterium_desmolans	green
Seq_1993_Porphyromonadaceae	green
Seq_2136_Ruminococcaceae	green
Seq_2266_Eubacterium	green
Seq_2327_Clostridium_XlVb	green
Seq_2330_Ruminococcaceae	green
Seq_2347_Anaerotruncus_colihominis	green
Seq_2375_Bilophila_wadsworthia	green

Seq_2420_Clostridium_XlVa	green
Seq_2421_Deltaproteobacteria	green
Seq_2447_Ruminococcaceae	green
Seq_2587_Ruminococcaceae	green
Seq_2593_Erysipelotrichaceae	green
Seq_2640_Enterorhabdus	green
Seq_2641_Bacteria	green
Seq_2642_Anaerostipes_butyraticus	green
Seq_2723_Ruminococcaceae	green
Seq_2724_Lachnospiraceae	green
Seq_2810_Clostridium_IV	green
Seq_2916_Ruminococcaceae	green
Seq_3195_Parvimonas_micra	green
Seq_3489_Bacteroides_coprocola	green
Seq_3531_Subdoligranulum	green
Seq_3533_Ruminococcaceae	green
Seq_9_Faecalibacterium_prausnitzii	greenyellow
Seq_26_Ruminococcus_bromii	greenyellow
Seq_46_Parabacteroides_merdae	greenyellow
Seq_73_Lachnospiraceae	greenyellow
Seq_151_Oscillibacter_valericigenes	greenyellow
Seq_190_Faecalibacterium_prausnitzii	greenyellow
Seq_218_Ruminococcus_bromii	greenyellow
Seq_247_Bacteroides_vulgatus	greenyellow
Seq_281_Eubacterium_rectale	greenyellow
Seq_305_Eubacterium_rectale	greenyellow
Seq_344_Lachnospiraceae	greenyellow
Seq_395_Bacteroides	greenyellow
Seq_515_Faecalibacterium_prausnitzii	greenyellow
Seq_546_Barnesiella_intestinihominis	greenyellow
Seq_603_Clostridium_XlVb	greenyellow
Seq_699_Bacteroides	greenyellow
Seq_739_Lachnospiraceae	greenyellow
Seq_755_Deltaproteobacteria	greenyellow
Seq_767_Roseburia_faecis	greenyellow
Seq_777_Lachnospiraceae	greenyellow
Seq_835_Firmicutes	greenyellow
Seq_894_Alistipes_senegalensis	greenyellow
Seq_948_Bifidobacterium_breve	greenyellow
Seq_1043_Lachnospiraceae	greenyellow
Seq_1114_Anaerostipes_hadrus	greenyellow
Seq_1120_Ruminococcus_callidus	greenyellow
Seq_1188_Ruminococcaceae	greenyellow
Seq_1218_Bifidobacterium_breve	greenyellow
Seq_1257_Lachnospiraceae	greenyellow

Seq_1278_Clostridium_leptum	greenyellow
Seq_1320_Bacteroides	greenyellow
Seq_1331_Parabacteroides_distasonis	greenyellow
Seq_1340_Lachnospiraceae	greenyellow
Seq_1367_Clostridium_leptum	greenyellow
Seq_1465_Ruminococcaceae	greenyellow
Seq_1475_Bacteroides_fragilis	greenyellow
Seq_1488_Lachnospiraceae	greenyellow
Seq_1512_Bacteroides_fragilis	greenyellow
Seq_1535_Clostridium_XlVa	greenyellow
Seq_1622_Anaerostipes_hadrus	greenyellow
Seq_1653_Parabacteroides_distasonis	greenyellow
Seq_1685_Ruminococcaceae	greenyellow
Seq_1698_Clostridium_XlVa	greenyellow
Seq_1740_Blautia_luti	greenyellow
Seq_1823_Clostridium_IV	greenyellow
Seq_1895_Ruminococcaceae	greenyellow
Seq_1912_Parabacteroides_distasonis	greenyellow
Seq_1913_Parasutterella_excrementihominis	greenyellow
Seq_1958_Bacteria	greenyellow
Seq_2034_Lachnospiraceae	greenyellow
Seq_2122_Ruminococcaceae	greenyellow
Seq_2123_Eubacterium_desmolans	greenyellow
Seq_2270_Peptococcus	greenyellow
Seq_2285_Dialister_invisus	greenyellow
Seq_2286_Megasphaera_micronuciformis	greenyellow
Seq_2324_Lachnospiraceae	greenyellow
Seq_2448_Ruminococcaceae	greenyellow
Seq_2618_Pseudoflavonifractor_capillosus	greenyellow
Seq_2683_Actinomyces	greenyellow
Seq_2796_Desulfovibrionaceae	greenyellow
Seq_2868_Ruminococcaceae	greenyellow
Seq_3021_Ruminococcaceae	greenyellow
Seq_3146_Roseburia	greenyellow
Seq_3382_Firmicutes	greenyellow
Seq_3384_Faecalibacterium_prausnitzii	greenyellow
Seq_3387_Lactococcus	greenyellow
Seq_3388_Porphyromonas_bennonis	greenyellow
Seq_3464_Bilophila_wadsworthia	greenyellow
Seq_1667_Ruminococcaceae	grey
Seq_2063_Staphylococcus	grey
Seq_29_Ruminococcus_bromii	grey60
Seq_84_Ruminococcus_albus	grey60
Seq_91_Clostridiales	grey60
Seq_130_Bacteroides_vulgatus	grey60

Seq_149_Lachnospiraceae	grey60
Seq_233_Eubacterium_ruminantium	grey60
Seq_330_Ruminococcaceae	grey60
Seq_396_Dialister_propionicifaciens	grey60
Seq_397_Lachnospiraceae	grey60
Seq_474_Clostridiales	grey60
Seq_493_Faecalibacterium_prausnitzii	grey60
Seq_536_Faecalibacterium_prausnitzii	grey60
Seq_591_Ruminococcaceae	grey60
Seq_604_Faecalibacterium_prausnitzii	grey60
Seq_631_Bacteroides_vulgatus	grey60
Seq_674_Bacteroides_vulgatus	grey60
Seq_687_Ruminococcus2	grey60
Seq_718_Dialister_propionicifaciens	grey60
Seq_759_Bacteroides	grey60
Seq_799_Gemmiger_formicilis	grey60
Seq_813_Clostridium_XlVa	grey60
Seq_864_Eubacterium_rectale	grey60
Seq_924_Clostridium_XlVa	grey60
Seq_1075_Clostridium_XVIII	grey60
Seq_1086_Roseburia	grey60
Seq_1112_Ruminococcaceae	grey60
Seq_1152_Lachnospiraceae	grey60
Seq_1286_Faecalibacterium_prausnitzii	grey60
Seq_1314_Ruminococcaceae	grey60
Seq_1414_Bacteroides	grey60
Seq_1464_Ruminococcaceae	grey60
Seq_1656_Roseburia_faecis	grey60
Seq_1683_Erysipelotrichaceae	grey60
Seq_1723_Roseburia_inulinivorans	grey60
Seq_2021_Clostridiales	grey60
Seq_2093_Ruminococcaceae	grey60
Seq_2175_Proteobacteria	grey60
Seq_2231_Streptophyta	grey60
Seq_2256_Lachnospiraceae	grey60
Seq_2318_Eubacterium_desmolans	grey60
Seq_2367_Lachnospiraceae	grey60
Seq_2368_Clostridiales	grey60
Seq_2452_Clostridium_IV	grey60
Seq_2551_Ruminococcaceae	grey60
Seq_2564_Clostridium_leptum	grey60
Seq_2565_Ruminococcaceae	grey60
Seq_2622_Ruminococcaceae	grey60
Seq_2623_Clostridiales	grey60
Seq_2707_Peptococcus_niger	grey60

Seq_3157_Pseudomonas	grey60
Seq_3184_Clostridiales	grey60
Seq_3406_Clostridiales	grey60
Seq_3468_Clostridiales	grey60
Seq_3472_Blautia_faecis	grey60
Seq_8_Dialister_invisus	lightcyan
Seq_69_Lachnospiraceae	lightcyan
Seq_77_Bacteroides_coprocola	lightcyan
Seq_158_Bacteroides_ovatus	lightcyan
Seq_180_Bacteroides_ovatus	lightcyan
Seq_386_Faecalibacterium_prausnitzii	lightcyan
Seq_441_Bacteroides_coprocola	lightcyan
Seq_455_Bacteroides	lightcyan
Seq_490_Bacteroides	lightcyan
Seq_498_Lachnospiraceae	lightcyan
Seq_537_Bacteroides	lightcyan
Seq_538_Lachnospiraceae	lightcyan
Seq_551_Oscillibacter	lightcyan
Seq_623_Ruminococcaceae	lightcyan
Seq_661_Firmicutes	lightcyan
Seq_689_Alistipes	lightcyan
Seq_720_Bacteroides_thetaiotaomicron	lightcyan
Seq_770_Clostridium_leptum	lightcyan
Seq_778_Lachnospiraceae	lightcyan
Seq_840_Bacteroides	lightcyan
Seq_1010_Parabacteroides	lightcyan
Seq_1024_Clostridium_XVIII	lightcyan
Seq_1178_Ruminococcaceae	lightcyan
Seq_1297_Porphyromonadaceae	lightcyan
Seq_1309_Bifidobacterium_dentium	lightcyan
Seq_1341_Bacteroides	lightcyan
Seq_1357_Bacteroides	lightcyan
Seq_1688_Clostridium_hathewayi	lightcyan
Seq_1707_Lachnospiraceae	lightcyan
Seq_1727_Faecalibacterium_prausnitzii	lightcyan
Seq_1728_Bacteroides	lightcyan
Seq_1825_Alistipes_shahii	lightcyan
Seq_1846_Ruminococcaceae	lightcyan
Seq_1856_Oscillospira_guilliermondii	lightcyan
Seq_1872_Bacteroides	lightcyan
Seq_1921_Lachnospiraceae	lightcyan
Seq_1944_Bacteroides	lightcyan
Seq_1990_Anaerofustis_stercorihominis	lightcyan
Seq_1991_Paraprevotella_clara	lightcyan
Seq_2098_Ruminococcaceae	lightcyan

Seq_2132_Lachnospiraceae	lightcyan
Seq_2290_Sutterella	lightcyan
Seq_2326_Clostridium_XlVa	lightcyan
Seq_2466_Parasutterella_secunda	lightcyan
Seq_2467_Firmicutes	lightcyan
Seq_2516_Alistipes_indistinctus	lightcyan
Seq_2584_Flavonifractor_plautii	lightcyan
Seq_2585_Succinatimonas_hippei	lightcyan
Seq_2714_Clostridium_ramosum	lightcyan
Seq_2801_Ruminococcaceae	lightcyan
Seq_2802_Ruminococcaceae	lightcyan
Seq_2803_Dialister_invisus	lightcyan
Seq_3030_Bacteroides	lightcyan
Seq_3191_Oxalobacteraceae	lightcyan
Seq_21_Roseburia_faecis	lightgreen
Seq_44_Roseburia_intestinalis	lightgreen
Seq_76_Roseburia	lightgreen
Seq_209_Eubacterium_rectale	lightgreen
Seq_442_Lachnospiraceae	lightgreen
Seq_460_Bacteroides_stercoris	lightgreen
Seq_469_Erysipelotrichaceae	lightgreen
Seq_504_Eubacterium_rectale	lightgreen
Seq_564_Roseburia_intestinalis	lightgreen
Seq_656_Coriobacteriaceae	lightgreen
Seq_662_Blautia	lightgreen
Seq_683_Faecalibacterium_prausnitzii	lightgreen
Seq_693_Bacteroides_massiliensis	lightgreen
Seq_695_Roseburia_intestinalis	lightgreen
Seq_962_Lachnospiraceae	lightgreen
Seq_1037_Lactobacillus	lightgreen
Seq_1080_Streptococcus	lightgreen
Seq_1096_Lachnospiraceae	lightgreen
Seq_1260_Faecalibacterium_prausnitzii	lightgreen
Seq_1426_Bacteria	lightgreen
Seq_1427_Eggerthella_lenta	lightgreen
Seq_1476_Megasphaera	lightgreen
Seq_1499_Lachnospiraceae	lightgreen
Seq_1514_Blautia	lightgreen
Seq_1548_Faecalibacterium_prausnitzii	lightgreen
Seq_1581_Ruminococcus_torques	lightgreen
Seq_1603_Weissella	lightgreen
Seq_1604_Megasphaera	lightgreen
Seq_1623_Lactobacillus	lightgreen
Seq_1655_Clostridium_XlVa	lightgreen
Seq_1687_Clostridiales	lightgreen

Seq_1703_Lactobacillus	lightgreen
Seq_1741_Eggerthella_lenta	lightgreen
Seq_1742_Butyricimonas_virosa	lightgreen
Seq_1801_Lachnospiraceae	lightgreen
Seq_1802_Coprococcus_comes	lightgreen
Seq_1824_Clostridiales	lightgreen
Seq_1853_Dorea_formicigenerans	lightgreen
Seq_1860_Butyricimonas_virosa	lightgreen
Seq_1867_Lactobacillus	lightgreen
Seq_1960_Coprococcus_comes	lightgreen
Seq_2065_Holdemania_filiformis	lightgreen
Seq_2066_Erysipelotrichaceae	lightgreen
Seq_2094_Blautia	lightgreen
Seq_2450_Lachnospiraceae	lightgreen
Seq_2503_Lachnospiraceae	lightgreen
Seq_2872_Lachnospiraceae	lightgreen
Seq_2873_Leuconostoc	lightgreen
Seq_2874_Erysipelotrichaceae	lightgreen
Seq_2875_Odoribacter_splanchnicus	lightgreen
Seq_2878_Ruminococcaceae	lightgreen
Seq_2989_Peptostreptococcus_anaerobius	lightgreen
Seq_100_Bacteroides_thetaiotaomicron	lightyellow
Seq_108_Bacteroides_dorei	lightyellow
Seq_137_Bacteroides_fragilis	lightyellow
Seq_191_Bacteroides_ovatus	lightyellow
Seq_252_Lachnospiraceae	lightyellow
Seq_265_Ruminococcaceae	lightyellow
Seq_315_Clostridium_IV	lightyellow
Seq_412_Ruminococcaceae	lightyellow
Seq_464_Bacteria	lightyellow
Seq_548_Coprobacillus_cateniformis	lightyellow
Seq_561_Anaerostipes	lightyellow
Seq_576_Veillonellaceae	lightyellow
Seq_598_Bacteroides_ovatus	lightyellow
Seq_667_Clostridium_lactatifermentans	lightyellow
Seq_670_Anaerotruncus_colihominis	lightyellow
Seq_756_Clostridium_XlVa	lightyellow
Seq_762_Bifidobacterium_dentium	lightyellow
Seq_858_Bacteria	lightyellow
Seq_983_Ruminococcaceae	lightyellow
Seq_1004_Ruminococcaceae	lightyellow
Seq_1081_Ruminococcaceae	lightyellow
Seq_1099_Sutterella_stercoricanis	lightyellow
Seq_1139_Oscillospira_guilliermondii	lightyellow
Seq_1189_Staphylococcus	lightyellow

Seq_1226_Pseudoflavonifractor	lightyellow
Seq_1602_Clostridium_XlVa	lightyellow
Seq_1914_Lachnospiraceae	lightyellow
Seq_1915_Ruminococcaceae	lightyellow
Seq_1959_Peptococcus	lightyellow
Seq_2024_Ruminococcaceae	lightyellow
Seq_2039_Clostridium_leptum	lightyellow
Seq_2153_Ruminococcaceae	lightyellow
Seq_2154_Clostridiales	lightyellow
Seq_2184_Enterococcus	lightyellow
Seq_2254_Ruminococcaceae	lightyellow
Seq_2287_Ruminococcaceae	lightyellow
Seq_2365_Clostridiales	lightyellow
Seq_2451_Oscillibacter_valericigenes	lightyellow
Seq_2502_Eubacterium_desmolans	lightyellow
Seq_2687_Clostridium_XlVb	lightyellow
Seq_2689_Lactobacillus_fermentum	lightyellow
Seq_2779_Ruminococcaceae	lightyellow
Seq_2869_Corynebacterium	lightyellow
Seq_2876_Clostridiales	lightyellow
Seq_2877_Ruminococcaceae	lightyellow
Seq_2990_Hydrogenoanaerobacterium	lightyellow
Seq_2991_Ruminococcaceae	lightyellow
Seq_2992_Ruminococcaceae	lightyellow
Seq_2993_Acetanaerobacterium_elongatum	lightyellow
Seq_3397_Clostridium_IV	lightyellow
Seq_3401_Lachnospiraceae	lightyellow
Seq_11_Bacteroides_dorei	magenta
Seq_13_Faecalibacterium_prausnitzii	magenta
Seq_70_Bacteroides_uniformis	magenta
Seq_78_Lachnospiraceae	magenta
Seq_95_Prevotella_copri	magenta
Seq_103_Eubacterium_eligens	magenta
Seq_133_Ruminococcus_lactaris	magenta
Seq_173_Lachnospiraceae	magenta
Seq_175_Blautia_faecis	magenta
Seq_189_Parabacteroides_distasonis	magenta
Seq_210_Lachnospiraceae	magenta
Seq_232_Parasutterella_excrementihominis	magenta
Seq_240_Clostridiales	magenta
Seq_254_Firmicutes	magenta
Seq_312_Lachnospiraceae	magenta
Seq_366_Bacteroides	magenta
Seq_369_Asteroleplasma	magenta
Seq_437_Lachnospiraceae	magenta

Seq_476_Ruminococcus	magenta
Seq_518_Bacteroides_intestinalis	magenta
Seq_530_Bacteria	magenta
Seq_557_Adlercreutzia_equolifaciens	magenta
Seq_572_Firmicutes	magenta
Seq_589_Bilophila_wadsworthia	magenta
Seq_624_Bacteria	magenta
Seq_627_Asteroleplasma	magenta
Seq_804_Lachnospiraceae	magenta
Seq_842_Ruminococcaceae	magenta
Seq_847_Lachnospiraceae	magenta
Seq_875_Clostridiales	magenta
Seq_884_Ruminococcaceae	magenta
Seq_922_Lachnospiraceae	magenta
Seq_950_Lachnospiraceae	magenta
Seq_990_Bacteria	magenta
Seq_1151_Faecalibacterium_prausnitzii	magenta
Seq_1271_Ruminococcaceae	magenta
Seq_1281_Parabacteroides_distasonis	magenta
Seq_1325_Faecalibacterium_prausnitzii	magenta
Seq_1349_Clostridium_XVIII	magenta
Seq_1370_Firmicutes	magenta
Seq_1401_Ruminococcaceae	magenta
Seq_1428_Ruminococcaceae	magenta
Seq_1440_Bacteroides_vulgatus	magenta
Seq_1469_Roseburia_faecis	magenta
Seq_1472_Firmicutes	magenta
Seq_1516_Parabacteroides_johnsonii	magenta
Seq_1637_Lachnospiraceae	magenta
Seq_1704_Eubacterium_desmolans	magenta
Seq_1725_Ruminococcaceae	magenta
Seq_1826_Butyricimonas_virosa	magenta
Seq_1941_Lachnospiraceae	magenta
Seq_1961_Prevotella_copri	magenta
Seq_2323_Bacteria	magenta
Seq_2370_Lachnospiraceae	magenta
Seq_2458_Lachnospiraceae	magenta
Seq_2507_Porphyromonadaceae	magenta
Seq_2508_Clostridium_lactatifermentans	magenta
Seq_2703_Clostridium_IV	magenta
Seq_2789_Pseudomonas	magenta
Seq_2790_Butyricimonas_virosa	magenta
Seq_2791_Candidatus_Saccharibacteria	magenta
Seq_2892_Bacteria	magenta
Seq_2893_Barnesiella_intestinihominis	magenta

Seq_3012_Clostridiales	magenta
Seq_3013_Ruminococcaceae	magenta
Seq_3171_Ruminococcaceae	magenta
Seq_3172_Ruminococcaceae	magenta
Seq_3173_Desulfovibrionaceae	magenta
Seq_3174_Firmicutes	magenta
Seq_3444_Clostridiales	magenta
Seq_3445_Butyricimonas_virosa	magenta
Seq_3446_Clostridiales	magenta
Seq_3447_Bacteria	magenta
Seq_3450_Buttiauxella	magenta
Seq_3575_Ruminococcaceae	magenta
Seq_93_Anaerostipes_hadrus	midnightblue
Seq_194_Megasphaera	midnightblue
Seq_222_Clostridium_XlVa	midnightblue
Seq_226_Megasphaera	midnightblue
Seq_300_Bacteroidales	midnightblue
Seq_327_Dialister_invisus	midnightblue
Seq_340_Bacteroides_vulgatus	midnightblue
Seq_379_Eubacterium_rectale	midnightblue
Seq_528_Roseburia_faecis	midnightblue
Seq_535_Blautia_luti	midnightblue
Seq_547_Burkholderiales	midnightblue
Seq_639_Erysipelotrichaceae	midnightblue
Seq_643_Faecalibacterium_prausnitzii	midnightblue
Seq_822_Megasphaera	midnightblue
Seq_849_Lachnospiraceae	midnightblue
Seq_871_Erysipelotrichaceae	midnightblue
Seq_1009_Roseburia_faecis	midnightblue
Seq_1017_Ruminococcus_torques	midnightblue
Seq_1057_Coriobacteriaceae	midnightblue
Seq_1060_Lachnospiraceae	midnightblue
Seq_1107_Lachnospiraceae	midnightblue
Seq_1124_Parabacteroides_distasonis	midnightblue
Seq_1159_Parabacteroides_distasonis	midnightblue
Seq_1179_Lachnospiraceae	midnightblue
Seq_1250_Coriobacteriaceae	midnightblue
Seq_1261_Blautia	midnightblue
Seq_1302_Coprococcus_comes	midnightblue
Seq_1315_Clostridium_glycolicum	midnightblue
Seq_1520_Clostridium_bartlettii	midnightblue
Seq_1606_Clostridium_scindens	midnightblue
Seq_1607_Lachnospiraceae	midnightblue
Seq_1608_Lachnospiraceae	midnightblue
Seq_1612_Bifidobacterium_pseudolongum	midnightblue

Seq_1674_Lachnospiraceae	midnightblue
Seq_1695_Ruminococcaceae	midnightblue
Seq_1726_Blautia	midnightblue
Seq_1785_Ruminococcus_torques	midnightblue
Seq_1794_Lachnospiraceae	midnightblue
Seq_1858_Eubacterium_desmolans	midnightblue
Seq_1892_Flavonifractor_plautii	midnightblue
Seq_1893_Clostridium_XlVa	midnightblue
Seq_1949_Bacteria	midnightblue
Seq_2097_Sutterella_stercoricanis	midnightblue
Seq_2129_Lachnospiraceae	midnightblue
Seq_2161_Clostridium_XlVa	midnightblue
Seq_2162_Lachnospiraceae	midnightblue
Seq_2170_Lachnospiraceae	midnightblue
Seq_2190_Bacteroidetes	midnightblue
Seq_2196_Actinomyces	midnightblue
Seq_2413_Lachnospiraceae	midnightblue
Seq_2414_Ruminococcus2	midnightblue
Seq_2461_Clostridiales	midnightblue
Seq_2473_Bacteria	midnightblue
Seq_2814_Lachnospiraceae	midnightblue
Seq_3175_Campylobacter_troglodytis	midnightblue
Seq_3454_Oscillibacter	midnightblue
Seq_19_Bacteroides_vulgatus	orange
Seq_43_Bacteroides_vulgatus	orange
Seq_54_Bacteroides_xylanisolvens	orange
Seq_79_Clostridium_XlVa	orange
Seq_141_Ruminococcaceae	orange
Seq_170_Flavonifractor_plautii	orange
Seq_257_Bacteroides_vulgatus	orange
Seq_285_Clostridium_symbiosum	orange
Seq_359_Odoribacter_splanchnicus	orange
Seq_368_Bacteroides_vulgatus	orange
Seq_376_Bacteroides_vulgatus	orange
Seq_428_Bacteroides_vulgatus	orange
Seq_578_Ruminococcaceae	orange
Seq_790_Clostridium_IV	orange
Seq_870_Clostridium_aldenense	orange
Seq_954_Clostridium_lavalense	orange
Seq_999_Clostridium_XlVa	orange
Seq_1014_Bacteria	orange
Seq_1026_Clostridium_XlVa	orange
Seq_1035_Butyricicoccus_pullicaecorum	orange
Seq_1044_Parabacteroides_merdae	orange
Seq_1056_Alistipes	orange

Seq_1063_Clostridium_aldenense	orange
Seq_1095_Roseburia_inulinivorans	orange
Seq_1200_Clostridium_aldenense	orange
Seq_1443_Lachnospiraceae	orange
Seq_1458_Clostridium_IV	orange
Seq_1494_Clostridium_citroniae	orange
Seq_1529_Ruminococcaceae	orange
Seq_1569_Firmicutes	orange
Seq_1689_Firmicutes	orange
Seq_1947_Eggerthella_lenta	orange
Seq_2003_Lachnospiraceae	orange
Seq_2092_Clostridium_lactatifermentans	orange
Seq_2468_Subdoligranulum_variabile	orange
Seq_2635_Ruminococcaceae	orange
Seq_2719_Bifidobacterium_pseudolongum	orange
Seq_3198_Actinomycetales	orange
Seq_3199_Erysipelotrichaceae	orange
Seq_3502_Firmicutes	orange
Seq_192_Barnesiella_intestinihominis	paleturquoise
Seq_405_Firmicutes	paleturquoise
Seq_434_Phascolarctobacterium_succinatutens	paleturquoise
Seq_517_Lachnospiraceae	paleturquoise
Seq_544_Parabacteroides_distasonis	paleturquoise
Seq_666_Parabacteroides_distasonis	paleturquoise
Seq_735_Lachnospiraceae	paleturquoise
Seq_826_Ruminococcus_callidus	paleturquoise
Seq_853_Oscillibacter	paleturquoise
Seq_1034_Faecalibacterium_prausnitzii	paleturquoise
Seq_1067_Ruminococcaceae	paleturquoise
Seq_1070_Blautia	paleturquoise
Seq_1105_Ruminococcaceae	paleturquoise
Seq_1258_Faecalibacterium_prausnitzii	paleturquoise
Seq_1312_Alistipes_indistinctus	paleturquoise
Seq_1338_Phascolarctobacterium_succinatutens	paleturquoise
Seq_1413_Barnesiella_intestinihominis	paleturquoise
Seq_1462_Clostridiales	paleturquoise
Seq_1483_Clostridium_IV	paleturquoise
Seq_1600_Faecalibacterium_prausnitzii	paleturquoise
Seq_1619_Ruminococcaceae	paleturquoise
Seq_1671_Ruminococcaceae	paleturquoise
Seq_1866_Coriobacteriaceae	paleturquoise
Seq_1937_Clostridiales	paleturquoise
Seq_2144_Prevotella_buccalis	paleturquoise
Seq_2150_Ruminococcaceae	paleturquoise
Seq_2214_Bacteria	paleturquoise

Seq_2498_Clostridiales	paleturquoise
Seq_2538_Oscillibacter	paleturquoise
Seq_2561_Lachnospiraceae	paleturquoise
Seq_2562_Clostridiales	paleturquoise
Seq_2600_Anaerotruncus_colihominis	paleturquoise
Seq_2686_Porphyromonas	paleturquoise
Seq_2778_Ruminococcaceae	paleturquoise
Seq_2870_Clostridiales	paleturquoise
Seq_2871_Ruminococcaceae	paleturquoise
Seq_3149_Clostridiales	paleturquoise
Seq_3151_Porphyromonas_somerae	paleturquoise
Seq_22_Bacteroides_uniformis	pink
Seq_40_Bacteroides_stercoris	pink
Seq_80_Coprococcus_eutactus	pink
Seq_85_Bacteroides_stercoris	pink
Seq_96_Acidaminococcus_intestini	pink
Seq_150_Roseburia_hominis	pink
Seq_179_Bacteroides_xylanisolvens	pink
Seq_215_Bacteroides_stercoris	pink
Seq_238_Bacteroides_vulgatus	pink
Seq_279_Ruminococcus_flavefaciens	pink
Seq_284_Ruminococcaceae	pink
Seq_325_Ruminococcaceae	pink
Seq_346_Lachnospiraceae	pink
Seq_409_Firmicutes	pink
Seq_436_Faecalibacterium_prausnitzii	pink
Seq_486_Barnesiella_intestinihominis	pink
Seq_508_Parabacteroides_distasonis	pink
Seq_569_Ruminococcaceae	pink
Seq_601_Lachnospiraceae	pink
Seq_616_Bacteroidales	pink
Seq_766_Eubacterium_desmolans	pink
Seq_816_Bacteroides	pink
Seq_944_Oscillibacter_valericigenes	pink
Seq_982_Lachnospiraceae	pink
Seq_996_Parabacteroides_distasonis	pink
Seq_1006_Ruminococcaceae	pink
Seq_1019_Lachnospiraceae	pink
Seq_1047_Lachnospiraceae	pink
Seq_1102_Ruminococcaceae	pink
Seq_1125_Parasutterella_excrementihominis	pink
Seq_1174_Ruminococcaceae	pink
Seq_1198_Phascolarctobacterium_succinatutens	pink
Seq_1245_Lachnospiraceae	pink
Seq_1251_Clostridiales	pink

Seq_1285_Clostridiales	pink
Seq_1390_Clostridiales	pink
Seq_1439_Oscillibacter_valericigenes	pink
Seq_1466_Streptococcus	pink
Seq_1517_Clostridium_indolis	pink
Seq_1538_Ruminococcaceae	pink
Seq_1627_Dorea_longicatena	pink
Seq_1684_Blautia_hydrogenotrophica	pink
Seq_1705_Streptococcus	pink
Seq_1743_Ruminococcaceae	pink
Seq_1760_Clostridium_leptum	pink
Seq_1784_Parabacteroides_distasonis	pink
Seq_2040_Clostridiales	pink
Seq_2041_Ruminococcaceae	pink
Seq_2067_Gemella_sanguinis	pink
Seq_2130_Ruminococcaceae	pink
Seq_2163_Bacteria	pink
Seq_2164_Bacteria	pink
Seq_2189_Clostridium_leptum	pink
Seq_2234_Oscillibacter	pink
Seq_2416_Lactobacillus_algidus	pink
Seq_2459_Clostridium_hiranonis	pink
Seq_2460_Firmicutes	pink
Seq_2576_Clostridiales	pink
Seq_2577_Lachnospiraceae	pink
Seq_2628_Leuconostocarnosum	pink
Seq_2704_Firmicutes	pink
Seq_2792_Ruminococcaceae	pink
Seq_2793_Ruminococcaceae	pink
Seq_2794_Clostridiales	pink
Seq_2795_Oscillibacter_valericigenes	pink
Seq_2895_Abiotrophia_defectiva	pink
Seq_2896_Actinomyces_graevenitzii	pink
Seq_3014_Firmicutes	pink
Seq_3015_Eubacterium	pink
Seq_3016_Actinomyces_lingnae	pink
Seq_3017_Clostridiales	pink
Seq_3176_Clostridiales	pink
Seq_3177_Clostridiales	pink
Seq_3178_Peptococcaceae_1	pink
Seq_3456_Clostridiales	pink
Seq_3457_Bacteria	pink
Seq_27_Lachnospiraceae	purple
Seq_83_Ruminococcaceae	purple
Seq_109_Lachnospiraceae	purple

Seq_115_Coprococcus_eutactus	purple
Seq_239_Eggerthella_lenta	purple
Seq_317_Erysipelotrichaceae	purple
Seq_424_Bacteroides_caccae	purple
Seq_430_Clostridia	purple
Seq_459_Blautia_hydrogenotrophica	purple
Seq_550_Anaerostipes_hadrus	purple
Seq_630_Coriobacteriaceae	purple
Seq_675_Clostridium_IV	purple
Seq_677_Ruminococcaceae	purple
Seq_707_Gordonibacter_pamelaeae	purple
Seq_732_Ruminococcaceae	purple
Seq_771_Eubacterium_desmolans	purple
Seq_852_Clostridiales	purple
Seq_860_Lachnospiraceae	purple
Seq_903_Bacteria	purple
Seq_920_Eubacterium	purple
Seq_936_Catenibacterium_mitsuokai	purple
Seq_945_Erysipelotrichaceae	purple
Seq_966_Holdemania_filiformis	purple
Seq_1071_Lachnospiraceae	purple
Seq_1072_Clostridium_methylpentosum	purple
Seq_1153_Ruminococcaceae	purple
Seq_1164_Bacteria	purple
Seq_1171_Clostridiales	purple
Seq_1224_Turicibacter_sanguinis	purple
Seq_1247_Clostridiales	purple
Seq_1263_Ruminococcaceae	purple
Seq_1276_Clostridiales	purple
Seq_1295_Ruminococcus2	purple
Seq_1351_Ruminococcus_obeum	purple
Seq_1532_Firmicutes	purple
Seq_1544_Clostridiales	purple
Seq_1550_Lachnospiraceae	purple
Seq_1589_Parabacteroides_distasonis	purple
Seq_1596_Clostridiales	purple
Seq_1613_Dialister_invisus	purple
Seq_1620_Lachnospiraceae	purple
Seq_1647_Clostridiales	purple
Seq_1736_Clostridiales	purple
Seq_1747_Clostridiales	purple
Seq_1748_Ruminococcus_bromii	purple
Seq_1762_Ruminococcaceae	purple
Seq_1769_Clostridiales	purple
Seq_1870_Ruminococcaceae	purple

Seq_1876_Ruminococcaceae	purple
Seq_1908_Clostridium_IV	purple
Seq_2043_Clostridiales	purple
Seq_2081_Firmicutes	purple
Seq_2139_Ruminococcaceae	purple
Seq_2284_Coriobacteriaceae	purple
Seq_2335_Ruminococcaceae	purple
Seq_2336_Clostridiales	purple
Seq_2337_Flavonifractor_plautii	purple
Seq_2338_Bacteria	purple
Seq_2432_Ruminococcaceae	purple
Seq_2525_Ruminococcaceae	purple
Seq_2595_Butyricimonas_virosa	purple
Seq_2646_Firmicutes	purple
Seq_2647_Lachnospiraceae	purple
Seq_2648_Lachnospiraceae	purple
Seq_2729_Ruminococcaceae	purple
Seq_2815_Clostridiales	purple
Seq_2816_Butyricimonas_virosa	purple
Seq_2921_Ruminococcaceae	purple
Seq_2922_Streptococcus	purple
Seq_2923_Butyricimonas_virosa	purple
Seq_2924_Clostridiales	purple
Seq_17_Bacteroides_vulgatus	red
Seq_35_Coprococcus_eutactus	red
Seq_52_Clostridiales	red
Seq_57_Roseburia_inulinivorans	red
Seq_60_Faecalibacterium_prausnitzii	red
Seq_64_Dorea_formicigenerans	red
Seq_105_Lachnospiraceae	red
Seq_128_Clostridium_XlVa	red
Seq_144_Ruminococcus_torques	red
Seq_159_Bacteroides_eggerthii	red
Seq_161_Clostridium_XlVa	red
Seq_181_Clostridium_XVIII	red
Seq_184_Clostridiales	red
Seq_185_Anaerostipes_hadrus	red
Seq_187_Anaerostipes_hadrus	red
Seq_207_Bacteroides_ovatus	red
Seq_228_Clostridium_XlVb	red
Seq_276_Clostridium_XlVa	red
Seq_282_Eubacterium_desmolans	red
Seq_336_Flavonifractor_plautii	red
Seq_374_Alistipes_finegoldii	red
Seq_390_Clostridiales	red

Seq_400_Blautia	red
Seq_470_Eubacterium_siraeum	red
Seq_487_Bacteroides_finegoldii	red
Seq_521_Lachnospiraceae	red
Seq_563_Bacteroides_vulgatus	red
Seq_685_Eubacterium_desmolans	red
Seq_690_Bacteria	red
Seq_692_Bacteroides_vulgatus	red
Seq_746_Lachnospiraceae	red
Seq_779_Clostridiales	red
Seq_785_Proteobacteria	red
Seq_817_Faecalibacterium_prausnitzii	red
Seq_832_Ruminococcaceae	red
Seq_918_Lachnospiraceae	red
Seq_931_Blautia	red
Seq_937_Firmicutes	red
Seq_981_Lachnospiraceae	red
Seq_1012_Faecalibacterium_prausnitzii	red
Seq_1018_Lachnospiraceae	red
Seq_1030_Parabacteroides_distasonis	red
Seq_1073_Parabacteroides_distasonis	red
Seq_1106_Clostridium_sensu_stricto	red
Seq_1140_Bifidobacterium	red
Seq_1172_Lachnospiraceae	red
Seq_1202_Lachnospiraceae	red
Seq_1233_Lachnospiraceae	red
Seq_1268_Erysipelotrichaceae	red
Seq_1378_Clostridium_saccharogumia	red
Seq_1391_Burkholderiales	red
Seq_1446_Clostridiales	red
Seq_1471_Erysipelotrichaceae	red
Seq_1484_Streptococcus	red
Seq_1519_Lachnospiraceae	red
Seq_1549_Lachnospiraceae	red
Seq_1571_Lachnospiraceae	red
Seq_1658_Lachnospiraceae	red
Seq_1659_Ruminococcus_obeum	red
Seq_1677_Coprococcus_comes	red
Seq_1793_Coprococcus_catus	red
Seq_1820_Bacteroides_nordii	red
Seq_1832_Faecalibacterium_prausnitzii	red
Seq_1948_Ruminococcaceae	red
Seq_1969_Lachnospiraceae	red
Seq_2102_Lachnospiraceae	red
Seq_2198_Ruminococcaceae	red

Seq_2332_Clostridiales	red
Seq_2333_Collinsella_tanakaei	red
Seq_2376_Dorea	red
Seq_2471_Collinsella	red
Seq_2522_Pediococcus	red
Seq_2523_Eubacterium_desmolans	red
Seq_2754_Clostridium_leptum	red
Seq_2811_Ruminococcaceae	red
Seq_2919_Coriobacteriaceae	red
Seq_3205_Clostridiales	red
Seq_3535_Solobacterium_moorei	red
Seq_28_Akkermansia_muciniphila	royalblue
Seq_66_Clostridium_sensu_stricto	royalblue
Seq_145_Clostridium_glycolicum	royalblue
Seq_236_Bifidobacterium_longum	royalblue
Seq_249_Firmicutes	royalblue
Seq_275_Akkermansia_muciniphila	royalblue
Seq_290_Akkermansia_muciniphila	royalblue
Seq_388_Bifidobacterium_animalis	royalblue
Seq_415_Ruminococcaceae	royalblue
Seq_495_Turicibacter_sanguinis	royalblue
Seq_532_Ruminococcaceae	royalblue
Seq_552_Ruminococcaceae	royalblue
Seq_705_Lachnospiraceae	royalblue
Seq_743_Ruminococcaceae	royalblue
Seq_791_Eubacterium_siraeum	royalblue
Seq_795_Holdemania_filiformis	royalblue
Seq_828_Clostridiales	royalblue
Seq_946_Clostridium_sensu_stricto	royalblue
Seq_1022_Lachnospiraceae	royalblue
Seq_1136_Bacteroides_fragilis	royalblue
Seq_1284_Eubacterium	royalblue
Seq_1500_Parabacteroides_johnsonii	royalblue
Seq_1539_Ruminococcaceae	royalblue
Seq_1565_Ruminococcaceae	royalblue
Seq_1628_Clostridium_baratii	royalblue
Seq_1719_Clostridiales	royalblue
Seq_1786_Alistipes_finegoldii	royalblue
Seq_1827_Clostridium_sensu_stricto	royalblue
Seq_1828_Flavonifractor_plautii	royalblue
Seq_1829_Desulfovibrio	royalblue
Seq_1894_Ruminococcaceae	royalblue
Seq_1918_Clostridium_XlVa	royalblue
Seq_1942_Ruminococcus	royalblue
Seq_1979_Ruminococcaceae	royalblue

Seq_2000_Pseudoflavonifractor	royalblue
Seq_2017_Bacteroides	royalblue
Seq_2143_Clostridiales	royalblue
Seq_2191_Bacteria	royalblue
Seq_2219_Clostridiales	royalblue
Seq_2258_Klebsiella	royalblue
Seq_2509_Butyricimonas_virosa	royalblue
Seq_2629_Clostridiales	royalblue
Seq_2630_Veillonella_dispar	royalblue
Seq_2705_Ruminococcaceae	royalblue
Seq_3019_Clostridiales	royalblue
Seq_3020_Firmicutes	royalblue
Seq_3180_Lachnospiraceae	royalblue
Seq_3459_Clostridiales	royalblue
Seq_3460_Clostridiales	royalblue
Seq_221_Erysipelotrichaceae	saddlebrown
Seq_223_Prevotella_stercorea	saddlebrown
Seq_259_Lachnospiraceae	saddlebrown
Seq_296_Parabacteroides_distasonis	saddlebrown
Seq_314_Gemmiger_formicilis	saddlebrown
Seq_367_Ruminococcus_callidus	saddlebrown
Seq_373_Lachnospiraceae	saddlebrown
Seq_481_Prevotella_copri	saddlebrown
Seq_595_Blautia	saddlebrown
Seq_680_Eubacterium_rectale	saddlebrown
Seq_697_Parasutterella_excrementihominis	saddlebrown
Seq_798_Clostridiales	saddlebrown
Seq_821_Prevotella_stercorea	saddlebrown
Seq_825_Allisonella_histaminiformans	saddlebrown
Seq_877_Prevotella	saddlebrown
Seq_939_Clostridium_XlVa	saddlebrown
Seq_947_Enterorhabdus	saddlebrown
Seq_991_Barnesiella_intestinihominis	saddlebrown
Seq_997_Phascolarctobacterium_succinatutens	saddlebrown
Seq_1038_Prevotella_stercorea	saddlebrown
Seq_1068_Blautia	saddlebrown
Seq_1166_Erysipelotrichaceae	saddlebrown
Seq_1221_Clostridiales	saddlebrown
Seq_1234_Prevotella_stercorea	saddlebrown
Seq_1272_Lachnospiraceae	saddlebrown
Seq_1369_Faecalibacterium_prausnitzii	saddlebrown
Seq_1382_Ruminococcus_callidus	saddlebrown
Seq_1657_Phascolarctobacterium_succinatutens	saddlebrown
Seq_1673_Slackia_isoflavoniconvertens	saddlebrown
Seq_1701_Clostridium_XlVb	saddlebrown

Seq_2015_Ruminococcaceae	saddlebrown
Seq_2159_Lachnospiraceae	saddlebrown
Seq_2320_Bacteroides_ovatus	saddlebrown
Seq_2573_Mogibacterium	saddlebrown
Seq_2701_Sutterella_wadsworthensis	saddlebrown
Seq_2788_Firmicutes	saddlebrown
Seq_2891_Bacteroides	saddlebrown
Seq_3439_Butyricimonas_virosa	saddlebrown
Seq_4_Bifidobacterium	salmon
Seq_67_Bifidobacterium	salmon
Seq_86_Prevotella_copri	salmon
Seq_104_Lachnospiraceae	salmon
Seq_160_Ruminococcus_callidus	salmon
Seq_169_Akkermansia_muciniphila	salmon
Seq_174_Prevotella_copri	salmon
Seq_211_Prevotella_copri	salmon
Seq_277_Bacteroides_caccae	salmon
Seq_302_Bifidobacterium_angulatum	salmon
Seq_323_Prevotella_copri	salmon
Seq_351_Anaerostipes_hadrus	salmon
Seq_429_Ruminococcaceae	salmon
Seq_471_Prevotella_copri	salmon
Seq_594_Erysipelotrichaceae	salmon
Seq_596_Prevotella_copri	salmon
Seq_645_Bacteroidetes	salmon
Seq_686_Lachnospiraceae	salmon
Seq_696_Eubacterium_desmolans	salmon
Seq_775_Ruminococcaceae	salmon
Seq_819_Lactobacillus_ruminis	salmon
Seq_906_Faecalibacterium_prausnitzii	salmon
Seq_929_Sutterella_wadsworthensis	salmon
Seq_986_Eubacterium_desmolans	salmon
Seq_995_Lachnospiraceae	salmon
Seq_1000_Prevotella_copri	salmon
Seq_1122_Barnesiella_intestinihominis	salmon
Seq_1205_Phascolarctobacterium_succinatutens	salmon
Seq_1319_Ruminococcaceae	salmon
Seq_1327_Phascolarctobacterium_succinatutens	salmon
Seq_1328_Peptococcus_niger	salmon
Seq_1358_Faecalibacterium_prausnitzii	salmon
Seq_1372_Prevotella_copri	salmon
Seq_1373_Prevotella_copri	salmon
Seq_1374_Ruminococcaceae	salmon
Seq_1383_Prevotella_copri	salmon
Seq_1404_Lachnospiraceae	salmon

Seq_1505_Bacteroides_fragilis	salmon
Seq_1585_Eubacterium_desmolans	salmon
Seq_1588_Prevotella_copri	salmon
Seq_1599_Ruminococcaceae	salmon
Seq_1609_Lachnospiraceae	salmon
Seq_1630_Eubacterium_desmolans	salmon
Seq_1709_Blautia_faecis	salmon
Seq_1788_Prevotella_copri	salmon
Seq_1798_Prevotella_copri	salmon
Seq_1896_Barnesiella_intestinihominis	salmon
Seq_1930_Coriobacteriaceae	salmon
Seq_1963_Eubacterium_desmolans	salmon
Seq_2118_Porphyromonadaceae	salmon
Seq_2181_Lachnospiraceae	salmon
Seq_2265_Clostridiales	salmon
Seq_2329_Prevotella_copri	salmon
Seq_2588_Clostridiales	salmon
Seq_2633_Lachnospiraceae	salmon
Seq_2634_Ruminococcaceae	salmon
Seq_2905_Butyricimonas_virosa	salmon
Seq_2906_Coriobacteriaceae	salmon
Seq_3033_Clostridium_lactatifermentans	salmon
Seq_3492_Pseudomonas	salmon
Seq_3494_Sutterella_stercoricanis	salmon
Seq_3495_Catenibacterium_mitsuokai	salmon
Seq_3496_Bacteroides	salmon
Seq_3514_Selenomonadales	salmon
Seq_47_Ruminococcus_torques	sienna3
Seq_138_Blautia	sienna3
Seq_263_Blautia	sienna3
Seq_320_Coprobacillus_cateniformis	sienna3
Seq_461_Blautia	sienna3
Seq_559_Gemmiger_formicilis	sienna3
Seq_597_Bacteria	sienna3
Seq_608_Bacteria	sienna3
Seq_649_Lachnospiraceae	sienna3
Seq_673_Firmicutes	sienna3
Seq_713_Bacteria	sienna3
Seq_727_Faecalibacterium_prausnitzii	sienna3
Seq_734_Firmicutes	sienna3
Seq_738_Streptococcus	sienna3
Seq_888_Bacteroides_ovatus	sienna3
Seq_1109_Ruminococcaceae	sienna3
Seq_1141_Eubacterium_desmolans	sienna3
Seq_1162_Lachnospira	sienna3

Seq_1173_Eubacterium_desmolans	sienna3
Seq_1209_Eubacterium_desmolans	sienna3
Seq_1220_Parasutterella_excrementihominis	sienna3
Seq_1243_Parabacteroides_distasonis	sienna3
Seq_1386_Blautia	sienna3
Seq_1430_Lachnospiraceae	sienna3
Seq_1447_Blautia	sienna3
Seq_1467_Blautia	sienna3
Seq_1511_Blautia	sienna3
Seq_1669_Blautia	sienna3
Seq_1670_Lachnospiraceae	sienna3
Seq_1851_Lachnospiraceae	sienna3
Seq_2227_Firmicutes	sienna3
Seq_2528_Eubacterium_desmolans	sienna3
Seq_2820_Eggerthella_lenta	sienna3
Seq_2982_Clostridiales	sienna3
Seq_3356_Bacteria	sienna3
Seq_3358_Lachnospiraceae	sienna3
Seq_94_Anaerostipes_hadrus	skyblue
Seq_307_Ruminococcaceae	skyblue
Seq_329_Bacteroides_ovatus	skyblue
Seq_385_Clostridiales	skyblue
Seq_402_Lachnospiraceae	skyblue
Seq_480_Alistipes_finegoldii	skyblue
Seq_499_Anaerostipes_hadrus	skyblue
Seq_519_Blautia	skyblue
Seq_523_Bacteria	skyblue
Seq_541_Bacteroides_ovatus	skyblue
Seq_653_Lactococcus	skyblue
Seq_723_Ruminococcus_albus	skyblue
Seq_772_Akkermansia_muciniphila	skyblue
Seq_810_Akkermansia_muciniphila	skyblue
Seq_971_Eubacterium_desmolans	skyblue
Seq_1160_Lachnospiraceae	skyblue
Seq_1311_Lactobacillus	skyblue
Seq_1584_Blautia	skyblue
Seq_1661_Clostridium_scindens	skyblue
Seq_1675_Bacteroides_intestinalis	skyblue
Seq_1706_Eubacterium_rectale	skyblue
Seq_1765_Lachnospiraceae	skyblue
Seq_1830_Bacteroides_intestinalis	skyblue
Seq_1873_Blautia_faecis	skyblue
Seq_1919_Anaerostipes_hadrus	skyblue
Seq_1989_Blautia_glucerasea	skyblue
Seq_2138_Lachnospiraceae	skyblue

Seq_2299_Clostridium_lactatifermentans	skyblue
Seq_2300_Clostridium_lavalense	skyblue
Seq_2417_Oscillibacter_valericigenes	skyblue
Seq_2645_Ruminococcaceae	skyblue
Seq_2706_Gordonibacter_pamelaeae	skyblue
Seq_2727_Ruminococcaceae	skyblue
Seq_2897_Holdemania_filiformis	skyblue
Seq_3022_Actinomycetales	skyblue
Seq_3043_Clostridiales	skyblue
Seq_3044_Staphylococcus	skyblue
Seq_3542_Ralstonia_insidiosa	skyblue
Seq_3543_Alloiococcus_otitis	skyblue
Seq_14_Bacteroides_uniformis	skyblue3
Seq_217_Bacteroides_uniformis	skyblue3
Seq_225_Lachnospiraceae	skyblue3
Seq_342_Coriobacteriaceae	skyblue3
Seq_360_Barnesiella_intestinihominis	skyblue3
Seq_423_Roseburia_intestinalis	skyblue3
Seq_478_Olsenella	skyblue3
Seq_565_Alistipes_massiliensis	skyblue3
Seq_679_Acidaminococcaceae	skyblue3
Seq_802_Gemmiger_formicilis	skyblue3
Seq_815_Roseburia_intestinalis	skyblue3
Seq_892_Eubacterium_rectale	skyblue3
Seq_942_Faecalibacterium_prausnitzii	skyblue3
Seq_943_Lachnospiraceae	skyblue3
Seq_1558_Streptophyta	skyblue3
Seq_1885_Clostridium_XlVa	skyblue3
Seq_2033_Faecalibacterium_prausnitzii	skyblue3
Seq_2105_Lachnospiraceae	skyblue3
Seq_2120_Collinsella	skyblue3
Seq_2121_Acidaminococcaceae	skyblue3
Seq_2211_Butyricimonas_virosa	skyblue3
Seq_2251_Erysipelotrichaceae	skyblue3
Seq_2403_Erysipelotrichaceae	skyblue3
Seq_2404_Ruminococcaceae	skyblue3
Seq_2477_Butyricimonas_virosa	skyblue3
Seq_2681_Lachnospiraceae	skyblue3
Seq_2862_Ruminococcaceae	skyblue3
Seq_2863_Butyricimonas_virosa	skyblue3
Seq_3359_Clostridiales	skyblue3
Seq_3571_Clostridiales	skyblue3
Seq_3572_Clostridiales	skyblue3
Seq_15_Collinsella_aerofaciens	steelblue
Seq_24_Blautia_faecis	steelblue

Seq_42_Ruminococcus_torques	steelblue
Seq_162_Firmicutes	steelblue
Seq_168_Lachnospiraceae	steelblue
Seq_251_Blautia_luti	steelblue
Seq_391_Dialister_succinatiphilus	steelblue
Seq_484_Coprococcus_eutactus	steelblue
Seq_612_Blautia_faecis	steelblue
Seq_626_Megasphaera	steelblue
Seq_721_Ruminococcus2	steelblue
Seq_736_Megasphaera	steelblue
Seq_803_Clostridiales	steelblue
Seq_913_Lachnospiraceae	steelblue
Seq_926_Slackia_piriformis	steelblue
Seq_988_Clostridiales	steelblue
Seq_1265_Ruminococcus_torques	steelblue
Seq_1399_Ruminococcaceae	steelblue
Seq_1468_Ruminococcaceae	steelblue
Seq_1931_Clostridiales	steelblue
Seq_1935_Clostridium_XlVb	steelblue
Seq_2171_Alistipes	steelblue
Seq_2197_Clostridiales	steelblue
Seq_2252_Actinomyces_odontolyticus	steelblue
Seq_2283_Clostridium_XlVa	steelblue
Seq_2316_Clostridiales	steelblue
Seq_2682_Ruminococcaceae	steelblue
Seq_2776_Ruminococcaceae	steelblue
Seq_2866_Clostridiales	steelblue
Seq_2983_Gordonibacter_pamelaeae	steelblue
Seq_2984_Erysipelotrichaceae	steelblue
Seq_3143_Ruminococcaceae	steelblue
Seq_3369_Dialister	steelblue
Seq_3370_Haemophilus_parainfluenzae	steelblue
Seq_3372_Clostridiales	steelblue
Seq_3373_Clostridiales	steelblue
Seq_3374_Clostridiales	steelblue
Seq_3376_Lachnospiraceae	steelblue
Seq_20_Streptococcus	tan
Seq_36_Ruminococcus_gnavus	tan
Seq_37_Clostridium_bartlettii	tan
Seq_38_Escherichia/Shigella	tan
Seq_113_Veillonella_dispar	tan
Seq_114_Streptococcus	tan
Seq_118_Lachnospiraceae	tan
Seq_154_Clostridium_spiroforme	tan
Seq_163_Ruminococcus_gnavus	tan

Seq_198_Clostridium_ramosum	tan
Seq_201_Lachnospiraceae	tan
Seq_214_Lachnospiraceae	tan
Seq_243_Klebsiella	tan
Seq_258_Lactobacillus	tan
Seq_286_Escherichia/Shigella	tan
Seq_308_Lachnospiraceae	tan
Seq_341_Veillonella_atypica	tan
Seq_372_Veillonella_parvula	tan
Seq_382_Streptococcus_mutans	tan
Seq_393_Veillonella_dispar	tan
Seq_401_Ruminococcaceae	tan
Seq_410_Faecalibacterium_prausnitzii	tan
Seq_411_Lachnospiraceae	tan
Seq_446_Veillonella_parvula	tan
Seq_447_Enterococcus	tan
Seq_453_Lachnospiraceae	tan
Seq_512_Streptococcus	tan
Seq_549_Butyricicoccus_pullicaecorum	tan
Seq_581_Butyricicoccus_pullicaecorum	tan
Seq_628_Ruminococcaceae	tan
Seq_648_Lactobacillus	tan
Seq_659_Lactobacillus	tan
Seq_663_Erysipelotrichaceae	tan
Seq_669_Clostridium_paraputrificum	tan
Seq_701_Lactobacillus	tan
Seq_703_Clostridium_XI	tan
Seq_747_Veillonella	tan
Seq_776_Streptococcus	tan
Seq_820_Bifidobacterium	tan
Seq_844_Rothia_mucilaginosa	tan
Seq_893_Clostridium_glycolicum	tan
Seq_1048_Streptococcus_cristatus	tan
Seq_1082_Clostridium_bartlettii	tan
Seq_1121_Clostridium_XI	tan
Seq_1131_Veillonella	tan
Seq_1181_Blautia	tan
Seq_1191_Bifidobacteriaceae	tan
Seq_1342_Streptococcus	tan
Seq_1441_Lactobacillus	tan
Seq_1629_Clostridium_paraputrificum	tan
Seq_1643_Lactobacillus	tan
Seq_1708_Clostridium_spiroforme	tan
Seq_1886_Alistipes_massiliensis	tan
Seq_2168_Enterococcus	tan

Seq_2228_Streptococcus	tan
Seq_2291_Rothia_mucilaginosa	tan
Seq_2292_Fusobacterium_nucleatum	tan
Seq_2400_Rothia_dentocariosa	tan
Seq_2716_Haemophilus	tan
Seq_2804_Scardovia_wiggsiae	tan
Seq_2805_Clostridium_XlVb	tan
Seq_3032_Campylobacter_gracilis	tan
Seq_3193_Megasphaera_micronuciformis	tan
Seq_3194_Eikenella_corrodens	tan
Seq_3579_Veillonella	tan
Seq_2_Faecalibacterium_prausnitzii	turquoise
Seq_6_Faecalibacterium_prausnitzii	turquoise
Seq_12_Lachnospiraceae	turquoise
Seq_33_Ruminococcaceae	turquoise
Seq_34_Dorea_longicatena	turquoise
Seq_39_Ruminococcaceae	turquoise
Seq_48_Lachnospiraceae	turquoise
Seq_49_Coprococcus_comes	turquoise
Seq_53_Faecalibacterium_prausnitzii	turquoise
Seq_58_Prevotella_copri	turquoise
Seq_71_Ruminococcaceae	turquoise
Seq_72_Faecalibacterium_prausnitzii	turquoise
Seq_74_Ruminococcaceae	turquoise
Seq_87_Clostridium_leptum	turquoise
Seq_88_Blautia	turquoise
Seq_107_Ruminococcaceae	turquoise
Seq_110_Bacteroides_coprocola	turquoise
Seq_117_Lachnospiraceae	turquoise
Seq_124_Clostridium_XlVa	turquoise
Seq_126_Catenibacterium_mitsuokai	turquoise
Seq_131_Firmicutes	turquoise
Seq_136_Eubacterium_desmolans	turquoise
Seq_139_Firmicutes	turquoise
Seq_140_Ruminococcaceae	turquoise
Seq_143_Coprococcus_catus	turquoise
Seq_148_Prevotella_copri	turquoise
Seq_165_Firmicutes	turquoise
Seq_178_Lachnospiraceae	turquoise
Seq_183_Alistipes_shahii	turquoise
Seq_196_Ruminococcaceae	turquoise
Seq_199_Clostridiales	turquoise
Seq_200_Barnesiella_intestinihominis	turquoise
Seq_216_Ruminococcaceae	turquoise
Seq_234_Clostridium_XlVa	turquoise

Seq_237_Phascolarctobacterium_succinatutens	turquoise
Seq_248_Sutterella_stercoricanis	turquoise
Seq_261_Flavonifractor	turquoise
Seq_262_Coriobacteriaceae	turquoise
Seq_278_Methanobrevibacter_smithii	turquoise
Seq_280_Blautia	turquoise
Seq_283_Firmicutes	turquoise
Seq_287_Lachnospiraceae	turquoise
Seq_294_Clostridiales	turquoise
Seq_297_Ruminococcaceae	turquoise
Seq_311_Blautia	turquoise
Seq_316_Ruminococcaceae	turquoise
Seq_319_Clostridium_XlVa	turquoise
Seq_321_Ruminococcaceae	turquoise
Seq_334_Phascolarctobacterium_succinatutens	turquoise
Seq_339_Bacteroides_uniformis	turquoise
Seq_343_Ruminococcaceae	turquoise
Seq_354_Lachnospiraceae	turquoise
Seq_370_Firmicutes	turquoise
Seq_378_Lachnospiraceae	turquoise
Seq_399_Ruminococcaceae	turquoise
Seq_421_Ruminococcaceae	turquoise
Seq_427_Alistipes_indistinctus	turquoise
Seq_432_Ruminococcaceae	turquoise
Seq_433_Prevotella_copri	turquoise
Seq_438_Bacteria	turquoise
Seq_439_Lachnospiraceae	turquoise
Seq_444_Ruminococcaceae	turquoise
Seq_449_Firmicutes	turquoise
Seq_463_Ruminococcaceae	turquoise
Seq_475_Clostridiales	turquoise
Seq_514_Erysipelotrichaceae	turquoise
Seq_516_Ruminococcaceae	turquoise
Seq_526_Flavonifractor_plautii	turquoise
Seq_560_Lachnospiraceae	turquoise
Seq_573_Firmicutes	turquoise
Seq_582_Lachnospiraceae	turquoise
Seq_617_Ruminococcaceae	turquoise
Seq_629_Sutterella_stercoricanis	turquoise
Seq_650_Lachnospiraceae	turquoise
Seq_651_Ruminococcaceae	turquoise
Seq_654_Lachnospiraceae	turquoise
Seq_658_Ruminococcaceae	turquoise
Seq_694_Ruminococcaceae	turquoise
Seq_704_Lachnospiraceae	turquoise

Seq_706_Bacteria	turquoise
Seq_711_Clostridiales	turquoise
Seq_729_Phascolarctobacterium_succinatutens	turquoise
Seq_730_Firmicutes	turquoise
Seq_750_Bacteria	turquoise
Seq_773_Ruminococcaceae	turquoise
Seq_788_Clostridiales	turquoise
Seq_836_Clostridiales	turquoise
Seq_846_Coprococcus_catus	turquoise
Seq_851_Clostridiales	turquoise
Seq_867_Firmicutes	turquoise
Seq_874_Haemophilus	turquoise
Seq_885_Clostridiales	turquoise
Seq_890_Oscillibacter	turquoise
Seq_891_Howardella_ureilytica	turquoise
Seq_895_Bacteria	turquoise
Seq_897_Lachnospiraceae	turquoise
Seq_899_Prevotella_copri	turquoise
Seq_901_Eubacterium_xylanophilum	turquoise
Seq_905_Prevotella_copri	turquoise
Seq_963_Ruminococcaceae	turquoise
Seq_968_Ruminococcaceae	turquoise
Seq_969_Clostridiales	turquoise
Seq_975_Clostridiales	turquoise
Seq_980_Clostridium_lactatifermentans	turquoise
Seq_985_Lachnospiraceae	turquoise
Seq_992_Ruminococcaceae	turquoise
Seq_1005_Lachnospiraceae	turquoise
Seq_1013_Ruminococcaceae	turquoise
Seq_1016_Ruminococcaceae	turquoise
Seq_1061_Ruminococcaceae	turquoise
Seq_1066_Clostridiales	turquoise
Seq_1084_Oscillibacter	turquoise
Seq_1098_Dorea_longicatena	turquoise
Seq_1117_Oscillibacter	turquoise
Seq_1119_Ruminococcaceae	turquoise
Seq_1123_Ruminococcaceae	turquoise
Seq_1135_Clostridium_IV	turquoise
Seq_1145_Dorea_longicatena	turquoise
Seq_1146_Phascolarctobacterium_succinatutens	turquoise
Seq_1150_Oscillibacter	turquoise
Seq_1180_Clostridiales	turquoise
Seq_1190_Dorea_longicatena	turquoise
Seq_1219_Lachnospiraceae	turquoise
Seq_1222_Clostridiales	turquoise

Seq_1230_Ruminococcaceae	turquoise
Seq_1254_Lachnospiraceae	turquoise
Seq_1300_Alistipes_massiliensis	turquoise
Seq_1326_Faecalibacterium_prausnitzii	turquoise
Seq_1348_Ruminococcaceae	turquoise
Seq_1354_Clostridium_XlVa	turquoise
Seq_1371_Peptococcus_niger	turquoise
Seq_1393_Ruminococcus_callidus	turquoise
Seq_1394_Ruminococcaceae	turquoise
Seq_1425_Ruminococcaceae	turquoise
Seq_1461_Ruminococcaceae	turquoise
Seq_1524_Clostridiales	turquoise
Seq_1559_Ruminococcaceae	turquoise
Seq_1567_Actinomyces_odontolyticus	turquoise
Seq_1805_Firmicutes	turquoise
Seq_1811_Ruminococcaceae	turquoise
Seq_1813_Clostridiales	turquoise
Seq_1814_Bacteroides_xylanisolvens	turquoise
Seq_1882_Bacteria	turquoise
Seq_1932_Ruminococcaceae	turquoise
Seq_1943_Bacteria	turquoise
Seq_1997_Ruminococcaceae	turquoise
Seq_2042_Firmicutes	turquoise
Seq_2083_Clostridium_IV	turquoise
Seq_2174_Ruminococcaceae	turquoise
Seq_2220_Lachnospiraceae	turquoise
Seq_2248_Clostridiales	turquoise
Seq_2261_Puniceicoccaceae	turquoise
Seq_2273_Clostridiales	turquoise
Seq_2280_Firmicutes	turquoise
Seq_2325_Ruminococcaceae	turquoise
Seq_2418_Ruminococcaceae	turquoise
Seq_2431_Clostridia	turquoise
Seq_2463_Firmicutes	turquoise
Seq_2464_Ruminococcaceae	turquoise
Seq_2488_Hydrogenoanaerobacterium_saccharovorans	turquoise
Seq_2513_Lachnospiraceae	turquoise
Seq_2514_Ruminococcaceae	turquoise
Seq_2578_Bacteroidales	turquoise
Seq_2583_Alloprevotella_rava	turquoise
Seq_2601_Clostridiales	turquoise
Seq_2632_Oscillibacter_valericigenes	turquoise
Seq_2710_Bacteroides	turquoise
Seq_2711_Ruminococcaceae	turquoise
Seq_2712_Ruminococcaceae	turquoise

Seq_2713_Dorea_longicatena	turquoise
Seq_2799_Bacteria	turquoise
Seq_2800_Ruminococcaceae	turquoise
Seq_2900_Clostridiales	turquoise
Seq_2901_Clostridiales	turquoise
Seq_2902_Anaerotruncus_colihominis	turquoise
Seq_2903_Firmicutes	turquoise
Seq_3027_Firmicutes	turquoise
Seq_3028_Anaerorhabdus_furcosa	turquoise
Seq_3029_Olsenella	turquoise
Seq_3189_Syntrophomonadaceae	turquoise
Seq_3480_Deltaproteobacteria	turquoise
Seq_3481_Bacteria	turquoise
Seq_132_Streptococcus	violet
Seq_356_Klebsiella	violet
Seq_362_Catenibacterium_mitsuokai	violet
Seq_483_Alistipes	violet
Seq_590_Klebsiella	violet
Seq_615_Ruminococcus_bromii	violet
Seq_622_Alistipes_finegoldii	violet
Seq_637_Catenibacterium_mitsuokai	violet
Seq_642_Klebsiella	violet
Seq_768_Bacteroides_salyersiae	violet
Seq_850_Dialister_invisus	violet
Seq_1138_Lachnospiraceae	violet
Seq_1177_Blautia	violet
Seq_1186_Klebsiella	violet
Seq_1212_Faecalibacterium_prausnitzii	violet
Seq_1274_Lachnospiraceae	violet
Seq_1329_Streptococcus	violet
Seq_1396_Bacteroides	violet
Seq_1445_Lachnospiraceae	violet
Seq_1509_Eubacterium_desmolans	violet
Seq_1533_Alistipes_shahii	violet
Seq_1666_Butyricimonas_virosa	violet
Seq_2091_Clostridium_XI	violet
Seq_2201_Paraprevotella_clara	violet
Seq_2213_Lachnospiraceae	violet
Seq_2253_Faecalibacterium_prausnitzii	violet
Seq_2297_Pyramidobacter_piscolens	violet
Seq_2364_Clostridiales	violet
Seq_2560_Blautia	violet
Seq_2619_Clostridiales	violet
Seq_2777_Lachnospiraceae	violet
Seq_2911_Ruminococcaceae	violet

Seq_2986_Clostridium_butyricum	violet
Seq_3037_Parabacteroides_distasonis	violet
Seq_3038_Bacteria	violet
Seq_3147_Rothia_mucilaginosa	violet
Seq_3511_Bacteroidales	violet
Seq_3580_Streptococcus	violet
Seq_253_Bacteroides_massiliensis	white
Seq_267_Eubacterium_rectale	white
Seq_271_Alistipes_shahii	white
Seq_361_Dialister_invisus	white
Seq_371_Ruminococcus_bromii	white
Seq_404_Bacteroides_plebeius	white
Seq_468_Ruminococcus_albus	white
Seq_473_Coprococcus_eutactus	white
Seq_503_Bacteroides_plebeius	white
Seq_614_Ruminococcaceae	white
Seq_644_Lachnospiraceae	white
Seq_725_Ruminococcus_callidus	white
Seq_774_Clostridiales	white
Seq_865_Faecalibacterium_prausnitzii	white
Seq_927_Blautia	white
Seq_951_Bacteroides_stercoris	white
Seq_964_Faecalibacterium_prausnitzii	white
Seq_1206_Bacteroides_plebeius	white
Seq_1246_Clostridium_disporicum	white
Seq_1296_Lachnospiraceae	white
Seq_1359_Clostridium_ruminantium	white
Seq_1375_Olsenella	white
Seq_1395_Coriobacteriaceae	white
Seq_1481_Faecalibacterium_prausnitzii	white
Seq_1552_Faecalibacterium_prausnitzii	white
Seq_1632_Ruminococcus_torques	white
Seq_1668_Ruminococcaceae	white
Seq_1729_Parasutterella_excrementihominis	white
Seq_1781_Bacteroides_plebeius	white
Seq_1966_Dorea_longicatena	white
Seq_2007_Ruminococcaceae	white
Seq_2226_Ruminococcaceae	white
Seq_2282_Actinomyces_odontolyticus	white
Seq_2374_Ruminococcaceae	white
Seq_2809_Firmicutes	white
Seq_2912_Ruminococcaceae	white
Seq_3355_Erysipelotrichaceae	white
Seq_3516_Peptostreptococcaceae	white
Seq_3582_Erysipelotrichaceae	white

Seq_30_Clostridium_ruminantium	yellow
Seq_41_Clostridiales	yellow
Seq_56_Clostridium_disporicum	yellow
Seq_65_Ruminococcaceae	yellow
Seq_182_Clostridium_leptum	yellow
Seq_203_Ruminococcaceae	yellow
Seq_241_Turicibacter_sanguinis	yellow
Seq_245_Clostridium_leptum	yellow
Seq_250_Alistipes	yellow
Seq_348_Clostridiales	yellow
Seq_352_Barnesiella_intestinihominis	yellow
Seq_407_Clostridiales	yellow
Seq_414_Alistipes	yellow
Seq_420_Bacteroides_massiliensis	yellow
Seq_431_Bacteria	yellow
Seq_485_Akkermansia_muciniphila	yellow
Seq_489_Clostridium_hathewayi	yellow
Seq_506_Lachnospiraceae	yellow
Seq_539_Firmicutes	yellow
Seq_588_Alistipes_indistinctus	yellow
Seq_634_Clostridiales	yellow
Seq_660_Ruminococcaceae	yellow
Seq_829_Ruminococcaceae	yellow
Seq_837_Flavonifractor_plautii	yellow
Seq_873_Clostridiales	yellow
Seq_882_Firmicutes	yellow
Seq_898_Lachnospiraceae	yellow
Seq_909_Ruminococcaceae	yellow
Seq_935_Ruminococcaceae	yellow
Seq_961_Lachnospiraceae	yellow
Seq_967_Pseudoflavonifractor	yellow
Seq_1089_Clostridiales	yellow
Seq_1236_Lachnospiraceae	yellow
Seq_1280_Bacteria	yellow
Seq_1321_Clostridium_XlVa	yellow
Seq_1322_Clostridia	yellow
Seq_1385_Bacteroides_vulgatus	yellow
Seq_1400_Flavonifractor_plautii	yellow
Seq_1403_Clostridium_XI	yellow
Seq_1406_Ruminococcaceae	yellow
Seq_1408_Clostridiales	yellow
Seq_1409_Clostridia	yellow
Seq_1478_Ruminococcaceae	yellow
Seq_1493_Lachnospiraceae	yellow
Seq_1503_Clostridium_IV	yellow

Seq_1504_Clostridiales	yellow
Seq_1531_Clostridium_IV	yellow
Seq_1543_Anaerotruncus_colihominis	yellow
Seq_1644_Bacteria	yellow
Seq_1735_Alistipes_indistinctus	yellow
Seq_1744_Eubacterium_rectale	yellow
Seq_1759_Clostridiales	yellow
Seq_1779_Clostridiales	yellow
Seq_1789_Clostridiales	yellow
Seq_1806_Ruminococcaceae	yellow
Seq_1946_Erysipelotrichaceae	yellow
Seq_2037_Holdemania_filiformis	yellow
Seq_2054_Clostridiales	yellow
Seq_2070_Clostridiales	yellow
Seq_2099_Clostridium_IV	yellow
Seq_2100_Ruminococcaceae	yellow
Seq_2134_Lachnospiraceae	yellow
Seq_2169_Firmicutes	yellow
Seq_2183_Ruminococcaceae	yellow
Seq_2193_Clostridiales	yellow
Seq_2194_Bacteria	yellow
Seq_2217_Clostridiales	yellow
Seq_2223_Bacteroides_thetaiotaomicron	yellow
Seq_2263_Clostridiales	yellow
Seq_2293_Clostridiales	yellow
Seq_2294_Ruminococcaceae	yellow
Seq_2362_Clostridiales	yellow
Seq_2394_Ruminococcaceae	yellow
Seq_2415_Ruminococcaceae	yellow
Seq_2430_Ruminococcaceae	yellow
Seq_2589_Alistipes	yellow
Seq_2590_Firmicutes	yellow
Seq_2717_Anaerotruncus_colihominis	yellow
Seq_2907_Clostridiales	yellow
Seq_2908_Lachnospiraceae	yellow
Seq_3497_Bacteria	yellow
Seq_3498_Clostridiales	yellow
Seq_3499_Clostridium_IV	yellow
Seq_270_Streptococcus	yellowgreen
Seq_288_Escherichia/Shigella_coli	yellowgreen
Seq_640_Ruminococcus2	yellowgreen
Seq_714_Dorea_longicatena	yellowgreen
Seq_784_Ruminococcus_bromii	yellowgreen
Seq_793_Faecalibacterium_prausnitzii	yellowgreen
Seq_808_Faecalibacterium_prausnitzii	yellowgreen

Seq_824_Blautia	yellowgreen
Seq_845_Clostridium_XlVa	yellowgreen
Seq_876_Faecalibacterium_prausnitzii	yellowgreen
Seq_1031_Faecalibacterium_prausnitzii	yellowgreen
Seq_1087_Catenibacterium_mitsuokai	yellowgreen
Seq_1097_Erysipelotrichaceae	yellowgreen
Seq_1134_Blautia_luti	yellowgreen
Seq_1149_Rothia_mucilaginosa	yellowgreen
Seq_1223_Anaerostipes_hadrus	yellowgreen
Seq_1534_Faecalibacterium_prausnitzii	yellowgreen
Seq_1536_Roseburia_intestinalis	yellowgreen
Seq_1566_Clostridium_XlVa	yellowgreen
Seq_1651_Blautia	yellowgreen
Seq_1654_Phascolarctobacterium_succinatutens	yellowgreen
Seq_1852_Ruminococcus2	yellowgreen
Seq_1911_Collinsella	yellowgreen
Seq_1985_Ruminococcus_lactaris	yellowgreen
Seq_2012_Prevotella	yellowgreen
Seq_2038_Phascolarctobacterium_succinatutens	yellowgreen
Seq_2125_Phascolarctobacterium_succinatutens	yellowgreen
Seq_2360_Bacteroides_caccae	yellowgreen
Seq_2361_Allisonella_histaminiformans	yellowgreen
Seq_2380_Erysipelotrichaceae	yellowgreen
Seq_2446_Paraprevotella_clara	yellowgreen
Seq_2864_Leuconostokimchii	yellowgreen
Seq_3368_Clostridiales	yellowgreen
Seq_3395_Roseburia	yellowgreen

Appendix 2: Skin modules taxa

Taxa	Colours
Seq_2_Corynebacterium	black
Seq_454_Prevotella_timonensis	black
Seq_780_Staphylococcus_aureus	black
Seq_930_Prevotella_bivia	black
Seq_951_Corynebacterium	black
Seq_955_Staphylococcus	black
Seq_966_Anaerococcus_murdochii	black
Seq_982_Parvimonas_micra	black
Seq_997_Corynebacterium	black
Seq_1024_Corynebacterium	black
Seq_1031_Staphylococcus	black
Seq_1050_Corynebacterium_jeikeium	black
Seq_1059_Actinomycetales	black
Seq_1089_Corynebacterium	black
Seq_1092_Corynebacterium	black
Seq_1105_Corynebacterium_aurimucosum	black
Seq_1111_Corynebacterium	black
Seq_1112_Akkermansia_muciniphila	black
Seq_1140_Corynebacterium	black
Seq_1141_Corynebacterium	black
Seq_1165_Corynebacterium_aurimucosum	black
Seq_1168_Peptoniphilus_coxii	black
Seq_1172_Corynebacterium	black
Seq_1173_Actinomycetales	black
Seq_1177_Corynebacterium	black
Seq_1182_Corynebacterium	black
Seq_1207_Prevotella_bivia	black
Seq_1227_Corynebacterium	black
Seq_1234_Prevotella_denticola	black
Seq_1257_Corynebacterium	black
Seq_1272_Prevotella_timonensis	black
Seq_1286_Corynebacterium	black
Seq_1296_Brevibacterium	black
Seq_1304_Corynebacterium	black
Seq_1333_Corynebacterium_aurimucosum	black
Seq_1356_Corynebacterium_aurimucosum	black
Seq_1357_Gallicola	black
Seq_1362_Staphylococcus	black
Seq_1363_Anaerococcus_vaginalis	black
Seq_1390_Corynebacterium_aurimucosum	black
Seq_1406_Corynebacterium	black
Seq_1445_Corynebacterium	black

Seq_1471_Corynebacterium	black
Seq_1476_Prevotella_bivia	black
Seq_1516_Klebsiella	black
Seq_1517_Prevotella_bivia	black
Seq_1533_Corynebacterium_aurimucosum	black
Seq_1564_Peptoniphilus	black
Seq_1581_Corynebacterium	black
Seq_1590_Corynebacterium_jeikeium	black
Seq_1673_Corynebacteriaceae	black
Seq_1681_Corynebacterium	black
Seq_1830_Corynebacterium	black
Seq_1898_Corynebacterium	black
Seq_1965_Corynebacterium	black
Seq_2024_Corynebacterium_jeikeium	black
Seq_2258_Thermomonas_hydrothermalis	black
Seq_2272_Saccharofermentans_acetigenes	black
Seq_2362_Gluconobacter	black
Seq_2749_Prevotella_buccalis	black
Seq_8_Corynebacterium	blue
Seq_11_Propionibacterium_acnes	blue
Seq_74_Anaerococcus_octavius	blue
Seq_95_Fusobacterium_nucleatum	blue
Seq_113_Prevotella_bivia	blue
Seq_118_Streptococcus	blue
Seq_162_Corynebacterium	blue
Seq_178_Streptococcus	blue
Seq_180_Gardnerella_vaginalis	blue
Seq_282_Actinobaculum_massiliense	blue
Seq_371_Staphylococcus	blue
Seq_397_Gardnerella_vaginalis	blue
Seq_399_Enterococcus	blue
Seq_457_Paracoccus_yeei	blue
Seq_523_Ruminococcaceae	blue
Seq_684_Prevotella_melaninogenica	blue
Seq_738_Pseudoxanthomonas_spadix	blue
Seq_739_Gardnerella_vaginalis	blue
Seq_799_Corynebacterium_durum	blue
Seq_812_Staphylococcus_massiliensis	blue
Seq_839_Moryella_indoligenes	blue
Seq_946_Acinetobacter_johnsonii	blue
Seq_970_Streptophyta	blue
Seq_1022_Streptococcus_equi	blue
Seq_1082_Photobacterium	blue
Seq_1135_Alloiococcus_otitis	blue
Seq_1295_Actinomyces	blue

Seq_1376_Dialister_propionicifaciens	blue
Seq_1490_Howardella_ureilytica	blue
Seq_1521_Aeromonas	blue
Seq_1569_Acinetobacter_johnsonii	blue
Seq_1660_Prevotella	blue
Seq_1662_Sneathia	blue
Seq_1748_Pantoea	blue
Seq_1820_Pseudomonas	blue
Seq_1873_Pantoea_calida	blue
Seq_1889_Acidaminococcus_intestini	blue
Seq_1969_Acidovorax_temperans	blue
Seq_1995_Aerococcus_christensenii	blue
Seq_2041_Megasphaera_elsdenii	blue
Seq_2098_Pseudomonas_luteola	blue
Seq_2268_Corynebacterium	blue
Seq_2343_Campylobacter_concisus	blue
Seq_2350_Amaricoccus	blue
Seq_2414_Veillonella_parvula	blue
Seq_2579_Dermacoccus_nishinomiyaensis	blue
Seq_2584_Solobacterium_moorei	blue
Seq_2619_Nocardioides_aquaticus	blue
Seq_2721_Coriobacteriaceae	blue
Seq_2773_Prevotella_histicola	blue
Seq_2795_Neisseria_bacilliformis	blue
Seq_2810_Actinomyces_lingnae	blue
Seq_2849_Prevotella_amnii	blue
Seq_2966_Blastocatella	blue
Seq_2969_Enterobacteriaceae	blue
Seq_3022_Prevotella	blue
Seq_3155_Haemophilus_parainfluenzae	blue
Seq_3188_Streptococcus	blue
Seq_3211_Anaerococcus_prevotii	blue
Seq_3364_GpI	blue
Seq_3417_Psychrobacter	blue
Seq_3458_Cyanobacteria	blue
Seq_3496_Brevibacterium	blue
Seq_3497_Psychrobacter	blue
Seq_3580_GpI	blue
Seq_3581_Zoogloea	blue
Seq_3582_Brevundimonas	blue
Seq_3630_Brachybacterium	blue
Seq_3690_Shinella	blue
Seq_3753_Neisseria	blue
Seq_3781_Cyanobacteria	blue
Seq_3882_Caulobacter	blue

Seq_4041_Propionibacteriaceae	blue
Seq_4042_Rhodospirillaceae	blue
Seq_4123_Streptococcus	blue
Seq_4142_Stenotrophomonas_maltophilia	blue
Seq_4206_Spirosoma	blue
Seq_4207_Proteobacteria	blue
Seq_4208_Marmoricola_bigeumensis	blue
Seq_4209_Pseudomonas	blue
Seq_4342_Leptotrichia	blue
Seq_4409_Pantoea	blue
Seq_4410_Cardiobacterium_hominis	blue
Seq_4411_Porphyrobacter	blue
Seq_4412_Hallella	blue
Seq_4413_Diaphorobacter	blue
Seq_4414_Rhodococcus	blue
Seq_4415_Flavobacterium	blue
Seq_4416_Prevotellaceae	blue
Seq_4640_Porphyromonas_gulae	blue
Seq_4641_Selenomonas_noxia	blue
Seq_4642_Enterobacteriaceae	blue
Seq_4643_Treponema_amylovorum	blue
Seq_4886_Rhodocyclaceae	blue
Seq_4887_Clostridiales	blue
Seq_4888_Rhizobiales	blue
Seq_4889_Lachnospiraceae	blue
Seq_5093_Lachnospiraceae	blue
Seq_5094_Mobiluncus_curtisii	blue
Seq_5215_Cyanobacteria	blue
Seq_5216_Tannerella_forsythia	blue
Seq_5218_Solirubrobacter	blue
Seq_5498_Veillonella_dispar	blue
Seq_5499_Jeotgalicoccus	blue
Seq_5575_Atopobium_vaginae	blue
Seq_5720_Hymenobacter	blue
Seq_6198_Sphingobacteriaceae	blue
Seq_6199_Actinomycetales	blue
Seq_6201_Staphylococcus	blue
Seq_6330_Roseburia_faecis	blue
Seq_6600_Sphingobacterium	blue
Seq_6601_Cyanobacteria	blue
Seq_64_Corynebacterium_appendicis	brown
Seq_94_Corynebacterium	brown
Seq_102_Corynebacterium_riegelii	brown
Seq_108_Faecalibacterium_prausnitzii	brown
Seq_142_Corynebacterium_genitalium	brown

Seq_160_Faecalibacterium_prausnitzii	brown
Seq_170_Weeksella_virosa	brown
Seq_184_Oligella_urethralis	brown
Seq_201_Corynebacterium_sundsvallense	brown
Seq_229_Peptoniphilus_koenoeneniae	brown
Seq_311_Corynebacterium_tuscaniense	brown
Seq_318_Propionibacterium_avidum	brown
Seq_327_Granulicatella_elegans	brown
Seq_330_Facklamia_ignava	brown
Seq_409_Bifidobacterium_longum	brown
Seq_416_Abiotrophia_defectiva	brown
Seq_420_Weeksella_virosa	brown
Seq_434_Alishewanella	brown
Seq_435_Pseudomonas	brown
Seq_447_Weeksella_virosa	brown
Seq_468_Staphylococcus_simulans	brown
Seq_472_Staphylococcus_simulans	brown
Seq_484_Clostridiales_Incertae_Sedis_XI	brown
Seq_491_Staphylococcus_simulans	brown
Seq_539_Micrococcaceae	brown
Seq_667_Micrococcaceae	brown
Seq_668_Anaerostipes_hadrus	brown
Seq_737_Ruminococcus_bromii	brown
Seq_804_Roseburia_faecis	brown
Seq_805_Corynebacterium_riegelii	brown
Seq_825_Staphylococcus_simulans	brown
Seq_832_Corynebacterium_genitalium	brown
Seq_880_Micrococcaceae	brown
Seq_885_Facklamia_ignava	brown
Seq_890_Clostridiales	brown
Seq_894_Anaerostipes_hadrus	brown
Seq_957_Anaerococcus_octavius	brown
Seq_993_Eubacterium_rectale	brown
Seq_1012_Roseburia_faecis	brown
Seq_1033_Prevotellaceae	brown
Seq_1039_Lachnospiraceae	brown
Seq_1060_Staphylococcus	brown
Seq_1076_Succiniclasticum_ruminis	brown
Seq_1139_Corynebacterium_riegelii	brown
Seq_1142_Clostridiales_Incertae_Sedis_XI	brown
Seq_1329_Lachnospiraceae	brown
Seq_1359_Porphyromonas_bennonis	brown
Seq_1430_Megasphaera	brown
Seq_1478_Ruminococcaceae	brown
Seq_1482_Oscillibacter	brown

Seq_1603_Acinetobacter	brown
Seq_1614_Clostridium_XlVb	brown
Seq_1654_Gardnerella_vaginalis	brown
Seq_1657_Anaerococcus	brown
Seq_1757_Ruminococcaceae	brown
Seq_1764_Ruminococcus_albus	brown
Seq_1798_Ruminococcus_torques	brown
Seq_1864_Parasutterella_excrementihominis	brown
Seq_1980_Brevibacterium	brown
Seq_2011_Ruminococcaceae	brown
Seq_2012_Prevotella_buccalis	brown
Seq_2130_Fastidiosipila_sanguinis	brown
Seq_2147_Microbacteriaceae	brown
Seq_2302_Clostridium_leptum	brown
Seq_2569_Bacteroides_ovatus	brown
Seq_2886_Lachnospiraceae	brown
Seq_2922_Facklamia_hominis	brown
Seq_3159_Actinomycetales	brown
Seq_3261_Barnesiella_intestinihominis	brown
Seq_3264_Blautia_glucerasea	brown
Seq_3396_Burkholderiales	brown
Seq_3427_Clostridium_XlVa	brown
Seq_3669_Varibaculum_cambriense	brown
Seq_3682_Streptophyta	brown
Seq_3874_Clostridium_scindens	brown
Seq_3875_Bacteroides	brown
Seq_3876_Oscillibacter	brown
Seq_4006_Flavonifractor_plautii	brown
Seq_4008_Nesterenkonia	brown
Seq_4009_Clostridium_hathewayi	brown
Seq_4154_Blastococcus_aggregatus	brown
Seq_4155_Lachnospiraceae	brown
Seq_4352_Ruminococcaceae	brown
Seq_4353_Eubacterium_desmolans	brown
Seq_4564_Alistipes_shahii	brown
Seq_4797_Rhodothermaceae	brown
Seq_4799_Erysipelotrichaceae	brown
Seq_5110_Eubacterium_rectale	brown
Seq_5516_Ruminococcaceae	brown
Seq_5518_Prevotella_buccalis	brown
Seq_5519_Bacteroidetes	brown
Seq_6232_Stenotrophomonas	brown
Seq_6233_Veillonellaceae	brown
Seq_6238_Faecalibacterium_prausnitzii	brown
Seq_42_Anaerococcus_vaginalis	cyan

Seq_109_Prevotella_buccalis	cyan
Seq_111_Prevotella_buccalis	cyan
Seq_122_Neisseriaceae	cyan
Seq_123_Peptoniphilus_coxii	cyan
Seq_128_Prevotella_buccalis	cyan
Seq_130_Porphyromonadaceae	cyan
Seq_199_Actinobaculum_schaalii	cyan
Seq_213_Dialister_invisus	cyan
Seq_222_Rhodobacteraceae	cyan
Seq_268_Peptoniphilus_coxii	cyan
Seq_290_Peptoniphilus_coxii	cyan
Seq_342_Acinetobacter_baumannii	cyan
Seq_376_Finegoldia_magna	cyan
Seq_388_Peptoniphilus	cyan
Seq_391_Trueperella_bernardiae	cyan
Seq_417_Peptoniphilus_coxii	cyan
Seq_542_Dialister_propionicifaciens	cyan
Seq_543_Streptophyta	cyan
Seq_569_Prevotella_corporis	cyan
Seq_620_Olsenella	cyan
Seq_699_Actinomyces_neuii	cyan
Seq_705_Actinomyces_neuii	cyan
Seq_743_Porphyromonadaceae	cyan
Seq_747_Prevotella_buccalis	cyan
Seq_748_Prevotella_buccalis	cyan
Seq_755_Empedobacter_brevis	cyan
Seq_757_Eremococcus_coleocola	cyan
Seq_769_Prevotella_buccalis	cyan
Seq_797_Anaerococcus_octavius	cyan
Seq_811_Clostridium_XVIII	cyan
Seq_853_Pseudomonas	cyan
Seq_1606_Fusobacterium_nucleatum	cyan
Seq_1771_Peptoniphilus_lacrimalis	cyan
Seq_2026_Sutterella_wadsworthensis	cyan
Seq_2230_Arthrobacter	cyan
Seq_2699_Acetobacteraceae	cyan
Seq_2706_Dietzia	cyan
Seq_3006_Cloacibacterium_normanense	cyan
Seq_3281_Varibaculum_cambriense	cyan
Seq_4192_Olsenella	cyan
Seq_4193_Capnocytophaga_gingivalis	cyan
Seq_4194_Murdochiella_asaccharolytica	cyan
Seq_4871_Sunxiuqinia	cyan
Seq_5197_Bacteria	cyan
Seq_5680_Hymenobacter	cyan

Seq_6539_Anaerococcus_vaginalis	cyan
Seq_6540_Anaerococcus_vaginalis	cyan
Seq_6546_Prevotella	cyan
Seq_6548_Clostridiales	cyan
Seq_6549_Anaerococcus_octavius	cyan
Seq_6550_Succinivibridextrinosolvens	cyan
Seq_87_Porphyromonas_bennonis	darkgreen
Seq_328_Brevundimonas	darkgreen
Seq_405_Corynebacterium	darkgreen
Seq_451_Staphylococcus	darkgreen
Seq_482_Porphyromonas_bennonis	darkgreen
Seq_493_Dialister_propionicifaciens	darkgreen
Seq_844_Corynebacterium_imitans	darkgreen
Seq_1030_Faecalibacterium_prausnitzii	darkgreen
Seq_1047_Porphyromonas_bennonis	darkgreen
Seq_1175_Clostridium_XI	darkgreen
Seq_1204_Streptophyta	darkgreen
Seq_1223_Sphingomonadaceae	darkgreen
Seq_1281_Porphyromonas_bennonis	darkgreen
Seq_1338_Atopobium_vaginae	darkgreen
Seq_1459_Bacteria	darkgreen
Seq_1474_Anaerococcus_prevotii	darkgreen
Seq_1588_Actinomycetales	darkgreen
Seq_1691_Prevotella_timonensis	darkgreen
Seq_1753_Clostridia	darkgreen
Seq_1823_Peptoniphilus_coxii	darkgreen
Seq_1841_GpI	darkgreen
Seq_1922_Sphingomonas	darkgreen
Seq_1962_Sphingomonadaceae	darkgreen
Seq_2001_Corynebacterium_imitans	darkgreen
Seq_2037_Bacillus_thermoamylovorans	darkgreen
Seq_2064_Finegoldia_magna	darkgreen
Seq_2127_Haemophilus	darkgreen
Seq_2128_Acidimicrobiales	darkgreen
Seq_2219_Actinomycetales	darkgreen
Seq_2240_Staphylococcus	darkgreen
Seq_2290_Bacteria	darkgreen
Seq_2339_Porphyromonas_bennonis	darkgreen
Seq_2358_Bacteroides	darkgreen
Seq_2624_Eubacterium_desmolans	darkgreen
Seq_2717_Rhizobium_giardinii	darkgreen
Seq_2816_Massilia_timonae	darkgreen
Seq_3105_Varibaculum_cambriense	darkgreen
Seq_3206_Bacteria	darkgreen
Seq_3872_Moraxella	darkgreen

Seq_4002_Acidobacteria_Gp4	darkgreen
Seq_4559_Propionibacteriaceae	darkgreen
Seq_126_Eubacterium_rectale	darkgrey
Seq_157_Anaerococcus_senegalensis	darkgrey
Seq_205_Blautia	darkgrey
Seq_227_Lachnospiraceae	darkgrey
Seq_249_Anaerococcus_hydrogenalis	darkgrey
Seq_299_Streptococcus	darkgrey
Seq_306_Peptoniphilus_coxii	darkgrey
Seq_334_Ruminococcaceae	darkgrey
Seq_383_Peptoniphilus_coxii	darkgrey
Seq_410_Porphyromonas_bennonis	darkgrey
Seq_477_Brevibacterium_paucivorans	darkgrey
Seq_497_Anaerococcus	darkgrey
Seq_511_Turicibacter_sanguinis	darkgrey
Seq_535_Anaerococcus_prevotii	darkgrey
Seq_692_Anaerococcus	darkgrey
Seq_763_Alistipes_putredinis	darkgrey
Seq_1038_Lachnospiraceae	darkgrey
Seq_1065_Peptococcus_niger	darkgrey
Seq_1602_Firmicutes	darkgrey
Seq_1729_Bacteroides	darkgrey
Seq_1857_Ruminococcaceae	darkgrey
Seq_2144_Blautia	darkgrey
Seq_2182_Roseburia_inulinivorans	darkgrey
Seq_2838_Parabacteroides	darkgrey
Seq_2924_Erysipelotrichaceae	darkgrey
Seq_3039_Bacteroides_ovatus	darkgrey
Seq_3088_Clostridium_XlVa	darkgrey
Seq_3144_Lachnospiraceae	darkgrey
Seq_3157_Faecalibacterium_prausnitzii	darkgrey
Seq_3207_Eggerthella_lenta	darkgrey
Seq_3326_Lachnospiraceae	darkgrey
Seq_3373_Asaccharobacter	darkgrey
Seq_3472_Parasutterella_excrementihominis	darkgrey
Seq_3557_Acinetobacter	darkgrey
Seq_3667_Blautia_faecis	darkgrey
Seq_4497_Ruminococcaceae	darkgrey
Seq_4560_Fastidiosipila_sanguinis	darkgrey
Seq_4791_Clostridiales	darkgrey
Seq_6214_Lactobacillales	darkgrey
Seq_6329_Bacteroides_vulgatus	darkgrey
Seq_179_Neisseria	darkmagenta
Seq_190_Corynebacterium_pseudogenitalium	darkmagenta
Seq_191_Clostridium_ruminantium	darkmagenta

Seq_344_Staphylococcus_auricularis	darkmagenta
Seq_387_Gallicola	darkmagenta
Seq_438_Porphyromonas_uenonis	darkmagenta
Seq_440_Rothia_mucilaginosa	darkmagenta
Seq_460_Anaerococcus	darkmagenta
Seq_544_Staphylococcus	darkmagenta
Seq_573_Clostridiales	darkmagenta
Seq_626_Staphylococcus	darkmagenta
Seq_772_Staphylococcus	darkmagenta
Seq_790_Finegoldia_magna	darkmagenta
Seq_944_Staphylococcus	darkmagenta
Seq_1099_Streptococcus	darkmagenta
Seq_1205_Staphylococcus	darkmagenta
Seq_1511_Abiotrophia_defectiva	darkmagenta
Seq_1553_Helcococcus_ovis	darkmagenta
Seq_1557_Atopobium_parvulum	darkmagenta
Seq_1595_Corynebacterium	darkmagenta
Seq_1669_Bacteroides_vulgatus	darkmagenta
Seq_1733_Finegoldia_magna	darkmagenta
Seq_1777_Staphylococcus_auricularis	darkmagenta
Seq_3474_Staphylococcus	darkmagenta
Seq_3605_Gaiella_occulta	darkmagenta
Seq_4010_Corynebacterium_durum	darkmagenta
Seq_4565_Enterobacteriaceae	darkmagenta
Seq_4800_Prevotella_disiens	darkmagenta
Seq_4801_Nocardioides	darkmagenta
Seq_5112_Megasphaera	darkmagenta
Seq_5113_Burkholderiales	darkmagenta
Seq_5114_Sphingobium	darkmagenta
Seq_5524_Lactobacillus_reuteri	darkmagenta
Seq_6245_Neisseria	darkmagenta
Seq_45_Acinetobacter	darkolivegreen
Seq_48_Peptoniphilus_harei	darkolivegreen
Seq_247_Anaerococcus_octavius	darkolivegreen
Seq_363_Acinetobacter_ursingii	darkolivegreen
Seq_407_Rothia_mucilaginosa	darkolivegreen
Seq_433_Acinetobacter	darkolivegreen
Seq_464_Staphylococcus	darkolivegreen
Seq_513_Staphylococcus	darkolivegreen
Seq_725_Pseudomonas	darkolivegreen
Seq_1034_Anaerococcus_octavius	darkolivegreen
Seq_1203_Haemophilus	darkolivegreen
Seq_1302_Massilia_timonae	darkolivegreen
Seq_1784_Corynebacterium	darkolivegreen
Seq_1855_Brevibacterium	darkolivegreen

Seq_1933_Porphyromonas	darkolivegreen
Seq_2049_Streptophyta	darkolivegreen
Seq_2227_Prevotella_nanceiensis	darkolivegreen
Seq_2233_Truepera_radiovictrix	darkolivegreen
Seq_2869_Bosea	darkolivegreen
Seq_3046_Corynebacterium	darkolivegreen
Seq_3106_Nesterenkonia_lacusekhoensis	darkolivegreen
Seq_3149_Lactococcus	darkolivegreen
Seq_3162_Amaricoccus	darkolivegreen
Seq_3566_Brachybacterium	darkolivegreen
Seq_4362_Ancylobacter_dichloromethanicus	darkolivegreen
Seq_4363_Corynebacterium_matruchotii	darkolivegreen
Seq_4364_Aureimonas	darkolivegreen
Seq_4578_Burkholderiales	darkolivegreen
Seq_5138_Sphingobacterium	darkolivegreen
Seq_5573_Blastocatella	darkolivegreen
Seq_6311_Murdochiella_asaccharolytica	darkolivegreen
Seq_6312_Spirosoma_rigui	darkolivegreen
Seq_6314_Comamonadaceae	darkolivegreen
Seq_6325_Finegoldia_magna	darkolivegreen
Seq_6328_Bacillariophyta	darkolivegreen
Seq_258_Corynebacterium	darkorange
Seq_266_Peptoniphilus_coxii	darkorange
Seq_293_Akkermansia_muciniphila	darkorange
Seq_822_Campylobacter_ureolyticus	darkorange
Seq_1019_Corynebacterium	darkorange
Seq_1055_Finegoldia_magna	darkorange
Seq_1113_Corynebacterium	darkorange
Seq_1116_Finegoldia_magna	darkorange
Seq_1129_Corynebacterium_aurimucosum	darkorange
Seq_1209_Anaerococcus	darkorange
Seq_1224_Anaerococcus_murdochii	darkorange
Seq_1291_Campylobacter_ureolyticus	darkorange
Seq_1299_Staphylococcus	darkorange
Seq_1305_Corynebacterium	darkorange
Seq_1306_Clostridiales_Incertae_Sedis_XI	darkorange
Seq_1342_Corynebacterium_jeikeium	darkorange
Seq_1398_Anaerococcus_murdochii	darkorange
Seq_1403_Akkermansia_muciniphila	darkorange
Seq_1446_Corynebacterium	darkorange
Seq_1487_Corynebacterium	darkorange
Seq_1488_Corynebacterium	darkorange
Seq_1496_Corynebacterium	darkorange
Seq_1547_Corynebacterium	darkorange
Seq_1640_Anaerococcus	darkorange

Seq_1650_Anaerococcus_murdochii	darkorange
Seq_1721_Corynebacterium	darkorange
Seq_1797_Prevotella_disiens	darkorange
Seq_1818_Corynebacterium	darkorange
Seq_1911_Anaerococcus	darkorange
Seq_1967_Anaerococcus_murdochii	darkorange
Seq_1994_Corynebacterium_jeikeium	darkorange
Seq_2025_Prevotella_bivia	darkorange
Seq_2039_Prevotella_disiens	darkorange
Seq_2067_Corynebacterium	darkorange
Seq_2115_Finegoldia_magna	darkorange
Seq_2176_Finegoldia_magna	darkorange
Seq_2575_Corynebacterium	darkorange
Seq_4402_Lachnospiraceae	darkorange
Seq_151_Anaerococcus_octavius	darkred
Seq_216_Negativicoccus_succinicivorans	darkred
Seq_252_Clostridium_disporicum	darkred
Seq_259_Lactococcus	darkred
Seq_385_Peptoniphilus	darkred
Seq_650_Staphylococcus	darkred
Seq_689_Corynebacterium	darkred
Seq_888_Streptococcus_mutans	darkred
Seq_915_Lachnospiraceae	darkred
Seq_1200_Anaerococcus_octavius	darkred
Seq_1472_Alphaproteobacteria	darkred
Seq_1563_Staphylococcus	darkred
Seq_1675_Leuconostoc	darkred
Seq_1840_Eubacterium_brachy	darkred
Seq_1993_Anaerococcus	darkred
Seq_2006_Staphylococcus	darkred
Seq_2143_Clostridium_XlVa	darkred
Seq_2304_Cyanobacteria	darkred
Seq_2489_Lachnospiraceae	darkred
Seq_2600_Microbacteriaceae	darkred
Seq_2920_Anaerococcus_vaginalis	darkred
Seq_3111_Leptotrichia_shahii	darkred
Seq_3478_Atopobium_rimae	darkred
Seq_3483_Corynebacterium_aurimucosum	darkred
Seq_3574_Bacteroides_coprocola	darkred
Seq_3770_Arthrobacter	darkred
Seq_3892_Selenomonas_noxia	darkred
Seq_3893_Pseudonocardiaceae	darkred
Seq_4173_Bacteroides_plebeius	darkred
Seq_4315_Blastocatella	darkred
Seq_4838_Prevotella_salivae	darkred

Seq_4839_Lachnospiraceae	darkred
Seq_5163_Dorea_longicatena	darkred
Seq_5165_Flavobacterium	darkred
Seq_5166_Candidatus_Saccharibacteria	darkred
Seq_5167_Flavobacteriaceae	darkred
Seq_5168_Zoogloea	darkred
Seq_5628_Chryseobacterium	darkred
Seq_5629_Xanthomonadaceae	darkred
Seq_5630_Eikenella_corrodens	darkred
Seq_6463_Actinobacteria	darkred
Seq_6464_Bacteroidetes	darkred
Seq_71_Prevotella_timonensis	darkturquoise
Seq_131_Prevotella_timonensis	darkturquoise
Seq_150_Dialister_micraerophilus	darkturquoise
Seq_161_Prevotella_disiens	darkturquoise
Seq_208_Staphylococcus	darkturquoise
Seq_220_Dialister_propionicifaciens	darkturquoise
Seq_226_Peptostreptococcus_anaerobius	darkturquoise
Seq_574_Roseomonas	darkturquoise
Seq_695_Leptotrichia_hongkongensis	darkturquoise
Seq_911_Dialister_micraerophilus	darkturquoise
Seq_1119_Dialister_propionicifaciens	darkturquoise
Seq_1147_Pantoea	darkturquoise
Seq_1167_Capnocytophaga_leadbetteri	darkturquoise
Seq_1534_Aureimonas_altamirensis	darkturquoise
Seq_1634_Varibaculum_cambriense	darkturquoise
Seq_1636_Prevotella_buccalis	darkturquoise
Seq_1904_Leptotrichia_shahii	darkturquoise
Seq_1939_Prevotella_bergensis	darkturquoise
Seq_2113_Actinomyces	darkturquoise
Seq_2221_Prevotella_buccalis	darkturquoise
Seq_2224_Corynebacterium	darkturquoise
Seq_2323_Rhodobacteraceae	darkturquoise
Seq_2447_Clostridium_leptum	darkturquoise
Seq_2558_Anaerococcus	darkturquoise
Seq_2570_Gemella_morbillorum	darkturquoise
Seq_2660_Janthinobacterium_lividum	darkturquoise
Seq_2742_Varibaculum_cambriense	darkturquoise
Seq_2846_Stenotrophomonas_rhizophila	darkturquoise
Seq_2921_Prevotella_melaninogenica	darkturquoise
Seq_3271_Rhizobium	darkturquoise
Seq_3484_Rubellimicrobium_aerolatum	darkturquoise
Seq_3485_Pasteurellaceae	darkturquoise
Seq_3772_Streptococcus	darkturquoise
Seq_3930_Vibrio	darkturquoise

Seq_4681_Porphyromonas_endodontalis	darkturquoise
Seq_4843_Pedobacter	darkturquoise
Seq_4844_Flavobacterium_johnsoniae	darkturquoise
Seq_5169_Novosphingobium	darkturquoise
Seq_5637_Acetobacteraceae	darkturquoise
Seq_6479_Haemophilus_parainfluenzae	darkturquoise
Seq_6482_Spartobacteria	darkturquoise
Seq_81_Streptococcus_agalactiae	green
Seq_125_Clostridiales	green
Seq_271_Fusobacterium_nucleatum	green
Seq_310_Dialister_invisus	green
Seq_364_Porphyromonas_bennonis	green
Seq_381_Porphyromonas_uenonis	green
Seq_390_Corynebacterium	green
Seq_485_Clostridiales	green
Seq_490_Gallicola	green
Seq_512_Lactobacillus	green
Seq_575_Corynebacterium_riegelii	green
Seq_631_Corynebacterium	green
Seq_736_Clostridiales	green
Seq_745_Alloprevotella_tannerae	green
Seq_774_Streptophyta	green
Seq_794_Bacteroides_dorei	green
Seq_798_Eubacterium_rectale	green
Seq_840_Ruminococcaceae	green
Seq_870_Parabacteroides_merdae	green
Seq_891_Peptostreptococcus_stomatis	green
Seq_905_Staphylococcus	green
Seq_947_Micrococcus_lylae	green
Seq_978_Prevotella_oris	green
Seq_1096_Atopobium_rimae	green
Seq_1270_Lachnospiraceae	green
Seq_1332_Alloprevotella_tannerae	green
Seq_1353_Olsenella_uli	green
Seq_1426_Corynebacterium_striatum	green
Seq_1442_Prevotella_oris	green
Seq_1536_Prevotella_oris	green
Seq_1853_Campylobacter_gracilis	green
Seq_1923_Anaerococcus_obesiensis	green
Seq_1924_Staphylococcus	green
Seq_2003_Dermabacter_hominis	green
Seq_2014_Anaerococcus_octavius	green
Seq_2065_Veillonella	green
Seq_2108_Lachnoanaerobaculum	green
Seq_2133_Prevotella_denticola	green

Seq_2242_Treponema_medium	green
Seq_2266_Eubacterium_desmolans	green
Seq_2285_Slackia_exigua	green
Seq_2293_Nosocomiicoccus_ampullae	green
Seq_2454_Porphyromonas_somerae	green
Seq_2547_Porphyromonas	green
Seq_2581_Peptoniphilus	green
Seq_2622_Selenomonas_infelix	green
Seq_2806_Helcobacillus_massiliensis	green
Seq_2963_Ruminococcus_callidus	green
Seq_3002_Prevotella_stercorea	green
Seq_3051_Selenomonas_infelix	green
Seq_3078_Eubacterium_sulci	green
Seq_3898_Treponema_socranskii	green
Seq_4034_Prevotellaceae	green
Seq_4180_Clostridiales	green
Seq_4181_Facklamia	green
Seq_4389_Ruminococcaceae	green
Seq_4455_Slackia_isoflavoniconvertens	green
Seq_4849_Clostridium_glycolicum	green
Seq_5176_Clostridiales	green
Seq_5177_Hymenobacter	green
Seq_5571_Clostridium_sensu_stricto	green
Seq_5648_Leptotrichia	green
Seq_5650_Acidovorax	green
Seq_5654_Prevotella_denticola	green
Seq_6309_Porphyromonas_somerae	green
Seq_6490_Gp16	green
Seq_6494_Butyricimonas_virosa	green
Seq_40_Micrococcus	greenyellow
Seq_43_Micrococcus	greenyellow
Seq_114_Corynebacterium_imitans	greenyellow
Seq_136_Corynebacterium_coyleae	greenyellow
Seq_200_Janibacter	greenyellow
Seq_236_Acinetobacter	greenyellow
Seq_237_Micrococcus	greenyellow
Seq_331_Arcanobacterium	greenyellow
Seq_370_Brachybacterium	greenyellow
Seq_372_Bacteria	greenyellow
Seq_422_Blautia_faecis	greenyellow
Seq_458_Streptophyta	greenyellow
Seq_549_Corynebacterium	greenyellow
Seq_656_Acinetobacter	greenyellow
Seq_746_Corynebacterium	greenyellow
Seq_754_Aerococcaceae	greenyellow

Seq_833_Pseudomonas	greenyellow
Seq_958_Diplorickettsia	greenyellow
Seq_986_Corynebacterium_imitans	greenyellow
Seq_1241_Murdochiella_asaccharolytica	greenyellow
Seq_1276_Corynebacterium	greenyellow
Seq_1367_Anaerococcus	greenyellow
Seq_1369_Acinetobacter	greenyellow
Seq_1544_Acinetobacter	greenyellow
Seq_1601_Helcococcus	greenyellow
Seq_1719_Actinomyces	greenyellow
Seq_1792_Anoxybacillus	greenyellow
Seq_1813_Acinetobacter	greenyellow
Seq_1932_Xanthobacter_autotrophicus	greenyellow
Seq_2043_Chryseobacterium	greenyellow
Seq_2418_Leuconostocarnosum	greenyellow
Seq_3067_Methylobacterium_adhaesivum	greenyellow
Seq_3115_Pseudomonas_stutzeri	greenyellow
Seq_3164_Corynebacterium	greenyellow
Seq_3407_Anaerococcus_prevotii	greenyellow
Seq_3481_Pseudomonas	greenyellow
Seq_3891_Janthinobacterium	greenyellow
Seq_4029_Sphingomonas	greenyellow
Seq_4168_Escherichia/Shigella	greenyellow
Seq_4169_Leucobacter	greenyellow
Seq_4379_Streptococcus	greenyellow
Seq_4831_Pseudomonas	greenyellow
Seq_4832_Flavobacterium_oncorhynchi	greenyellow
Seq_4833_Porphyromonas	greenyellow
Seq_4834_Pseudomonas	greenyellow
Seq_4835_Stenotrophomonas	greenyellow
Seq_5612_Cellulomonas	greenyellow
Seq_5616_Aeromonas	greenyellow
Seq_5617_Negativicoccus_succinicivorans	greenyellow
Seq_5618_Prevotella	greenyellow
Seq_6445_Clostridiaceae_1	greenyellow
Seq_6446_Prevotella	greenyellow
Seq_6447_Ruminococcaceae	greenyellow
Seq_6448_Novispirillum_itersonii	greenyellow
Seq_6450_Butyricimonas_virosa	greenyellow
Seq_1_Staphylococcus	grey
Seq_3_Staphylococcus	grey
Seq_4_Finegoldia_magna	grey
Seq_5_Staphylococcus	grey
Seq_6_Staphylococcus	grey
Seq_7_Staphylococcus	grey

Seq_9_Staphylococcus_epidermidis	grey
Seq_10_Anaerococcus_octavius	grey
Seq_12_Peptoniphilus	grey
Seq_13_Corynebacterium	grey
Seq_14_Corynebacterium	grey
Seq_15_Corynebacterium	grey
Seq_16_Proteus	grey
Seq_18_Peptoniphilus_asaccharolyticus	grey
Seq_19_Corynebacterium	grey
Seq_20_Anaerococcus_octavius	grey
Seq_21_Campylobacter_ureolyticus	grey
Seq_22_Dolosigranulum_pigrum	grey
Seq_24_Peptoniphilus_lacrimalis	grey
Seq_25_Corynebacterium	grey
Seq_26_Actinomycetales	grey
Seq_27_Moraxella_nonliquefaciens	grey
Seq_28_Corynebacterium	grey
Seq_31_Corynebacterium	grey
Seq_33_Staphylococcus	grey
Seq_34_Clostridiales	grey
Seq_36_Staphylococcus	grey
Seq_44_Porphyromonas_bennonis	grey
Seq_47_Streptococcus	grey
Seq_49_Actinomycetales	grey
Seq_53_Proteus	grey
Seq_54_Staphylococcus_hominis	grey
Seq_57_Peptoniphilus_coxii	grey
Seq_59_Corynebacterium	grey
Seq_61_Anaerococcus_murdochii	grey
Seq_68_Anaerococcus	grey
Seq_69_Corynebacterium	grey
Seq_72_Peptoniphilus_duerdenii	grey
Seq_73_Corynebacterium	grey
Seq_80_Porphyromonas_bennonis	grey
Seq_83_Staphylococcus_epidermidis	grey
Seq_86_Porphyromonas_bennonis	grey
Seq_96_Streptococcus	grey
Seq_101_Porphyromonas_somerae	grey
Seq_107_Streptococcus_sanguinis	grey
Seq_112_Corynebacterium_pseudogenitalium	grey
Seq_120_Corynebacterium	grey
Seq_121_Prevotella_corporis	grey
Seq_138_Anaerococcus_prevotii	grey
Seq_141_Fusobacterium_nucleatum	grey
Seq_152_Sneathia	grey

Seq_158_Staphylococcus_epidermidis	grey
Seq_159_Staphylococcus	grey
Seq_165_Staphylococcus	grey
Seq_171_Dolosigranulum_pigrum	grey
Seq_173_Fusobacterium_nucleatum	grey
Seq_175_Prevotella_corporis	grey
Seq_177_Dolosigranulum_pigrum	grey
Seq_182_Anaeroglobus_geminatus	grey
Seq_186_Anaerococcus_octavius	grey
Seq_192_Dermabacter_hominis	grey
Seq_193_Prevotella_timonensis	grey
Seq_194_Facklamia	grey
Seq_206_Actinomyces_neuii	grey
Seq_209_Corynebacterium	grey
Seq_210_Gemella_haemolysans	grey
Seq_214_Peptoniphilus_coxii	grey
Seq_232_Campylobacter_curvus	grey
Seq_240_Prevotella_denticola	grey
Seq_241_Ruminococcaceae	grey
Seq_243_Porphyromonas_bennonis	grey
Seq_245_Corynebacterium	grey
Seq_254_Facklamia_languida	grey
Seq_255_Corynebacterium	grey
Seq_257_Staphylococcus	grey
Seq_263_Corynebacterium	grey
Seq_270_Streptophyta	grey
Seq_272_Dolosigranulum_pigrum	grey
Seq_275_Clostridiales	grey
Seq_276_Anaerococcus_octavius	grey
Seq_280_Aerococcus	grey
Seq_283_Porphyromonas_bennonis	grey
Seq_303_Corynebacterium_kroppenstedtii	grey
Seq_309_Clostridium_sensu_stricto	grey
Seq_317_Staphylococcus	grey
Seq_320_Faecalibacterium_prausnitzii	grey
Seq_324_Mobiluncus_curtisii	grey
Seq_325_Corynebacterium	grey
Seq_340_Finegoldia_magna	grey
Seq_343_Actinomyces_radingae	grey
Seq_345_Porphyromonas_bennonis	grey
Seq_350_Prevotella_timonensis	grey
Seq_351_Corynebacterium_kroppenstedtii	grey
Seq_354_Actinomycetales	grey
Seq_355_Prevotella_timonensis	grey
Seq_360_Corynebacterium	grey

Seq_362_Prevotella_denticola	grey
Seq_366_Clostridiales	grey
Seq_373_Prevotella_buccalis	grey
Seq_377_Prevotella_oris	grey
Seq_378_Prevotella_bergensis	grey
Seq_380_Finegoldia_magna	grey
Seq_384_Streptococcus	grey
Seq_393_Prevotella_buccalis	grey
Seq_396_Chryseobacterium	grey
Seq_401_Corynebacterium	grey
Seq_402_Dolosigranulum_pigrum	grey
Seq_404_Atopobium_minutum	grey
Seq_411_Neisseria	grey
Seq_427_Negativicoccus_succinicivorans	grey
Seq_429_Enhydrobacter	grey
Seq_431_Facklamia_languida	grey
Seq_432_Enterobacteriaceae	grey
Seq_436_Porphyromonas_uenonis	grey
Seq_449_Prevotella_oris	grey
Seq_456_Staphylococcus	grey
Seq_467_Brochothrix_thermosphacta	grey
Seq_470_Negativicoccus_succinicivorans	grey
Seq_488_Finegoldia_magna	grey
Seq_489_Prevotella_oris	grey
Seq_494_Prevotella_oris	grey
Seq_495_Haemophilus	grey
Seq_507_Corynebacterium	grey
Seq_514_Finegoldia_magna	grey
Seq_515_Prevotella_denticola	grey
Seq_516_Fusobacterium_nucleatum	grey
Seq_521_Staphylococcus	grey
Seq_525_Staphylococcus	grey
Seq_526_Gordonia	grey
Seq_527_Coprococcus_comes	grey
Seq_532_Paracoccus	grey
Seq_533_Staphylococcus	grey
Seq_536_Staphylococcus_epidermidis	grey
Seq_540_Corynebacterium	grey
Seq_546_Enterobacteriaceae	grey
Seq_554_Enterobacter	grey
Seq_561_Corynebacterium_mucifaciens	grey
Seq_565_Dialister_propionicifaciens	grey
Seq_567_Corynebacterium	grey
Seq_571_Prevotella_bergensis	grey
Seq_579_Enterobacteriaceae	grey

Seq_585_Corynebacterium_kroppenstedtii	grey
Seq_589_Corynebacterium_kroppenstedtii	grey
Seq_591_Sphingomonas	grey
Seq_592_Finegoldia_magna	grey
Seq_593_Lactobacillus_iners	grey
Seq_594_Fusobacterium_nucleatum	grey
Seq_601_Corynebacterium_durum	grey
Seq_607_Leptotrichia	grey
Seq_608_Corynebacterium_jeikeium	grey
Seq_612_Petrobacter_succinatimandens	grey
Seq_614_Veillonella_atypica	grey
Seq_623_Dialister_pneumosintes	grey
Seq_627_Porphyromonas_catoniae	grey
Seq_628_Negativicoccus_succinicivorans	grey
Seq_630_Bifidobacterium_breve	grey
Seq_640_Micrococcaceae	grey
Seq_649_Haemophilus_parainfluenzae	grey
Seq_652_Corynebacterium	grey
Seq_654_Veillonella_parvula	grey
Seq_657_Lactobacillus	grey
Seq_662_Xanthomonadaceae	grey
Seq_666_Corynebacterium	grey
Seq_669_Staphylococcus	grey
Seq_671_Staphylococcus	grey
Seq_673_Staphylococcus	grey
Seq_674_Anaerococcus_octavius	grey
Seq_679_Fastidiosipila_sanguinis	grey
Seq_686_Murdochiella_asaccharolytica	grey
Seq_687_Acinetobacter_johnsonii	grey
Seq_688_Staphylococcus	grey
Seq_697_Parvimonas_micra	grey
Seq_700_Porphyromonas_bennonis	grey
Seq_702_Staphylococcus	grey
Seq_710_Peptoniphilus	grey
Seq_711_Peptoniphilus_coxii	grey
Seq_715_Actinobacteria	grey
Seq_717_Bacillus_thermoamylovorans	grey
Seq_718_Murdochiella_asaccharolytica	grey
Seq_721_Lachnospiraceae	grey
Seq_729_Staphylococcus	grey
Seq_740_Corynebacterium	grey
Seq_750_Staphylococcus	grey
Seq_759_Corynebacterium_imitans	grey
Seq_760_Staphylococcus	grey
Seq_762_Hydrogenophilus	grey

Seq_766_Fusobacterium_nucleatum	grey
Seq_767_Fusobacterium_nucleatum	grey
Seq_782_Anaerococcus	grey
Seq_787_Porphyromonas_bennonis	grey
Seq_792_Lactobacillus_iners	grey
Seq_796_Tetracoccus_cechii	grey
Seq_813_Escherichia/Shigella	grey
Seq_819_Acinetobacter	grey
Seq_826_Pseudomonas	grey
Seq_828_Anaerococcus_prevotii	grey
Seq_829_Clostridiales	grey
Seq_831_Corynebacterium	grey
Seq_849_Actinomyces	grey
Seq_854_Schlegelella_aquatica	grey
Seq_869_Anaerococcus_prevotii	grey
Seq_874_Gallicola	grey
Seq_879_Varibaculum_cambriense	grey
Seq_883_Helcococcus_sueciensis	grey
Seq_889_Acinetobacter	grey
Seq_899_Neisseria_elongata	grey
Seq_906_Haemophilus	grey
Seq_917_Staphylococcus	grey
Seq_924_Corynebacterium	grey
Seq_928_Actinomyces_europaeus	grey
Seq_929_Varibaculum_cambriense	grey
Seq_935_Clostridiales	grey
Seq_941_Actinobaculum_schaalii	grey
Seq_952_Coprococcus_catus	grey
Seq_953_Veillonella_atypica	grey
Seq_954_Anaerococcus_octavius	grey
Seq_969_Carnobacterium	grey
Seq_972_Planctomycetaceae	grey
Seq_973_Prevotella_bergensis	grey
Seq_989_Corynebacterium	grey
Seq_994_Porphyromonas	grey
Seq_996_Corynebacterium	grey
Seq_1002_Actinomyces_turicensis	grey
Seq_1011_Clostridiales	grey
Seq_1013_Pseudomonas	grey
Seq_1015_Pseudomonas	grey
Seq_1023_Aerococcus_sanguinicola	grey
Seq_1025_Prevotella_timonensis	grey
Seq_1032_Porphyromonas	grey
Seq_1036_Staphylococcus	grey
Seq_1042_Pseudomonas	grey

Seq_1043_Staphylococcus	grey
Seq_1045_Staphylococcus	grey
Seq_1051_Veillonella_parvula	grey
Seq_1052_Kocuria	grey
Seq_1070_Corynebacterium_jeikeium	grey
Seq_1075_Pseudomonas	grey
Seq_1080_Aeromonas	grey
Seq_1083_Peptoniphilus	grey
Seq_1095_Dialister_micraerophilus	grey
Seq_1101_Dermabacter_hominis	grey
Seq_1107_Rhizobium	grey
Seq_1108_Proteus	grey
Seq_1109_Anaerococcus	grey
Seq_1121_Prevotella_timonensis	grey
Seq_1133_Chryseobacterium	grey
Seq_1138_Corynebacterium_amycolatum	grey
Seq_1143_Peptostreptococcus_stomatis	grey
Seq_1159_Helcococcus	grey
Seq_1170_Fusobacterium_nucleatum	grey
Seq_1179_Peptoniphilus_asaccharolyticus	grey
Seq_1184_Paracoccus	grey
Seq_1190_Murdochiella_asaccharolytica	grey
Seq_1197_Peptococcus_niger	grey
Seq_1206_Dialister_propionicifaciens	grey
Seq_1211_Enterobacter	grey
Seq_1218_Staphylococcus	grey
Seq_1219_Staphylococcus	grey
Seq_1222_Prevotella_corporis	grey
Seq_1231_Negativicoccus_succinicivorans	grey
Seq_1239_Methylobacterium_radiotolerans	grey
Seq_1249_Staphylococcaceae	grey
Seq_1250_Deinococcus	grey
Seq_1251_Staphylococcus	grey
Seq_1260_Brevibacterium_paucivorans	grey
Seq_1263_Prevotella_bivia	grey
Seq_1271_Proteus_mirabilis	grey
Seq_1273_Actinobaculum_schaalii	grey
Seq_1278_Corynebacterium	grey
Seq_1288_Microbacteriaceae	grey
Seq_1289_Corynebacterium	grey
Seq_1301_Alishewanella_jeotgali	grey
Seq_1318_Porphyromonas_asaccharolytica	grey
Seq_1319_Clostridiales_Incertae_Sedis_XI	grey
Seq_1320_Corynebacterium	grey
Seq_1322_Staphylococcus_epidermidis	grey

Seq_1326_Flavobacteriaceae	grey
Seq_1330_Peptoniphilus_duerdenii	grey
Seq_1334_Staphylococcus	grey
Seq_1343_Aerococcus_urinae	grey
Seq_1352_Veillonella_dispar	grey
Seq_1360_Anaerococcus_octavius	grey
Seq_1364_Prevotella_denticola	grey
Seq_1366_Streptophyta	grey
Seq_1374_Luteimonas	grey
Seq_1375_Corynebacterium	grey
Seq_1377_Moraxella	grey
Seq_1392_Peptococcus_niger	grey
Seq_1393_Haemophilus_parainfluenzae	grey
Seq_1420_Corynebacterium_riegelii	grey
Seq_1422_Alishewanella_aestuarii	grey
Seq_1428_Gemella_haemolysans	grey
Seq_1429_Peptoniphilus	grey
Seq_1433_Veillonella	grey
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Seq_1448_Staphylococcus	grey
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Seq_1466_Staphylococcus	grey
Seq_1473_Staphylococcus	grey
Seq_1485_Gp6	grey
Seq_1537_Corynebacterium	grey
Seq_1548_Clostridiales_Incertae_Sedis_XI	grey
Seq_1566_Clostridiales	grey
Seq_1587_Facklamia_ignava	grey
Seq_1612_Staphylococcus_epidermidis	grey
Seq_1617_Streptococcus	grey
Seq_1629_Corynebacterium	grey
Seq_1630_Staphylococcus_pettenkoferi	grey
Seq_1631_Campylobacter_hominis	grey
Seq_1642_Ruminococcaceae	grey
Seq_1649_Finegoldia_magna	grey
Seq_1665_Micrococcaceae	grey
Seq_1683_Aerococcus_christensenii	grey
Seq_1699_Moraxella_lincolnii	grey
Seq_1711_Prevotella	grey
Seq_1720_Campylobacter_ureolyticus	grey
Seq_1742_Actinomyces_gerencseriae	grey
Seq_1752_Prevotella_buccalis	grey
Seq_1755_Prevotella_bergensis	grey
Seq_1756_Corynebacterium_aurimucosum	grey
Seq_1772_Negativicoccus_succinicivorans	grey

Seq_1775_Streptophyta	grey
Seq_1786_Novosphingobium	grey
Seq_1787_Staphylococcus_pettenkoferi	grey
Seq_1805_Moraxella	grey
Seq_1814_Prevotella_oulorum	grey
Seq_1824_Acinetobacter	grey
Seq_1828_Pyramidobacter_piscolens	grey
Seq_1833_Cyanobacteria	grey
Seq_1842_Prevotella_bergensis	grey
Seq_1843_Corynebacterium_pseudogenitalium	grey
Seq_1844_Moraxella_lincolnii	grey
Seq_1850_Clostridiales	grey
Seq_1852_Schlegelella_aquatica	grey
Seq_1874_Xanthomonadaceae	grey
Seq_1878_Skermanella_aerolata	grey
Seq_1880_Xanthobacter	grey
Seq_1882_Clostridiales	grey
Seq_1884_Enterococcus_cecorum	grey
Seq_1908_Prevotella	grey
Seq_1913_Stenotrophomonas	grey
Seq_1926_Dialister_propionicifaciens	grey
Seq_1936_Finegoldia_magna	grey
Seq_1957_Staphylococcus_epidermidis	grey
Seq_1964_Facklamia_languida	grey
Seq_1966_Staphylococcus	grey
Seq_1979_Aerococcus	grey
Seq_1981_Anaerococcus_octavius	grey
Seq_1992_Hydrogenophilus	grey
Seq_1999_Flavobacteriaceae	grey
Seq_2002_Kocuria_kristinae	grey
Seq_2007_Brevibacterium	grey
Seq_2018_Pseudomonas	grey
Seq_2020_Anaerococcus_murdochii	grey
Seq_2023_Anoxybacillus	grey
Seq_2028_Leptotrichia_buccalis	grey
Seq_2038_Veillonella_parvula	grey
Seq_2042_Luteimonas	grey
Seq_2055_Corynebacterium_confusum	grey
Seq_2080_Haemophilus_parainfluenzae	grey
Seq_2083_Anaerococcus_octavius	grey
Seq_2089_Dialister	grey
Seq_2094_Capnocytophaga_gingivalis	grey
Seq_2099_Veillonella	grey
Seq_2109_Actinomyces_naeslundii	grey
Seq_2120_Jeotgalicoccus	grey

Seq_2129_Corynebacterium	grey
Seq_2134_Propionibacterium_granulosum	grey
Seq_2135_Anaerococcus_octavius	grey
Seq_2142_Acinetobacter_johnsonii	grey
Seq_2168_Proteobacteria	grey
Seq_2203_Facklamia_ignava	grey
Seq_2206_Clostridium_sensu_stricto	grey
Seq_2220_Clostridium_disporicum	grey
Seq_2241_Streptococcus	grey
Seq_2243_Staphylococcus_epidermidis	grey
Seq_2244_Anaerococcus_octavius	grey
Seq_2274_Anaerococcus	grey
Seq_2286_Facklamia	grey
Seq_2307_Actinomycetales	grey
Seq_2310_Staphylococcus	grey
Seq_2311_Prevotella_timonensis	grey
Seq_2326_Prevotella_buccalis	grey
Seq_2327_Porphyromonadaceae	grey
Seq_2333_Peptococcus_niger	grey
Seq_2342_Atopobium_minutum	grey
Seq_2356_Pantoea_agglomerans	grey
Seq_2359_Marmoricola	grey
Seq_2365_Porphyromonas_uenonis	grey
Seq_2393_Clostridiales	grey
Seq_2395_Bacteria	grey
Seq_2397_Prevotella	grey
Seq_2408_Campylobacter_gracilis	grey
Seq_2411_Anaerococcus	grey
Seq_2453_Staphylococcaceae	grey
Seq_2455_Staphylococcus_lugdunensis	grey
Seq_2469_Facklamia_languida	grey
Seq_2470_Porphyromonas_somerae	grey
Seq_2472_Peptoniphilus_coxii	grey
Seq_2492_Photobacterium_phosphoreum	grey
Seq_2494_Corynebacterium	grey
Seq_2496_Kingella_oralis	grey
Seq_2500_Streptococcus	grey
Seq_2518_Morganella_morganii	grey
Seq_2521_Staphylococcus_aureus	grey
Seq_2534_Ethanoligenens	grey
Seq_2541_Anaerococcus_octavius	grey
Seq_2566_Lachnospiraceae	grey
Seq_2567_Facklamia_languida	grey
Seq_2578_Staphylococcus_epidermidis	grey
Seq_2598_Corynebacterium_coyleae	grey

Seq_2606_Bacteria	grey
Seq_2618_Porphyromonas_asaccharolytica	grey
Seq_2625_Corynebacterium	grey
Seq_2626_Corynebacterium_amycolatum	grey
Seq_2627_Acinetobacter_lwoffii	grey
Seq_2630_Corynebacterium_imitans	grey
Seq_2650_Facklamia_languida	grey
Seq_2654_Bacteroidetes	grey
Seq_2662_Rheinheimera_perlucida	grey
Seq_2684_Porphyromonas_asaccharolytica	grey
Seq_2687_Facklamia_languida	grey
Seq_2696_Veillonella	grey
Seq_2697_Cardiobacterium_hominis	grey
Seq_2724_Nesterenkonia	grey
Seq_2729_Aeromonas	grey
Seq_2743_Aerococcus_urinae	grey
Seq_2751_Ruminococcaceae	grey
Seq_2769_Streptococcus	grey
Seq_2770_Anaerococcus_octavius	grey
Seq_2804_Porphyromonas	grey
Seq_2809_Streptococcus	grey
Seq_2840_Conexibacter	grey
Seq_2841_Lachnospiraceae	grey
Seq_2842_Porphyromonadaceae	grey
Seq_2843_Bacteroidales	grey
Seq_2848_Corynebacterium_jeikeium	grey
Seq_2850_Mesorhizobium	grey
Seq_2877_Streptophyta	grey
Seq_2916_Prevotella_intermedia	grey
Seq_2919_Aerococcus_sanguinicola	grey
Seq_2940_Streptophyta	grey
Seq_2951_Peptoniphilus	grey
Seq_2952_Prevotella_buccalis	grey
Seq_2998_Blautia_luti	grey
Seq_3005_Peptoniphilus_coxii	grey
Seq_3008_Brevundimonas	grey
Seq_3009_Pasteurellaceae	grey
Seq_3014_Capnocytophaga_leadbetteri	grey
Seq_3045_Roseomonas_vinacea	grey
Seq_3049_Peptoniphilus_koenoeneniae	grey
Seq_3054_Clostridiales_Incertae_Sedis_XI	grey
Seq_3055_Brachybacterium	grey
Seq_3057_Brevibacterium	grey
Seq_3108_Corynebacterium_frankenforstense	grey
Seq_3112_Pseudomonas	grey

Seq_3139_Sphingomonadaceae	grey
Seq_3209_Prevotellaceae	grey
Seq_3210_Megasphaera_micronuciformis	grey
Seq_3219_Prevotella_timonensis	grey
Seq_3259_Oligella_urethralis	grey
Seq_3268_Dermabacter_hominis	grey
Seq_3329_Blautia_faecis	grey
Seq_3330_Campylobacter_curvus	grey
Seq_3336_Micrococcaceae	grey
Seq_3337_Anaeroglobus_geminatus	grey
Seq_3340_Corynebacterium	grey
Seq_3385_Brevibacterium	grey
Seq_3393_Prevotella	grey
Seq_3395_Actinomyces	grey
Seq_3398_Actinomycetales	grey
Seq_3400_Prevotella_buccalis	grey
Seq_3401_Rhizobium	grey
Seq_3408_Haemophilus_parainfluenzae	grey
Seq_3416_Rothia_mucilaginosa	grey
Seq_3462_Prevotella	grey
Seq_3465_Lysobacter_gummosus	grey
Seq_3473_Nocardioides	grey
Seq_3475_Actinobaculum_schaalii	grey
Seq_3480_Petrobacter_succinatimandens	grey
Seq_3487_Bacteroidetes	grey
Seq_3489_Anaerococcus	grey
Seq_3553_Scardovia_wiggsiae	grey
Seq_3562_Prevotella_bergensis	grey
Seq_3564_Ruminococcus	grey
Seq_3567_Eubacterium_rectale	grey
Seq_3570_Porphyromonas_bennonis	grey
Seq_3583_Rhodobacteraceae	grey
Seq_3584_Moraxellaceae	grey
Seq_3585_Prevotella_oulorum	grey
Seq_3671_Helcococcus	grey
Seq_3673_Corynebacterium	grey
Seq_3675_Dialister_propionicifaciens	grey
Seq_3759_Nocardioides_islandensis	grey
Seq_3760_Sphingomonas	grey
Seq_3777_Bacteroides_uniformis	grey
Seq_3782_Peptoniphilus	grey
Seq_3783_Rhizobium_giardinii	grey
Seq_3886_Corynebacterium	grey
Seq_3903_Corynebacterium_doosanense	grey
Seq_3907_Aquabacterium	grey

Seq_4007_Dialister_propionicifaciens	grey
Seq_4012_Brevibacterium	grey
Seq_4013_Prevotella	grey
Seq_4014_Selenomonas_noxia	grey
Seq_4015_Prevotella_oris	grey
Seq_4017_Stenotrophomonas_maltophilia	grey
Seq_4022_Lachnospiraceae	grey
Seq_4023_Ruminococcaceae	grey
Seq_4024_Lachnoanaerobaculum_saburreum	grey
Seq_4031_Enhydrobacter	grey
Seq_4038_Actinomyces_odontolyticus	grey
Seq_4058_Treponema_amylovorum	grey
Seq_4077_Bacteria	grey
Seq_4079_Chloroplast	grey
Seq_4158_Murdochiella_asaccharolytica	grey
Seq_4159_Anaerococcus_vaginalis	grey
Seq_4160_Megasphaera_elsdenii	grey
Seq_4164_Pantoea	grey
Seq_4167_Bacteria	grey
Seq_4183_Prevotella_buccalis	grey
Seq_4186_Akkermansia_muciniphila	grey
Seq_4190_Treponema_lecithinolyticum	grey
Seq_4201_Firmicutes	grey
Seq_4203_Prevotella_melaninogenica	grey
Seq_4204_Clostridiales_Incertae_Sedis_XI	grey
Seq_4205_Clostridiales	grey
Seq_4210_Actinomycetales	grey
Seq_4211_Porphyromonas_catoniae	grey
Seq_4349_Rathayibacter	grey
Seq_4365_Blautia	grey
Seq_4373_Neisseria_bacilliformis	grey
Seq_4376_Lactobacillus	grey
Seq_4384_Capnocytophaga_sputigena	grey
Seq_4385_Gemella_palaticanis	grey
Seq_4386_Porphyromonas_catoniae	grey
Seq_4390_Streptococcus_agalactiae	grey
Seq_4392_Lactobacillus_jensenii	grey
Seq_4398_Finegoldia_magna	grey
Seq_4417_Staphylococcus	grey
Seq_4461_Campylobacter_ureolyticus	grey
Seq_4568_Mogibacterium_timidum	grey
Seq_4569_Facklamia	grey
Seq_4577_Prevotella	grey
Seq_4583_Clostridiales	grey
Seq_4587_Phyllobacteriaceae	grey

Seq_4588_Prevotella_timonensis	grey
Seq_4599_Actinomyces_odontolyticus	grey
Seq_4611_Lysobacter	grey
Seq_4613_Prevotella_copri	grey
Seq_4614_Chryseobacterium	grey
Seq_4615_Cellulomonas	grey
Seq_4616_Alphaproteobacteria	grey
Seq_4623_Psychrobacter	grey
Seq_4645_Clostridiales_Incertae_Sedis_XI	grey
Seq_4766_Mogibacterium	grey
Seq_4785_Parvimonas_micra	grey
Seq_4802_Ruminococcus_torques	grey
Seq_4808_Anaerococcus_murdochii	grey
Seq_4809_Anaerococcus	grey
Seq_4821_Micrococcaceae	grey
Seq_4855_Rothia_mucilaginosa	grey
Seq_4856_Propionibacterium_acnes	grey
Seq_4857_Oligella_urethralis	grey
Seq_4861_Corynebacterium	grey
Seq_4865_Rhizobiales	grey
Seq_4882_Prevotellaceae	grey
Seq_4883_Brevibacterium	grey
Seq_4884_Moryella_indoligenes	grey
Seq_4885_Rhodobacteraceae	grey
Seq_4893_Firmicutes	grey
Seq_5105_Howardella_ureilytica	grey
Seq_5106_Acinetobacter	grey
Seq_5107_Peptoniphilus_lacrimalis	grey
Seq_5118_Bifidobacterium	grey
Seq_5119_Bacteria	grey
Seq_5120_Atopobium_minutum	grey
Seq_5128_Luteibacter_rhizovicinus	grey
Seq_5135_Jeotgalicoccus_pinnipedialis	grey
Seq_5137_Capnocytophaga_ochracea	grey
Seq_5146_Selenomonas_noxia	grey
Seq_5147_Porphyromonas	grey
Seq_5149_Bacteria	grey
Seq_5150_Mogibacterium	grey
Seq_5151_Ilumatobacter	grey
Seq_5162_Fusobacterium	grey
Seq_5188_Parvimonas_micra	grey
Seq_5191_Bifidobacterium_longum	grey
Seq_5198_Ruminococcus_flavefaciens	grey
Seq_5207_Facklamia_languida	grey
Seq_5209_Veillonella_parvula	grey

Seq_5213_Staphylococcus_lugdunensis	grey
Seq_5214_Staphylococcus	grey
Seq_5219_Nocardioides	grey
Seq_5221_Neisseriaceae	grey
Seq_5532_Corynebacterium	grey
Seq_5535_Bacteria	grey
Seq_5536_Bacteria	grey
Seq_5538_Corynebacterium	grey
Seq_5541_Staphylococcus_aureus	grey
Seq_5542_Ruminococcaceae	grey
Seq_5549_Bacteria	grey
Seq_5550_Bacteroidetes	grey
Seq_5552_Anaerostipes_hadrus	grey
Seq_5555_Pseudoxanthomonas_taiwanensis	grey
Seq_5561_Alloprevotella_rava	grey
Seq_5562_Mycoplasma_salivarium	grey
Seq_5566_Clostridiales	grey
Seq_5567_Prevotella_oulorum	grey
Seq_5568_Clostridiales	grey
Seq_5569_Prevotella	grey
Seq_5600_Hymenobacter	grey
Seq_5609_Porphyromonas	grey
Seq_5611_Porphyromonas	grey
Seq_5625_Flavobacterium	grey
Seq_5626_Barnesiella	grey
Seq_5627_Porphyromonas_circumdentaria	grey
Seq_5675_Acinetobacter_baumannii	grey
Seq_5678_Clostridiales	grey
Seq_5681_Pseudomonas	grey
Seq_5707_Acinetobacter	grey
Seq_5709_Ruminococcaceae	grey
Seq_5711_Conexibacter_arvalis	grey
Seq_5713_Bacillus_circulans	grey
Seq_5715_Flavobacterium_noncentrifugens	grey
Seq_5716_Staphylococcus	grey
Seq_5717_Bacteria	grey
Seq_5723_Clostridia	grey
Seq_5725_Psychrobacter	grey
Seq_5726_Bacteria	grey
Seq_6197_Lactobacillales	grey
Seq_6210_Brevibacterium	grey
Seq_6227_Ruminococcaceae	grey
Seq_6228_Sphingomonas	grey
Seq_6259_Prevotella_corporis	grey
Seq_6262_Anaeroglobus_geminatus	grey

Seq_6269_Porphyromonas_uenonis	grey
Seq_6273_Clostridiales	grey
Seq_6276_Firmicutes	grey
Seq_6286_Succinivibridextrinosolvens	grey
Seq_6288_Butyricicoccus	grey
Seq_6289_Actinomycetales	grey
Seq_6290_Murdochiella_asaccharolytica	grey
Seq_6292_Actinomycetales	grey
Seq_6298_Lachnospiraceae	grey
Seq_6302_Bacteroidetes	grey
Seq_6336_Oribacterium_sinus	grey
Seq_6381_Firmicutes	grey
Seq_6392_Treponema_socranskii	grey
Seq_6397_Stenotrophomonas	grey
Seq_6398_Bacteria	grey
Seq_6403_Brevundimonas	grey
Seq_6404_Gammaproteobacteria	grey
Seq_6408_Ruminococcus_champanellensis	grey
Seq_6437_Peptoniphilus_lacrimalis	grey
Seq_6439_Porphyromonas_bennonis	grey
Seq_6442_Clostridiales	grey
Seq_6462_Clostridiales	grey
Seq_6495_Bacteria	grey
Seq_6496_Bacteria	grey
Seq_6500_Prevotella_copri	grey
Seq_6504_Barnesiella_intestinihominis	grey
Seq_6534_Lactobacillus_algidus	grey
Seq_6538_Streptophyta	grey
Seq_6541_Actinomycetales	grey
Seq_6542_Deinococcus	grey
Seq_6545_Sphingobacterium	grey
Seq_6567_Enterobacteriaceae	grey
Seq_6568_Selenomonas_artemidis	grey
Seq_6572_Sutterella_stercoricanis	grey
Seq_6576_Clostridium_XlVa	grey
Seq_6580_Staphylococcaceae	grey
Seq_6581_Cyanobacteria	grey
Seq_6583_Clostridiales	grey
Seq_6584_Bacteria	grey
Seq_6590_Prevotella	grey
Seq_6591_Candidatus_Saccharibacteria	grey
Seq_6593_Porphyromonas_endodontalis	grey
Seq_6610_Clostridiales	grey
Seq_6611_Firmicutes	grey
Seq_6614_Bacteria	grey

Seq_6615_Enterobacteriaceae	grey
Seq_6618_Ilumatobacter	grey
Seq_6620_Porphyromonas	grey
Seq_6621_Firmicutes	grey
Seq_6651_Actinomycetales	grey
Seq_6670_Staphylococcus	grey
Seq_6675_Stenotrophomonas_maltophilia	grey
Seq_23_Lactobacillus_iners	grey60
Seq_46_Anaerococcus_octavius	grey60
Seq_79_Staphylococcus	grey60
Seq_93_Pseudomonas	grey60
Seq_143_Faecalibacterium_prausnitzii	grey60
Seq_149_Atopobium_vaginae	grey60
Seq_155_Dermacoccus_nishinomiyaensis	grey60
Seq_188_Dermacoccus	grey60
Seq_423_Corynebacterium_pseudogenitalium	grey60
Seq_430_Corynebacterium_pseudogenitalium	grey60
Seq_444_Dialister	grey60
Seq_459_Staphylococcus_hominis	grey60
Seq_698_Staphylococcus	grey60
Seq_742_Anaerococcus	grey60
Seq_851_Pseudomonas	grey60
Seq_881_Staphylococcus	grey60
Seq_1413_Nevskia_ramosa	grey60
Seq_1414_Anaerococcus_prevotii	grey60
Seq_2296_Gemella_asaccharolytica	grey60
Seq_2507_Bacteria	grey60
Seq_2542_Aerococcus_urinae	grey60
Seq_2573_Enterobacteriaceae	grey60
Seq_2621_Veillonella_montpellierensis	grey60
Seq_2628_Porphyromonas_somerae	grey60
Seq_2771_Porphyromonas_somerae	grey60
Seq_2896_Pseudomonas	grey60
Seq_2948_Ochrobactrum	grey60
Seq_3163_Stenotrophomonas	grey60
Seq_3212_Anaerococcus_senegalensis	grey60
Seq_3213_Mycoplasma_hominis	grey60
Seq_3764_Prevotella_timonensis	grey60
Seq_3765_Propionimicrobium_lymphophilum	grey60
Seq_3863_Clostridiales_Incertae_Sedis_XI	grey60
Seq_4162_Neisseria	grey60
Seq_4163_Clostridiales	grey60
Seq_4366_Prevotella	grey60
Seq_4367_Lachnospiraceae	grey60
Seq_4813_Parabacteroides_distasonis	grey60

Seq_4814_Enterobacteriaceae	grey60
Seq_4815_Roseomonas	grey60
Seq_5140_Bacteroides_xylanisolvens	grey60
Seq_5141_Parvimonas_micra	grey60
Seq_5579_Enterobacteriaceae	grey60
Seq_6340_Actinomyces_odontolyticus	grey60
Seq_38_Corynebacterium_jeikeium	lightcyan
Seq_50_Corynebacterium_aurimucosum	lightcyan
Seq_60_Corynebacterium_aurimucosum	lightcyan
Seq_135_Corynebacterium_aurimucosum	lightcyan
Seq_181_Lactobacillus_jensenii	lightcyan
Seq_196_Dermabacter_hominis	lightcyan
Seq_359_Acinetobacter_baumannii	lightcyan
Seq_408_Jonquetella_anthropi	lightcyan
Seq_415_Staphylococcus	lightcyan
Seq_465_Micrococcaceae	lightcyan
Seq_503_Prevotella_bivia	lightcyan
Seq_508_Corynebacterium	lightcyan
Seq_600_Micrococcaceae	lightcyan
Seq_709_Klebsiella	lightcyan
Seq_749_Coprococcus_eutactus	lightcyan
Seq_753_Prevotella_bergensis	lightcyan
Seq_848_Bacteroides_uniformis	lightcyan
Seq_882_Enterobacteriaceae	lightcyan
Seq_931_Ruminococcaceae	lightcyan
Seq_1100_Blautia	lightcyan
Seq_1178_Klebsiella	lightcyan
Seq_1293_Micrococcaceae	lightcyan
Seq_1347_Acinetobacter	lightcyan
Seq_1437_Phascolarctobacterium_faecium	lightcyan
Seq_1552_Corynebacterium	lightcyan
Seq_1562_Bacteroides_coprocola	lightcyan
Seq_2345_Enterobacteriaceae	lightcyan
Seq_2357_Pseudomonas	lightcyan
Seq_2572_Paraprevotella_clara	lightcyan
Seq_2686_Enterococcus	lightcyan
Seq_3103_Ruminococcaceae	lightcyan
Seq_3104_Catenibacterium_mitsuokai	lightcyan
Seq_3260_Gallicola	lightcyan
Seq_3391_Ruminococcus_albus	lightcyan
Seq_3471_Coriobacteriaceae	lightcyan
Seq_3666_Blautia	lightcyan
Seq_3871_Anaerococcus_octavius	lightcyan
Seq_4000_Lachnospiraceae	lightcyan
Seq_4001_Sphingomonadales	lightcyan

Seq_4145_Erysipelotrichaceae	lightcyan
Seq_4343_Porphyromonadaceae	lightcyan
Seq_4344_Bifidobacterium	lightcyan
Seq_4789_Coriobacteriaceae	lightcyan
Seq_5098_Coprobacillus_cateniformis	lightcyan
Seq_5099_Prevotellaceae	lightcyan
Seq_5505_Planifilum_fimeticola	lightcyan
Seq_5506_Exiguobacterium	lightcyan
Seq_6209_Prevotella_disiens	lightcyan
Seq_29_Moraxella	lightgreen
Seq_100_Corynebacterium_appendicis	lightgreen
Seq_174_Porphyromonas_bennonis	lightgreen
Seq_361_Peptoniphilus	lightgreen
Seq_367_Porphyromonas	lightgreen
Seq_382_Corynebacterium	lightgreen
Seq_398_Gallicola	lightgreen
Seq_478_Anaerococcus_octavius	lightgreen
Seq_531_Anaerococcus_octavius	lightgreen
Seq_562_Anaerococcus_octavius	lightgreen
Seq_703_Anaerococcus_octavius	lightgreen
Seq_803_Clostridiales	lightgreen
Seq_836_Anaerococcus	lightgreen
Seq_945_Corynebacterium	lightgreen
Seq_977_Anaerococcus_octavius	lightgreen
Seq_1037_Anaerococcus_octavius	lightgreen
Seq_1067_Peptoniphilus	lightgreen
Seq_1226_Anaerococcus_octavius	lightgreen
Seq_1290_Anaerococcus_octavius	lightgreen
Seq_1543_Anaerococcus_octavius	lightgreen
Seq_1618_Peptoniphilus	lightgreen
Seq_1712_Clostridiales	lightgreen
Seq_1713_Anaerococcus_octavius	lightgreen
Seq_1734_Clostridiales	lightgreen
Seq_1810_Corynebacterium	lightgreen
Seq_1909_Corynebacterium	lightgreen
Seq_2004_Anaerococcus_octavius	lightgreen
Seq_2005_Corynebacterium	lightgreen
Seq_2013_Anaerococcus_octavius	lightgreen
Seq_2257_Anaerococcus_octavius	lightgreen
Seq_2382_Firmicutes	lightgreen
Seq_2428_Corynebacterium	lightgreen
Seq_2471_Anaerococcus_octavius	lightgreen
Seq_2520_Anaerococcus_octavius	lightgreen
Seq_2722_Clostridiales	lightgreen
Seq_2932_Ruminococcaceae	lightgreen

Seq_3000_Clostridiales	lightgreen
Seq_3215_Anaerococcus_octavius	lightgreen
Seq_3335_Dialister_propionicifaciens	lightgreen
Seq_3479_Anaerococcus_octavius	lightgreen
Seq_3571_Corynebacterium_riegelii	lightgreen
Seq_3890_Clostridiales	lightgreen
Seq_4026_Clostridiales_Incertae_Sedis_XI	lightgreen
Seq_37_Corynebacterium	lightyellow
Seq_62_Staphylococcus	lightyellow
Seq_76_Anaerococcus_octavius	lightyellow
Seq_91_Staphylococcus	lightyellow
Seq_119_Anaerococcus	lightyellow
Seq_139_Staphylococcus_haemolyticus	lightyellow
Seq_197_Staphylococcus_epidermidis	lightyellow
Seq_278_Gardnerella_vaginalis	lightyellow
Seq_294_Corynebacterium	lightyellow
Seq_394_Finegoldia_magna	lightyellow
Seq_455_Clostridium_bartlettii	lightyellow
Seq_588_Streptococcus	lightyellow
Seq_636_Corynebacterium	lightyellow
Seq_727_Staphylococcus	lightyellow
Seq_845_Staphylococcus_epidermidis	lightyellow
Seq_1086_Staphylococcus	lightyellow
Seq_1378_Staphylococcus	lightyellow
Seq_1436_Sutterella_wadsworthensis	lightyellow
Seq_1452_Bifidobacterium_longum	lightyellow
Seq_1594_Corynebacterium	lightyellow
Seq_1644_Ruminococcus	lightyellow
Seq_1664_Clostridiales	lightyellow
Seq_1785_Anaerococcus_senegalensis	lightyellow
Seq_1989_Ruminococcus	lightyellow
Seq_2165_Amaricoccus_tamworthensis	lightyellow
Seq_2433_Clostridium_sensu_stricto	lightyellow
Seq_2491_Porphyromonas_gingivalis	lightyellow
Seq_2559_Ruminococcaceae	lightyellow
Seq_2678_Veillonellaceae	lightyellow
Seq_3486_Burkholderiales	lightyellow
Seq_3771_Bacilli	lightyellow
Seq_3773_Leptotrichia	lightyellow
Seq_3896_Rhizobium	lightyellow
Seq_4033_Actinomyces_odontolyticus	lightyellow
Seq_4346_Prevotellaceae	lightyellow
Seq_4847_Capnocytophaga_granulosa	lightyellow
Seq_4848_Candidatus_Saccharibacteria	lightyellow
Seq_5171_Streptococcus	lightyellow

Seq_5180_Gemella_bergeri	lightyellow
Seq_5642_Eubacterium_eligens	lightyellow
Seq_5643_Clostridiales	lightyellow
Seq_5644_Chitinophagaceae	lightyellow
Seq_5657_Corynebacterium	lightyellow
Seq_84_Atopobium_minutum	magenta
Seq_92_Anaerococcus_murdochii	magenta
Seq_116_Peptoniphilus_coxii	magenta
Seq_129_Jonquetella_anthropi	magenta
Seq_133_Porphyromonas	magenta
Seq_134_Porphyromonas	magenta
Seq_146_Clostridiales_Incertae_Sedis_XI	magenta
Seq_163_Anaerococcus_lactolyticus	magenta
Seq_166_Porphyromonas_asaccharolytica	magenta
Seq_286_Bifidobacterium	magenta
Seq_295_Veillonella_dispar	magenta
Seq_308_Corynebacterium_kroppenstedtii	magenta
Seq_313_Porphyromonadaceae	magenta
Seq_323_Porphyromonadaceae	magenta
Seq_333_Prevotella	magenta
Seq_341_Prevotella	magenta
Seq_474_Porphyromonas_bennonis	magenta
Seq_505_Prevotella	magenta
Seq_732_Prevotella	magenta
Seq_843_Haemophilus	magenta
Seq_852_Clostridiales	magenta
Seq_892_Peptoniphilus_lacrimalis	magenta
Seq_1003_Prevotella	magenta
Seq_1208_Fastidiosipila_sanguinis	magenta
Seq_1279_Prevotella	magenta
Seq_1399_Murdochiella	magenta
Seq_1542_Pyramidobacter_piscolens	magenta
Seq_1568_Lachnospiraceae	magenta
Seq_1646_Gemmatimonas_aurantiaca	magenta
Seq_1671_Mogibacterium	magenta
Seq_1765_Porphyromonas	magenta
Seq_1788_Firmicutes	magenta
Seq_2019_Peptoniphilus_lacrimalis	magenta
Seq_2174_Varibaculum_cambriense	magenta
Seq_2175_Hymenobacter_arizonensis	magenta
Seq_2189_Varibaculum_cambriense	magenta
Seq_2308_Noviherbaspirillum	magenta
Seq_2394_Noviherbaspirillum	magenta
Seq_2495_Bacteroidales	magenta
Seq_2543_Gallicola_barnesae	magenta

Seq_2688_Pyramidobacter_piscolens	magenta
Seq_2880_Prevotella	magenta
Seq_2917_Porphyromonas	magenta
Seq_3047_Ruminococcaceae	magenta
Seq_3138_Lysobacter_thermophilus	magenta
Seq_3332_Enterobacteriaceae	magenta
Seq_3333_Bacteria	magenta
Seq_3766_Veillonellaceae	magenta
Seq_3883_Moraxella_nonliquefaciens	magenta
Seq_4018_Faecalibacterium_prausnitzii	magenta
Seq_4369_Bacteroidales	magenta
Seq_4579_Armatimonadetes_gp5	magenta
Seq_4817_Bacteria	magenta
Seq_5142_Clostridiales	magenta
Seq_5584_Peptoniphilus_lacrimalis	magenta
Seq_6350_Corynebacterium_imitans	magenta
Seq_570_Prevotella_bivia	midnightblue
Seq_603_Corynebacterium	midnightblue
Seq_622_Prevotella_bivia	midnightblue
Seq_784_Staphylococcus	midnightblue
Seq_908_Lachnospiraceae	midnightblue
Seq_914_Staphylococcus	midnightblue
Seq_987_Corynebacterium	midnightblue
Seq_1040_Corynebacterium_jeikeium	midnightblue
Seq_1048_Staphylococcus	midnightblue
Seq_1049_Staphylococcus	midnightblue
Seq_1054_Corynebacterium	midnightblue
Seq_1091_Corynebacterium	midnightblue
Seq_1157_Peptoniphilus	midnightblue
Seq_1164_Clostridiales_Incertae_Sedis_XI	midnightblue
Seq_1180_Finegoldia_magna	midnightblue
Seq_1181_Peptoniphilus_harei	midnightblue
Seq_1194_Clostridiales_Incertae_Sedis_XI	midnightblue
Seq_1233_Corynebacterium_aurimucosum	midnightblue
Seq_1240_Corynebacterium_jeikeium	midnightblue
Seq_1244_Corynebacterium_jeikeium	midnightblue
Seq_1246_Anaerococcus_murdochii	midnightblue
Seq_1252_Staphylococcus_epidermidis	midnightblue
Seq_1253_Corynebacterium_aurimucosum	midnightblue
Seq_1254_Bacteria	midnightblue
Seq_1282_Corynebacterium	midnightblue
Seq_1384_Corynebacterium_aurimucosum	midnightblue
Seq_1397_Corynebacterium	midnightblue
Seq_1416_Corynebacterium_aurimucosum	midnightblue
Seq_1435_Prevotella_bivia	midnightblue

Seq_1444_Anaerococcus_murdochii	midnightblue
Seq_1469_Corynebacterium_amycolatum	midnightblue
Seq_1470_Corynebacterium_aurimucosum	midnightblue
Seq_1475_Staphylococcus	midnightblue
Seq_1495_Actinomycetales	midnightblue
Seq_1545_Corynebacterium	midnightblue
Seq_1546_Staphylococcus	midnightblue
Seq_1573_Corynebacterium	midnightblue
Seq_1607_Corynebacterium	midnightblue
Seq_1608_Prevotella_bivia	midnightblue
Seq_1714_Corynebacterium_aurimucosum	midnightblue
Seq_1766_Corynebacterium	midnightblue
Seq_1806_Staphylococcus	midnightblue
Seq_1817_Corynebacterium_jeikeium	midnightblue
Seq_2270_Porphyromonas_uenonis	midnightblue
Seq_2292_Staphylococcus	midnightblue
Seq_2847_Murdochiella_asaccharolytica	midnightblue
Seq_5175_Pseudomonadaceae	midnightblue
Seq_6489_Clostridiales	midnightblue
Seq_32_Corynebacterium	orange
Seq_67_Anaerococcus_octavius	orange
Seq_115_Anaerococcus_octavius	orange
Seq_156_Corynebacterium	orange
Seq_239_Corynebacterium	orange
Seq_277_Streptophyta	orange
Seq_300_Hydrogenophilus	orange
Seq_322_Staphylococcus	orange
Seq_661_Anaerococcus_octavius	orange
Seq_664_Anaerococcus_octavius	orange
Seq_714_Brevundimonas	orange
Seq_771_Microbacteriaceae	orange
Seq_793_Porphyromonas_uenonis	orange
Seq_1028_Candidatus_Saccharibacteria	orange
Seq_1350_Veillonella_rogosae	orange
Seq_1395_Corynebacterium	orange
Seq_1423_Intrasporangiaceae	orange
Seq_1518_Corynebacterium	orange
Seq_1710_Lactobacillus	orange
Seq_1815_Corynebacterium_urealyticum	orange
Seq_1930_Blastococcus_aggregatus	orange
Seq_2131_Rheinheimera_tangshanensis	orange
Seq_2392_Prevotella_intermedia	orange
Seq_2519_Micrococcaceae	orange
Seq_2540_Rhizobiales	orange
Seq_2596_Erwinia_rhapontici	orange

Seq_2656_Corynebacterium_kroppenstedtii	orange
Seq_2657_Paracoccus_yeei	orange
Seq_2719_Prevotella_timonensis	orange
Seq_2720_Streptococcus	orange
Seq_2744_Neisseria	orange
Seq_2794_Caulobacter_vibrioides	orange
Seq_2879_Peptoniphilus_coxii	orange
Seq_3042_Corynebacterium_appendicis	orange
Seq_3043_Arthrobacter	orange
Seq_3160_Hymenobacter	orange
Seq_3877_Lactobacillus_jensenii	orange
Seq_3878_Anaerococcus	orange
Seq_4567_Chryseobacterium	orange
Seq_35_Corynebacterium	paleturquoise
Seq_419_Rothia_mucilaginosa	paleturquoise
Seq_424_Streptococcus	paleturquoise
Seq_471_Streptococcus	paleturquoise
Seq_529_Ruminococcus_bromii	paleturquoise
Seq_558_Actinomyces	paleturquoise
Seq_808_Lactobacillus	paleturquoise
Seq_821_Veillonella	paleturquoise
Seq_876_Pantoea	paleturquoise
Seq_1114_Anaerococcus	paleturquoise
Seq_1189_Corynebacterium_kroppenstedtii	paleturquoise
Seq_1192_Kingella_oralis	paleturquoise
Seq_1509_Sphingomonas	paleturquoise
Seq_1730_Bifidobacterium_longum	paleturquoise
Seq_1983_Haemophilus_influenzae	paleturquoise
Seq_2016_Aggregatibacter_segnis	paleturquoise
Seq_2299_Pseudomonas	paleturquoise
Seq_2385_Jeotgalicoccus_huakuii	paleturquoise
Seq_2386_Capnocytophaga_granulosa	paleturquoise
Seq_2413_Actinomyces_odontolyticus	paleturquoise
Seq_2429_Enterobacteriaceae	paleturquoise
Seq_2448_Brachybacterium	paleturquoise
Seq_2909_Streptobacillus_moniliformis	paleturquoise
Seq_2962_Selenomonas_sputigena	paleturquoise
Seq_3217_Lachnospiraceae	paleturquoise
Seq_3362_Treponema_medium	paleturquoise
Seq_3776_Prevotella_pallens	paleturquoise
Seq_4185_Clostridiales	paleturquoise
Seq_4394_Prevotella_veroralis	paleturquoise
Seq_4395_Candidatus_Saccharibacteria	paleturquoise
Seq_4610_Saccharofermentans	paleturquoise
Seq_4858_Brochothrix_thermosphacta	paleturquoise

Seq_5185_Stenotrophomonas	paleturquoise
Seq_5186_Helcococcus_sueciensis	paleturquoise
Seq_5187_Murdochiella_asaccharolytica	paleturquoise
Seq_6510_Firmicutes	paleturquoise
Seq_6514_Gp6	paleturquoise
Seq_77_Staphylococcus_pettenkoferi	pink
Seq_78_Porphyromonas	pink
Seq_228_Parvimonas_micra	pink
Seq_230_Clostridiales	pink
Seq_274_Peptoniphilus	pink
Seq_329_Saccharofermentans_acetigenes	pink
Seq_353_Solobacterium_moorei	pink
Seq_357_Mobiluncus_curtisii	pink
Seq_368_Prevotella_buccalis	pink
Seq_400_Porphyromonas	pink
Seq_428_Clostridiales_Incertae_Sedis_XI	pink
Seq_439_Clostridiales	pink
Seq_469_Peptoniphilus_coxii	pink
Seq_480_Prevotella	pink
Seq_605_Clostridiales	pink
Seq_680_Pyramidobacter_piscolens	pink
Seq_691_Porphyromonas	pink
Seq_712_Fusobacterium	pink
Seq_776_Saccharofermentans_acetigenes	pink
Seq_834_Porphyromonas_somerae	pink
Seq_1035_Prevotella_corporis	pink
Seq_1127_Prevotella_corporis	pink
Seq_1215_Porphyromonas_somerae	pink
Seq_1349_Treponema_refringens	pink
Seq_1523_Corynebacterium_frankenforstense	pink
Seq_1647_Fusobacterium_nucleatum	pink
Seq_1698_Prevotella_corporis	pink
Seq_1744_Prevotella	pink
Seq_1829_Fusobacterium_nucleatum	pink
Seq_1856_Porphyromonas	pink
Seq_1897_Clostridium_symbiosum	pink
Seq_2149_Dialister_micraerophilus	pink
Seq_2163_Corynebacterium_frankenforstense	pink
Seq_2164_Eggerthia_catenaformis	pink
Seq_2204_Porphyromonas_bennonis	pink
Seq_2262_Clostridiales	pink
Seq_2291_Anaeroglobus_geminatus	pink
Seq_2383_Bacteroidetes	pink
Seq_2427_Porphyromonas_bennonis	pink
Seq_2844_Barnesiella	pink

Seq_3266_Ruminococcaceae	pink
Seq_3267_Porphyromonas_somerae	pink
Seq_3404_Bacteroidetes	pink
Seq_3767_Prevotella_buccalis	pink
Seq_3885_Saccharofermentans	pink
Seq_4021_Prevotella_buccalis	pink
Seq_4372_Lachnospiraceae	pink
Seq_5145_Prevotellaceae	pink
Seq_5592_Jonquetella_anthropi	pink
Seq_5595_Bacteroidetes	pink
Seq_6365_Bacteria	pink
Seq_6370_Prevotella	pink
Seq_6372_Bacteria	pink
Seq_6376_Saccharofermentans_acetigenes	pink
Seq_6377_Bacteroidetes	pink
Seq_6378_Prevotella_timonensis	pink
Seq_41_Anaerococcus	purple
Seq_97_Anaerococcus	purple
Seq_99_Acinetobacter_junii	purple
Seq_104_Porphyromonas_bennonis	purple
Seq_235_Anaerococcus_prevotii	purple
Seq_262_Acinetobacter_johnsonii	purple
Seq_269_Actinomyces_hominis	purple
Seq_297_Kocuria_rhizophila	purple
Seq_346_Pseudomonas	purple
Seq_448_Porphyromonas_bennonis	purple
Seq_566_Psychrobacter_sanguinis	purple
Seq_587_Acinetobacter	purple
Seq_595_Stenotrophomonas	purple
Seq_642_Paracoccus	purple
Seq_783_Staphylococcus	purple
Seq_817_Caulobacteraceae	purple
Seq_878_Anaerococcus_prevotii	purple
Seq_895_Actinomyces	purple
Seq_934_Brevibacterium	purple
Seq_959_Bacteroides_vulgatus	purple
Seq_1018_Enterobacter	purple
Seq_1216_Sphingobacterium_multivorum	purple
Seq_1386_Fusobacterium_nucleatum	purple
Seq_1465_Mycobacterium	purple
Seq_1639_Acinetobacter_calcoaceticus	purple
Seq_1851_Staphylococcus_epidermidis	purple
Seq_1877_Pseudomonas	purple
Seq_1890_Williamsia	purple
Seq_1902_Novosphingobium	purple

Seq_1952_Campylobacter_ureolyticus	purple
Seq_2231_Shewanella	purple
Seq_2372_Anaerostipes_hadrus	purple
Seq_2417_Brevundimonas	purple
Seq_2545_Rhodobacteraceae	purple
Seq_2745_Streptobacillus	purple
Seq_2747_Mycobacterium	purple
Seq_2881_Rhodobacteraceae	purple
Seq_3270_Acinetobacter	purple
Seq_3575_Aurantimonadaceae	purple
Seq_3679_Prevotella_melaninogenica	purple
Seq_3680_Enterobacteriaceae	purple
Seq_3681_Neisseriaceae	purple
Seq_3895_Conchiformibius_steedae	purple
Seq_4174_Leptotrichia	purple
Seq_4175_Enterobacteriaceae	purple
Seq_4176_Ruminococcus_bromii	purple
Seq_4387_Gardnerella_vaginalis	purple
Seq_4388_Cobetia_crustatorum	purple
Seq_4603_Pedobacter	purple
Seq_4604_Skermanella_aerolata	purple
Seq_4840_GpI	purple
Seq_5635_Moraxellaceae	purple
Seq_6467_Cardiobacteriaceae	purple
Seq_6468_Acidobacteria_Gp4	purple
Seq_6471_Capnocytophaga	purple
Seq_51_Anaerococcus_octavius	red
Seq_58_Staphylococcus_epidermidis	red
Seq_75_Neisseriaceae	red
Seq_202_Corynebacterium_sundsvallense	red
Seq_212_Streptococcus	red
Seq_219_Moraxella	red
Seq_224_Kocuria_rhizophila	red
Seq_281_Paracoccus	red
Seq_285_Gemmiger_formicilis	red
Seq_418_Acinetobacter_johnsonii	red
Seq_452_Finegoldia_magna	red
Seq_466_Dietzia	red
Seq_509_Acinetobacter	red
Seq_518_Peptoniphilus	red
Seq_557_Veillonella	red
Seq_677_Chryseobacterium_hispanicum	red
Seq_707_Actinomyces_europaeus	red
Seq_866_Kocuria_kristinae	red
Seq_1066_Pantoea	red

Seq_1084_Wautersiella_falsenii	red
Seq_1236_Acinetobacter_junii	red
Seq_1269_Porphyromonas_catoniae	red
Seq_1409_Finegoldia_magna	red
Seq_1591_Enterobacteriaceae	red
Seq_1616_Wautersiella_falsenii	red
Seq_1726_Acinetobacter	red
Seq_1807_Psychrobacter	red
Seq_1832_Haemophilus	red
Seq_1948_Staphylococcus	red
Seq_2053_Nosocomiicoccus_ampullae	red
Seq_2322_Rhizobium	red
Seq_2341_Acinetobacter	red
Seq_2461_Comamonas	red
Seq_2761_Pseudoxanthomonas	red
Seq_2772_Neisseria_mucosa	red
Seq_2815_Janthinobacterium	red
Seq_3004_Pantoea	red
Seq_3052_Enterobacteriaceae	red
Seq_3053_Enterobacteriaceae	red
Seq_3131_Bosea	red
Seq_3225_Streptococcus_sobrinus	red
Seq_3491_Paracoccus	red
Seq_3577_Neisseria_flavescens	red
Seq_3684_Acinetobacter	red
Seq_3685_Brevundimonas	red
Seq_4011_Actinomyces_odontolyticus	red
Seq_4187_Enterobacteriaceae	red
Seq_4189_Pseudomonas	red
Seq_4400_Enterobacteriaceae	red
Seq_4401_Pseudomonas	red
Seq_4618_Fusobacterium_nucleatum	red
Seq_4619_Staphylococcus_sciuri	red
Seq_4620_Flavobacterium	red
Seq_5192_Achromobacter	red
Seq_5193_Rhizobium	red
Seq_5194_Gp16	red
Seq_5668_Ruminococcus_bromii	red
Seq_5669_Betaproteobacteria	red
Seq_5671_Bacteria	red
Seq_5673_Corynebacteriaceae	red
Seq_6520_Betaproteobacteria	red
Seq_6521_Bacteria	red
Seq_6525_Bacteria	red
Seq_6530_Solirubrobacter_ginsenosidimutans	red

Seq_6667_Firmicutes	red
Seq_6668_Pseudomonas	red
Seq_223_Prevotella_timonensis	royalblue
Seq_291_Brevibacterium	royalblue
Seq_375_Corynebacterium	royalblue
Seq_462_Staphylococcus_pettenkoferi	royalblue
Seq_475_Porphyromonas_bennonis	royalblue
Seq_635_Dialister_propionicifaciens	royalblue
Seq_741_Porphyromonas	royalblue
Seq_860_Anaerococcus_octavius	royalblue
Seq_984_Clostridiales	royalblue
Seq_1008_Gallicola	royalblue
Seq_1064_Clostridiales	royalblue
Seq_1074_Bacteria	royalblue
Seq_1106_Coriobacteriaceae	royalblue
Seq_1126_Sutterella_stercoricanis	royalblue
Seq_1150_Clostridiales	royalblue
Seq_1232_Clostridiales	royalblue
Seq_1506_Anaerococcus_prevotii	royalblue
Seq_1633_Porphyromonas	royalblue
Seq_1661_Veillonellaceae	royalblue
Seq_2137_Clostridiales	royalblue
Seq_2162_Porphyromonas	royalblue
Seq_2181_Porphyromonas	royalblue
Seq_2384_Clostridiales	royalblue
Seq_2655_Actinomyces_turicensis	royalblue
Seq_2685_Porphyromonas_somerae	royalblue
Seq_2995_Porphyromonas	royalblue
Seq_3156_Porphyromonas	royalblue
Seq_3559_Treponema_refringens	royalblue
Seq_3754_Porphyromonas	royalblue
Seq_3884_Clostridiales	royalblue
Seq_4143_Ruminococcaceae	royalblue
Seq_4144_Peptoniphilus_coxii	royalblue
Seq_4370_Murdochiella_asaccharolytica	royalblue
Seq_4557_Bacteria	royalblue
Seq_4580_Barnesiella_intestinihominis	royalblue
Seq_4787_Firmicutes	royalblue
Seq_4818_Bacteria	royalblue
Seq_5144_Clostridiales	royalblue
Seq_6204_Bacteria	royalblue
Seq_6360_Varibaculum_cambriense	royalblue
Seq_6361_Bacteria	royalblue
Seq_6364_Bacteroidetes	royalblue
Seq_39_Anaerococcus	saddlebrown

Seq_148_Murdochiella_asaccharolytica	saddlebrown
Seq_153_Anaerococcus_octavius	saddlebrown
Seq_248_Corynebacterium_pseudogenitalium	saddlebrown
Seq_267_Finegoldia_magna	saddlebrown
Seq_289_Corynebacterium_pseudogenitalium	saddlebrown
Seq_305_Anaerococcus_prevotii	saddlebrown
Seq_461_Ruminococcus_obeum	saddlebrown
Seq_550_Peptoniphilus_coxii	saddlebrown
Seq_598_Gallicola	saddlebrown
Seq_777_Peptococcus_niger	saddlebrown
Seq_967_Streptococcus	saddlebrown
Seq_979_Dialister_propionicifaciens	saddlebrown
Seq_1053_Bacteroides_uniformis	saddlebrown
Seq_1117_Lachnospiraceae	saddlebrown
Seq_1373_Ruminococcaceae	saddlebrown
Seq_1501_Ruminococcus_bromii	saddlebrown
Seq_1538_Clostridium_XlVa	saddlebrown
Seq_1839_Oxalobacteraceae	saddlebrown
Seq_1905_Ruminococcus_callidus	saddlebrown
Seq_1940_Lachnospiraceae	saddlebrown
Seq_2340_Neisseria	saddlebrown
Seq_2676_Roseburia_intestinalis	saddlebrown
Seq_2831_Ruminococcaceae	saddlebrown
Seq_2996_Ruminococcaceae	saddlebrown
Seq_3208_Olsenella_uli	saddlebrown
Seq_3262_Lactobacillus	saddlebrown
Seq_3312_Eggerthella_lenta	saddlebrown
Seq_3392_Lachnospiraceae	saddlebrown
Seq_3560_Parabacteroides	saddlebrown
Seq_3561_Corynebacterium	saddlebrown
Seq_3757_Flavobacteriaceae	saddlebrown
Seq_4150_Pseudomonas	saddlebrown
Seq_4562_Veillonella	saddlebrown
Seq_4794_Oscillibacter	saddlebrown
Seq_5103_Gp1	saddlebrown
Seq_6218_Treponema	saddlebrown
Seq_30_Enhydrobacter	salmon
Seq_63_Acinetobacter	salmon
Seq_127_Anaerococcus_obesiensis	salmon
Seq_145_Prevotella_buccalis	salmon
Seq_242_Chryseobacterium	salmon
Seq_292_Peptoniphilus_lacrimalis	salmon
Seq_304_Acinetobacter	salmon
Seq_307_Jeotgalicoccus_pinnipedialis	salmon
Seq_338_Acinetobacter_parvus	salmon

Seq_412_Acinetobacter	salmon
Seq_421_Acinetobacter	salmon
Seq_426_Chryseobacterium_anthropi	salmon
Seq_473_Acinetobacter	salmon
Seq_499_Chryseobacterium_anthropi	salmon
Seq_502_Ochrobactrum	salmon
Seq_519_Chryseobacterium	salmon
Seq_653_Chryseobacterium_anthropi	salmon
Seq_676_Acinetobacter	salmon
Seq_704_Acinetobacter	salmon
Seq_706_Acinetobacter_tjernbergiae	salmon
Seq_823_Acinetobacter	salmon
Seq_827_Globicatella	salmon
Seq_873_Acinetobacter	salmon
Seq_971_Acinetobacter	salmon
Seq_988_Clostridium_IV	salmon
Seq_999_Bacteroides_vulgatus	salmon
Seq_1027_Prevotella_buccalis	salmon
Seq_1068_Microbacterium_lacticum	salmon
Seq_1198_Aerococcaceae	salmon
Seq_1486_Chryseobacterium	salmon
Seq_1625_Peptoniphilus	salmon
Seq_1727_Bosea	salmon
Seq_1837_Rhodobacter	salmon
Seq_1998_Helcococcus	salmon
Seq_2319_Dialister_invisus	salmon
Seq_2512_Stenotrophomonas_maltophilia	salmon
Seq_2588_Brevibacterium	salmon
Seq_2599_Vogesella	salmon
Seq_2893_Bacteroides_stercoris	salmon
Seq_2953_Staphylococcus_simulans	salmon
Seq_3165_Burkholderia	salmon
Seq_3239_Corynebacterium	salmon
Seq_3269_Staphylococcus	salmon
Seq_3572_Massilia_timonae	salmon
Seq_4030_Delftia	salmon
Seq_4171_Sphingopyxis	salmon
Seq_4383_Enterobacteriaceae	salmon
Seq_4597_Pseudomonas	salmon
Seq_4598_Xanthobacter_autotrophicus	salmon
Seq_5161_Vagococcus	salmon
Seq_5621_Terrimonas	salmon
Seq_5622_Neisseria_bacilliformis	salmon
Seq_6452_Porphyromonas	salmon
Seq_56_Clostridiales	skyblue

Seq_103_Chryseobacterium_hominis	skyblue
Seq_244_Clostridiales_Incertae_Sedis_XI	skyblue
Seq_301_Brachybacterium	skyblue
Seq_453_Bacteroides_uniformis	skyblue
Seq_479_Dorea_longicatena	skyblue
Seq_530_Brevibacterium_pityocampae	skyblue
Seq_560_Moryella_indoligenes	skyblue
Seq_577_Saccharofermentans_acetigenes	skyblue
Seq_584_Clostridiales_Incertae_Sedis_XI	skyblue
Seq_616_Helcococcus	skyblue
Seq_926_Corynebacterium_pseudogenitalium	skyblue
Seq_938_Staphylococcus	skyblue
Seq_968_Clostridiales	skyblue
Seq_1016_Porphyromonas_asaccharolytica	skyblue
Seq_1046_Porphyromonadaceae	skyblue
Seq_1195_Finegoldia_magna	skyblue
Seq_1292_Staphylococcus	skyblue
Seq_1586_Peptoniphilus	skyblue
Seq_1610_Corynebacterium_pseudogenitalium	skyblue
Seq_1611_Porphyromonadaceae	skyblue
Seq_1620_Acinetobacter	skyblue
Seq_1659_Porphyromonas_uenonis	skyblue
Seq_1682_Peptoniphilus	skyblue
Seq_2119_Slackia_exigua	skyblue
Seq_2177_Prevotella_buccalis	skyblue
Seq_2187_Haemophilus	skyblue
Seq_2191_Campylobacter_ureolyticus	skyblue
Seq_3492_Clostridiales	skyblue
Seq_3578_Clostridiales	skyblue
Seq_3904_Moryella_indoligenes	skyblue
Seq_3905_Aureimonas_altamirensis	skyblue
Seq_4626_Comamonadaceae	skyblue
Seq_4627_Clostridium_sensu_stricto	skyblue
Seq_4872_Pseudomonas	skyblue
Seq_4873_Aeromonas	skyblue
Seq_5691_Firmicutes	skyblue
Seq_6673_Prevotellaceae	skyblue
Seq_211_Corynebacterium_massiliense	steelblue
Seq_316_Corynebacterium_frankenforstense	steelblue
Seq_349_Corynebacterium_glucuronolyticum	steelblue
Seq_483_Corynebacterium	steelblue
Seq_563_Corynebacterium_frankenforstense	steelblue
Seq_578_Fusobacterium_periodonticum	steelblue
Seq_648_Staphylococcus	steelblue
Seq_660_Clostridium_glycolicum	steelblue

Seq_751_Peptoniphilus	steelblue
Seq_838_Porphyromonas_catoniae	steelblue
Seq_1155_Pseudomonas	steelblue
Seq_1225_Anaerococcus_vaginalis	steelblue
Seq_1238_Prevotella_salivae	steelblue
Seq_1297_Peptoniphilus	steelblue
Seq_1308_Pantoea	steelblue
Seq_1323_Streptococcus	steelblue
Seq_1361_Megasphaera_elsdenii	steelblue
Seq_1382_Gallicola	steelblue
Seq_1421_Prevotella_nanceiensis	steelblue
Seq_1567_Abiotrophia_defectiva	steelblue
Seq_1728_Actinomyces	steelblue
Seq_1938_Staphylococcus_epidermidis	steelblue
Seq_2150_Parasutterella_excrementihominis	steelblue
Seq_2155_Olsenella	steelblue
Seq_2361_Leptotrichia	steelblue
Seq_2498_Bacteroidetes	steelblue
Seq_2574_Lactobacillus	steelblue
Seq_2882_Corynebacterium	steelblue
Seq_3158_Lactobacillus	steelblue
Seq_3199_Prevotella_loescheii	steelblue
Seq_3296_Mogibacterium	steelblue
Seq_4035_Kocuria	steelblue
Seq_4608_Chryseobacterium	steelblue
Seq_4609_Piscicoccus_intestinalis	steelblue
Seq_5184_GpI	steelblue
Seq_5658_Sphingomonas	steelblue
Seq_6508_Prevotella_melaninogenica	steelblue
Seq_82_Staphylococcus	tan
Seq_132_Corynebacterium	tan
Seq_250_Staphylococcus	tan
Seq_260_Brevibacterium_paucivorans	tan
Seq_326_Corynebacterium	tan
Seq_374_Finegoldia_magna	tan
Seq_386_Blautia_luti	tan
Seq_395_Brevibacterium_luteolum	tan
Seq_441_Corynebacterium_jeikeium	tan
Seq_496_Anaerococcus_vaginalis	tan
Seq_537_Micrococcaceae	tan
Seq_541_Staphylococcus_pettenkoferi	tan
Seq_552_Corynebacterium_jeikeium	tan
Seq_599_Prevotella_copri	tan
Seq_602_Ruminococcus_torques	tan
Seq_621_Peptococcus_niger	tan

Seq_624_Brachybacterium	tan
Seq_765_Lachnospiraceae	tan
Seq_788_Ruminococcus	tan
Seq_807_Dorea_formicigenerans	tan
Seq_850_Kytococcus	tan
Seq_1088_Corynebacterium	tan
Seq_1104_Catenibacterium_mitsuokai	tan
Seq_1210_Clostridiales	tan
Seq_1310_Brevibacterium_luteolum	tan
Seq_1327_Bifidobacterium_angulatum	tan
Seq_1351_Faecalibacterium_prausnitzii	tan
Seq_1385_Clostridiales	tan
Seq_1515_Staphylococcus_pettenkoferi	tan
Seq_1702_Lachnospiraceae	tan
Seq_1780_Lachnospiraceae	tan
Seq_1881_Clostridium_XlVa	tan
Seq_1945_Flavonifractor	tan
Seq_2033_Bifidobacterium_bifidum	tan
Seq_2148_Staphylococcus_pettenkoferi	tan
Seq_2173_Prevotella_copri	tan
Seq_2367_Lactobacillus_ruminis	tan
Seq_2452_Staphylococcus	tan
Seq_2522_Erysipelotrichaceae	tan
Seq_2658_Prevotella_copri	tan
Seq_3044_Prevotella_copri	tan
Seq_3476_Ruminococcus_obeum	tan
Seq_4572_Anaerostipes_hadrus	tan
Seq_4573_Propionibacterium_acnes	tan
Seq_4574_Erysipelotrichaceae	tan
Seq_4803_Burkholderiales	tan
Seq_4805_Barnesiella_intestinihominis	tan
Seq_5547_Eubacterium_desmolans	tan
Seq_5548_Candidatus_Saccharibacteria	tan
Seq_6280_Bacteria	tan
Seq_6282_Lachnospiraceae	tan
Seq_6283_Roseburia	tan
Seq_6284_Acidaminococcus_intestini	tan
Seq_17_Streptococcus	turquoise
Seq_70_Staphylococcus	turquoise
Seq_85_Streptophyta	turquoise
Seq_140_Micrococcaceae	turquoise
Seq_167_Rothia_dentocariosa	turquoise
Seq_187_Staphylococcus	turquoise
Seq_198_Acinetobacter	turquoise
Seq_221_Staphylococcus_epidermidis	turquoise

Seq_233_Veillonella_dispar	turquoise
Seq_238_Streptococcus	turquoise
Seq_256_Dialister	turquoise
Seq_264_Granulicatella	turquoise
Seq_279_Streptococcus	turquoise
Seq_314_Kocuria	turquoise
Seq_319_Staphylococcus	turquoise
Seq_336_Acinetobacter	turquoise
Seq_358_Rothia_mucilaginosa	turquoise
Seq_369_Staphylococcus_epidermidis	turquoise
Seq_463_Alloprevotella	turquoise
Seq_506_Fusobacterium	turquoise
Seq_510_Porphyromonas_asaccharolytica	turquoise
Seq_582_Actinomyces	turquoise
Seq_611_Aggregatibacter	turquoise
Seq_643_Corynebacterium_singulare	turquoise
Seq_693_Staphylococcus	turquoise
Seq_764_Veillonella	turquoise
Seq_781_Staphylococcus_epidermidis	turquoise
Seq_795_Tetracoccus_cechii	turquoise
Seq_810_Staphylococcus	turquoise
Seq_835_Acinetobacter	turquoise
Seq_855_Fusobacterium_nucleatum	turquoise
Seq_859_Parvimonas_micra	turquoise
Seq_898_Staphylococcus	turquoise
Seq_922_Rothia_mucilaginosa	turquoise
Seq_933_Corynebacterium_matruchotii	turquoise
Seq_936_Saccharofermentans_acetigenes	turquoise
Seq_983_Leptotrichia_buccalis	turquoise
Seq_991_Prevotella	turquoise
Seq_995_Lachnospiraceae	turquoise
Seq_1021_Leptotrichia	turquoise
Seq_1081_Actinomyces_odontolyticus	turquoise
Seq_1093_Streptococcus	turquoise
Seq_1097_Ruminococcus_bromii	turquoise
Seq_1102_Gemella	turquoise
Seq_1162_Gemella_morbillorum	turquoise
Seq_1169_Leptotrichia_amnionii	turquoise
Seq_1187_Methylobacterium	turquoise
Seq_1199_Pasteurellaceae	turquoise
Seq_1214_Enterobacteriaceae	turquoise
Seq_1324_Kocuria	turquoise
Seq_1391_Acinetobacter	turquoise
Seq_1440_Actinomyces_georgiae	turquoise
Seq_1443_Leptotrichia_wadei	turquoise

Seq_1582_Actinomycetales	turquoise
Seq_1599_Acinetobacter_guillouiae	turquoise
Seq_1651_Sphingomonadales	turquoise
Seq_1653_Actinomycetales	turquoise
Seq_1679_Leptotrichia	turquoise
Seq_1687_Lachnoanaerobaculum	turquoise
Seq_1717_Brevibacterium	turquoise
Seq_1735_Staphylococcus_pasteuri	turquoise
Seq_1745_Corynebacterium_matruchotii	turquoise
Seq_1866_Bacteria	turquoise
Seq_1869_Selenomonas_noxia	turquoise
Seq_1891_Campylobacter	turquoise
Seq_1942_Leptotrichia	turquoise
Seq_1973_Aureimonas_jatrophae	turquoise
Seq_1977_Actinomyces	turquoise
Seq_2027_Lachnoanaerobaculum_saburreum	turquoise
Seq_2056_Rhizobium	turquoise
Seq_2075_Prevotella_melaninogenica	turquoise
Seq_2103_Acinetobacter	turquoise
Seq_2118_Leptotrichia	turquoise
Seq_2139_Serratia	turquoise
Seq_2209_Pseudomonas	turquoise
Seq_2273_Pasteurellaceae	turquoise
Seq_2282_Porphyromonas_catoniae	turquoise
Seq_2320_Chryseobacterium	turquoise
Seq_2324_Tannerella_forsythia	turquoise
Seq_2325_Lachnospiraceae	turquoise
Seq_2376_Corynebacterium_durum	turquoise
Seq_2377_Porphyromonas_endodontalis	turquoise
Seq_2479_Capnocytophaga_ochracea	turquoise
Seq_2501_Capnocytophaga	turquoise
Seq_2552_Leuconostoc	turquoise
Seq_2576_Fusobacterium_nucleatum	turquoise
Seq_2577_Porphyromonas_catoniae	turquoise
Seq_2593_Pseudomonas	turquoise
Seq_2632_Fusobacterium	turquoise
Seq_2661_Haemophilus_haemolyticus	turquoise
Seq_2666_Rhodococcus	turquoise
Seq_2690_Selenomonas	turquoise
Seq_2808_Lachnospiraceae	turquoise
Seq_2883_Flavobacteriaceae	turquoise
Seq_2905_Enterobacteriaceae	turquoise
Seq_2936_Filifactor_alocis	turquoise
Seq_2955_Haemophilus	turquoise
Seq_2956_Prevotella_nigrescens	turquoise

Seq_3001_Porphyromonadaceae	turquoise
Seq_3191_Olsenella_profusa	turquoise
Seq_3218_Prevotella_pleuritidis	turquoise
Seq_3272_Porphyromonas_bennonis	turquoise
Seq_3339_Capnocytophaga_ochracea	turquoise
Seq_3413_Selenomonas_sputigena	turquoise
Seq_3414_Prevotella_oulorum	turquoise
Seq_3415_Prevotella_saccharolytica	turquoise
Seq_3470_Tannerella_forsythia	turquoise
Seq_3493_Corynebacterium_imitans	turquoise
Seq_3494_Alloprevotella_rava	turquoise
Seq_3495_Capnocytophaga_ochracea	turquoise
Seq_3579_Prevotella_maculosa	turquoise
Seq_3687_Actinomyces	turquoise
Seq_3688_Stenotrophomonas	turquoise
Seq_3696_Eubacterium_saphenum	turquoise
Seq_3779_Porphyromonas_catoniae	turquoise
Seq_3780_Sphingomonadaceae	turquoise
Seq_3902_Ilumatobacter_fluminis	turquoise
Seq_3938_Deinococcus_aerolatus	turquoise
Seq_4196_Haemophilus	turquoise
Seq_4197_Cardiobacterium_valvarum	turquoise
Seq_4198_Selenomonas_artemidis	turquoise
Seq_4200_Citrobacter	turquoise
Seq_4323_Bacteria	turquoise
Seq_4403_SR1	turquoise
Seq_4404_Pseudomonas	turquoise
Seq_4405_Flavobacteriaceae	turquoise
Seq_4406_Corynebacterium_riegelii	turquoise
Seq_4629_Prevotella_saccharolytica	turquoise
Seq_4630_Nakamurella_multipartita	turquoise
Seq_4633_Clostridiales	turquoise
Seq_4874_Treponema_amylovorum	turquoise
Seq_4875_Leptotrichia	turquoise
Seq_4878_Aurantimonadaceae	turquoise
Seq_5202_Peptococcus_niger	turquoise
Seq_5204_Candidatus_Saccharibacteria	turquoise
Seq_5205_Treponema	turquoise
Seq_5206_Prevotella_marshii	turquoise
Seq_5693_Sinobacteraceae	turquoise
Seq_5694_Veillonellaceae	turquoise
Seq_5696_Sphingobacterium	turquoise
Seq_5697_Actinobacteria	turquoise
Seq_5698_Bacteria	turquoise
Seq_5699_Bacteria	turquoise

Seq_5702_Vibrio	turquoise
Seq_5703_Veillonellaceae	turquoise
Seq_5705_Clostridiales	turquoise
Seq_6555_Proteobacteria	turquoise
Seq_6558_Micrococcaceae	turquoise
Seq_6564_SR1	turquoise
Seq_88_Propionibacterium_granulosum	violet
Seq_176_Propionibacterium	violet
Seq_215_Staphylococcus_epidermidis	violet
Seq_288_Corynebacterium_kroppenstedtii	violet
Seq_302_Spirosoma	violet
Seq_315_Staphylococcus	violet
Seq_678_Propionibacterium_acnes	violet
Seq_713_Neisseria	violet
Seq_733_Enterococcus	violet
Seq_744_Wautersiella_falsenii	violet
Seq_961_Marmoricola_scoriae	violet
Seq_1149_Bacteroides_uniformis	violet
Seq_1220_Sphingomonas_glacialis	violet
Seq_1337_Turicella_otitidis	violet
Seq_1528_Prevotella_histicola	violet
Seq_1556_Phenylobacterium	violet
Seq_1560_Pseudomonas	violet
Seq_1572_Veillonella	violet
Seq_1638_Gp4	violet
Seq_1759_Pseudomonas	violet
Seq_1875_Sphingomonadales	violet
Seq_1912_Actinomycetales	violet
Seq_1984_Enterococcus	violet
Seq_2068_Candidatus_Saccharibacteria	violet
Seq_2085_Blastocatella	violet
Seq_2136_Lactobacillus_versmoldensis	violet
Seq_2391_Comamonadaceae	violet
Seq_2398_Enterococcus	violet
Seq_2537_Sphingomonas	violet
Seq_2691_Pseudomonas	violet
Seq_2811_Rudaeicoccus_suwonensis	violet
Seq_2885_Bacteria	violet
Seq_3908_Sphingomonas	violet
Seq_4647_Comamonadaceae	violet
Seq_5727_Capnocytophaga_ochracea	violet
Seq_90_Porphyromonas	white
Seq_147_Haemophilus_parainfluenzae	white
Seq_183_Finegoldia_magna	white
Seq_610_Haemophilus	white

Seq_638_Burkholderiales	white
Seq_735_Alloprevotella_rava	white
Seq_768_Alloprevotella	white
Seq_871_Rhizobium	white
Seq_896_Streptococcus_sanguinis	white
Seq_1069_Alloprevotella_rava	white
Seq_1264_Bacillaceae_2	white
Seq_1522_Finegoldia_magna	white
Seq_1535_Lactobacillus_delbrueckii	white
Seq_1667_Alloprevotella_rava	white
Seq_1868_Treponema_lecithinolyticum	white
Seq_1990_Actinomyces	white
Seq_2077_Leptotrichia	white
Seq_2467_Porphyromonas_catoniae	white
Seq_2612_Capnocytophaga_sputigena	white
Seq_2727_Pseudomonas	white
Seq_2839_Conchiformibius_steedae	white
Seq_2915_Granulicatella	white
Seq_3755_Rubellimicrobium_aerolatum	white
Seq_3756_Prevotella_nigrescens	white
Seq_3873_Oxalobacteraceae	white
Seq_4004_Leuconostoc	white
Seq_4147_Naxibacter	white
Seq_4148_Acetobacter_lovaniensis	white
Seq_4149_Intrasporangiaceae	white
Seq_4347_Armatimonadetes_gp5	white
Seq_4348_GpI	white
Seq_4561_Candidatus_Saccharibacteria	white
Seq_4792_Chlorophyta	white
Seq_4793_Rubellimicrobium	white
Seq_5102_Erwinia	white
Seq_5510_Chryseobacterium	white
Seq_5512_Clostridiales_Incertae_Sedis_XI	white
Seq_6217_Chloroplast	white
Seq_89_Brevibacterium	yellow
Seq_137_Lactobacillus	yellow
Seq_204_Neisseria_meningitidis	yellow
Seq_218_Nosocomiicoccus_ampullae	yellow
Seq_225_Corynebacterium_urealyticum	yellow
Seq_234_Neisseriaceae	yellow
Seq_261_Prevotella_copri	yellow
Seq_298_Anaerococcus	yellow
Seq_332_Anaerococcus_prevotii	yellow
Seq_335_Clostridiales_Incertae_Sedis_XI	yellow
Seq_337_Corynebacterium_urealyticum	yellow

Seq_392_Collinsella_aerofaciens	yellow
Seq_437_Corynebacterium_urealyticum	yellow
Seq_476_Anaerococcus	yellow
Seq_522_Pseudomonas	yellow
Seq_559_Micrococcaceae	yellow
Seq_580_Anaerococcus	yellow
Seq_632_Peptoniphilus_coxii	yellow
Seq_644_Clostridiales	yellow
Seq_645_Staphylococcus	yellow
Seq_791_Ruminococcus_torques	yellow
Seq_806_Anaerococcus	yellow
Seq_814_Anaerococcus_octavius	yellow
Seq_903_Clostridiales	yellow
Seq_1077_Actinomyces_odontolyticus	yellow
Seq_1325_Carnobacteriaceae	yellow
Seq_1480_Pseudomonas	yellow
Seq_1551_Anaerococcus_prevotii	yellow
Seq_1626_Brevundimonas	yellow
Seq_1648_Porphyromonas_bennonis	yellow
Seq_1658_Streptococcus	yellow
Seq_1725_Staphylococcus	yellow
Seq_1731_Prevotella_copri	yellow
Seq_1816_Dialister_propionicifaciens	yellow
Seq_2054_Clostridiales	yellow
Seq_2138_Dietzia_timorensis	yellow
Seq_2141_Anaerococcus	yellow
Seq_2375_Comamonas_kerstersii	yellow
Seq_2412_Dialister_propionicifaciens	yellow
Seq_2549_Prevotella_copri	yellow
Seq_2610_Capnocytophaga_sputigena	yellow
Seq_2659_Anaerococcus	yellow
Seq_2667_Mogibacterium	yellow
Seq_2723_Flavobacterium	yellow
Seq_2731_Negativicoccus_succinicivorans	yellow
Seq_2746_Clostridiales	yellow
Seq_2796_Lachnospiraceae	yellow
Seq_2845_Enterobacteriaceae	yellow
Seq_2999_Saccharofermentans_acetigenes	yellow
Seq_3110_Porphyromonas_bennonis	yellow
Seq_3214_Dietzia	yellow
Seq_3463_Cloacibacterium_normanense	yellow
Seq_3676_Micrococcaceae	yellow
Seq_3704_Micrococcaceae	yellow
Seq_3768_Actinomycetales	yellow
Seq_3889_Corynebacterium	yellow

Seq_4378_Massilia	yellow
Seq_4589_Peptococcus_niger	yellow
Seq_4590_Actinomycetales	yellow
Seq_4593_Veillonella	yellow
Seq_4594_Eubacterium_desmolans	yellow
Seq_4795_Bacteroidetes	yellow
Seq_4822_Sphingobacterium_faecium	yellow
Seq_4824_Prevotella_bergensis	yellow
Seq_4825_Chryseobacterium	yellow
Seq_4827_Megasphaera_elsdenii	yellow
Seq_4829_Selenomonas_artemidis	yellow
Seq_4830_Bacteroidetes	yellow
Seq_5069_Clostridiales_Incertae_Sedis_XI	yellow
Seq_5104_Facklamia	yellow
Seq_5152_Prevotella_nanceiensis	yellow
Seq_5153_Atopostipes_suicloacalis	yellow
Seq_5154_Prosthecobacter	yellow
Seq_5155_Stenotrophomonas_maltophilia	yellow
Seq_5603_Prevotella_buccalis	yellow
Seq_5604_Bacteria	yellow
Seq_5605_Sphingomonadaceae	yellow
Seq_5606_Moheibacter	yellow
Seq_5607_Moraxella	yellow
Seq_6221_Staphylococcus	yellow
Seq_6222_Ruminococcus_champanellensis	yellow
Seq_6410_Peptostreptococcus_anaerobius	yellow
Seq_6417_Burkholderiales	yellow
Seq_6418_Porphyromonas	yellow
Seq_6432_Bacteria	yellow