General background of pathway production	MetaCyc metabolic pathway	Enzyme Classifications and Kegg Orthologs (gene ID)	Bacteria genus associated with pathways (D=Drops; ND=No-Drops)
Predominant pathways in Drops and No-Drops samples compared to Control samples			
Heptose sugar synthesis: lipopolysaccharides (LPS), capsules, and O-antigens of gram-negative bacteria	- GDP-D-glycero-α-D-manno-heptose biosynthesis - Superpathway of GDP-mannose-derived O-antigen building blocks biosynthesis	- D-sedoheptulose 7-phosphate isomerase (gmhA) - GDP-4-dehydro-6-deoxy-D-mannose reductase (rmd) - GDP-mannose 4,6-dehydratase (gmd) - D-glycero-β-D-manno-heptose 1,7-bisphosphate 7-phosphatase (gmhB) - D-glycero-α-D-manno-heptose-1,7-bisphosphate 7-phosphatase (gmhB) -D-glycero-α-D-manno-heptose 1-phosphate guanylyltransferase (gmhD, hddC) - GDP-L-fucose synthase (fcl) - mannose-1-phosphate guanylyltransferase (gmpp)	- Akkermansia (ND and D) - Anaerococcus (D) - Bacteroides (ND and D) - Bradyrhizobium (ND) - Incertae sedis (D) - Lachnoclostridium (D) - Lachnospira (D) - Lawsonella (D) - Ochrobactrum (ND)
Synthesis of Lipid A, component that anchors LPS into the outer membrane of gram-negative bacteria	- Lipid IVa biosynthesis - Kdo transfer to lipid IVa III	- Acyl-[acyl-carrier-protein]-phospholipid O-acyltransferase (aas) - Lipid-A-disaccharide synthase (ipxB) - Lipid IV(A) 3-deoxy-D-manno-octulosonic acid transferase (gseA, waaA) - (Kdo)-lipid IV(A) 3-deoxy-D-manno-octulosonic acid transferase (gseA, waaA) - (Kdo)(2)-lipid IV(A) (2-8) 3-deoxy-D-manno-octulosonic acid transferase (gseA, waaA) - (Kdo)(3)-lipid IV(A) (2-4) 3-deoxy-D-manno-octulosonic acid transferase (gseA, waaA) - (Kdo)(2)-lipid IV(A) lauroyltransferase (ipxL)	- Akkermansia (ND) - Bradyrhizobium (ND) - Christensenellaceae R-7 group (ND) - Gluconobacter (D) - Komagataeibacter (D) - Ochrobactrum (ND) - Rosemonas gilerdii (ND)
Synthesis of polysaccharide component of bacterial LPS	- CMP-3-deoxy-D-manno-octulosonate biosynthesis I	- Arabinose-5-phosphate isomerase (gutQ) - 3-deoxy-8-phosphooctulonate synthase (kdsA1) -3-deoxy-manno-octulosonate cytidylyltransferase (cks)	- Akkermansia (ND) - Bradyrhizobium (ND) - Christensenellaceae R-7 group (ND) - Gluconobacter (D) - Komagataetibacter (D) - Ochrobactrum (ND) - Rosemonas gilardii (ND) - Sphingobium (ND)
Synthesis of 7-deazapurines from nucleotide GTP	- PreQ0 biosynthesis	- 6-carboxytetrahydropterin synthase (queD) - 7-carboxy-7-deazaguanine synthase (queC) - 7-cyano-7-deazaguanine reductase (queF) - 7-carboxy-7-deazaguanine synthase (queE)	- Akkermansia (ND) - Bradyrhizobium (ND) - Christensenellaceae R-7 group (ND) - Gluconobacter (D) - Komagataeibacter (D) - Ochrobactrum (ND) - Rosemonas gilardii (ND) - Ruminococcus torques group (ND)
Heptose sugar synthesis: lipopolysaccharides (LPS), capsules, and O-antigens of gram-negative bacteria	- GDP-D-glycero-α-D-manno-heptose biosynthesis - ADP-L-glycero-β-D-manno-heptose biosynthesis	- D-glycero-α-D-manno-heptose 1-phosphate guanylyltransferase (hddC) - D-glycero-β-D-manno-heptose 1,7-bisphosphate 7-phosphatase (gmhB) - D-glycero-α-D-manno-heptose-1,7-bisphosphate 7-phosphatase (gmhB) - D-sedoheptulose 7-phosphate isomerase (gmhA)	- Bradyrhizobium (ND) - Christensenellaceae R-7 group (D) - Lachnoclostridium (D) - Lachnospiraceae groups (D) - Lachnospiraceae NK4A136 group (D) - Ruminococcus sp. (D)

Bacterial anaerobic biosynthesis of unsaturated fatty acids	- Gondoate biosynthesis (anaerobic) - cis-vaccenate biosynthesis	- Enoyl-[acyl-carrier-protein] reductase (fabK) - 2,4-dienoyl-CoA NADH reductase (fadH)	- Agathobacter (D) - Akkermansia (D+ND) - Bradyrhizobium (D+ND) - Coprococcus (ND) - Faecalibacterium (D+ND) - Fusobacterium (D) - Lachnoclostridium (ND) - Lachnospiraceae NK4A136 group (D) - Oscillabacter (ND) - Oscillospiraceae UCG-005 (D) - Roseburia (D+ND) - Ruminococcus sp. (D+ND)
Predominant pathways in Control samples compared to Drops and No-Drops samples			
Heme and tetrapyrrole biosynthesis	- Heme biosynthesis I (aerobic) - Heme biosynthesis II (anaerobic) - Superpathway of heme biosynthesis from glutamate	- Uroporphyrinogen decarboxylase (hemE, urod) - Protoporphyrinogen oxidase (hemF) - Ferrochelatase (hemH) - Glutamate-tRNA ligase (gltX) - heme iron utilization protein (hugZ) - heme oxygenase 1 (hmox1) - putative heme uptake system protein - coproporphyrinogen III oxidase (hemF) - uroporphyrinogen-III synthase (hemD) - coproporphyrin ferrochelatase (hemH) - uroporphyrin-III C-methyltransferase (cobA)	- Brevibacter - Corynebacterium - Cutibacterium - Gluconobacter - Kocuria - Komagaetibacter - Methylobacterium - Rothia - Sphingomonas
Synthesis of thiols (e.g., glutathione, mycothiol)	- Mycothiol biosynthesis	- S-(hydroxymethyl)-mycothiol dehydrogenase (E1.1.1.306) - Myocothiol synthase (mshD) - Aresnate-mycothiol transferase (arsC) - Mycothiol S-conjugate amidase (mca) - D-inositol-3-phosphate glycosyltransferase (mshA)	- Brevibacterium - Corynebacterium - Kocuria - Lawsonella - Rothia
Synthesis of biotin, a heterocyclic cofactor for CO2 transfer during many cellular pathways including fatty acid and carbohydrate metabolism	- Biotin biosynthesis II	- Dethiobiotin synthase (bioD) - 6-carboxyhexanoate-CoA ligase (bioW) - Adenosylmethionine-8-amino-7-oxononanoate transaminase (bioA) - biotin carboxylase, biotin carboxyl carrier protein (bccA, pccA) - biotin transport system permease protein (bioN) - biotin transport system ATP-binding protein (bioM)	- Bacteroides - Corynebacterium - Methylobacterium - Shigella

Supplemental Table 3. Differentially abundant metabolic pathways - inference of microbial community functional profiles using PICRUSt2. The differentially abundant predicted metabolic pathways that are shared by the microbial communities on both the patients' treated and untreated eyes and the predominant pathways for the healthy control subject microbiome are summarized in this table. Predicted metagenome functional pathways were identified for microbial communities using 16S amplicon marker gene sequences. Differentially abundant pathways found in patient eye samples treated with eyedrops ("Drops/D") and patient eye samples not treated with eyedrops ("No Drops/ND") when compared to health controls ("Control") were identified using ALDEx2. The listed MetaCyc metabolic pathways with associated Enzyme Classifications and Kegg Orthologs had statistically significant difference in functional abundance when comparing Drops vs. Controls and No Drops vs. Controls. Statistical significance was determined using a Wilcoxon rank-sum test with p-values < 0.05 following correction using the Benjamini and Hochberg method. The genus classifications associated with each metabolic pathway are labeled with the corresponding patient eye sample (Drops "D" or No Drops "ND") where the bacteria is predicted to be functionally active. The genus classifications associated with pathways that are predominant in healthy control eye samples are inferred to be functionally active on control samples and therefore, do not have a corresponding label.