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ULTRA-HIGH MAGNIFICATION ENDOCYTOSCOPY AND MOLECULAR MARKERS FOR DEFINING ENDOSCOPIC AND HISTOLOGIC REMISSION IN ULCERATIVE COLITIS – AN EXPLORATORY STUDY TO DEFINE DEEP REMISSION

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ABSTRACT

Background

Endoscopic and histological remission are both important treatment goals in patients with ulcerative colitis (UC). We aimed to define cellular architecture, expression of molecular markers and their correlation with endoscopic scores assessed by ultra -high magnification endocytoscopy (ECS) and histological scores.

Methods

UC patients (n=29) were prospectively recruited. The correlation between ECS score (ECSS) and Mayo Endoscopic Score (MES) and with histological scores were determined.

AUC were plotted to determine the best thresholds for ECSS that predicted histological remission by Robarts (RHI) and Nancy Histological Index (NHI).

Soluble analytes relevant to inflammation were measured in serum and mucosal culture supernatants using Procartaplex Luminex assays and studied by Partial Least Square Discriminant Analysis and logistic model.

Mucosal RNA sequencing and bioinformatics analysis were performed to define differentially expressed genes /pathways.

Results

ECSS correlated strongly with RHI (r= 0.89 [95% CI 0.51- 0.98] and NHI (r= 0.86 [95% CI 0.42- 0.98] but correlated poorly with MES (r= 0.28 [95% CI-0.27 – 0.70]). We identified soluble BDNF, MIP-1 α and sVCAM-1 predicted histological remission. Mucosal biopsy cultures also identified sVCAM-1 associated with healed mucosa. RNA-seq analysis identified gene expressions shared between ECSS, RHI or NHI defined healing. A number of gene expressions and pathways were identified including inflammation, metabolic and tumour suppressors that discriminated healed from non-healed mucosa .

Conclusions

ECS represents an interesting tool that may sit between endoscopy and histology but closer to the latter, identifies gene expression markers and pathways that are also identified by histology.

INTRODUCTION

Achieving mucosal healing (MH) is considered to be a primary target in the treatment of inflammatory bowel disease (IBD)[1-3]. MH increasingly incorporates both endoscopic remission (ER) and histologic remission (HR). Nevertheless, ER does not necessarily correspond to HR [4-6]. Indeed, there is an increasing evidence that patients with ER have histological inflammation accounting for relapse and adverse outcomes at follow-up[7,8]. This discrepancy between HR and ER might be explained by the use of conventional endoscopes that cannot detect accurately subtle inflammation.[9,10]

Several studies have shown that HR is associated with reduced steroid use, lower risk of complication, hospitalization and colorectal cancer development, suggesting it is an important endpoint to achieve especially in ulcerative colitis (UC). [11-14]

The advanced endoscopy technologies are getting closer to histology by introducing the new concepts of mucosal and vascular healing patterns. [15,16] Several studies have demonstrated that with widely available advanced technologies such as virtual electronic chromoendoscopy (VEC) and high definition (HD) imaging, endoscopic and histologic scores correlate more strongly and reduced discrepancy between the two[17-19]. This has also been shown using artificial intelligence approach utilizing deep neural network approach [20,21].

Among these new endoscopic armamentarium , endocytoscopy (ECS; CF- Y-0058-1 prototype, Olympus Japan) is a new technique which provides " *in vivo* microscopic" imaging during endoscopy, with ultra-high magnification ranging from 450 -fold to 1400-fold, looking at cells and nuclei of mucosal surfaces. ECS is a reliable technique to assess precisely ER and HR potentially reducing the need for biopsy specimens**.** Notably, biopsies can assess only a limited area whereas ECS is an optical diagnosis tool, which can sample a wider area *in vivo* of the colonic mucosa [22]. Studies with ECS have shown high reproducibility between endoscopists and demonstrated that it predicts accurately histological inflammation and HR [22-25]. Therefore, ECS is a bridge between endoscopy and histology but further studies are required.

The identification of non-invasive molecular markers to monitor IBD patients by predicting MH and the risk of flare-up is a growing area of interest. Frequent endoscopic examinations are costly and uncomfortable for the patient , thereby a need exists for blood-based biomarkers that accurately assess MH which correlates well with endoscopic findings[26]. Recently a commercial panel based on blood levels of 13 proteins, called the endoscopic healing index [27], was developed and preliminary evidence supports that it can identify endoscopic healing favouring the non-invasive monitoring and management of Crohn's disease (CD) patients .[28] Despite the encouraging results of EHI, it did not include histological assessment to confirm MH and has not been reproduced in UC.

While, many studies have explored the gene expression profiles in the context of specific therapies [29,30], few studies have investigated ultrastructural and molecular mechanisms of intestinal healing beyond absence of inflammation. Whether advanced endoscopic techniques such as ECS and histology share molecular footprints of intestinal restitution and repair requires further evidence. Importantly, MH is not just an absence of inflammation but an active process of restitution and repair at the cellular and molecular level. [31]

AIM

The main objectives of this exploratory study was to understand ER and HR in UC determined by ultra- high magnification “in vivo microscopy “ECS, determine the correlation between endocytoscopy and histology, and to define cellular architecture, expression of molecular and genomic markers and their correlation with endoscopic score defined by ultra -high magnification and with histology scores.

MATERIALS AND METHODS

Patients

We conducted a prospective study enrolling consecutive 29 UC patients, 18 males (62%); mean age 41 years ± SD 15) referred for assessing ER achieved after treatment or for surveillance, between January 2018 and July 2019, at a tertiary academic centre (Queen Elizabeth II) Birmingham (UK).

We collected demographic data, including patient characteristics and clinical data detailing age at diagnosis and disease characteristics (extent of disease, Montreal classification), treatments (corticosteroids, immunosuppressive therapy, biologics) clinical disease activity scores (Full and partial Mayo score [32]) and endoscopic activity scores (Mayo endoscopic score (MES) [33], Ulcerative Colitis Endoscopic Index (UCEIS)[34] and Paddington International virtual chromoendoscopy score (PICaSSO)[35-37]. (Table 1)

Endoscopic procedure

All the patients recruited underwent colonoscopies with endocytoscope (ECS; CF- Y-0058-1 prototype Olympus, Japan) with 520 -fold magnification in order to obtain ultra-magnified images and to define inflamed and healed areas. For consistency of technique all of the procedures were performed by one colonoscopist (MI) experienced in ECS and optical diagnosis in IBD to harmonize and accurately assess the grade of inflammation but the endoscopic findings were scored by 2 endoscopists during the procedure and also video recorded. The agreed score between the two endoscopists was recorded and analysed.

The colonic mucosa was initially assessed using HD white light endoscopy (WLE) and Narrow Banding Imaging (NBI) with and without magnification. The inflammatory activity was scored using the MES and we defined ER as MES 0.[2] Biopsies were taken targeting either the worst affected area of inflammation or the most representative area of endoscopic healing. Following washing of the mucosa with water plus simethicone and staining with 10mL of 1% methylene blue solution, ECS was performed in the same area of the colon where endoscopic activity was scored. The following endoscopic parameters for ECSS were assessed to grade the inflammation (table 2) : (a) the shape of the crypts (normal round, elongated, irregular, necrosis); (b) infiltration of the cell between the crypts (≤50% vs ≥50%); (c) the distance between the crypts (normal, 3 or more crypts in a visual field (VF), ≤ 2 crypts in a VF, intermediate 2 ≤ crypts ≥ 3 in a

VF with infiltrating cells in lamina propria , drop-out /necrosis) and (d) the visibility of superficial microvessels (not visible vs visible).We set an overall score of 3-9 and we defined the following subscores : the shape of crypts (range: 1 – 3), infiltration between the crypts (range: 1-2), distance between the crypts (range: 1 – 3), and the visibility of superficial microvessels (range: 0 – 1). This score was adapted from Nakazato *et al* by including endoscopic findings representative of disease activity (infiltration of cells). [22](Figure 1).

Pictures and videos collected under HD-WLE, NBI and then ECS from each patient were all recorded and digitally stored for subsequent analyses by using the Olympus recording system IMH-20.

Histological Scoring

Histological assessment of inflammatory activity was scored by an expert pathologist blinded to clinical and endoscopic information. The following histological scores were used: NHI score (0-4 range) [38] and Robarts Histological Index (RHI) [39](0-33 range). HR was defined as NHI ≤ 1[38], and RHI ≤ 3 without neutrophils in the epithelium and lamina propria (LP)[40].

Analysis of Soluble Markers

A. Serum Collection

Serum samples were collected from all patients at the time of the colonoscopy in BD SST vacutainer tubes and processed within 4 hours. Samples were spun at 1300 *g* for 10 minutes and serum removed and stored at -80C prior to analysis.

B. Culture of Mucosal Biopsies

Endoscopic biopsies were cultured in 10% fetal bovine serum, 50U/ml Penicillin/Streptomycin, 200µM L-Glutamine, 50µg/ml Gentamicin, 2.5µg/ml Amphotericin B, 50µM 2-mercaptoethanol in RPMI (1640) at mass to volume ratio of 20ug/ml. At 24 hours, supernatants were harvested, centrifuged for 10 mins at 10000g and stored at -80C prior to analysis.

Serum and mucosal biopsy culture supernatants were thawed on ice and analysed for 56 soluble markers (Table 3) using ProcartaPlex Luminex assays (ThermoFisher Scientific, UK) according to manufacturer guidelines. Serum samples were diluted 2 fold for all analytes except for MMP-2, MMP9, iICAM-1 and sVCAM-1 which were diluted 100 fold. Culture supernatants were used neat.

RNA Extraction, Library Preparation and Sequencing

Endoscopic biopsies of the colon were stored in RNA later prior to RNeasy on-column RNA extraction and purification (Qiagen). RNA was quantified by Qubit (Life Technologies) and 0.5*ng* used to prepare uniquely indexed cDNA QIAseq UPX 3’ Transcriptome libraries according to manufacturer’s instructions. Libraries were quantified and quality-controlled using the QIAseq Library Quant Assay Kit and tapestation analysis and sequenced on the Miseq and Nextseq Illumina platforms to a depth of 1-3milion reads/sample. Fastq files were obtained through BaseSpace and reads de-multiplexed aligned, quantified and normalised using the CLC Genomics Workbench (Qiagen, UK). The RNA seq data has been deposited and the raw data should be available at Array Express through accession number E-MATB-9731.

STATISTICAL ANALYSIS AND INFORMATICS

A. Demographic, clinical and endoscopic data

Demographic, clinical and endoscopic data were collected using the REDCap platform and the results transferred to a Microsoft Excel database.

Pearson correlation between MES and ECSS and histological scores and between Picasso total score and UCEIS and ECSS was calculated. Very strong correlation was considered as a value of 0.8-1.0, strong as 0.6-0.79, moderate as 0.40-0.59 and weak as 0.2-0.39

We determined diagnostic accuracy, sensitivity and specificity of MES and ECSS assessed by HD-NBI to predict HR. Receiver operating characteristic (ROC) curves were plotted as sensitivity versus 1-specificity to explore the ability of endoscopic scores to predict HR .The area under the receiver operating characteristic curve (AUROC) was determined to accurately identify the cut-off of MES and ECSS that reflect HR.

B. Cytokine panel analysis from blood samples

A total of 56 soluble analytes relevant to inflammation or shown to be altered in UC were measured in serum (Table 3). Measurements that did not fall within the standard range of the assay were assigned the maximum or lower limits of the assay as appropriate and analytes that were not detected in at least 40% of patients in one group were excluded from analysis to reduce type 1 errors. Those not detected in serum or culture supernatants are marked in Table 3. Detected analytes were used to train a logistic regression model.

C. Luminex soluble marker analysis from mucosal culture supernatants

Luminex data were initially analysed using t-test across all the comparisons separately. The selected analytes were then included in a regression model utilising Partial Least Square -Discriminant analysis (PLS-DA). A False Discovery Rate (FDR) corrected p value (q value) was considered for significance. Significant cytokines/soluble markers were then further analysed using PLS-DA modelling.[41] We used Variable Importance in Projection |(VIP) to prioritise the features. VIP is a measure of a variable's importance in the PLS-DA model. It summarizes the contribution a variable makes to the model. Markers with a VIP score of more than 1.5 were used.[42]Area under the curve (AUC) for each comparison was calculated to show the sensitivity and specificity of each combinations of the markers.

D. RNA sequencing data

Bioinformatics analysis of the RNA sequencing data was performed. The following differential expression procedure was performed for participants classified as healed versus non-healed according to each of the scoring procedures. Transcripts per million (TPM) normalised values [43] were log-transformed with a pseudocount of 1 added. Transcripts with < 1 transformed count in any sample were excluded from further analysis, as were transcripts with low variance (defined as less than 10% unique counts across both conditions and greater than a 19:1 ratio of the most frequent count to the second most frequent across both conditions). Differential expression analysis between conditions was conducted with the limma package [44]. Library size was estimated using reduced maximum likelihood estimator with 500 iterations. Initial fitting was performed using a robust M-estimation, and moderated test statistics computed by empirical Bayes. A FDR corrected p value <0.05 was considered and filtered for further downstream data analysis. Partial least squares discriminant analysis (PLS-DA) modelling was performed on these genes. A VIP score was used to further filter the genes and measured a variable's importance in the PLS-DA model. For gene expression analysis we used genes VIP score more than 1. To understand the biological significance and pathways, we also performed enrichment analysis using EnrichR [45] . Pathway enrichment was done using Gene ontology and Kyoto Encyclopaedia of Genes and Genomes (KEGG).[27] Differentially expressed up and down regulated genes were visualised using volcano plots. We considered Fold change >2.0 and FDR corrected p value <0.05 across healed vs. non healed samples.

The RNA sequencing data was loaded into ArrayExpress (ArrayExpress accession:E-MTAB-9731)

RESULTS

Patient characteristics

The demographic characteristics of the patients are summarised in Table 1. Eighty-six % (25/29) of UC patients had pancolitis, and 52% (15/29) were in clinical remission according to partial Mayo Clinical score, while 38% (11/29) showed endoscopic MES 0 and 28% (8/29) MES 1.; 45% (13/29) and 52% (15/29) were in histologic remission (HR) according to NHI ≤ 1 [38] and RHI ≤ 3[40] respectively.

Correlations of endocytoscopy and histology (Nancy and RHI) scores in UC

The ECS total score had very strong correlation with HR as defined by NHI r= 0.86 (95% CI 0.42- 0.98) and RHI r= 0.89 (95% CI 0.51- 0.98). While ECS total score correlated weakly with MES r= 0.28 (95% CI-0.27 – 0.70). MES correlated strongly with NHI r= 0.73 (95%CI 95% 0.35-090) and RHI r=0.63 (95% CI 0.18-0.86), though less strongly than with ECSS. (Table.4)

Correlations of endocytoscopy and endoscopic PICASSO and UCEIS scores in UC

The ECS total score showed a strong correlation with PICaSSO total score r= 0.67 (95% CI 0.40- 0.83) and with UCEIS r = 0.74 (95% CI 0.51- 0.87), better than MES but less strong than HR defined by NHI.

Diagnostic accuracy of endocytoscopy score system (ECSS) in UC patients for RHI ≤ 3 and NHI ≤1

Using the defined threshold of HR, we analysed the diagnostic accuracy of each ECSS endoscopic features and the total score in the colonic area and from where biopsies were taken . (Table 4 -5). A ROC curve was used to calculate the best value of total ECSS to predict HR. The best value of ECSS total score was ≤ 3 for predicting HR with RHI≤3 with no neutrophilis in epithelium/LP with an AUROC 0.81 (95% CI :0.66-0.97), specificity 0.89 (95% CI: 0.52-1), sensitivity 0.62 (95% CI: 0.31-0.86) and an accuracy 0.80 (95% CI:0.57-0.87). Similarly, an ECSS total score ≤3 was the best cut-off for predict HR defined as NHI ≤1 with an AUROC of 0.77(95% CI :0.59-0.95), specificity of 0.86 (95% CI-43-1) , sensitivity of 0.64 % (95% CI: 27-91), and an accuracy of 0.80% (95% CI: 49- 90). (Table 5-6)

Serum soluble markers

By downstream modelling and logistic regression we identified Brain-Derived Neurotrophic Factor (BDNF) and Macrophage Inflammatory Proteins (MIP-1 α) that when combined together showed the highest predictive ability for RHI≤3 (no neutrophils) and NHI ≤ 1 with an AUROC of 0.82 (95% CI: 0.69-0.97) (Figure 2) . When we investigated analytes separately for predicting HR, univariate logistic regression was significant for two other markers: Leukemia Inhibitory Factor (LIF) and soluble Vascular Cell Adhesion Molecule 1 (sVCAM1), both showing higher values associated with active inflammation by histology. The AUROC was 0.74 for LIF (95%CI: 0.591-0.89) and 0.72 for sVCAM1 (95% CI: 0.53-0.90). Serum soluble markers did not correlate significantly at $p<0.05$ with ECSS (LIF vs ECSS r= 0.31); sVCAM vs ECSS 0.37.

Culture supernatant of UC mucosal biopsies

The supernatants from the mucosal biopsy cultures were analysed for a panel of soluble markers. The following markers were identified as distinguishing healed from non-healed mucosa. (Table 7). Both RHI ≤ 3 and NHI ≤ 1 identified the same set of molecules MMP9, TNFR2, IL-1RA and HGF as a panel being associated with HR. AUROC was 0.82 (95% CI :0.5-1) for a panel of 4 analytes to predict HR by RHI or NHI. The ECSS score ≤ 3 identified sVCAM-1, TNFR2 and IL-1Ra as a panel (the latter two being the same identified by HR) – for predicting healing with an AUROC 0.75 (95% CI:0.25-1). For prediction of ER assessed by MES=0, the AUROC was 0.91 (95% CI:0.5-1) for 4 analytes panel of sICAM-1, IL-6, IL-1Ra and IL-15.

RNA Sequence analysis

We performed RNA sequence analysis using each of the scores (MES, ECSS, RHI, NHI) and identified up and down regulated genes in each of the outcome variables (Supplementary table 1). Moreover, Principal component analysis (PCA) shows clear separation of the healing vs non healing samples for all the scores, including ECSS and MES as well as RHI and NHI index scores (Figure 3). Comparing ECCS scores healing vs. non-healing, we found 116 genes upregulated and 14 genes downregulated. By RHI scores 68 genes were upregulated and 15 genes were found down regulated. NHI scores for healing vs non healing resulted in 188 upregulated and 7 downregulated genes. Those commonly identified by ECSS and RHI scores are summarised by the Venn diagram in figure 4. Twenty-five genes were overlapping between healed mucosa defined by ECSS and RHI score; 79 genes were overlapping between healed mucosa defined by ECSS and NHI index. (Supplementary table 2)

We listed all the important genes prioritized Variable Importance in Projection (VIP) more than 1 in the PLS-DA model. We found that healing and non-healing samples were separated by differentially expressed genes. For healing vs. non healing comparison as defined by RHI, Nancy, Mayo and ECCS we found 32, 83, 127 and 60 differentially genes respectively (Supplementary table 3). All those genes were highly predictive. For example, AUC value using 60 genes together for healing vs. non healing defined by ECCS were 1. The AUC value for each of the genes are listed in the supplementary table 4.

As shown by the volcano plots in figure 5 these included genes relevant to TGF- β signaling such as TGFBR2, PDZK1IP1, USP2, YOD1, macrophage recruitment into tissues such as RNASET2, neutrophil and plasma cell function RNF4 and PIM2 and tumour suppressor genes HECA, BIN3. A number of those identified were shared by MES and ECSS defined healing as well as histological criteria defined healing (NHI index and RHI).

Gene Enrichment analysis

To investigate the roles of the gene pathways that might be involved in the healing process we used gene enrichment analysis on the overlapping genes with KEGG and Gene-Ontology (GO). Supplementary tables 5 and 6 summarise the enriched pathways ($p<0.05$) identified by KEGG and Go Biological process analysis respectively for the differentially expressed genes as defined by each score. Those identified for the 25 differentially expressed genes that were commonly upregulated according to ECSS vs. RHI scores and the 79 genes commonly upregulated between ECSS and NHI scores are illustrated in figure 6 and summarised in supplementary table 7. In summary, the Constitutive Androstane receptor (CAR) and Pregnane X Receptor (PXR) pathways as well as metabolic pathways related to aminoacids, terpinoid andarachidonic acid and the tricarboxylic acid (TCA) cycle were identified and considered mechanistically plausible. The biological relevance of these pathways to MH is presented in the discussion.

DISCUSSION

Both ER and HR are considered therapeutic targets to prevent long term complication in IBD. However, ER may not always translate accurately to HR especially when previous generation of endoscopes is used, though with the current generation of HD and VCE endoscopes, discrepancy between endoscopy and histology is smaller [17]. Advances in endoscopy technologies have dramatically improved the way to assess the intestinal mucosa allowing *"in vivo"* micro-structural mucosal features to be visualised. The endocytoscope , although only available in limited number of centres, currently operates in a similar way to a standard endoscope and can be switched to electronic chromoendoscopy and ultra-high magnification "*in vivo* microscopic" mode at the press of a button on the handset. For ultra-high magnification methylene blue spray is required, a technique familiar to gastroenterologists for dye spray endoscopy.

In this study we explored if the latest generation endocytoscope with ultra-high magnification can accurately assess subtle inflammatory changes in the colonic mucosa and better determine HR of patients in UC. We confirmed that mucosal ER defined by the latest-generation endocytoscope did correlate strongly with HR in UC. The best value of ECSS for predicting HR with RHI and NHI was ≤ 3. We further sought to detect the best predictors among each endocytoscope score items for their ability to differentiate between MH and mild inflammation. The best predictors were the distance between crypts and total ECSS (table 4). Similarly, Natazako et al have shown a good diagnostic accuracy of ECSS with sensitivity of 77% (95% CI:59-89) , specificity of 97% (95% CI 83-99) and accuracy of 86 % (95% CI 75-93) to predict HR in patients with UC [22]. Bessho et al had developed the first ECSS score and had shown good correlation of each item and histopathological grade [25]. Therefore, our study also confirmed that endocytoscopy features such as crypt architecture, distance between crypts, cellular infiltration and visibility of micro-vessels at endoscopy were strongly correlated with histological scores. Furthermore, each of these features could accurately predict histology defined using the validated scores such as RHI and NHI for UC. (Tables 4,5,6)
Of note, Maeda et al have described a computer-aided diagnosis (CAD) endocytoscopy system to predict persistent histologic activity [46]. It is likely that CAD diagnosis may also be related to long-term clinical prognoses. However, this requires a prospective longitudinal follow-up study with specific therapies. Recently Iacucci et al reported that, even with high definition and electronic chromoendoscopy, endoscopic remission and histologic remission equally predict clinical outcomes at 1 year [37]. So endoscopy is getting closer to histology and AI might enable efficient use of endocytoscopy with minimal training and time.

We also investigated if the introduction of soluble markers in blood could provide a non-invasive method to predict HR in UC. We found that serum levels of BDNF + MIP-1α predicted HR defined by histological scores of RHI and NHI. LIF and sVCAM1 showed higher values associated with active disease by histology. Interestingly, BDNF and MIP-1α have been associated with healing in different tissues and derived from specific subsets of macrophages and plasma cells and so could be mechanistically relevant.

In our study sVCAM-1 concentration was related to HR in UC. A mechanistic explanation might be that mucosal VCAM-1 adheres to monocyte-expressed α4β7 integrin and directs *in vivo* gut homing [47]. This facilitates recruitment of subtypes of macrophages that have been identified as important in restitution and repair in IBD and hence soluble markers such as sVCAM and MIP-1α are of interest [31]. In the future this may minimize and avoid invasive procedures to monitor response to therapy and assess MH. However, in this study we have not compared soluble markers with faecal calprotectin. Recently, a new Monitr®serological test was developed to assess mucosal inflammation by evaluating 13 biomarkers in CD patients [28,48]. There is no obvious overlap between this panel in CD and our panel in UC, except VCAM and further large studies are required to replicate and validate these preliminary findings.

We also identified a panel of cytokines and soluble proteins from mucosal biopsy cultures that could predict MH by endoscopic, endocytoscopic and histologic criteria (table 4). This was aimed at mechanistic assessment of MH and the process of mucosal restitution and repair. Several of these molecules (IL-1Ra, TNFR2) have been associated with healing by antagonising inflammatory cytokines. [49,50]Matrix Metalloproteinase (MMP) 9 has been demonstrated to be involved in wound healing and angiogenesis. MMP9 has been shown to be involved in intestinal healing in mice. It has also been implicated in inflammation though blocking MMP9 did not improve active UC. [51] MMPs including MMP9 play a role in tissue remodelling but further studies are required regarding MMP9 in MH . [51,52] Notably, MMP9 expression regulates epithelial barrier function as evident by decreased paracellular permeability and reorganization of claudins and it acts as a tumor suppressor in colitis associate cancer by sustaining the epithelial mucosal integrity though the activation of EGFR-Sp1 signaling pathway [52] .
Hepatocyte Growth Factor (HGF) is a paracrine multifunctional protein involved in angiogenesis and regeneration of tissues. [53]
It is of note that sVCAM 1 was associated with HR in both the serum and biopsy culture supernatants.

RNA-seq analysis identified genes expressed in colonic biopsies that discriminated between healed and non-healed mucosa and overlapped gene expression between ECSS defined healing and histology defined healing (Fig 4-5). These gene expression profiles relate to a number of metabolic pathways involved in vital tissue functions that may be damaged in inflammation related to tissue destruction (Figure 6 and supplementary table 7) or involved in intestinal restitutive and repair processes triggered by damage.

PLS-DA, Volcano plot and gene enrichment and Gene Ontology (GO) analysis , Kyoto Encyclopedia of Gene and genomes (KEGG) analysis identified a number of genes and pathways that are biologically plausible to be involved in MH . It is interesting that a number of tumor suppressor genes are upregulated in healed mucosa (HECA, BIN3) compared with non -healed inflamed mucosa. This may be relevant to dysplasia risk. In our study, the TGF-β pathway, neutrophil function and macrophage recruitment were identified as important in defining healing by histological indices (RHI and Nancy) as well as by ECSS. (Figure 5). In addition, biological processes and pathway enrichment (GO, KEGG and WIKI) identified a number of molecular functions and pathways that may be relevant for MH including the Pregane X receptor (PXR) -JNK axis which has been shown to be involved in healing in other organ such as skin.[54] . Constitutive Androstane Receptor (CAR) pathway regulates intestinal mucosal response to injury [55] in mice . Activation of PXR which is a close relative of CAR may also enhance intestinal epithelial wound healing [56]. Therefore, a small molecule inhibitor of the xenobiotic receptor CAR such as CINPA1 [57] may be useful in MH and needs further translational studies. As well as these pathways, our study identified several metabolic pathways including those involving arachidonic acid, amino acids, terpenoid biosynthesis and the TCA cycle, whose involvement in healing is already recognised [51,53,54]. Interestingly, the involvement of amino acids histidine and arginine in intestinal cell restitution may also involve TGF-β pathways[58]. TGF-β promotes protein translation at least in part by increasing the mitochondrial oxidation of glucose and glutamine carbons to support the energy demand of translation. In addition to stimulating the entry of glucose and glutamine carbon into the TCA cycle, TGFβ induced the biosynthesis of proline from glutamine in a Smad4-dependent fashion. [59] Oxidoreductase activity is an important molecular function in intestinal healing due to intestinal damage resulting from neutrophil derived reactive oxygen [60]. Terpenoids are bioactive and can help anchor proteins to cell membranes and shown to affect wound healing[61] .

The strengths of this study include the use of ultra-high magnification “in vivo microscopy” to identify ultrastructural features of ER, the application of two validated histology scores (RHI and NHI), the study of molecular markers from mucosal biopsy culture and RNA sequencing analysis of mucosal biopsies and bioinformatics to identify potential molecules and molecular pathways that are relevant. In addition, our study has examined potential molecular pathways and soluble markers that might be relevant to the healing process and therefore indicators of healing or targets for therapy. The MES acted as a comparator of a routinely used endoscopy score in clinical practice, which poorly correlated with ECSS.

Limitations of the study include a relatively small number of patients giving large confidence intervals for results, thus validation in a larger independent cohort is needed . We did not have fecal calprotectin assays from all our patients as this was not an aim for this study but we have reported this biomarker extensively in the context of advanced endoscopies recently. [62] We also did not study CD patients though mucosal biopsies may not represent molecular events in CD as well as in UC. Of note, we did not focus on the mechanistic effect of the selected genes on the mucosal architecture since it was beyond the scope of this exploratory study and it will require mini-gut organoids, molecular imaging and animal models using conditional gene knockdowns, a task for future studies.

In conclusion, ultra-high magnification endocytoscopy score strongly correlated with either RHI or NHI but not with MES. A number of soluble markers were identified which could predict HR including molecules such as sVCAM1 which was elevated in both peripheral blood and mucosal biopsy cultures. RNA transcriptomics analysis identified differentially expressed genes that were shared between ECSS and histological score defined healing.

Table 1 Demographic and clinical data of IBD patients enrolled

UC	Demographic and clinical characteristics
Sex	11 F; 18 M (62%M and 38% F)
Mean age ± SD (range)	41± 15 (20-66)
Disease duration median years (range)	12 (1-38)
Localization	
Pancolitis (E3)	25 (86%)
Left colitis (E2)	4 (15%)
Proctosigmoiditis (E1)	0
Mayo Endoscopy score (MES):	
Mayo 0	11 (38%)
Mayo 1	8 (27,5%)
Mayo 2	8 (27,5%)
Mayo 3	2 (7%)
Clinical Mayo	
Remission < 2 remission	15 (52%)
Mild 2 - 4 mild activity	7 (24%)
Moderate 5 - 7 moderate activity	3 (10%)
Severe > 7 severe activity	4 (14%)
Biological therapy	
Adalimumab	3 (10.3%)
Infliximab	1 (3.5%)
Vedolizumab	3 (10.3%)
Ustekinumab	1 (3.5%)
No biological therapy	21 (72.4%)
Medication	
Mesalazine	24 (83%)
Steroids	7 (24%)
Immunosuppressants	6 (20%)
CRP mean (range) mg/dL	9 (1-33)
FC mean (range) mcg/gram	656 (30-2363)

Table 2 Endocytoscopy scoring system

Endocytoscopy items	Score
Crypts architecture: Normal, elongated Irregular Necrosis	 **1** **2** **3**
Infiltration of the cell between the crypts: ≤50% ≥50%	 **1** **2**
Distance between the crypts : Normal: 3 or more crypts in a VF Elongated = <2 crypts in a VF Intermediate= 2 ≤ crypts ≥ 3 in a VF with infiltrating cells in LP Drop-out /necrosis	 **1** **1** **2** **3**
Visibility of superficial microvessels: Not visible Visible	 **0** **1**
ECS total score	**3-9**

VF= visual field

Table 3: ProcartaPlex Luminex arrays used to analyse serum and endoscopy biopsy culture supernatants

ProcartaPlex array	Analytes
4 Plex (customized)	MMP-2; MMP-9; sICAM-1; sVCAM-1
7 Plex (customized)	BLC; IL-12p40; MMP-1; OSM*ϒ; TNFR1; TNFR2; TREM-1*ϒ
45 Plex (ProcartaPlex Hu) Cytokine/Chemokine/GF 1 45plex (Cat no. EPX450-12171-901))	BDNFϒ; Eotaxin/CCL11; EGFϒ; FGF-2*ϒ; GM-CSF*; GRO alpha/CXCL1*; HGF; NGF beta*ϒ; LIF; IFN alpha*ϒ; IFN gamma*; IL-1 beta*; IL-1 alpha*; IL-1RA*; IL-2*; IL-4*ϒ; IL-5*ϒ; IL-6*; IL-7; IL-8/CXCL8*; IL-9 *ϒ; IL-10*; IL-12 p70*; IL-13*; IL-15*; IL-17A*; IL-18*; IL-21*ϒ; IL-22*; IL-23 *ϒ; IL-27*; IL-31*ϒ; IP-10/CXCL10; MCP-1/CCL2; MIP-1 alpha/CCL3; MIP-1 beta/CCL4; RANTES/CCL5; SDF-1 alpha/CXCL12; TNF alpha*; TNF beta/LTA*ϒ; PDGF-BBϒ; PLGF; SCF; VEGF-A; VEGF-D*ϒ

* Not detected in serum; ϒ Not detected in culture supernatant

Table 4. Correlations of ECS with Nancy and RHI score in UC patients perhaps

Correlations of endocytoscopy scores and Nancy score of UC patients	
Crypts architecture	76.4%; 95% CI 12.9- 95.4
Infiltration of the cell between the crypts	66.1%; 95% CI 8.11 -93.2
Distance between the crypts	86.6%; 95% CI 41.52- 97.5
Visibility of vessels	75.0%; 95% CI 9.61 -95.2
Endocytoscopy total score	86.6%; 95% CI 41.5- 97.5
Correlations of endocytoscopy scores and RHI score of UC patients	
Crypts architecture	66.3%; 95% CI 7.7- 93.2
Infiltration of the cell between the crypts	82.7%; 95% CI 29.4- 96.7
Distance between the crypts	89.6%; 95% CI 52.05- 98.1
Visibility of vessels	86.7%; 95% CI 41.9- 97.6
Endocytoscopy total score	89.3 %; 95% CI 50.8 -98.0

Table 5 Diagnostic accuracy of the best threshold ECSS total to predict histological healing

UC	Sensitivity 95% CI	Specificity 95% CI	Accuracy 95% CI	AUROC 95% CI
ECS total score ≤ 3 and RHI ≤ 3	61.5% (31- 85)	88.5 % (52-100)	79.5% (57-87)	81.2% (66-97)
ECS total score ≤ 3 and Nancy≤1	64% (27-91)	86% (43-100)	79.5% (49-90)	77% (59-95)

Table 6. Diagnostic accuracy of the best threshold of each ECS ≤ 3 item to predict histological healing in UC defined by RHI and Nancy scores

ECS item in UC	Sensitivity 95% CI	Specificity 95% CI	Accuracy 95% CI	AUROC 95% CI
Crypt architecture ≤ 0 and RHI ≤ 3	46% (11.5-71)	96% (52-100)	80% (50-82.5)	74% (57-91)
Infiltration of the cell ≤ 1 between the crypts and RHI ≤ 3	69% (33-92)	81.5% (42- 94)	77.5% (51-85.5)	75% (60-90)
Distance between the crypts ≤ 1 and RHI ≤ 3	92% (69-100)	56% (8-75)	67.5% (36-82)	82% (68-95.5)
Visibility of superficial microvessels ≤ 0 and RHI ≤ 3	92% (64-100)	48% (15-67)	62% (52.5-65)	70% (57-83)

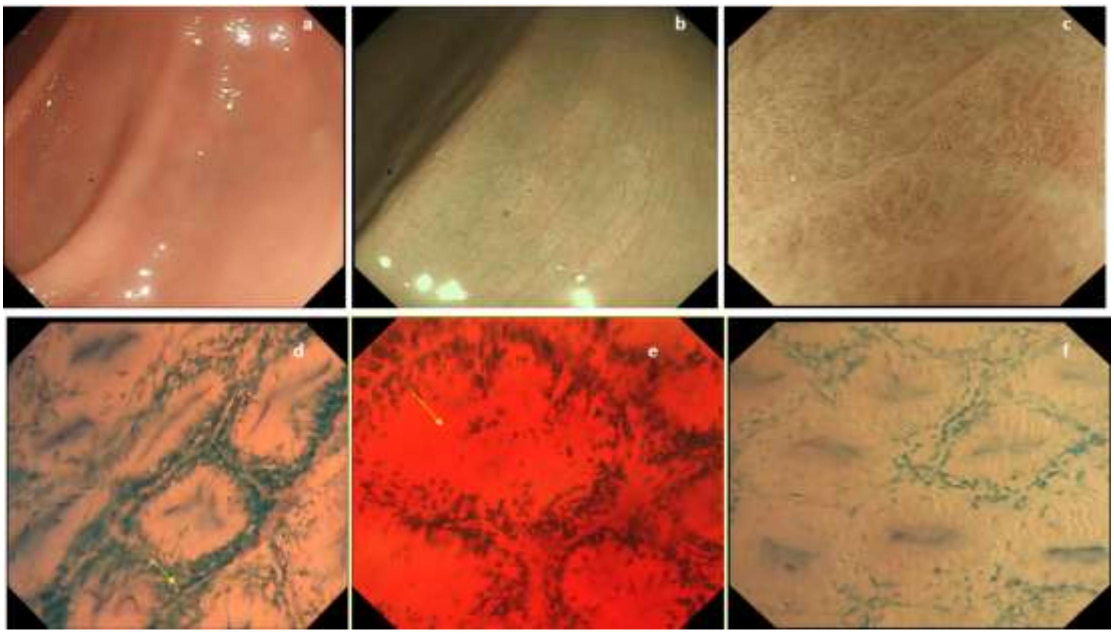
ECS item in UC	Sensitivity 95% CI	Specificity 95% CI	Accuracy 95% CI	AUROC 95% CI
Crypt architecture ≤ 0 and Nancy≤1	45.5% (12-74)	93% (52-100)	80% (50-85)	72% (54-91)
Infiltration of the cell ≤1 between the crypts and Nancy≤1	64% (29-91)	76% (39-91)	72.5% (46-83)	70% (53-87)
Distance between the crypts ≤ 1 and Nancy≤1	91% (65-100)	52% (8-72)	62.5% (31-78)	78% (62-94)
Visibility of superficial microvessels ≤ 0 and Nancy≤1	57% (49-59)	90% (61-100)	44% (15-63)	67% (54-81)

Table 7: Biopsy culture derived selected makers from PLS-DA modelling and combined marker AUC values. Markers were selected based on VIP> 1.5.

Score used	Markers selected from PLS-DA model (VIP>1.5)	AUC(95% CI)
RHI	MMP-9, TNFR2, IL-1ra, HGF	0.82 (0.54-1)
Nancy	MMP-9, TNFR2, IL-1ra, HGF	0.82 (0.5-1)
Mayo	sICAM-1 IL-6 IL-1ra IL-15	0.91 (0.5-1)
ECCS	sVCAM-1, TNFR2, IL-1ra	0.75 (0.25-1)

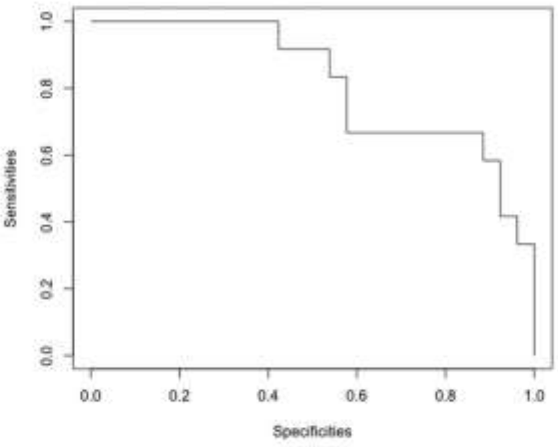
Figures legends:

Figure 1.



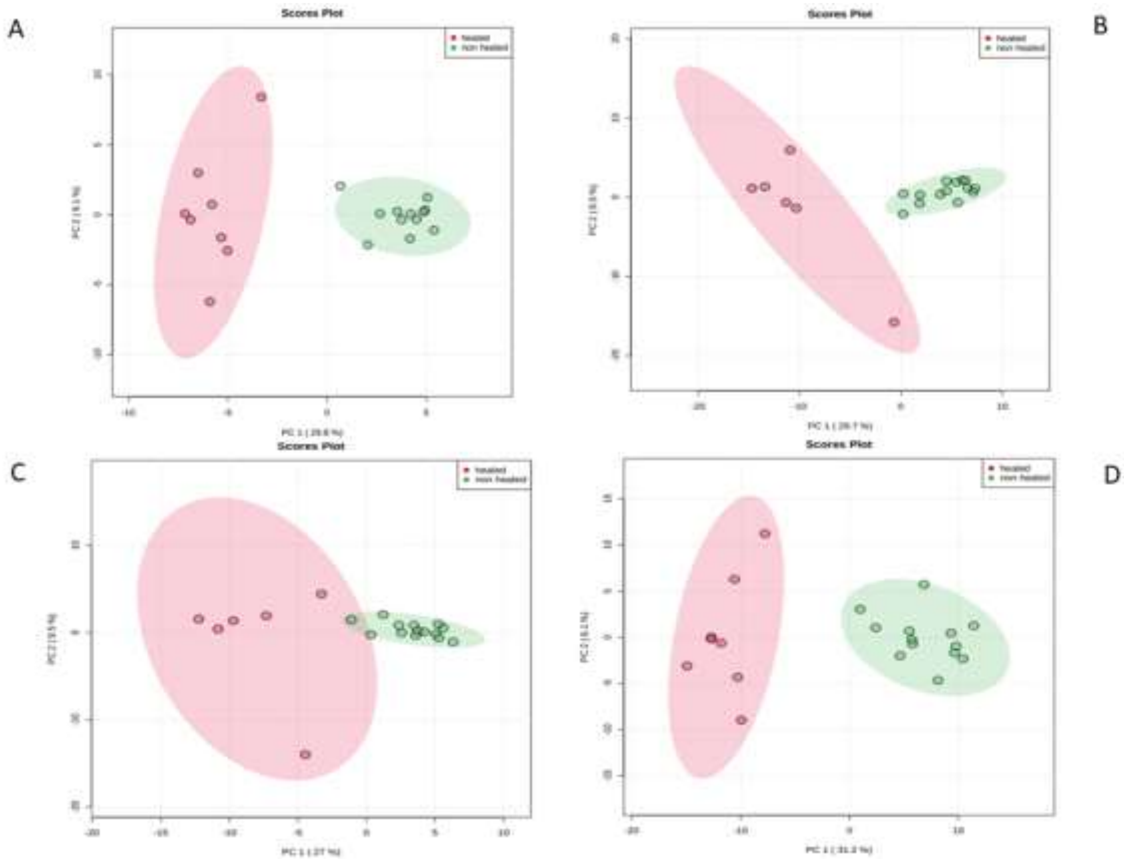
a-c) Endoscopic MH assessed by HD-mwhite light endoscopy and NBI with and without magnification showing elongated crypts as observed in Endoscopic mucosal healing in UC d-f) ultra-high magnification Endocytoscope (ECS)after using Dye Chromoendoscopy with Methylene blue 1% showed increase infiltration with cells between the crypts (arrow) and elongated distorted crypts (arrow) as per historical healing changes.

Figure 2.



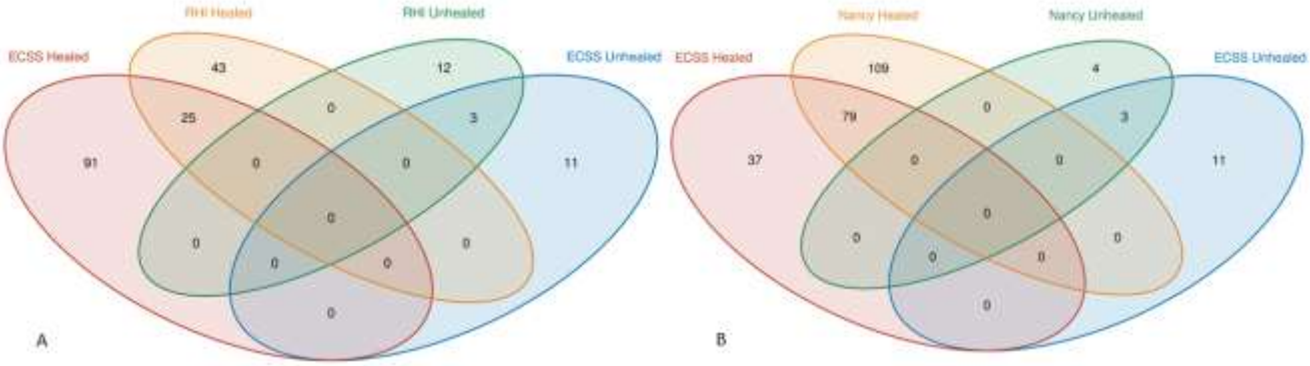
ROC curves of serum BDNF and MIP-1 that, when combined together, were best at predicting histological healing (RHI ≤3 and Nancy ≤ 1) with an AUROC of 0.82

Figure 3.



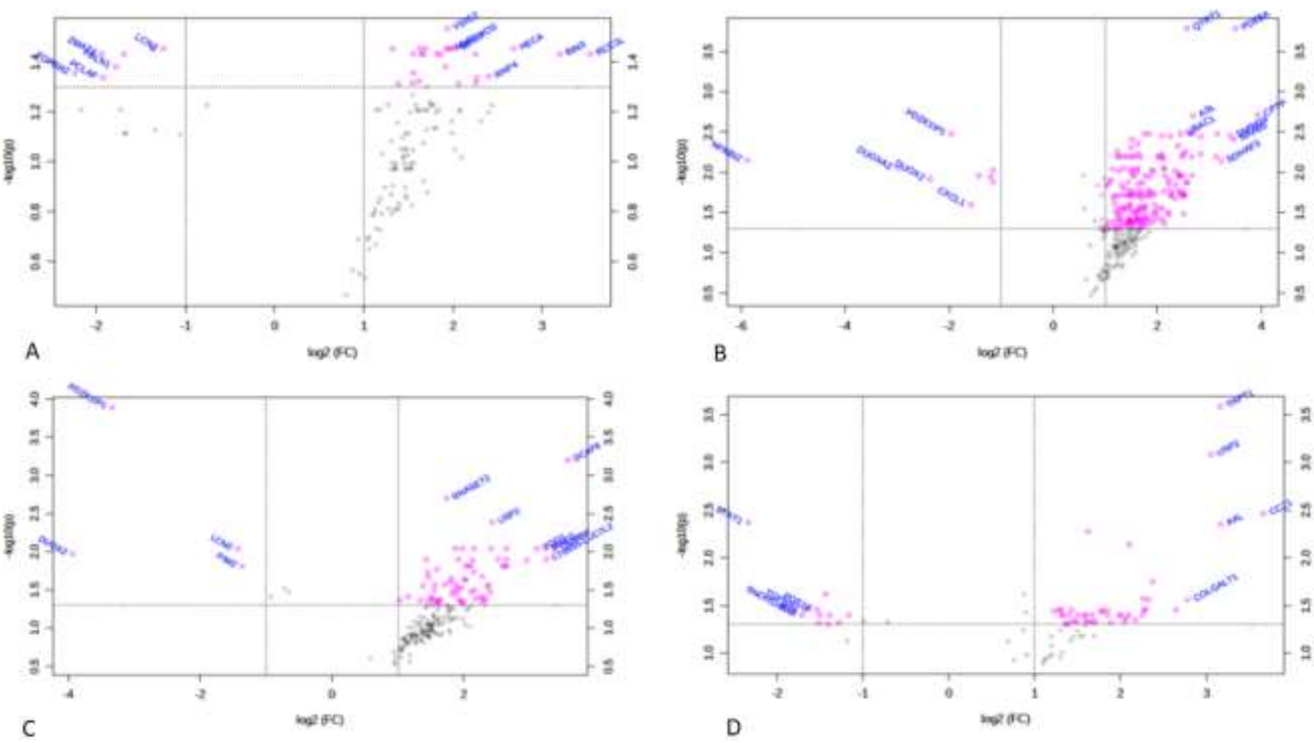
Principal component analysis [PCA] score plots represented on the differentially expressed transcriptome datasets. Each of the plots demonstrating clustering of patients according to the healed vs non healed categories. Each of the dots (Red or green) represent samples (or patients) and are coloured according to the subject cohort (healed vs non healed). Ellipses represent 95% confidence healed or non-healed patients. Results are plotted according to the top two principal components (PC) scores: principal component 1 (PC1) and principal component 2 (PC2) .PC1 and PC2 scores, with the percent variation explained by the x and y axis. Four different definitions of the healed vs non healed defined A) RHI scores B) Nancy scores C) ECCS scores D) Mayo score

Figure 4.



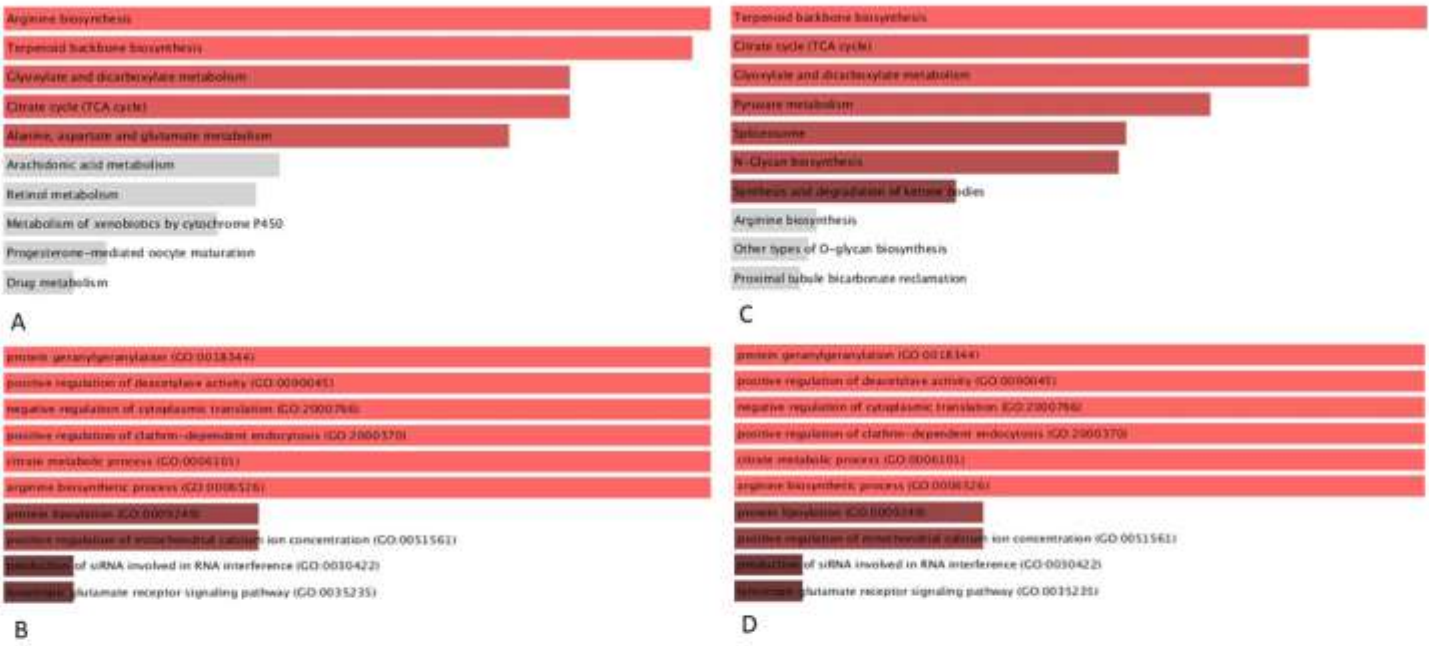
Overlap of upregulated genes in healed and non-healed mucosa as defined by A) ECSS and RHI scores B) ECSS and Nancy scores.

Figure 5.



Volcano plot representations of the differentially expressed genes in healed vs non-healed mucosa as defined by A) ECSS, B) Mayo, C) Nancy and D) RHI scores.

Figure 6



GO and KEGG pathway enrichment analysis of commonly upregulated genes in healed mucosa defined by ECSS and RHI scores (A and B) and ECSS and Nancy scores (C and D). Pathways for which $p<0.05$ are shaded red.

REFERENCES

1. Agrawal M, Colombel JF. Treat-to-Target in Inflammatory Bowel Diseases, What Is the Target and How Do We Treat? *Gastrointest Endosc Clin N Am.* 2019;29(3):421-436.
2. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. *Am J Gastroenterol.* 2015;110(9):1324-1338.
3. Pineton de Chambrun G, Blanc P, Peyrin-Biroulet L. Current evidence supporting mucosal healing and deep remission as important treatment goals for inflammatory bowel disease. *Expert Rev Gastroenterol Hepatol.* 2016;10(8):915-927.
4. Baert F, Moortgat L, Van Assche G, et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. *Gastroenterology.* 2010;138(2):463-468; quiz e410-461.
5. Shah SC, Colombel JF, Sands BE, Narula N. Mucosal Healing Is Associated With Improved Long-term Outcomes of Patients With Ulcerative Colitis: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol.* 2016;14(9):1245-1255 e1248.
6. Shah SC, Colombel JF, Sands BE, Narula N. Systematic review with meta-analysis: mucosal healing is associated with improved long-term outcomes in Crohn's disease. *Aliment Pharmacol Ther.* 2016;43(3):317-333.
7. Bryant RV, Winer S, Travis SP, Riddell RH. Systematic review: histological remission in inflammatory bowel disease. Is 'complete' remission the new treatment paradigm? An IOIBD initiative. *J Crohns Colitis.* 2014;8(12):1582-1597.
8. Bryant RV, Burger DC, Delo J, et al. Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up. *Gut.* 2016;65(3):408-414.
9. Froslie KF, Jahnsen J, Moum BA, Vatn MH, Group I. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. *Gastroenterology.* 2007;133(2):412-422.
10. Iacucci M, Fort Gasia M, Hassan C, et al. Complete mucosal healing defined by endoscopic Mayo subscore still demonstrates abnormalities by novel high definition colonoscopy and refined histological gradings. *Endoscopy.* 2015;47(8):726-734.
11. Narang V, Kaur R, Garg B, et al. Association of endoscopic and histological remission with clinical course in patients of ulcerative colitis. *Intest Res.* 2018;16(1):55-61.
12. Park S, Abdi T, Gentry M, Laine L. Histological Disease Activity as a Predictor of Clinical Relapse Among Patients With Ulcerative Colitis: Systematic Review and Meta-Analysis. *Am J Gastroenterol.* 2016;111(12):1692-1701.
13. Ozaki R, Kobayashi T, Okabayashi S, et al. Histological Risk Factors to Predict Clinical Relapse in Ulcerative Colitis With Endoscopically Normal Mucosa. *J Crohns Colitis.* 2018;12(11):1288-1294.
14. Christensen B EJ, Gibson PR, Rubin T.D. Histological healing is associated with decreased clinical relapse in patients with ileal Crohn's disease *Gastroenterology* 2018;154(6):S-128-S-129.
15. Nardone OM, Cannatelli R, Zardo D, Ghosh S, Iacucci M. Can advanced endoscopic techniques for assessment of mucosal inflammation and healing approximate histology in inflammatory bowel disease? *Therap Adv Gastroenterol.* 2019;12:1756284819863015.
16. Iacucci M, Furfaro F, Matsumoto T, et al. Advanced endoscopic techniques in the assessment of inflammatory bowel disease: new technology, new era. *Gut.* 2018.
17. Iacucci M, Cannatelli R, Gui XS, et al. Assessment of endoscopic healing by using advanced technologies reflects histologic healing in ulcerative colitis. *J Crohns Colitis.* 2020.
18. Iacucci M SSC, Bazarova A. , Shivaji U.N., Bhandari P. , Cannatelli R., Daperno M, Ferraz J.G., Goetz M, Gui X., Hayee B, De Hertogh G., Lazarev M, Li J., Nardone O.M., Occhipinti V., Panaccione R, Parra-Blanco A., Pastorelli L., Rath T., Tontini G. , Vieth M., Villanacci V. , Zardo D., Kiesslich R., Bisschops R., Ghosh S. OP26 The first real-life multicentre prospective validation study of the electronic chromoendoscopy score (Paddington International Virtual ChromoendoScopy ScOre) and its outcome in ulcerative colitis. *Journal of Crohn's and Colitis.* 2020;Volume 14.
19. Iacucci M SSC, Bazarova A. , Shivaji U.N., Bhandari P. , Cannatelli R., Daperno M, Ferraz J.G., Goetz M, Gui X., Hayee B, De Hertogh G., Lazarev M, Li J., Nardone O.M., Occhipinti V., Panaccione R, Parra-Blanco A., Pastorelli L., Rath T., Tontini G. , Vieth M., Villanacci V. , Zardo D., Kiesslich R., Bisschops R., Ghosh S. The first real-life multicentre prospective validation study

of the electronic chromoendoscopy score (Paddington International Virtual ChromoendoScopy ScOre) and its outcome in ulcerative colitis. *Gastrointestinal Endoscopy.* 2020;Volume 91(6).

20. Takenaka K, Ohtsuka K, Fujii T, et al. Development and Validation of a Deep Neural Network for Accurate Evaluation of Endoscopic Images From Patients With Ulcerative Colitis. *Gastroenterology.* 2020;158(8):2150-2157.
21. Le Berre C, Sandborn WJ, Aridhi S, et al. Application of Artificial Intelligence to Gastroenterology and Hepatology. *Gastroenterology.* 2020;158(1):76-94 e72.
22. Nakazato Y, Naganuma M, Sugimoto S, et al. Endocytoscopy can be used to assess histological healing in ulcerative colitis. *Endoscopy.* 2017;49(6):560-563.
23. Nishiyama S, Oka S, Tanaka S, et al. Clinical usefulness of endocytoscopy in the remission stage of ulcerative colitis: a pilot study. *J Gastroenterol.* 2015;50(11):1087-1093.
24. Ueda N, Isomoto H, Ikebuchi Y, et al. Endocytoscopic classification can be predictive for relapse in ulcerative colitis. *Medicine (Baltimore).* 2018;97(10):e0107.
25. Bessho R, Kanai T, Hosoe N, et al. Correlation between endocytoscopy and conventional histopathology in microstructural features of ulcerative colitis. *J Gastroenterol.* 2011;46(10):1197-1202.
26. Nardone OM, Shivaji UN, Ferruzza V, Ghosh S, Iacucci M. Soluble Blood Markers of Mucosal Healing in Inflammatory Bowel Disease: The Future of Noninvasive Monitoring. *Inflamm Bowel Dis.* 2019.
27. Kanehisa M, Goto S. KEGG: kyoto encyclopedia of genes and genomes. *Nucleic Acids Res.* 2000;28(1):27-30.
28. D'Haens G, Kelly O, Battat R, et al. Development and Validation of a Test to Monitor Endoscopic Activity in Patients With Crohn's Disease Based on Serum Levels of Proteins. *Gastroenterology.* 2020;158(3):515-526 e510.
29. Verstockt B, Verstockt S, Veny M, et al. Expression Levels of 4 Genes in Colon Tissue Might Be Used to Predict Which Patients Will Enter Endoscopic Remission After Vedolizumab Therapy for Inflammatory Bowel Diseases. *Clin Gastroenterol Hepatol.* 2020;18(5):1142-1151 e1110.
30. Arijs I, De Hertogh G, Lemmens B, et al. Effect of vedolizumab (anti-alpha4beta7-integrin) therapy on histological healing and mucosal gene expression in patients with UC. *Gut.* 2018;67(1):43-52.
31. Ho GT, Cartwright JA, Thompson EJ, Bain CC, Rossi AG. Resolution of Inflammation and Gut Repair in IBD: Translational Steps Towards Complete Mucosal Healing. *Inflamm Bowel Dis.* 2020.
32. Dhanda AD, Creed TJ, Greenwood R, Sands BE, Probert CS. Can endoscopy be avoided in the assessment of ulcerative colitis in clinical trials? *Inflamm Bowel Dis.* 2012;18(11):2056-2062.
33. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med.* 1987;317(26):1625-1629.
34. Travis SP, Schnell D, Krzeski P, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). *Gut.* 2012;61(4):535-542.
35. Trivedi PJ, Kiesslich R, Hodson J, et al. The Paddington International Virtual Chromoendoscopy Score in ulcerative colitis exhibits very good inter-rater agreement after computerized module training: a multicenter study across academic and community practice (with video). *Gastrointest Endosc.* 2018;88(1):95-106 e102.
36. Iacucci M, Daperno M, Lazarev M, et al. Development and reliability of the new endoscopic virtual chromoendoscopy score: the PICaSSO (Paddington International Virtual ChromoendoScopy ScOre) in ulcerative colitis. *Gastrointest Endosc.* 2017;86(6):1118-1127 e1115.
37. Iacucci M, Smith SC, Bazarova A, et al. An international multicenter real-life prospective study of electronic chromoendoscopy score PICaSSO in Ulcerative Colitis. *Gastroenterology.* 2020.
38. Marchal-Bressenot A, Salleron J, Boulagnon-Rombi C, et al. Development and validation of the Nancy histological index for UC. *Gut.* 2017;66(1):43-49.
39. Klenske E, Atreya R, Hartmann A, et al. Magnification endoscopy with optical chromoendoscopy shows strong correlation with histologic inflammation in patients with inflammatory bowel disease. *Endosc Int Open.* 2019;7(8):E1018-E1026.
40. Pai RK, Khanna R, D'Haens GR, et al. Definitions of response and remission for the Robarts Histopathology Index. *Gut.* 2019;68(11):2101-2102.
41. Garthwaite PH. An Interpretation of Partial Least Squares. *Journal of the American Statistical Association.* 1994;89(424).

42. Wold H. Estimation of Principal Components and Related Models by Iterative Least Squares. *Academic Press, New York.* 1966:391-420.
43. Li B, Ruotti V, Stewart RM, Thomson JA, Dewey CN. RNA-Seq gene expression estimation with read mapping uncertainty. *Bioinformatics.* 2010;26(4):493-500.
44. Ritchie ME, Phipson B, Wu D, et al. limma powers differential expression analyses for RNA-sequencing and microarray studies. *Nucleic Acids Res.* 2015;43(7):e47.
45. Chen EY, Tan CM, Kou Y, et al. Enrichr: interactive and collaborative HTML5 gene list enrichment analysis tool. *BMC Bioinformatics.* 2013;14:128.
46. Maeda Y, Kudo S-E, Mori Y, et al. Fully automated diagnostic system with artificial intelligence using endocytoscopy to identify the presence of histologic inflammation associated with ulcerative colitis (with video). *Gastrointestinal endoscopy.* 2019;89(2):408-415.
47. Schleier L, Wiendl M, Heidbreder K, et al. Non-classical monocyte homing to the gut via alpha4beta7 integrin mediates macrophage-dependent intestinal wound healing. *Gut.* 2020;69(2):252-263.
48. Sandborn WJ, Abreu MT, Dubinsky MC. A Noninvasive Method to Assess Mucosal Healing in Patients* With Crohn's Disease. *Gastroenterol Hepatol (N Y).* 2018;14(5 Suppl 2):1-12.
49. Bersudsky M, Luski L, Fishman D, et al. Non-redundant properties of IL-1alpha and IL-1beta during acute colon inflammation in mice. *Gut.* 2014;63(4):598-609.
50. Bradford EM, Ryu SH, Singh AP, et al. Epithelial TNF Receptor Signaling Promotes Mucosal Repair in Inflammatory Bowel Disease. *J Immunol.* 2017;199(5):1886-1897.
51. Neumann PA, Twardy V, Becker F, et al. Assessment of MMP-2/-9 expression by fluorescence endoscopy for evaluation of anastomotic healing in a murine model of anastomotic leakage. *PLoS One.* 2018;13(3):e0194249.
52. Pujada A, Walter L, Patel A, et al. Matrix metalloproteinase MMP9 maintains epithelial barrier function and preserves mucosal lining in colitis associated cancer. *Oncotarget.* 2017;8(55):94650-94665.
53. Fajardo-Puerta AB, Mato Prado M, Frampton AE, Jiao LR. Gene of the month: HGF. *J Clin Pathol.* 2016;69(7):575-579.
54. Tanaka Y, Uchi H, Ito T, Furue M. Indirubin-pregnane X receptor-JNK axis accelerates skin wound healing. *Sci Rep.* 2019;9(1):18174.
55. Hudson GM, Flannigan KL, Erickson SL, et al. Constitutive androstane receptor regulates the intestinal mucosal response to injury. *Br J Pharmacol.* 2017;174(12):1857-1871.
56. Terc J, Hansen A, Alston L, Hirota SA. Pregnane X receptor agonists enhance intestinal epithelial wound healing and repair of the intestinal barrier following the induction of experimental colitis. *Eur J Pharm Sci.* 2014;55:12-19.
57. Cherian MT, Chai SC, Wright WC, et al. CINPA1 binds directly to constitutive androstane receptor and inhibits its activity. *Biochem Pharmacol.* 2018;152:211-223.
58. Matsui T, Ichikawa H, Fujita T, et al. Histidine and arginine modulate intestinal cell restitution via transforming growth factor-beta1. *Eur J Pharmacol.* 2019;850:35-42.
59. Schworer S, Berisa M, Violante S, et al. Proline biosynthesis is a vent for TGFbeta-induced mitochondrial redox stress. *EMBO J.* 2020;39(8):e103334.
60. Matthews JD, Owens JA, Naudin CR, et al. Neutrophil-Derived Reactive Oxygen Orchestrates Epithelial Cell Signaling Events during Intestinal Repair. *Am J Pathol.* 2019;189(11):2221-2232.
61. Barreto RS, Albuquerque-Junior RL, Araujo AA, et al. A systematic review of the wound-healing effects of monoterpenes and iridoid derivatives. *Molecules.* 2014;19(1):846-862.
62. Cannatelli R, Bazarova A, Zardo D, et al. Fecal Calprotectin Thresholds to Predict Endoscopic Remission Using Advanced Optical Enhancement Techniques and Histological Remission in IBD Patients. *Inflamm Bowel Dis.* 2020.

Supplementary tables legend:

Supplementary Table 1: Differentially (Up and down) expressed genes in healed versus non-healed mucosa as defined by A) ECSS, B) Mayo, C) RHI and D) Nancy scores

A) ECCS Score

Gene	logFC	CI.L	CI.R	AveExpr	t	P.Value	adj.P.Val	B
RBM19	2.044353	1.116333	2.972373	0.883196	152.0693	4.10E-30	9.59E-28	57.21332
QTRT2	2.500183	1.992547	3.007819	1.121663	119.7676	3.38E-28	6.73E-26	52.55863
SVBP	2.806107	2.510506	3.101708	1.640306	62.14957	6.12E-23	8.77E-21	39.7553
USP2	2.933185	2.365593	3.500777	1.322209	59.38294	1.41E-22	1.97E-20	38.70751
HECA	2.187658	1.479372	2.895944	0.656094	48.5896	7.25E-21	9.13E-19	34.82907
LACTB2	2.54801	0.978397	4.117623	1.073903	37.62444	6.13E-19	6.65E-17	31.56301
RNF4	2.70509	2.192251	3.217928	0.907569	36.2566	1.21E-18	1.29E-16	31.51774
CCZ1	2.553754	1.91243	3.195077	1.021038	32.39274	9.98E-18	1.02E-15	27.14156
ZNF581	2.714869	2.049755	3.379983	0.979933	28.62194	8.90E-17	8.54E-15	26.93485
CYP2B6	2.290757	-0.69481	5.276326	1.161438	31.15583	1.91E-17	1.89E-15	26.32576
TRNP	3.733059	3.182252	4.283866	1.489721	30.18452	3.61E-17	3.52E-15	25.5099
AIMP2	3.459043	2.206548	4.711538	0.868984	25.28981	8.32E-16	7.40E-14	25.44484
PEPD	3.364649	2.743272	3.986025	1.327562	27.76661	1.64E-16	1.52E-14	24.01114
ATPAF1	4.063603	3.53749	4.589717	1.741297	27.67168	1.78E-16	1.64E-14	23.75224
RCC1L	2.085837	1.740788	2.430887	0.569284	23.43631	3.27E-15	2.76E-13	22.08107
RMDN2	2.190249	1.552459	2.828039	0.861871	23.1537	4.75E-15	3.96E-13	20.46097
TSNAX	3.170193	2.551519	3.788867	1.487764	22.62958	6.47E-15	5.29E-13	20.14427
UBFD1	3.078114	1.106412	5.049817	0.974677	17.59026	5.30E-13	3.93E-11	18.4169
DHX8	2.13624	0.77594	3.49654	0.897775	20.4134	4.43E-14	3.47E-12	18.23961
AKIRIN2	3.132657	2.559279	3.706035	1.235573	20.19476	5.23E-14	4.08E-12	17.90485

SLC22A18AS	2.427324	1.996222	2.858425	1.098352	19.3042	1.13E-13	8.64E-12	17.26576
FSIP2-AS1	2.538045	2.231385	2.844705	0.812913	15.29682	5.99E-12	4.16E-10	16.61552
ANGEL2	2.318862	1.746083	2.89164	0.85416	14.40591	1.68E-11	1.10E-09	15.28387
MPP7	2.674475	1.078823	4.270127	1.174432	17.24219	8.45E-13	6.16E-11	14.97573
ENPP4	2.191354	2.191322	2.191387	1.035684	16.62234	1.60E-12	1.16E-10	14.25335
BIN3	3.529334	3.210426	3.848243	0.803558	16.33373	2.17E-12	1.55E-10	14.07418
WEE1	2.079114	1.738722	2.419507	0.656271	16.3161	2.21E-12	1.57E-10	14.03614
TRNI	2.810699	1.838388	3.78301	1.220718	13.0676	8.73E-11	5.39E-09	12.70529
TUSC2	2.963634	2.538834	3.388434	1.260674	15.14867	7.90E-12	5.46E-10	12.66635
EEF1E1	3.249916	1.850422	4.649411	1.56335	15.01392	9.03E-12	6.18E-10	12.51874
MED31	2.943466	2.56789	3.319043	1.213335	14.88753	1.06E-11	7.16E-10	12.40289
C1orf35	3.700921	3.250473	4.151369	1.553506	14.69477	1.33E-11	8.76E-10	12.09741
BTN3A1	2.060327	1.630121	2.490534	1.018597	14.50001	1.66E-11	1.09E-09	11.86975
CPTP	2.454969	2.008764	2.901173	0.937513	13.73866	4.14E-11	2.62E-09	10.88354
FEM1C	2.168002	1.33555	3.000455	1.233111	13.42129	6.04E-11	3.76E-09	10.54138
ANKLE2	2.24581	-1.03958	5.531202	1.040567	12.836	1.29E-10	7.90E-09	9.691726
STAT6	2.104962	1.668676	2.541248	0.773144	9.597838	1.30E-08	6.64E-07	9.227968
NTAN1	3.200848	2.515339	3.886357	1.616328	11.94191	4.23E-10	2.53E-08	8.550779
DENND2A	2.002039	1.533173	2.470906	0.70024	11.38297	9.28E-10	5.36E-08	7.906954
MCU	2.398353	1.307934	3.488772	1.195997	11.56166	7.20E-10	4.21E-08	7.902982
RAB32	3.685852	3.114968	4.256736	1.265912	11.43687	8.59E-10	5.00E-08	7.760085
GEMIN6	2.220184	1.312218	3.12815	1.346597	11.17728	1.24E-09	7.07E-08	7.392286
POLR3GL	3.730165	1.787087	5.673243	2.103339	10.97982	1.66E-09	9.38E-08	7.014975
RNASET2	3.813432	2.687211	4.939652	2.67838	10.76361	2.28E-09	1.27E-07	6.548834
BIN1	2.095973	0.710333	3.481613	0.93652	10.55876	3.10E-09	1.70E-07	6.398415

SNAPIN	3.663573	1.447871	5.879274	1.599302	10.58326	2.99E-09	1.65E-07	6.327282
C6orf203	3.365172	2.820174	3.910171	1.559197	10.34479	4.29E-09	2.32E-07	6.018038
C1orf123	3.465322	2.664821	4.265824	1.578687	10.24949	4.96E-09	2.66E-07	5.781661
LY96	3.020784	2.18904	3.852528	1.393876	10.06976	6.56E-09	3.46E-07	5.69782
SLC35B1	2.00445	0.527743	3.481156	0.990241	10.10326	6.22E-09	3.31E-07	5.658887
PLRG1	2.942645	2.374229	3.511061	1.043451	7.789984	2.97E-07	1.31E-05	5.120305
TNIP2	2.835446	2.075904	3.594989	1.259205	9.621056	1.33E-08	6.79E-07	5.02605
AP1AR	2.097359	2.097274	2.097443	0.98335	9.395108	1.92E-08	9.62E-07	4.48124
INSIG1	2.721966	1.448222	3.995711	1.490891	9.344891	2.09E-08	1.04E-06	4.413448
KIAA1522	2.085089	1.725738	2.44444	0.962693	9.284152	2.31E-08	1.15E-06	4.409443
AKAP1	2.993598	2.563517	3.42368	1.436996	9.434641	1.80E-08	9.05E-07	4.399287
LCN2	-4.65975	-6.48264	-2.83687	4.924502	-9.27705	2.34E-08	1.15E-06	4.209871
RCN2	3.006828	2.404383	3.609273	1.41372	8.624381	7.03E-08	3.34E-06	3.080181
ACAT1	2.812549	0.397801	5.227297	1.317663	8.526152	8.34E-08	3.92E-06	2.833017
PPP2R3C	3.379457	0.875809	5.883105	1.578451	8.427482	9.91E-08	4.62E-06	2.668195
SHKBP1	2.903541	1.566629	4.240452	1.343222	8.308066	1.22E-07	5.64E-06	2.540237
FNTA	3.093005	2.272423	3.913587	1.543854	8.211334	1.45E-07	6.63E-06	2.260459
TMEM171	3.307068	2.654412	3.959725	1.53924	7.915541	2.47E-07	1.10E-05	1.709427
GLRX5	3.926558	3.349388	4.503728	1.926578	7.867183	2.70E-07	1.19E-05	1.653165
TMEM56	2.216914	1.516645	2.917183	1.040859	7.7165	3.56E-07	1.56E-05	1.562078
CSE1L	2.353413	2.352159	2.354666	1.186302	7.69338	3.72E-07	1.62E-05	1.302135
CRYL1	2.574171	0.584418	4.563924	1.402709	7.636687	4.13E-07	1.79E-05	1.250575
SIRT6	2.342843	2.342823	2.342863	1.279651	7.299488	7.78E-07	3.25E-05	0.989804
MMP24OS	4.018274	3.703297	4.33325	1.962005	7.408871	6.33E-07	2.70E-05	0.677336
CRYZL1	2.936727	2.356852	3.516602	1.443914	7.330937	7.33E-07	3.09E-05	0.656205

RNASE6	2.02006	1.059716	2.980404	1.036319	7.343701	7.16E-07	3.02E-05	0.592286
EDEM1	2.326945	1.098154	3.555736	1.147248	7.322101	7.46E-07	3.13E-05	0.509772
PPID	2.834726	2.486594	3.182857	1.417196	7.120982	1.10E-06	4.50E-05	0.160021
PQBP1	2.545887	0.640088	4.451686	1.231564	7.071331	1.21E-06	4.93E-05	0.118905
UMAD1	2.78878	2.788731	2.788829	1.077013	5.106448	6.79E-05	0.001996	-0.2002
TUFM	2.842723	2.300926	3.38452	2.125172	6.92576	1.60E-06	6.37E-05	-0.29034
FAM104B	2.039369	1.095508	2.98323	1.113283	6.803856	2.03E-06	8.04E-05	-0.32903
PPP1R35	3.956437	3.521764	4.391109	1.032592	4.803125	0.000133	0.003675	-0.35351
FLOT1	2.207133	1.933999	2.480268	1.210963	6.705476	2.47E-06	9.60E-05	-0.499
SDHAF3	2.403949	2.060778	2.747121	0.923721	6.723027	2.38E-06	9.35E-05	-0.51366
PCLAF	-3.16645	-4.07282	-2.26009	2.525913	-6.71029	2.44E-06	9.54E-05	-0.74725
PTPRCAP	2.911392	2.608748	3.214037	1.556755	6.639252	2.82E-06	0.000109	-0.81622
NR3C2	2.279403	1.506352	3.052453	1.179453	6.617856	2.94E-06	0.000113	-0.89331
GINS2	2.667458	2.179674	3.155242	1.13673	6.310668	5.46E-06	0.0002	-1.3956
HOXB9	2.072191	1.316101	2.82828	1.329053	6.307175	5.50E-06	0.000201	-1.4846
PDZK1IP1	-4.49771	-4.49785	-4.49758	4.006909	-6.32967	5.25E-06	0.000193	-1.54133
GTF3A	3.74885	3.030238	4.467462	2.858464	6.299026	5.59E-06	0.000204	-1.6372
ALG3	2.436639	1.123307	3.74997	1.307249	5.991992	1.05E-05	0.000365	-2.04125
VSIG2	3.680443	2.230037	5.13085	2.007373	5.988658	1.06E-05	0.000366	-2.28218
NUDC	2.372985	0.956802	3.789169	1.740297	5.8451	1.43E-05	0.000481	-2.49247
POGLUT1	2.230454	1.850632	2.610276	0.570013	3.735506	0.001456	0.033023	-2.53831
ASL	3.140256	1.938284	4.342227	1.610077	5.708434	1.90E-05	0.000632	-2.82054
GCNT3	-2.26342	-3.24085	-1.28599	3.67741	-5.61656	2.31E-05	0.000751	-3.004
ACO2	2.113277	1.401618	2.824937	1.316509	5.604662	2.37E-05	0.000768	-3.05205
TGFBR2	-2.3281	-3.05997	-1.59623	1.720101	-5.59644	2.41E-05	0.000778	-3.12285

FZD5	2.176893	1.641974	2.711812	1.306024	5.544673	2.70E-05	0.000858	-3.23433
CCDC124	3.584463	3.065455	4.103471	2.037902	5.468355	3.17E-05	0.000998	-3.38698
VSIG10	2.081888	1.403044	2.760733	1.270378	5.418477	3.53E-05	0.001098	-3.47837
R3HCC1	2.035309	1.474976	2.595642	1.011615	5.167585	6.07E-05	0.00182	-3.72733
DUOX2	-2.70628	-2.7069	-2.70566	2.121494	-5.1522	6.28E-05	0.001873	-4.07936
COMMD4	2.956851	1.015696	4.898005	1.694066	5.141614	6.42E-05	0.001908	-4.11925
LSM14A	-2.20224	-2.67968	-1.7248	1.907003	-5.12404	6.67E-05	0.00197	-4.13684
OXSR1	2.038853	1.363474	2.714231	1.161741	5.043004	7.96E-05	0.00232	-4.25057
CCT8	2.661845	0.483494	4.840197	1.472151	4.97226	9.30E-05	0.002668	-4.41191
DPM2	2.50036	2.169522	2.831198	1.319774	4.907122	0.000107	0.003045	-4.47075
TRPT1	2.815742	2.81308	2.818404	1.718767	4.959394	9.57E-05	0.002732	-4.47434
TXNL4A	3.280097	0.232872	6.327323	1.959008	4.900434	0.000109	0.003077	-4.65583
TTC38	2.329782	1.671477	2.988087	1.566354	4.817851	0.000131	0.00363	-4.86865
PCK1	2.293387	1.681215	2.905559	1.497706	4.782835	0.000141	0.003889	-4.92314
ERI3	2.329428	1.637618	3.021238	1.506631	4.677703	0.000178	0.004828	-5.10822
TBCC	2.3716	1.720187	3.023013	1.454201	4.632804	0.000197	0.005249	-5.17766
DAAM1	-2.19259	-3.74964	-0.63554	1.599992	-4.64212	0.000193	0.005162	-5.24066
CPEB4	2.335422	-0.43306	5.103907	1.534287	4.6438	0.000192	0.005159	-5.27049
SCYL2	2.053542	-0.96678	5.073859	1.227669	4.566437	0.000228	0.006047	-5.34163
PRDM1	-2.06882	-3.68521	-0.45243	2.440991	-4.58194	0.00022	0.005854	-5.40429
YIPF6	2.380613	1.886943	2.874282	1.470888	4.474145	0.00028	0.007326	-5.61929
B4GALT5	2.268608	1.789039	2.748177	1.297247	4.444259	0.000299	0.007786	-5.67928
ZMAT2	-2.58039	-4.05927	-1.10152	2.412718	-4.29361	0.000419	0.010636	-6.05215
TMEM208	3.433656	1.358988	5.508323	2.647198	4.159178	0.000567	0.014138	-6.32329
SNORA16A	-2.34988	-3.09815	-1.6016	2.065895	-4.16176	0.000564	0.014083	-6.3275

PKP3	2.281578	1.513092	3.050065	1.657891	4.127334	0.000609	0.015018	-6.43159
NSD3	-2.02584	-2.50037	-1.55132	2.017893	-4.0894	0.000663	0.016204	-6.47639
PSMD3	2.222183	2.017898	2.426469	1.509329	3.97369	0.00086	0.020421	-6.65177
DHRSX_1	2.633795	1.965426	3.302164	1.658882	3.941504	0.000925	0.021684	-6.8282
FBLN1	-2.15995	-3.09809	-1.22181	1.991384	-3.94069	0.000927	0.021686	-6.84792
APOC1	2.428941	0.260529	4.597353	1.899563	3.641852	0.001814	0.040404	-7.41234
SMIM24	2.205442	1.61878	2.792104	1.195596	3.604961	0.001971	0.043601	-7.46222
AHR	-2.00219	-2.69203	-1.31236	2.240724	-3.60397	0.001975	0.043625	-7.58488
PCCB	2.290676	1.846339	2.735012	1.577295	3.569708	0.002133	0.046343	-7.6349
NUDCD2	2.118842	0.055209	4.182476	1.593866	3.550107	0.002229	0.048112	-7.69202

B) Mayo Score

Gene	logFC	CI.L	CI.R	AveExpr	t	P.Value	adj.P.Val	B
IFI35	3.81213	2.709277	4.914983	1.35181	160.0525	5.20E-32	2.24E-29	63.68156
IL6R	2.38608	1.242511	3.529649	0.889591	154.5484	1.03E-31	4.29E-29	63.00309
CCZ1	2.427393	2.426635	2.42815	0.972417	127.9454	4.16E-30	1.52E-27	59.25316
SLC16A9	2.509788	1.16473	3.854846	1.114532	124.1351	7.52E-30	2.66E-27	58.64044
CDS1	3.213184	2.762118	3.664249	1.303199	121.9818	1.06E-29	3.63E-27	58.33087
NSUN2	2.316363	1.421229	3.211498	1.164852	115.4933	3.09E-29	9.72E-27	57.18276
C6orf203	3.700584	2.719135	4.682032	1.48495	98.14872	7.45E-28	2.17E-25	53.75342
C5orf51	3.097821	2.771519	3.424124	1.469766	82.80612	2.07E-26	5.60E-24	50.39084
GINS2	3.58299	1.28423	5.881749	1.250605	78.06734	6.53E-26	1.69E-23	49.19201
SMIM24	3.597224	3.25418	3.940267	1.309807	75.89623	1.13E-25	2.84E-23	49.09286
PEPD	3.744219	3.478287	4.010151	1.486938	75.84919	1.15E-25	2.84E-23	48.49344
GMPPB	2.89751	0.815772	4.979248	1.506204	68.76586	7.78E-25	1.78E-22	46.57878

METTL7B	3.550573	1.744268	5.356879	1.285729	68.62506	8.10E-25	1.81E-22	46.48247
TRNP	3.653698	3.243021	4.064375	1.418782	66.98538	1.30E-24	2.85E-22	46.08393
SSRP1	2.24064	1.60227	2.87901	0.976933	60.94665	8.20E-24	1.77E-21	44.24517
STX10	3.707534	2.429258	4.98581	1.334305	52.68165	1.40E-22	2.77E-20	41.97753
EMC2	2.680362	0.618868	4.741857	1.000875	52.44487	1.53E-22	2.97E-20	40.98563
EHHADH	2.224983	2.154053	2.295913	0.748809	43.33901	6.67E-21	1.09E-18	37.0141
KDM1A	2.571702	2.197611	2.945794	1.003076	42.84543	7.80E-21	1.24E-18	36.93486
TPSB2	3.851953	3.333078	4.370828	2.014786	43.20272	6.62E-21	1.09E-18	36.84314
DCAF11	2.538222	2.047576	3.028869	0.999963	42.17972	1.12E-20	1.71E-18	36.4318
UBE2D1	3.010271	2.538591	3.481951	1.454046	41.29398	1.59E-20	2.40E-18	36.20461
RPA2	3.554161	1.766482	5.341841	1.694258	38.50748	6.15E-20	8.83E-18	34.69293
UBP1	2.646686	2.646667	2.646705	1.262138	38.48611	6.22E-20	8.83E-18	34.67733
AP1AR	2.754229	2.135495	3.372963	1.083713	37.39509	1.16E-19	1.58E-17	33.97911
ELAVL1	2.165178	1.70654	2.623816	0.761008	37.00949	1.41E-19	1.91E-17	33.84603
CRYL1	3.60478	3.174428	4.035133	1.57977	35.40139	3.12E-19	4.14E-17	33.06312
COMT	2.785729	2.218543	3.352915	1.075839	34.74066	4.78E-19	6.18E-17	32.52022
QTRT1	4.277155	2.656463	5.897847	2.147958	33.95247	7.36E-19	9.33E-17	31.86571
UBAC1	3.34443	2.899612	3.789247	1.544884	30.71572	4.84E-18	5.76E-16	30.08277
MGAT1	2.793909	2.215027	3.372792	1.551716	30.62158	5.11E-18	6.01E-16	29.96342
RCOR1	2.197091	1.387772	3.006409	0.774117	30.57017	5.58E-18	6.50E-16	29.94961
ISOC1	3.214549	2.73698	3.692118	1.745207	29.36287	1.14E-17	1.29E-15	29.20222
GCHFR	4.382337	2.860813	5.903861	1.929309	28.40045	2.24E-17	2.44E-15	28.54509
PICALM	2.508703	1.943153	3.074253	0.928804	25.13422	2.23E-16	2.22E-14	27.73191
CPTP	3.046462	2.343441	3.749483	1.069698	26.70145	7.41E-17	7.64E-15	27.10533
NIPSNAP3A	3.58658	1.766912	5.406249	1.480322	24.63434	3.43E-16	3.36E-14	25.58758

HRCT1	3.390992	2.438035	4.343949	1.7973	24.35176	4.07E-16	3.95E-14	25.55902
RMND5A	2.109962	1.778944	2.44098	1.270568	24.29042	4.38E-16	4.22E-14	25.31225
CYP2B6	2.313181	1.151238	3.475123	1.106131	24.11333	5.15E-16	4.91E-14	25.24244
UGT2A3	2.775578	2.459482	3.091674	1.265528	24.03472	5.47E-16	5.19E-14	25.14209
C1orf123	4.041846	3.674865	4.408826	1.503512	23.60209	7.72E-16	7.26E-14	24.57638
KLHDC3	2.969751	2.121091	3.818411	1.176795	22.66835	1.66E-15	1.51E-13	23.95003
EDIL3	3.109006	3.08937	3.128643	1.613949	22.69385	1.62E-15	1.50E-13	23.9122
DHX8	2.119304	1.655522	2.583086	0.997975	22.48799	1.93E-15	1.74E-13	23.83181
SNHG6	3.570333	2.390385	4.750281	1.916656	22.4463	1.99E-15	1.79E-13	23.72219
MT1H	4.828434	4.305371	5.351497	1.899374	21.93606	3.07E-15	2.67E-13	23.20686
GON7	4.364283	2.607778	6.120787	2.211136	21.87368	3.24E-15	2.80E-13	23.11003
KLHL24	2.280189	1.859959	2.700418	1.15928	21.68252	3.83E-15	3.28E-13	22.93861
PPID	3.278712	0.899326	5.658097	1.349711	21.4851	4.55E-15	3.87E-13	22.87312
HOXB9	2.492461	1.65971	3.325212	1.265765	21.0622	6.60E-15	5.53E-13	22.50281
PDE8A	2.526607	1.529064	3.52415	1.011164	19.92914	1.86E-14	1.52E-12	21.25222
POLR2G	3.225841	2.592118	3.859564	1.748929	19.43002	2.99E-14	2.40E-12	21.01812
METAP1	2.165615	0.756234	3.574995	0.796519	18.94324	4.79E-14	3.79E-12	20.49525
ST20-MTHFS	2.413194	2.044643	2.781744	1.444491	18.83517	5.32E-14	4.16E-12	20.34026
ZNF703	2.849812	1.39277	4.306853	1.456374	18.73601	5.87E-14	4.56E-12	20.09334
AXL	2.234778	1.556791	2.912765	1.163575	17.92656	1.33E-13	1.01E-11	19.38932
DCTN3	2.767126	2.188439	3.345814	1.437411	17.67059	1.74E-13	1.31E-11	19.00382
ABCG2	2.272444	1.748544	2.796343	1.210788	17.01961	3.47E-13	2.56E-11	18.22351
POLR2B	2.521145	2.288938	2.753352	1.271944	16.8248	4.28E-13	3.12E-11	18.05307
EGLN2	3.23813	2.819456	3.656805	1.434663	16.19795	8.58E-13	6.17E-11	17.32045
GTF2B	3.160028	2.535178	3.784878	1.140545	16.02395	1.04E-12	7.42E-11	17.11223

TMEM87B	3.115862	0.654439	5.577286	1.514928	15.73169	1.46E-12	1.03E-10	16.7399
RMDN2	2.096451	1.65944	2.533462	0.820829	15.50005	1.91E-12	1.31E-10	16.43505
APOC1	4.269745	1.43317	7.10632	1.809108	15.41195	2.12E-12	1.45E-10	16.39729
GDPD3	3.380005	2.066475	4.693535	1.675791	14.85846	4.11E-12	2.77E-10	15.83581
JUP	2.659902	1.332486	3.987318	1.287695	14.52814	6.16E-12	4.10E-10	15.17961
RNASET2	3.769172	3.17281	4.365535	2.778469	14.31608	8.03E-12	5.31E-10	14.85875
TRNL2	3.249239	2.895854	3.602624	1.88589	14.11415	1.04E-11	6.66E-10	14.72313
NUDC	2.76272	2.187744	3.337696	1.686914	14.03616	1.14E-11	7.26E-10	14.70426
HBB	4.504794	3.55275	5.456838	1.80157	14.18375	9.48E-12	6.20E-10	14.70168
PTPA	2.101996	0.944142	3.259851	0.876405	14.03376	1.15E-11	7.26E-10	14.6194
AKAP1	2.542423	1.699333	3.385513	1.368567	14.03888	1.14E-11	7.26E-10	14.61507
DHRSX_1	2.962739	0.738356	5.187123	1.579888	13.8596	1.43E-11	9.02E-10	14.33733
SLC22A18AS	2.360073	2.358622	2.361525	1.19562	13.76647	1.62E-11	1.01E-09	14.33176
GEMIN6	2.230654	1.970449	2.490859	1.282473	13.6158	1.96E-11	1.22E-09	14.15574
RBM19	2.127396	2.127229	2.127563	0.841139	13.60894	1.98E-11	1.23E-09	14.13576
TULP4	2.366759	2.156843	2.576674	1.383276	13.53519	2.18E-11	1.34E-09	13.82481
ASL	3.778875	1.90886	5.648891	1.758782	13.51108	2.25E-11	1.37E-09	13.77286
FNTA	3.149908	2.610374	3.689443	1.470337	13.36091	2.75E-11	1.67E-09	13.70339
WDR82	2.156375	1.496326	2.816425	1.17754	13.28963	3.02E-11	1.80E-09	13.67529
PTPRR	2.503541	1.823214	3.183867	1.336919	13.02069	4.33E-11	2.54E-09	13.29222
MIR200CHG	4.351649	3.235042	5.468256	1.965887	12.62096	7.50E-11	4.30E-09	12.61469
CDKN2B-AS1	2.279781	1.897688	2.661874	1.286727	12.4561	9.44E-11	5.31E-09	12.38239
PDZK1IP1	-4.9404	-7.73611	-2.14468	3.876659	-12.4044	1.01E-10	5.66E-09	12.1684
NCEH1	2.078717	0.753769	3.403665	1.098455	12.25654	1.25E-10	6.90E-09	12.11041
DHX9	2.270945	1.857732	2.684158	1.187952	12.19581	1.36E-10	7.46E-09	12.014

PCK1	2.97274	1.914884	4.030595	1.662883	12.17344	1.41E-10	7.63E-09	11.86426
VPS4A	3.383841	1.016586	5.751095	1.853375	12.18928	1.38E-10	7.49E-09	11.86176
EPS8L3	2.70447	1.98811	3.42083	1.37344	12.02552	1.74E-10	9.34E-09	11.73268
SAFB2	2.14293	1.251768	3.034093	0.874248	12.01532	1.77E-10	9.44E-09	11.70135
SEC23B	2.216806	1.346739	3.086874	1.306142	11.83936	2.28E-10	1.20E-08	11.53295
NRDE2	2.03272	0.468988	3.596453	0.69734	11.72187	2.71E-10	1.41E-08	11.47314
CHORDC1	2.132197	1.558722	2.705673	0.859779	11.62282	3.13E-10	1.61E-08	11.21632
MSMO1	2.580988	2.039975	3.122002	1.346873	11.60938	3.20E-10	1.63E-08	11.19388
ENDOD1	2.209804	1.489946	2.929663	1.099391	11.54878	3.50E-10	1.77E-08	10.9964
CDK1	2.217946	0.834661	3.60123	1.204917	11.23049	5.64E-10	2.75E-08	10.42379
DDT	3.653811	2.022977	5.284644	3.649753	11.01818	7.80E-10	3.77E-08	10.11206
KRTCAP3	4.382291	2.86385	5.900732	1.816872	10.9691	8.42E-10	4.05E-08	9.997693
MCU	2.267021	1.242524	3.291517	1.139044	10.83029	1.04E-09	4.99E-08	9.868723
TBC1D15	2.010804	-0.45177	4.473383	0.991343	10.38657	2.11E-09	9.98E-08	9.184823
MEP1A	2.971993	1.748593	4.195392	1.561482	10.33833	2.28E-09	1.07E-07	9.100863
CAPN7	2.421791	1.180803	3.662779	1.218891	10.30808	2.39E-09	1.11E-07	9.010872
NDUFS2	2.5687	1.887132	3.250268	1.561587	10.35622	2.21E-09	1.04E-07	8.977252
TBCC	2.595216	1.685796	3.504636	1.497952	9.938386	4.38E-09	1.98E-07	8.321841
BIN1	2.063841	0.343497	3.784185	0.891924	9.866327	4.94E-09	2.16E-07	8.284155
DPP7	2.502624	2.115685	2.889563	1.362659	9.894798	4.71E-09	2.09E-07	8.245976
SMIM26	4.223594	3.466123	4.981065	3.92523	9.903227	4.64E-09	2.08E-07	8.225271
DENR	2.755666	2.462633	3.0487	1.407055	9.746094	6.04E-09	2.63E-07	8.001609
TMEM209	2.112862	1.394212	2.831512	0.928052	9.516977	8.90E-09	3.87E-07	7.646688
RBMX2	2.87727	0.655741	5.098798	1.601598	9.511563	8.98E-09	3.89E-07	7.577739
TRIM25	2.100822	0.529186	3.672458	1.374375	9.467198	9.69E-09	4.17E-07	7.517458

USF2	2.092815	0.962363	3.223268	1.357562	9.365801	1.15E-08	4.87E-07	7.407158
FAM3B	2.631898	1.914849	3.348947	1.281982	9.357987	1.17E-08	4.90E-07	7.396624
VSIG10	2.025469	0.980631	3.070308	1.332005	9.44115	1.01E-08	4.32E-07	7.39645
DNAJC2	2.849515	2.128011	3.571019	1.529434	9.35826	1.17E-08	4.90E-07	7.236794
DUOX2	-3.20995	-4.27972	-2.14017	2.020471	-9.34469	1.20E-08	5.00E-07	7.212729
SEMA5A	2.259509	0.855222	3.663795	1.308777	8.952808	2.38E-08	9.35E-07	6.562141
FAM120AOS	2.804813	0.954221	4.655406	1.531234	8.897614	2.62E-08	1.02E-06	6.403628
HEXB	2.659623	2.081079	3.238167	1.621662	8.780592	3.23E-08	1.24E-06	6.222549
ACY1	3.233039	3.162951	3.303127	1.887555	8.768603	3.30E-08	1.27E-06	6.190719
NAA60	2.274401	1.891634	2.657168	0.909134	8.630444	4.24E-08	1.59E-06	5.988539
WASL	3.01237	1.775154	4.249586	1.908825	8.678902	3.88E-08	1.47E-06	5.979991
GSTM4	2.095161	1.474303	2.71602	1.087826	8.568633	4.74E-08	1.76E-06	5.899534
GGCT	3.141801	2.738239	3.545364	1.850985	8.579498	4.65E-08	1.74E-06	5.890665
DHRS11	3.463438	1.205335	5.721542	2.360587	8.575079	4.69E-08	1.75E-06	5.788515
RHOF	3.113268	1.830658	4.395878	1.899445	8.552337	4.89E-08	1.80E-06	5.787411
ALDH6A1	2.421922	1.915792	2.928052	1.48238	8.512368	5.26E-08	1.92E-06	5.763965
MRPL39	2.74205	0.646018	4.838083	2.304083	8.483816	5.54E-08	2.02E-06	5.639038
RBM7	2.048493	2.033246	2.06374	1.21035	8.33107	7.34E-08	2.63E-06	5.526453
ASNA1	3.120116	1.330311	4.909921	1.79675	8.356107	7.01E-08	2.52E-06	5.455621
SQLE	2.40892	1.625445	3.192395	1.187621	8.304944	7.71E-08	2.75E-06	5.352156
CD14	3.228474	2.803788	3.65316	2.104191	8.22877	8.88E-08	3.13E-06	5.171648
NAAA	2.624839	1.818549	3.431128	1.753833	8.236114	8.76E-08	3.09E-06	5.125568
GOT1	2.089117	2.089088	2.089147	1.075095	8.03142	1.29E-07	4.35E-06	4.933915
IDH3G	3.097601	2.616924	3.578279	1.714499	8.053938	1.23E-07	4.20E-06	4.872652
TMEM170A	2.506949	1.468569	3.545329	1.723101	8.103409	1.12E-07	3.85E-06	4.867786

ALG2	2.45518	1.584282	3.326078	1.79052	8.043763	1.26E-07	4.26E-06	4.823251
ETFDH	2.45396	-5.1E+10	5.05E+10	1.3846	8.028066	1.30E-07	4.36E-06	4.758491
SDHAF3	2.645626	2.287163	3.004089	1.131932	7.910958	1.62E-07	5.39E-06	4.606017
CBX1	2.353133	1.295522	3.410744	1.35995	7.884401	1.70E-07	5.66E-06	4.597429
CTSA	2.997917	2.545724	3.45011	1.682387	7.878723	1.72E-07	5.70E-06	4.50686
WDR76	2.078544	1.543009	2.614079	1.118039	7.807443	1.97E-07	6.43E-06	4.476394
AVPI1	2.490747	1.913512	3.067981	1.464245	7.839037	1.86E-07	6.08E-06	4.469332
EMC10	2.801643	1.67193	3.931357	1.730104	7.84348	1.84E-07	6.05E-06	4.39603
TMC4	2.23297	1.569498	2.896443	1.266361	7.664409	2.60E-07	8.33E-06	4.13207
FRMD1	2.208894	0.60428	3.813509	1.461439	7.692992	2.46E-07	7.91E-06	4.103194
TSNAX	2.427658	2.111656	2.743661	1.536256	7.462122	3.87E-07	1.20E-05	3.701055
GLIPR2	2.226456	1.255941	3.196971	1.558569	7.468906	3.82E-07	1.19E-05	3.684874
CNDP2	2.151342	1.421078	2.881606	1.321477	7.480402	3.73E-07	1.16E-05	3.667321
TMEM220	2.586355	0.983657	4.189052	1.386511	7.387453	4.48E-07	1.37E-05	3.505768
DERA	2.753326	1.460227	4.046425	2.536157	7.374307	4.60E-07	1.40E-05	3.44003
SURF1	3.150912	2.649333	3.652492	2.841486	7.386158	4.49E-07	1.37E-05	3.42142
AAMDC	3.09191	2.841921	3.341899	1.516078	7.315322	5.17E-07	1.57E-05	3.343767
VPS28	3.397973	3.134684	3.661261	2.916194	7.314033	5.19E-07	1.57E-05	3.301342
TOR1AIP1	2.381197	0.964916	3.797478	1.405983	7.297388	5.36E-07	1.61E-05	3.267319
OSBPL1A	2.243912	0.074655	4.413169	1.159407	7.272305	5.64E-07	1.69E-05	3.199127
TUFM	2.647824	1.125266	4.170381	2.229522	7.24925	5.90E-07	1.76E-05	3.169104
HSD17B2	3.554527	2.347388	4.761666	2.050393	7.203819	6.46E-07	1.91E-05	3.087958
SLC38A1	2.026942	1.581235	2.472649	1.656473	7.189716	6.65E-07	1.96E-05	3.01441
SAMD13	2.323792	0.452136	4.195447	1.187624	7.079699	8.30E-07	2.40E-05	2.951015

CRK	2.040108	0.783944	3.296272	1.253374	7.045106	8.90E-07	2.56E-05	2.826589
NUDT19	2.267359	0.803483	3.731236	1.511936	7.065839	8.54E-07	2.46E-05	2.791979
CUTA	3.214536	2.763573	3.6655	3.317159	7.041614	8.96E-07	2.57E-05	2.727376
ZHX1	2.011036	0.542515	3.479557	1.186531	6.911713	1.17E-06	3.30E-05	2.558568
PCGF5	2.303893	0.156108	4.451678	1.425258	6.861663	1.29E-06	3.63E-05	2.338789
RARRES3	2.811636	2.499595	3.123677	1.502137	6.747696	1.64E-06	4.51E-05	2.199945
SNX2	2.038931	1.556562	2.5213	1.464372	6.67959	1.88E-06	5.13E-05	1.95447
NOB1	2.400336	1.978632	2.82204	1.365484	6.629186	2.09E-06	5.60E-05	1.910452
CREG1	2.353018	-0.36597	5.072007	1.335665	6.632584	2.08E-06	5.58E-05	1.877562
RGS10	3.095706	3.074386	3.117025	1.537646	6.568315	2.38E-06	6.33E-05	1.754538
CNOT1	2.046916	1.222125	2.871707	1.418955	6.528415	2.58E-06	6.84E-05	1.603029
AIP	2.792925	1.806215	3.779636	1.142675	6.478214	2.87E-06	7.51E-05	1.599579
LCN2	-4.29177	-4.80555	-3.77799	4.752504	-6.49879	2.75E-06	7.23E-05	1.588486
PQBP1	2.658083	0.92163	4.394535	1.172918	6.429656	3.18E-06	8.28E-05	1.496309
TLK1	2.263834	1.386696	3.140973	1.628956	6.425613	3.21E-06	8.34E-05	1.406737
SMIM31	2.954233	1.107271	4.801194	2.023474	6.41416	3.28E-06	8.50E-05	1.395006
MT1G	4.546925	4.208851	4.884999	4.649754	6.419261	3.25E-06	8.43E-05	1.378188
MT1F	4.259469	3.753884	4.765054	2.208922	6.406498	3.34E-06	8.62E-05	1.369809
REP15	3.033199	1.932429	4.133969	2.735606	6.396021	3.41E-06	8.78E-05	1.355553
SCIN	2.190109	1.099575	3.280644	1.52838	6.325107	3.96E-06	0.000101	1.25388
PSMG2	3.159388	2.510438	3.808339	1.802924	6.311551	4.08E-06	0.000103	1.216825
RAB4B	2.198232	1.986056	2.410409	1.498087	6.262671	4.53E-06	0.000113	1.187994
ANAPC5	2.243913	1.965057	2.52277	1.427675	6.267312	4.48E-06	0.000112	1.150458
EPB41L4B	2.019451	1.566974	2.471928	1.217863	6.275018	4.41E-06	0.00011	1.097075
C1orf115	2.308287	1.743402	2.873173	1.454249	6.250897	4.64E-06	0.000115	1.022

PABPN1	2.446337	1.967203	2.925471	1.89907	6.239065	4.76E-06	0.000117	0.966488
USP2	2.105157	-0.39798	4.608291	1.259246	6.179989	5.40E-06	0.000133	0.9304
TRMT10C	2.646964	2.468229	2.825698	1.645522	6.069186	6.85E-06	0.000166	0.742142
GOLGA5	2.413181	1.974364	2.851998	1.198381	6.01531	7.70E-06	0.000186	0.541526
FRA10AC1	2.49868	1.782121	3.215239	1.890328	5.970625	8.48E-06	0.000203	0.379245
RAB11B	3.112027	1.311563	4.912491	2.165634	5.92332	9.40E-06	0.000223	0.267539
PLIN3	2.982609	2.267094	3.698124	2.473966	5.920072	9.46E-06	0.000224	0.259613
SFT2D1	3.660535	3.530818	3.790253	3.292997	5.900918	9.86E-06	0.000232	0.240878
B3GNT3	2.157871	1.770258	2.545484	1.351462	5.813051	1.19E-05	0.000277	0.113425
TEX264	2.461619	2.016966	2.906272	1.330928	5.794122	1.25E-05	0.000286	0.07098
TM2D3	2.000059	-0.55653	4.556649	1.483152	5.683959	1.59E-05	0.000357	-0.07691
ERI3	2.335942	2.029368	2.642517	1.593841	5.691795	1.56E-05	0.000353	-0.14751
GRPEL1	2.992974	2.605364	3.380583	2.33467	5.724792	1.45E-05	0.000329	-0.15827
RBBP8	2.163771	-0.50428	4.831827	1.064359	5.643565	1.73E-05	0.000388	-0.1986
NFKBIZ	-2.77804	-3.4394	-2.11668	1.507165	-5.59643	1.92E-05	0.000426	-0.44976
CSNK2A1	2.246974	0.989489	3.504459	1.78731	5.591062	1.95E-05	0.00043	-0.45779
RAB10	2.067494	-0.17113	4.306121	3.102669	5.567047	2.05E-05	0.000451	-0.49479
SCGB2A1	3.076714	1.68196	4.471468	1.76205	5.521866	2.27E-05	0.000496	-0.52268
ACP5	2.034824	1.105118	2.964531	1.225476	5.486241	2.46E-05	0.000532	-0.63158
DCTN6	2.721257	2.450373	2.99214	1.640891	5.460951	2.60E-05	0.000559	-0.66584
HSD11B2	2.453495	0.971747	3.935242	1.571458	5.482981	2.47E-05	0.000535	-0.69212
CAMLG	2.318806	2.312485	2.325128	1.283769	5.36543	3.21E-05	0.000679	-0.84466
TCEAL8	2.84198	2.205847	3.478112	2.238952	5.403129	2.96E-05	0.000632	-0.8674
MICU1	2.542093	1.97413	3.110056	1.646492	5.381378	3.10E-05	0.000658	-0.89163
PPP1R2	2.412873	0.424197	4.40155	1.687844	5.374533	3.15E-05	0.000666	-0.94141

NUCB1	2.118127	2.118085	2.11817	1.407478	5.330652	3.47E-05	0.000727	-0.98209
ECHDC1	2.275178	1.759934	2.790422	1.559403	5.294962	3.76E-05	0.000783	-1.08842
EFNA1	2.781345	0.281601	5.281088	1.808627	5.2696	3.98E-05	0.000823	-1.13756
DUOXA2	-3.08296	-4.11024	-2.05568	2.24527	-5.24289	4.23E-05	0.000869	-1.24219
THYN1	3.035184	3.029653	3.040716	2.203594	5.189171	4.77E-05	0.000969	-1.365
GSN	-2.40557	-3.28037	-1.53078	2.453364	-5.19478	4.71E-05	0.00096	-1.37154
FUCA2	2.571891	1.930309	3.213473	1.752289	5.180771	4.87E-05	0.000983	-1.38019
CUL3	2.016938	1.69653	2.337345	1.326686	5.168617	5.00E-05	0.001003	-1.39137
CCL5	3.20274	2.445547	3.959933	2.062241	5.118803	5.60E-05	0.001105	-1.48415
CCDC124	2.849704	1.689602	4.009805	1.940859	5.114499	5.65E-05	0.001114	-1.48551
ALDH3A2	2.417598	1.713577	3.12162	1.992443	5.077639	6.14E-05	0.001207	-1.62127
FIS1	3.177036	2.740012	3.614061	3.155817	5.022674	6.96E-05	0.001344	-1.73776
OAF	2.800186	1.805476	3.794897	1.948356	5.012568	7.12E-05	0.001362	-1.75026
CFTR	2.283704	1.826024	2.741384	2.035253	5.02991	6.84E-05	0.001324	-1.75867
LEO1	2.218259	1.422328	3.01419	1.727513	4.998242	7.35E-05	0.0014	-1.77089
ARCN1	2.445365	1.78792	3.10281	1.745105	4.936888	8.45E-05	0.001588	-1.95514
MISP	2.824194	2.472112	3.176276	2.316248	4.939784	8.40E-05	0.001581	-1.96879
MBOAT1	2.06409	1.472302	2.655878	1.885916	4.922342	8.74E-05	0.001634	-1.98321
JUN	-2.30367	-2.65096	-1.95638	2.745356	-4.86551	9.95E-05	0.001836	-2.1264
PDCD6	2.559205	1.539612	3.578799	2.831536	4.850862	0.000103	0.001884	-2.16367
SERINC3	2.764837	2.324077	3.205597	2.072232	4.841282	0.000105	0.001919	-2.1984
MT1M	3.412285	2.436821	4.387749	2.22102	4.804034	0.000114	0.002067	-2.22839
HIST1H1C	3.713998	3.38133	4.046665	2.886076	4.808676	0.000113	0.002052	-2.22919
TXNL4A	2.587991	0.511485	4.664498	1.865722	4.791755	0.000118	0.002116	-2.25635
TFAM	2.131513	1.655924	2.607103	1.417571	4.754157	0.000128	0.002288	-2.33221

MB	2.033137	-0.32049	4.386768	1.319524	4.633974	0.000169	0.002951	-2.50301
AK6	2.6649	1.965073	3.364728	2.826331	4.671661	0.000155	0.002719	-2.51355
LACTB	2.078689	1.505678	2.6517	1.469511	4.613965	0.000177	0.003071	-2.67449
MTIF3	2.597731	1.964495	3.230966	2.085317	4.584171	0.000189	0.003265	-2.78567
CAT	3.069179	2.604507	3.53385	2.678741	4.526631	0.000216	0.0037	-2.92487
UBXN1	2.522243	1.262767	3.78172	2.12293	4.4547	0.000255	0.004284	-3.0429
MKRN1	2.452401	1.515779	3.389022	1.992011	4.415428	0.000279	0.00465	-3.17724
CCL2	3.257504	3.190672	3.324335	2.504038	4.374086	0.000307	0.005072	-3.22197
LEPROTL1	2.231479	1.755336	2.707623	1.721721	4.385941	0.000299	0.00495	-3.22449
CLCN3	2.000289	1.029934	2.970643	1.760372	4.331861	0.000339	0.005556	-3.33923
DNAJC1	2.198136	1.508259	2.888012	1.926814	4.240776	0.000418	0.006666	-3.56829
AKR1B10	2.451956	1.434059	3.469852	2.434046	4.199418	0.00046	0.007236	-3.66526
MRPS34	3.165582	2.925414	3.40575	2.740135	4.193928	0.000466	0.007309	-3.67071
MRPL50	2.44726	-0.0759	4.97042	1.994857	4.172634	0.00049	0.007647	-3.7128
NOSIP	2.195432	1.050878	3.339986	1.741842	4.149011	0.000517	0.008045	-3.74454
POLR3GL	2.536324	2.106239	2.966409	2.052716	4.10777	0.000569	0.008803	-3.84602
PPP2CB	2.475692	1.98568	2.965704	1.846391	4.109277	0.000567	0.008784	-3.85509
PSMD8	2.696705	1.777912	3.615498	2.118568	4.104463	0.000573	0.008859	-3.88969
WASHC3	3.16387	2.418596	3.909144	2.557657	4.062413	0.000632	0.00967	-3.94749
MTHFS	2.082718	0.620448	3.544988	1.637732	4.049919	0.00065	0.00992	-3.97408
CENPV	2.516683	2.084395	2.94897	1.908838	4.021741	0.000694	0.010519	-4.05766
TRPT1	2.369377	1.896312	2.842442	1.636921	3.99311	0.000742	0.011082	-4.07932
RIOK3	2.570696	1.992926	3.148465	2.518952	4.010326	0.000713	0.01069	-4.13334
GINM1	2.707617	1.241943	4.173291	2.220697	3.97112	0.000781	0.011571	-4.22069
SDF4	2.242175	1.741515	2.742836	1.856597	3.900327	0.00092	0.013476	-4.36125

CS	2.20779	2.046722	2.368859	1.735868	3.899202	0.000922	0.013476	-4.38389
PLD3	2.030092	0.976929	3.083255	2.214734	3.783553	0.001205	0.017178	-4.62292
PRKACB	2.111075	1.622899	2.59925	2.128957	3.787886	0.001193	0.017049	-4.63516
LGALS2	3.609555	3.100026	4.119085	3.054542	3.777752	0.001221	0.017368	-4.63576
UBL3	2.220294	0.242522	4.198067	1.713003	3.746462	0.001312	0.0184	-4.73793
HADHB	2.676563	2.19824	3.154886	2.443162	3.743767	0.001321	0.01846	-4.75133
DUSP23	2.368486	1.548847	3.188124	3.358994	3.717875	0.001402	0.019491	-4.76453
MPST	2.729302	2.300547	3.158058	2.832505	3.701063	0.001457	0.020166	-4.84484
PIM2	-2.37988	-3.01189	-1.74787	3.157232	-3.67665	0.001542	0.021283	-4.89979
MT2A	3.001102	0.813853	5.188352	4.313885	3.659577	0.001604	0.022033	-4.92711
CHP2	2.050242	1.125041	2.975443	2.493356	3.636102	0.001693	0.023041	-4.97068
NOP53	2.49899	0.657569	4.34041	3.311144	3.621248	0.001752	0.023788	-5.01285
DDRGK1	2.6094	2.257471	2.96133	2.25895	3.574733	0.00195	0.026051	-5.10036
SLC20A1	2.311949	1.751494	2.872405	1.956708	3.511036	0.002257	0.029816	-5.26482
TOMM7	2.210883	-0.29474	4.716508	4.711357	3.467487	0.002494	0.03258	-5.36075
GUCA2A	3.083389	2.292911	3.873867	3.884702	3.451519	0.002587	0.033606	-5.41128
SPTSSA	2.308714	1.745421	2.872007	2.844345	3.427498	0.002734	0.03527	-5.45168
ARL8B	2.456741	1.738536	3.174945	2.146121	3.423641	0.002758	0.035544	-5.47525
MSRB2	2.149326	0.493179	3.805472	1.9014	3.384664	0.003015	0.038517	-5.50669
UBE2I	2.102909	-0.34137	4.547187	2.36129	3.37004	0.003117	0.039695	-5.57671
MT1X	2.099136	0.039158	4.159114	5.600482	3.371197	0.003109	0.039634	-5.5817
LTB	2.716037	2.233168	3.198907	2.353622	3.322524	0.003474	0.043762	-5.6509
GRAMD2B	2.050927	0.144836	3.957018	1.907566	3.333032	0.003392	0.042772	-5.67031
SCO2	2.39592	1.723721	3.068118	2.07891	3.3086	0.003586	0.045075	-5.70868
SEC13	2.703729	0.711021	4.696438	2.538779	3.279988	0.003828	0.047594	-5.78664

TST	2.452017	1.84682	3.057213	3.721221	3.274126	0.003879	0.04813	-5.79301
CEBPG	2.059055	0.866524	3.251586	2.161297	3.265415	0.003957	0.048937	-5.81591
TCEA3	2.734556	2.732428	2.736683	2.308541	3.266377	0.003948	0.048882	-5.81946
CXCL1	-2.74943	-3.28559	-2.21326	2.841187	-3.2589	0.004016	0.049614	-5.83582

C) RHI Score

Gene	logFC	CI.L	CI.R	AveExpr	t	P.Value	adj.P.Val	B
COLGALT1	2.448437	1.287695	3.609179	0.854771	133.8343	3.56E-29	3.17E-26	56.83971
AXL	2.809427	1.900998	3.717855	1.04306	94.14676	2.42E-26	1.62E-23	50.05356
CCZ1	2.662905	2.247912	3.077897	1.021038	89.46849	6.23E-26	3.78E-23	48.93296
MCU	2.633375	1.984741	3.282008	1.195997	81.42972	3.56E-25	2.07E-22	46.97422
USP2	3.063964	2.282935	3.844992	1.322209	68.28226	9.27E-24	4.95E-21	43.79647
CYP2B6	2.477012	1.433219	3.520806	1.161438	67.50043	1.15E-23	5.88E-21	43.57976
CDK11B	2.280687	1.387327	3.174047	1.269938	57.93331	1.93E-22	8.84E-20	40.25036
SNORD89	3.288007	2.518838	4.057176	1.733113	57.84613	1.99E-22	8.84E-20	40.20446
TSNAX	3.262442	2.913089	3.611795	1.487764	37.35855	6.23E-19	2.25E-16	31.67218
FNTA	3.77068	3.119835	4.421526	1.543854	37.68046	5.32E-19	1.97E-16	31.65076
ECHDC1	2.869572	2.438665	3.30048	1.421871	20.37056	3.70E-14	9.67E-12	19.95997
TRNY	3.747186	2.338096	5.156277	2.250054	17.37944	6.13E-13	1.49E-10	16.85812
RMDN2	2.077343	1.641188	2.513499	0.861871	16.22082	2.05E-12	4.55E-10	15.68228
TUSC2	2.997918	2.537783	3.458053	1.260674	15.69503	3.63E-12	7.80E-10	15.17195
SLC52A2	3.179016	0.775827	5.582205	1.306519	15.22431	6.14E-12	1.26E-09	14.59268
DCTN3	2.401108	2.093894	2.708321	1.317697	15.11622	6.94E-12	1.40E-09	14.37497
NCEH1	2.091172	1.429724	2.75262	1.153378	14.16496	2.12E-11	3.92E-09	13.26254
MED31	2.757586	2.101858	3.413315	1.213335	13.34268	5.85E-11	1.04E-08	12.19444

UBP1	2.336538	0.752199	3.920877	1.096856	13.08268	8.15E-11	1.41E-08	11.9008
ARRDC1	2.60054	1.756701	3.444379	1.342597	12.09071	3.04E-10	4.83E-08	10.47093
ENPP4	2.202717	1.190456	3.214977	1.035684	12.11223	2.96E-10	4.75E-08	10.41172
ACO2	2.499574	1.997658	3.00149	1.316509	11.14704	1.16E-09	1.73E-07	9.012808
TRPT1	3.941203	3.601082	4.281323	1.718767	11.08127	1.27E-09	1.89E-07	8.814524
PTPN18	2.884837	2.88476	2.884914	1.543403	10.70163	2.24E-09	3.24E-07	8.301359
MRPS9	3.251539	2.105933	4.397146	1.723736	9.930204	7.37E-09	1.00E-06	7.017412
P4HTM	2.51378	2.027298	3.000261	1.305442	9.285492	2.10E-08	2.67E-06	6.068406
RNASET2	3.706666	2.405789	5.007544	2.67838	9.242938	2.26E-08	2.81E-06	5.839428
LUZP1	2.305325	1.462749	3.1479	1.268563	8.258746	1.24E-07	1.46E-05	4.037207
GALE	3.338605	2.56122	4.11599	1.562478	8.230661	1.30E-07	1.52E-05	4.026588
CTCF	2.192899	0.996964	3.388834	1.300226	7.651132	3.75E-07	4.04E-05	3.028586
GSTM4	2.034871	1.585114	2.484629	1.142218	7.534297	4.68E-07	4.80E-05	2.748886
STAT1	-2.86201	-4.80319	-0.92083	2.103253	-7.58761	4.23E-07	4.44E-05	2.713932
RHOF	2.979916	2.187616	3.772216	1.751	7.437187	5.62E-07	5.72E-05	2.478323
RNPS1	-2.6085	-2.87046	-2.34654	1.97136	-7.40112	6.02E-07	6.08E-05	2.39208
NUDT19	2.340475	2.340377	2.340572	1.547869	7.30119	7.28E-07	7.20E-05	2.214708
CCDC28A	2.70434	0.782514	4.626167	1.675085	7.25234	8.00E-07	7.85E-05	2.100491
ASL	2.74243	2.18036	3.3045	1.610077	7.152311	9.70E-07	9.38E-05	2.026058
SNORD47	-3.77433	-5.04639	-2.50227	2.689265	-7.14624	9.82E-07	9.42E-05	1.851693
MRPL1	2.49601	1.920505	3.071515	1.304657	7.099315	1.08E-06	0.0001	1.846544
TMEM56	2.263489	1.769788	2.75719	1.040859	6.980714	1.36E-06	0.000126	1.666687
SCYL2	2.024057	1.732167	2.315947	1.227669	6.912677	1.55E-06	0.000142	1.470867
ERI3	2.532138	2.282368	2.781907	1.506631	6.765543	2.07E-06	0.000184	1.174109
GATA6	2.25594	1.854613	2.657266	1.090087	6.608187	2.84E-06	0.000245	0.984401

FAM104B	2.135061	0.491856	3.778267	1.113283	6.444472	3.96E-06	0.000334	0.598621
NUDT16	2.15245	1.837376	2.467525	1.123216	6.493513	3.58E-06	0.000304	0.590711
DCTN6	2.711836	2.109516	3.314155	1.722936	6.293621	5.38E-06	0.000443	0.196032
NUDC	2.386658	1.838586	2.934731	1.740297	6.165839	7.01E-06	0.00056	-0.06869
PDZK1IP1	-4.27711	-4.70096	-3.85325	4.006909	-6.1693	6.96E-06	0.000559	-0.14769
ANAPC5	2.424776	1.698403	3.15115	1.499058	5.987883	1.01E-05	0.000774	-0.47304
WWP1	-2.43861	-2.90071	-1.9765	2.078839	-5.90628	1.20E-05	0.000907	-0.72288
HEPACAM2	2.758108	2.072547	3.443669	2.04585	5.848822	1.36E-05	0.001017	-0.8705
CASP5	-3.13102	-3.70178	-2.56026	2.674777	-5.6184	2.22E-05	0.001556	-1.35102
TUFM	2.383816	2.224527	2.543105	2.125172	5.53015	2.68E-05	0.001841	-1.49993
C1orf210	2.614948	2.32017	2.909726	2.031779	5.524543	2.71E-05	0.001854	-1.53121
CPEB4	2.041106	1.809122	2.27309	1.534287	5.32803	4.14E-05	0.002736	-2.00794
AK2	-2.23196	-5.02828	0.564354	2.192713	-5.25646	4.84E-05	0.003135	-2.1686
TGFBR2	-2.20349	-2.63462	-1.77236	1.720101	-5.20286	5.44E-05	0.003473	-2.30211
MRPL54	2.530108	1.870616	3.189599	2.903509	5.131535	6.36E-05	0.003983	-2.39607
GLRX5	2.963585	2.179231	3.747939	1.926578	5.054231	7.54E-05	0.004633	-2.50828
FIS1	2.992747	1.453327	4.532168	3.313608	5.01044	8.30E-05	0.005009	-2.69166
BZW2	2.047876	-0.08112	4.176871	0.994719	4.776815	0.000139	0.008178	-3.13516
DHRSX_1	2.40107	0.08533	4.716809	1.658882	4.671179	0.000176	0.010124	-3.45128
NMI	-2.66251	-3.26277	-2.06226	2.120964	-4.66221	0.00018	0.010241	-3.5135
ANP32A	2.321131	1.91442	2.727843	2.993507	4.43022	0.000302	0.016309	-4.04041
SBDS	2.193404	1.363331	3.023476	3.633575	4.392038	0.000329	0.017418	-4.12096
DYNC1LI2	2.7302	0.683578	4.776821	2.105871	4.403642	0.000321	0.017105	-4.13022
HNF4G	-2.00194	-2.40374	-1.60013	1.67976	-4.30819	0.000397	0.020545	-4.28997
SLC25A1	2.568915	2.056027	3.081802	1.792055	4.280549	0.000423	0.021449	-4.31281

LXN	-2.77299	-3.62682	-1.91916	2.539336	-4.28191	0.000422	0.021449	-4.35401
MGAT1	2.141514	-0.32581	4.608837	1.487852	4.270835	0.000432	0.021841	-4.37863
DUOX2	-2.41709	-4.28455	-0.54963	2.121494	-4.25488	0.000448	0.02247	-4.40015
FERMT1	2.375085	1.979159	2.771011	2.145787	4.255541	0.000447	0.02247	-4.43323
UBXN1	2.441601	1.986914	2.896287	1.998288	4.208712	0.000497	0.024207	-4.4799
PLEKHJ1	3.032695	2.668536	3.396854	2.589318	4.173841	0.000538	0.025627	-4.62688
NUDCD2	2.210172	1.641529	2.778814	1.593866	4.112137	0.000618	0.028442	-4.73626
RNPEP	2.494355	2.090464	2.898246	1.835929	4.036981	0.000733	0.033246	-4.8742
MMP24OS	2.313257	2.022827	2.603686	1.962005	3.986317	0.000822	0.036533	-4.95112
POF1B	-2.36615	-3.36627	-1.36603	2.157271	-3.98965	0.000815	0.03638	-5.06196
HERPUD1	2.304271	2.03267	2.575871	3.386884	3.957943	0.000876	0.038567	-5.0805
IFI6	-2.05529	-2.55977	-1.55082	4.201512	-3.9208	0.000953	0.04167	-5.11411
KRCC1	2.763519	2.20942	3.317619	2.255007	3.896246	0.001007	0.043761	-5.24842
RNF114	2.033581	1.301424	2.765739	1.503655	3.847728	0.001124	0.048032	-5.32398
NDUFB5	-3.06875	-6.31655	0.179039	3.649938	-3.84488	0.001131	0.048053	-5.38419

D) Nancy Score

Gene	logFC	CI.L	CI.R	AveExpr	t	P.Value	adj.P.Val	B
C7orf55-LUC7L2	2.973356	2.60268	3.344032	0.853482	973.1416	6.52E-45	3.48E-42	92.43679
BTN2A1	2.589775	2.287399	2.892151	0.902246	433.8996	1.93E-38	3.67E-36	77.13244
WEE1	2.320904	0.384721	4.257088	0.656271	398.4486	9.29E-38	1.55E-35	76.99243
CCZ1	2.683669	0.415992	4.951345	1.021038	245.9757	6.79E-34	9.24E-32	66.21257
MED31	3.315601	1.335997	5.295206	1.213335	242.3434	8.93E-34	1.20E-31	65.68843
EDN3	2.888385	1.701879	4.07489	0.746363	205.131	1.93E-32	2.39E-30	64.46794

SLC16A9	2.510903	1.832845	3.188962	1.170259	205.8292	1.81E-32	2.28E-30	62.26269
USP2	3.063715	0.485283	5.642147	1.322209	170.4111	5.90E-31	6.40E-29	58.95116
CPTP	2.919831	1.717799	4.121863	0.937513	123.0577	2.38E-28	2.13E-26	53.81366
RNF4	2.705159	1.970925	3.439394	0.907569	120.0257	3.77E-28	3.31E-26	53.44855
TMEM97	3.306198	1.558131	5.054265	1.031917	95.05034	2.77E-26	2.11E-24	48.85804
COLGALT1	2.462431	2.059514	2.865347	0.854771	91.66869	5.40E-26	4.03E-24	48.69441
AIMP2	3.487156	2.736872	4.237441	0.868984	89.3522	8.66E-26	6.38E-24	48.47704
CYP2B6	2.477085	1.237846	3.716324	1.161438	69.48567	8.84E-24	5.89E-22	42.48504
CRACR2B	2.282575	0.185604	4.379545	0.662691	57.30274	3.05E-22	1.84E-20	41.28492
DNMBP	2.326228	-1.05072	5.703172	0.576117	65.63341	3.39E-23	2.22E-21	39.64474
RMDN2	2.408938	1.434472	3.383405	0.861871	58.32415	2.92E-22	1.78E-20	37.247
HOXB9	2.682496	2.00064	3.364352	1.329053	56.53259	3.91E-22	2.33E-20	36.96108
EHHADH	2.223402	1.567511	2.879294	0.763597	53.99182	1.19E-21	6.91E-20	35.89604
MAFG	2.228223	1.819736	2.63671	0.598625	42.24393	8.11E-20	4.22E-18	34.29909
MCU	2.729448	1.482053	3.976844	1.195997	48.02243	8.31E-21	4.56E-19	33.70988
TRIP10	3.009567	3.009267	3.009867	1.262253	40.38897	1.84E-19	9.48E-18	32.5676
C1orf174	2.29682	1.319431	3.27421	1.01741	36.53863	1.14E-18	5.59E-17	31.02043
TRNP	3.790563	2.02831	5.552816	1.489721	39.28826	3.36E-19	1.70E-17	29.80364
KNOP1	3.555052	0.229917	6.880186	1.075287	29.31891	6.21E-17	2.87E-15	27.2852
POLR1C	2.41116	1.815291	3.007028	0.981427	27.17174	2.45E-16	1.09E-14	25.83447
TCEANC2	2.114084	1.536106	2.692061	0.640683	30.3227	4.12E-17	1.91E-15	24.8894
YOD1	2.251726	1.40002	3.103432	0.630349	22.08382	1.01E-14	4.16E-13	23.72576
FNTA	3.8008	3.188863	4.412737	1.543854	27.94975	1.69E-16	7.67E-15	23.2208
TSNAX	3.213507	0.379325	6.047689	1.487764	27.66631	1.96E-16	8.83E-15	23.16127
RMI1	2.092177	0.053513	4.130841	0.809893	22.23836	8.90E-15	3.70E-13	22.99896

SLC35B1	2.732088	1.038645	4.425532	0.990241	22.54165	6.99E-15	2.93E-13	22.59159
KIAA1191	2.777883	1.416633	4.139133	1.296049	23.14282	4.37E-15	1.86E-13	22.38208
CARNMT1	2.395839	1.601053	3.190626	0.882447	24.6258	1.71E-15	7.49E-14	20.8106
PEPD	3.375827	2.716792	4.034861	1.327562	22.5639	7.96E-15	3.33E-13	19.25178
RCOR1	2.207431	0.766057	3.648805	0.695448	22.06852	1.19E-14	4.90E-13	18.87775
ESCO1	2.410864	1.589855	3.231874	0.989235	21.22402	2.38E-14	9.62E-13	18.12087
SLC22A18AS	2.451748	2.451727	2.45177	1.098352	21.03564	2.75E-14	1.11E-12	18.09003
ANGEL2	2.320377	1.747174	2.893581	0.85416	16.94474	1.07E-12	3.95E-11	18.08162
DHX8	2.126274	0.458546	3.794001	0.897775	21.13826	2.55E-14	1.03E-12	18.06963
NRARP	2.43004	1.962687	2.897392	1.068269	17.46356	6.33E-13	2.35E-11	17.72656
AXL	2.237418	2.026419	2.448417	1.04306	20.58388	4.08E-14	1.63E-12	17.58648
RNASET2	4.249637	3.913789	4.585486	2.67838	20.56747	4.14E-14	1.65E-12	17.31053
PDZK1IP1	-5.60813	-6.03222	-5.18403	4.006909	-20.0512	6.47E-14	2.54E-12	16.86215
SLC52A2	3.270025	0.55141	5.988641	1.306519	19.79658	8.08E-14	3.14E-12	16.84347
TWSG1	2.486368	0.923375	4.049361	1.029715	15.76793	3.72E-12	1.30E-10	16.11874
SURF2	2.783291	2.276591	3.289991	0.868903	14.25796	2.09E-11	7.06E-10	15.22762
CDK11B	2.228709	0.945362	3.512057	1.269938	17.82835	4.94E-13	1.86E-11	14.89304
TUSC2	2.999059	2.989158	3.00896	1.260674	16.68282	1.59E-12	5.78E-11	13.66459
ELAVL1	2.187195	1.595485	2.778905	0.799058	16.48699	1.95E-12	7.02E-11	13.41318
SSRP1	2.41651	2.112921	2.720099	1.02578	16.27372	2.44E-12	8.74E-11	13.21645
KLHDC2	2.078547	1.39049	2.766605	1.009655	15.91742	3.56E-12	1.25E-10	13.0265
ENPP4	2.179243	-0.10535	4.46383	1.035684	16.15862	2.75E-12	9.84E-11	13.00227
SLC27A2	2.976645	2.03798	3.915309	1.290051	15.94305	3.47E-12	1.22E-10	12.90597
SCML1	2.151266	1.948615	2.353916	0.890799	15.94217	3.47E-12	1.22E-10	12.76882
EMC2	2.457522	2.153252	2.761793	1.028416	15.2968	7.03E-12	2.45E-10	12.07289

BTN3A1	2.078392	1.233696	2.923088	1.018597	15.25522	7.37E-12	2.55E-10	12.04292
RBM19	2.147287	0.323798	3.970777	0.883196	14.68492	1.41E-11	4.82E-10	11.4609
TOMM40	3.174469	2.811968	3.536971	1.44834	11.51221	7.37E-10	2.23E-08	10.39573
UBE2D1	2.816295	2.594203	3.038387	1.314221	13.8573	3.75E-11	1.24E-09	10.32199
PPP1R35	4.043265	1.469199	6.617332	1.032592	10.76411	2.18E-09	6.25E-08	10.2874
C1orf35	3.660725	3.408885	3.912565	1.553506	13.80063	4.01E-11	1.32E-09	10.20995
PSMF1	2.115044	1.612514	2.617574	1.100495	13.81859	3.93E-11	1.29E-09	10.14865
MGAT4B	2.096633	1.643736	2.54953	0.818526	13.68205	4.64E-11	1.51E-09	10.06462
POGLUT1	2.248572	0.981399	3.515744	0.570013	11.97195	3.88E-10	1.21E-08	10.05983
CAPN7	2.341091	2.061652	2.62053	1.091799	13.33016	7.17E-11	2.32E-09	9.792124
RAB32	3.785741	3.309704	4.261778	1.265912	12.97195	1.13E-10	3.63E-09	9.221832
NTAN1	3.185764	1.823052	4.548477	1.616328	12.78952	1.43E-10	4.54E-09	9.016292
ANKLE2	2.235264	1.822963	2.647566	1.040567	12.37396	2.46E-10	7.77E-09	8.332503
SNHG25	3.301412	2.68459	3.918234	1.4569	10.05838	6.41E-09	1.74E-07	8.298405
C5orf51	2.530155	1.277495	3.782815	1.35589	11.94619	4.39E-10	1.35E-08	7.679155
THAP1	2.074863	0.986198	3.163527	1.114663	11.70405	6.12E-10	1.87E-08	7.428032
EPS8L3	2.850031	2.253827	3.446235	1.279373	11.72497	5.95E-10	1.83E-08	7.353802
DUOX2	-3.33027	-3.68371	-2.97684	2.121494	-11.609	6.99E-10	2.13E-08	7.080796
UBFD1	2.689606	2.689558	2.689653	0.974677	8.842133	4.68E-08	1.16E-06	7.078165
PDE8A	2.271803	0.97669	3.566915	0.896731	11.16351	1.32E-09	3.87E-08	6.535539
GTF2B	2.912327	2.912247	2.912406	1.197572	10.82742	2.15E-09	6.24E-08	6.06125
NCEH1	2.002233	1.339632	2.664834	1.153378	10.81695	2.18E-09	6.25E-08	5.979975
GLRX5	4.280981	3.75816	4.803802	1.926578	10.82551	2.15E-09	6.24E-08	5.963599
UGT2A3	2.532018	2.078919	2.985116	1.145835	10.68313	2.66E-09	7.52E-08	5.838591
UBP1	2.285544	-0.15752	4.728604	1.096856	10.55124	3.24E-09	9.00E-08	5.64475

C1orf123	3.495482	2.708355	4.282609	1.578687	10.60944	2.97E-09	8.34E-08	5.636488
VSIG10	2.364122	1.981099	2.747145	1.270378	10.58769	3.07E-09	8.59E-08	5.583776
CNNM4	2.097288	2.097254	2.097322	0.91612	10.53647	3.31E-09	9.18E-08	5.536932
DHRSX_1	3.258274	2.775611	3.740937	1.658882	10.57878	3.11E-09	8.69E-08	5.50189
SNX14	2.1982	1.257286	3.139114	1.103197	10.38995	4.13E-09	1.14E-07	5.395501
BIN1	2.114224	1.494234	2.734214	0.93652	10.37461	4.23E-09	1.16E-07	5.368496
RCN2	3.096913	1.704593	4.489234	1.41372	10.22543	5.31E-09	1.45E-07	5.105555
AP1AR	2.120758	1.025418	3.216097	0.98335	9.952441	8.12E-09	2.17E-07	4.648369
NELFCD	2.771497	0.69712	4.845875	1.232264	9.937995	8.30E-09	2.22E-07	4.594104
MIR22HG	2.913346	2.06404	3.762652	0.868125	7.055286	1.22E-06	2.52E-05	4.517802
C6orf203	3.154998	2.338211	3.971785	1.559197	9.724124	1.16E-08	3.08E-07	4.247387
AKAP1	2.996021	2.491645	3.500397	1.436996	9.739193	1.14E-08	3.01E-07	4.201744
POLR3GL	3.526519	3.184796	3.868242	2.103339	9.482831	1.72E-08	4.49E-07	3.859821
TMEM209	2.103622	-0.15381	4.361055	0.974455	9.355783	2.11E-08	5.46E-07	3.633699
ASL	3.588122	3.205127	3.971117	1.610077	9.253373	2.50E-08	6.40E-07	3.359054
LCN2	-4.8817	-6.88305	-2.88035	4.924502	-9.20957	2.68E-08	6.83E-07	3.346671
GSTM4	2.119042	1.85711	2.380974	1.142218	9.069587	3.39E-08	8.56E-07	3.14862
OXSR1	2.53886	0.29241	4.785311	1.161741	8.891075	4.57E-08	1.14E-06	2.741917
ISOC1	2.743681	1.984805	3.502558	1.601496	8.764776	5.66E-08	1.39E-06	2.687141
ZFYVE21	2.97238	2.971923	2.972838	1.317557	8.694322	6.39E-08	1.55E-06	2.433465
TMEM56	2.407083	1.545139	3.269028	1.040859	8.412209	1.04E-07	2.48E-06	2.093342
HSPA14	2.585395	1.539956	3.630835	0.853805	5.803582	1.53E-05	0.000273	2.062648
CRYL1	2.642929	2.017582	3.268277	1.402709	8.447708	9.79E-08	2.35E-06	2.000301
GOT1	2.099817	0.34234	3.857295	1.12885	8.347945	1.17E-07	2.76E-06	1.964918
TNIP2	2.721967	1.340159	4.103776	1.259205	8.257663	1.37E-07	3.20E-06	1.880354

TMEM171	3.36368	3.363421	3.363939	1.53924	8.387995	1.09E-07	2.59E-06	1.877229
ITGB1BP1	2.074926	0.64479	3.505063	1.100548	8.164326	1.61E-07	3.71E-06	1.779527
TUFM	3.034215	1.739648	4.328781	2.125172	8.223816	1.45E-07	3.38E-06	1.487497
PCK1	2.605471	-0.80546	6.016405	1.497706	8.166244	1.61E-07	3.70E-06	1.372002
ACAT1	2.719574	2.100674	3.338474	1.317663	8.035478	2.03E-07	4.64E-06	1.232942
ZNF703	2.436165	1.513695	3.358636	1.301567	7.901053	2.59E-07	5.85E-06	0.999204
DCAF6	2.070073	1.483048	2.657099	0.599172	5.075775	7.33E-05	0.001185	0.935852
CSE1L	2.34291	1.375322	3.310499	1.186302	7.832599	2.94E-07	6.59E-06	0.869885
RSBN1L	2.424064	2.104211	2.743917	1.320355	7.82726	2.97E-07	6.64E-06	0.824219
DUSP3	2.064711	1.475769	2.653653	0.862563	7.592072	4.58E-07	1.00E-05	0.713651
RNF11	2.332395	1.667296	2.997495	1.062682	7.528117	5.16E-07	1.12E-05	0.492373
TRPT1	3.647179	1.701423	5.592936	1.718767	7.640164	4.19E-07	9.26E-06	0.401975
CDK1	2.112382	1.884341	2.340423	1.239469	7.529813	5.14E-07	1.12E-05	0.20739
SULT1A1	2.016674	0.362954	3.670394	0.816475	4.890616	0.00011	0.001731	0.189336
P4HTM	2.408499	1.148882	3.668116	1.305442	7.381554	6.79E-07	1.46E-05	0.065232
ACTR1B	2.32397	0.692559	3.955382	0.791875	7.361093	7.06E-07	1.51E-05	0.062269
PPID	2.876656	2.473251	3.280061	1.417196	7.395204	6.62E-07	1.43E-05	-0.00659
CEP70	2.110711	0.634833	3.58659	1.176033	7.283588	8.17E-07	1.73E-05	-0.15888
MSMO1	2.617393	2.613929	2.620858	1.38079	7.238338	8.91E-07	1.87E-05	-0.25953
MRPS9	3.044866	2.418714	3.671019	1.723736	7.194536	9.69E-07	2.03E-05	-0.41486
FLOT1	2.289003	1.796035	2.781971	1.210963	7.041368	1.30E-06	2.67E-05	-0.52858
SDHAF3	2.47459	0.170415	4.778765	0.923721	7.028835	1.33E-06	2.73E-05	-0.60883
TMED5	2.18228	1.589209	2.775351	1.40524	7.044483	1.29E-06	2.66E-05	-0.72353
PQBP1	2.56265	1.952007	3.173292	1.231564	7.001052	1.41E-06	2.87E-05	-0.73686
UMAD1	2.369403	0.682056	4.05675	1.077013	4.828917	0.000126	0.001965	-0.93346

ACO2	2.268683	0.140477	4.396889	1.316509	6.858664	1.86E-06	3.74E-05	-1.09854
QTRT1	3.442982	1.88831	4.997653	1.977843	6.8593	1.85E-06	3.74E-05	-1.12608
FAM104B	2.007063	0.993456	3.02067	1.113283	6.704513	2.51E-06	4.97E-05	-1.23871
GCHFR	3.709967	2.513954	4.90598	2.025775	6.460125	4.09E-06	7.87E-05	-1.85542
GINS2	2.709001	-0.638	6.056003	1.13673	6.416866	4.47E-06	8.51E-05	-1.88028
MMP24OS	3.529966	2.75141	4.308523	1.962005	6.365356	4.96E-06	9.43E-05	-2.12635
R3HCC1	2.362893	1.924178	2.801609	1.011615	6.218686	6.68E-06	0.000125	-2.18902
GMFB	2.212609	0.952692	3.472526	0.875928	3.634836	0.001833	0.022912	-2.59653
CBX1	2.439385	1.680544	3.198227	1.427948	6.043383	9.57E-06	0.000176	-2.68758
PET117	2.959902	1.948051	3.971753	1.858143	6.078905	8.90E-06	0.000165	-2.78756
SFXN4	2.166839	1.661853	2.671826	1.249208	6.016005	1.01E-05	0.000186	-2.82505
NR3C2	2.205622	-0.72971	5.140952	1.179453	6.028719	9.87E-06	0.000182	-2.82904
ALG3	2.436979	2.140497	2.733462	1.307249	5.908004	1.27E-05	0.00023	-2.91305
C8orf82	2.802414	2.802328	2.8025	1.064694	3.703489	0.001571	0.019956	-3.01453
ECSIT	3.420267	2.866547	3.973987	1.219854	3.718712	0.001518	0.01932	-3.10885
ZNF22	3.060888	2.431157	3.690618	1.888848	5.874973	1.36E-05	0.000245	-3.16983
RHOF	2.94349	2.240266	3.646713	1.751	5.83653	1.47E-05	0.000264	-3.26822
MRPL1	2.759888	1.463961	4.055816	1.304657	5.78498	1.64E-05	0.000292	-3.33834
SCYL2	2.188636	2.187996	2.189276	1.227669	5.771178	1.69E-05	0.0003	-3.34408
SRSF2	2.003466	2.003156	2.003776	0.967469	5.697387	1.97E-05	0.000348	-3.3664
VAMP3	2.230182	1.602781	2.857583	1.242426	5.739752	1.80E-05	0.000319	-3.46064
ZAR1	2.055048	1.657868	2.452227	1.145776	5.66365	2.12E-05	0.000373	-3.54314
ECHDC1	2.405591	1.798266	3.012916	1.421871	5.700651	1.96E-05	0.000346	-3.56433
VSIG2	3.599777	2.004296	5.195259	2.007373	5.639449	2.23E-05	0.000391	-3.72519
NIPSNAP3A	3.069046	0.44227	5.695823	1.554338	5.589474	2.48E-05	0.000433	-3.7396

POLR2G	2.79577	1.809943	3.781598	1.836376	5.573093	2.57E-05	0.000447	-3.76254
FUCA2	2.728046	2.263576	3.192516	1.631229	5.600982	2.42E-05	0.000423	-3.78953
ATPAF1	3.00056	2.628135	3.372985	1.741297	5.545591	2.72E-05	0.000472	-3.86223
NUDC	2.355102	1.744796	2.965408	1.740297	5.511019	2.93E-05	0.000505	-3.92898
DPM2	2.634481	1.835302	3.433661	1.319774	5.273361	4.87E-05	0.000816	-4.36661
GOLGA5	2.336888	1.828551	2.845225	1.2583	5.292422	4.68E-05	0.000785	-4.42948
CCDC124	3.404749	2.985173	3.824324	2.037902	5.15842	6.25E-05	0.001025	-4.762
APOC1	3.401035	2.850621	3.951449	1.899563	5.11662	6.85E-05	0.001112	-4.78699
MT1H	3.695767	2.195583	5.19595	1.737959	5.077434	7.46E-05	0.001204	-4.89096
MYO1B	2.06177	1.470182	2.653359	1.212623	5.052306	7.88E-05	0.001269	-4.92469
CTSA	2.573179	2.276685	2.869672	1.506444	5.04328	8.03E-05	0.00129	-4.94791
NOB1	2.176812	1.325793	3.027831	1.433758	5.013069	8.58E-05	0.001372	-5.02925
ERI3	2.418652	1.933861	2.903443	1.506631	4.937971	0.000101	0.001602	-5.2146
RNF167	2.092779	0.997214	3.188344	1.518743	4.916788	0.000106	0.001673	-5.28941
FZD5	2.074947	1.660916	2.488978	1.306024	4.879538	0.000115	0.001804	-5.39514
SMIM24	2.509003	1.932175	3.085832	1.195596	4.79683	0.000138	0.002132	-5.41253
CDCA7	2.007039	1.321438	2.69264	1.342108	4.815575	0.000132	0.002053	-5.52106
SLAIN2	2.503268	0.517553	4.488983	1.654989	4.692049	0.000174	0.002638	-5.77225
RAMP2	2.562878	2.246831	2.878926	1.407561	4.470399	0.000284	0.004183	-6.15971
PLA2G2A	-2.40297	-2.67877	-2.12716	5.445552	-4.47957	0.000279	0.004103	-6.26186
FRA10AC1	2.597565	1.932592	3.262537	1.784234	4.489994	0.000272	0.004022	-6.29118
DCTN6	2.46058	0.933868	3.987293	1.722936	4.421763	0.000317	0.004621	-6.38547
ANAPC5	2.244461	1.894544	2.594378	1.499058	4.376223	0.000351	0.005088	-6.47927
CPEB4	2.170472	1.590245	2.750698	1.534287	4.40705	0.000328	0.004762	-6.48573
UBAC1	2.422318	1.903208	2.941427	1.533242	4.307527	0.000409	0.005913	-6.66032

CCT8	2.262592	2.262455	2.262729	1.472151	4.236113	0.00048	0.006834	-6.80559
FIS1	3.15974	2.676863	3.642618	3.313608	4.178578	0.000546	0.007684	-6.98974
S100P	-2.40653	-4.4701	-0.34296	5.361695	-4.08701	0.000671	0.00925	-7.17508
PIM2	-2.71056	-3.37664	-2.04447	3.27922	-4.09061	0.000665	0.009185	-7.20864
MRPL54	2.197727	2.18798	2.207474	2.903509	3.985897	0.000841	0.011361	-7.37421
PKP3	2.242736	1.948856	2.536617	1.657891	3.966333	0.000879	0.011847	-7.47729
TXNL4A	2.740742	1.254701	4.226782	1.959008	3.904483	0.00101	0.013476	-7.59001
PSMD7	-2.76606	-3.09546	-2.43666	3.974223	-3.88269	0.001061	0.014054	-7.61306
PKIG	2.294194	1.043281	3.545106	1.626934	3.825928	0.001205	0.015793	-7.70669
DHRS11	2.832458	-0.06152	5.726434	2.232465	3.704095	0.001584	0.02011	-8.05798
GTF3A	3.181624	3.178957	3.18429	2.858464	3.635697	0.001847	0.02305	-8.22108
FERMT1	2.566723	1.933945	3.199501	2.145787	3.422914	0.002973	0.035575	-8.70165
TTC19	2.010088	1.557543	2.462633	1.394691	3.387022	0.003221	0.038333	-8.74945
MGAT1	2.046709	1.495983	2.597434	1.487852	3.269718	0.004182	0.04838	-9.00111

Supplementary Table 2: Differentially expressed genes common in healed mucosa defined by A) ECSS and RHI and B) ECSS and Nancy scores

A) Overlapping between healed mucosa defined by ECSS and RHI score

Overlapping between healed mucosa defined by ECSS and RHI score
USP2
CCZ1
CYP2B6
RMDN2
TSNAX
ENPP4
TUSC2
MED31
MCU

RNASET2
FNTA
GLRX5
TMEM56
MMP24OS
TUFM
FAM104B
NUDC
ASL
ACO2
TRPT1
ERI3
CPEB4
SCYL2
DHRSX_1
NUDCD2

B) Overlapping between healed mucosa defined by ECSS and NHI index

RBM19
USP2
RNF4
CCZ1
CYP2B6
TRNP
AIMP2
PEPD
ATPAF1
RMDN2
TSNAX
UBFD1
DHX8
SLC22A18AS
ANGEL2
ENPP4
WEE1
TUSC2
MED31
C1orf35
BTN3A1
CPTP
ANKLE2
NTAN1
MCU
RAB32
POLR3GL

RNASET2
BIN1
C6orf203
C1orf123
SLC35B1
TNIP2
AP1AR
AKAP1
RCN2
ACAT1
FNTA
TMEM171
GLRX5
TMEM56
CSE1L
CRYL1
MMP24OS
PPID
PQBP1
UMAD1
TUFM
FAM104B
PPP1R35
FLOT1
SDHAF3
NR3C2
GINS2
HOXB9
GTF3A
ALG3
VSIG2
NUDC
POGLUT1
ASL
ACO2
FZD5
CCDC124
VSIG10
R3HCC1
OXSR1
CCT8
DPM2
TRPT1
TXNL4A
PCK1
ERI3

CPEB4
SCYL2
PKP3
DHRSX_1
APOC1
SMIM24

Supplementary Table 3: Partial Least Square Discriminant Analysis (PLS/DA) of healed vs non-healed mucosa defined by A)ECSS, B)Mayo, C) RHI and D) Nancy scores. Differentially expressed genes for which VIP>1 are listed

A) ECSS

Sample	VIP score	logFC	CI.L	CI.R	AveExpr	t	P.Value	adj.P.Val	B
VSIG2	1.5303	3.6804	2.2300	5.1309	2.0074	5.9887	0.0000	0.0004	-2.2822
CPEB4	1.4385	2.3354	-0.4331	5.1039	1.5343	4.6438	0.0002	0.0052	-5.2705
HECA	1.3919	2.1877	1.4794	2.8959	0.6561	48.5896	0.0000	0.0000	34.8291
MMP24OS	1.3518	4.0183	3.7033	4.3332	1.9620	7.4089	0.0000	0.0000	0.6773
LCN2	1.3464	-4.6598	-6.4826	-2.8369	4.9245	-9.2771	0.0000	0.0000	4.2099
EDEM1	1.3400	2.3269	1.0982	3.5557	1.1472	7.3221	0.0000	0.0000	0.5098
GTF3A	1.3378	3.7488	3.0302	4.4675	2.8585	6.2990	0.0000	0.0002	-1.6372
PRDM1	1.3348	-2.0688	-3.6852	-0.4524	2.4410	-4.5819	0.0002	0.0059	-5.4043
MPP7	1.3183	2.6745	1.0788	4.2701	1.1744	17.2422	0.0000	0.0000	14.9757
B4GALT5	1.3159	2.2686	1.7890	2.7482	1.2972	4.4443	0.0003	0.0078	-5.6793
FZD5	1.3096	2.1769	1.6420	2.7118	1.3060	5.5447	0.0000	0.0009	-3.2343
TTC38	1.2866	2.3298	1.6715	2.9881	1.5664	4.8179	0.0001	0.0036	-4.8687
AKAP1	1.2815	2.9936	2.5635	3.4237	1.4370	9.4346	0.0000	0.0000	4.3993
PDZK1IP1	1.2762	-4.4977	-4.4978	-4.4976	4.0069	-6.3297	0.0000	0.0002	-1.5413
ATPAF1	1.2603	4.0636	3.5375	4.5897	1.7413	27.6717	0.0000	0.0000	23.7522
YIPF6	1.2512	2.3806	1.8869	2.8743	1.4709	4.4741	0.0003	0.0073	-5.6193
UMAD1	1.2477	2.7888	2.7887	2.7888	1.0770	5.1064	0.0001	0.0020	-0.2002
BIN3	1.2415	3.5293	3.2104	3.8482	0.8036	16.3337	0.0000	0.0000	14.0742
ZMAT2	1.2383	-2.5804	-4.0593	-1.1015	2.4127	-4.2936	0.0004	0.0106	-6.0522
CCDC124	1.2366	3.5845	3.0655	4.1035	2.0379	5.4684	0.0000	0.0010	-3.3870
RCC1L	1.2326	2.0858	1.7408	2.4309	0.5693	23.4363	0.0000	0.0000	22.0811
ENPP4	1.2114	2.1914	2.1913	2.1914	1.0357	16.6223	0.0000	0.0000	14.2534
FBLN1	1.2081	-2.1599	-3.0981	-1.2218	1.9914	-3.9407	0.0009	0.0217	-6.8479
TGFBR2	1.1950	-2.3281	-3.0600	-1.5962	1.7201	-5.5964	0.0000	0.0008	-3.1228
TXNL4A	1.1902	3.2801	0.2329	6.3273	1.9590	4.9004	0.0001	0.0031	-4.6558
RNF4	1.1816	2.7051	2.1923	3.2179	0.9076	36.2566	0.0000	0.0000	31.5177
PCLAF	1.1739	-3.1665	-4.0728	-2.2601	2.5259	-6.7103	0.0000	0.0001	-0.7473
UBFD1	1.1706	3.0781	1.1064	5.0498	0.9747	17.5903	0.0000	0.0000	18.4169
COMMD4	1.1617	2.9569	1.0157	4.8980	1.6941	5.1416	0.0001	0.0019	-4.1192
ANGEL2	1.1537	2.3189	1.7461	2.8916	0.8542	14.4059	0.0000	0.0000	15.2839
DHRSX_1	1.1512	2.6338	1.9654	3.3022	1.6589	3.9415	0.0009	0.0217	-6.8282
PKP3	1.1457	2.2816	1.5131	3.0501	1.6579	4.1273	0.0006	0.0150	-6.4316

KIAA1522	1.1415	2.0851	1.7257	2.4444	0.9627	9.2842	0.0000	0.0000	4.4094
USP2	1.1334	2.9332	2.3656	3.5008	1.3222	59.3829	0.0000	0.0000	38.7075
VSIG10	1.1198	2.0819	1.4030	2.7607	1.2704	5.4185	0.0000	0.0011	-3.4784
RCN2	1.1063	3.0068	2.4044	3.6093	1.4137	8.6244	0.0000	0.0000	3.0802
CCT8	1.0923	2.6618	0.4835	4.8402	1.4722	4.9723	0.0001	0.0027	-4.4119
GCNT3	1.0883	-2.2634	-3.2409	-1.2860	3.6774	-5.6166	0.0000	0.0008	-3.0040
CRYZL1	1.0866	2.9367	2.3569	3.5166	1.4439	7.3309	0.0000	0.0000	0.6562
TMEM208	1.0829	3.4337	1.3590	5.5083	2.6472	4.1592	0.0006	0.0141	-6.3233
DENND2A	1.0782	2.0020	1.5332	2.4709	0.7002	11.3830	0.0000	0.0000	7.9070
TRPT1	1.0775	2.8157	2.8131	2.8184	1.7188	4.9594	0.0001	0.0027	-4.4743
DHX8	1.0768	2.1362	0.7759	3.4965	0.8978	20.4134	0.0000	0.0000	18.2396
LSM14A	1.0654	-2.2022	-2.6797	-1.7248	1.9070	-5.1240	0.0001	0.0020	-4.1368
RNASET2	1.0614	3.8134	2.6872	4.9397	2.6784	10.7636	0.0000	0.0000	6.5488
TUFM	1.0537	2.8427	2.3009	3.3845	2.1252	6.9258	0.0000	0.0001	-0.2903
DAAM1	1.0516	-2.1926	-3.7496	-0.6355	1.6000	-4.6421	0.0002	0.0052	-5.2407
AKIRIN2	1.0493	3.1327	2.5593	3.7060	1.2356	20.1948	0.0000	0.0000	17.9049
RNASE6	1.0493	2.0201	1.0597	2.9804	1.0363	7.3437	0.0000	0.0000	0.5923
RAB32	1.0442	3.6859	3.1150	4.2567	1.2659	11.4369	0.0000	0.0000	7.7601
GLRX5	1.0421	3.9266	3.3494	4.5037	1.9266	7.8672	0.0000	0.0000	1.6532
ANKLE2	1.0415	2.2458	-1.0396	5.5312	1.0406	12.8360	0.0000	0.0000	9.6917
PPP2R3C	1.0353	3.3795	0.8758	5.8831	1.5785	8.4275	0.0000	0.0000	2.6682
CSE1L	1.0344	2.3534	2.3522	2.3547	1.1863	7.6934	0.0000	0.0000	1.3021
LACTB2	1.0307	2.5480	0.9784	4.1176	1.0739	37.6244	0.0000	0.0000	31.5630
STAT6	1.0237	2.1050	1.6687	2.5412	0.7731	9.5978	0.0000	0.0000	9.2280
SCYL2	1.0236	2.0535	-0.9668	5.0739	1.2277	4.5664	0.0002	0.0060	-5.3416
CCZ1	1.0209	2.5538	1.9124	3.1951	1.0210	32.3927	0.0000	0.0000	27.1416
SDHAF3	1.0034	2.4039	2.0608	2.7471	0.9237	6.7230	0.0000	0.0001	-0.5137
FSIP2-AS1	1.0021	2.5380	2.2314	2.8447	0.8129	15.2968	0.0000	0.0000	16.6155

B) Mayo

Sample	VIP score	logFC	CI.L	CI.R	AveExpr	t	P.Value	adj.P.Val	B
IFI35	1.3778	3.8121	2.7093	4.9150	1.3518	160.0525	0.0000	0.0000	63.6816
IL6R	1.0552	2.3861	1.2425	3.5297	0.8896	154.5484	0.0000	0.0000	63.0031
CDS1	1.2857	3.2132	2.7621	3.6643	1.3032	121.9818	0.0000	0.0000	58.3309
C6orf203	1.1594	3.7006	2.7191	4.6820	1.4850	98.1487	0.0000	0.0000	53.7534
C5orf51	1.0052	3.0978	2.7715	3.4241	1.4698	82.8061	0.0000	0.0000	50.3908
GINS2	1.0722	3.5830	1.2842	5.8818	1.2506	78.0673	0.0000	0.0000	49.1920
SMIM24	1.3663	3.5972	3.2542	3.9403	1.3098	75.8962	0.0000	0.0000	49.0929
PEPD	1.1416	3.7442	3.4783	4.0102	1.4869	75.8492	0.0000	0.0000	48.4934
METTL7B	1.0931	3.5506	1.7443	5.3569	1.2857	68.6251	0.0000	0.0000	46.4825
STX10	1.0637	3.7075	2.4293	4.9858	1.3343	52.6817	0.0000	0.0000	41.9775
EMC2	1.0558	2.6804	0.6189	4.7419	1.0009	52.4449	0.0000	0.0000	40.9856
EHHADH	1.2524	2.2250	2.1541	2.2959	0.7488	43.3390	0.0000	0.0000	37.0141
TPSB2	1.1268	3.8520	3.3331	4.3708	2.0148	43.2027	0.0000	0.0000	36.8431
DCAF11	1.1634	2.5382	2.0476	3.0289	1.0000	42.1797	0.0000	0.0000	36.4318
UBP1	1.1794	2.6467	2.6467	2.6467	1.2621	38.4861	0.0000	0.0000	34.6773

AP1AR	1.1187	2.7542	2.1355	3.3730	1.0837	37.3951	0.0000	0.0000	33.9791
ELAVL1	1.1616	2.1652	1.7065	2.6238	0.7610	37.0095	0.0000	0.0000	33.8460
CRYL1	1.3015	3.6048	3.1744	4.0351	1.5798	35.4014	0.0000	0.0000	33.0631
COMT	1.0662	2.7857	2.2185	3.3529	1.0758	34.7407	0.0000	0.0000	32.5202
QTRT1	1.5812	4.2772	2.6565	5.8979	2.1480	33.9525	0.0000	0.0000	31.8657
UBAC1	1.4008	3.3444	2.8996	3.7893	1.5449	30.7157	0.0000	0.0000	30.0828
MGAT1	1.0870	2.7939	2.2150	3.3728	1.5517	30.6216	0.0000	0.0000	29.9634
RCOR1	1.1313	2.1971	1.3878	3.0064	0.7741	30.5702	0.0000	0.0000	29.9496
PICALM	1.0578	2.5087	1.9432	3.0743	0.9288	25.1342	0.0000	0.0000	27.7319
CPTP	1.4722	3.0465	2.3434	3.7495	1.0697	26.7015	0.0000	0.0000	27.1053
NIPSNAP3A	1.0894	3.5866	1.7669	5.4063	1.4803	24.6343	0.0000	0.0000	25.5876
C1orf123	1.2944	4.0419	3.6749	4.4088	1.5035	23.6021	0.0000	0.0000	24.5764
MT1H	1.3961	4.8284	4.3054	5.3515	1.8994	21.9361	0.0000	0.0000	23.2069
GON7	1.1908	4.3643	2.6078	6.1208	2.2111	21.8737	0.0000	0.0000	23.1100
KLHL24	1.4107	2.2802	1.8600	2.7004	1.1593	21.6825	0.0000	0.0000	22.9386
PDE8A	1.5866	2.5266	1.5291	3.5242	1.0112	19.9291	0.0000	0.0000	21.2522
METAP1	1.1693	2.1656	0.7562	3.5750	0.7965	18.9432	0.0000	0.0000	20.4953
DCTN3	1.0851	2.7671	2.1884	3.3458	1.4374	17.6706	0.0000	0.0000	19.0038
ABCG2	1.2701	2.2724	1.7485	2.7963	1.2108	17.0196	0.0000	0.0000	18.2235
POLR2B	1.2430	2.5212	2.2889	2.7534	1.2719	16.8248	0.0000	0.0000	18.0531
GTF2B	1.1257	3.1600	2.5352	3.7849	1.1406	16.0240	0.0000	0.0000	17.1122
TMEM87B	1.2126	3.1159	0.6544	5.5773	1.5149	15.7317	0.0000	0.0000	16.7399
APOC1	1.0119	4.2697	1.4332	7.1063	1.8091	15.4120	0.0000	0.0000	16.3973
JUP	1.0521	2.6599	1.3325	3.9873	1.2877	14.5281	0.0000	0.0000	15.1796
RNASET2	1.1120	3.7692	3.1728	4.3655	2.7785	14.3161	0.0000	0.0000	14.8588
HBB	1.3560	4.5048	3.5528	5.4568	1.8016	14.1838	0.0000	0.0000	14.7017
RBM19	1.0868	2.1274	2.1272	2.1276	0.8411	13.6089	0.0000	0.0000	14.1358
ASL	1.4580	3.7789	1.9089	5.6489	1.7588	13.5111	0.0000	0.0000	13.7729
CDKN2B-AS1	1.0002	2.2798	1.8977	2.6619	1.2867	12.4561	0.0000	0.0000	12.3824
PDZK1IP1	1.3849	-4.9404	-7.7361	-2.1447	3.8767	-12.4044	0.0000	0.0000	12.1684
DHX9	1.0501	2.2710	1.8577	2.6842	1.1880	12.1958	0.0000	0.0000	12.0140
PCK1	1.2858	2.9727	1.9149	4.0306	1.6629	12.1734	0.0000	0.0000	11.8643
VPS4A	1.2702	3.3838	1.0166	5.7511	1.8534	12.1893	0.0000	0.0000	11.8618
SAFB2	1.1189	2.1429	1.2518	3.0341	0.8743	12.0153	0.0000	0.0000	11.7014
ENDOD1	1.2616	2.2098	1.4900	2.9297	1.0994	11.5488	0.0000	0.0000	10.9964
DDT	1.2041	3.6538	2.0230	5.2846	3.6498	11.0182	0.0000	0.0000	10.1121
KRTCAP3	1.2595	4.3823	2.8639	5.9007	1.8169	10.9691	0.0000	0.0000	9.9977
MEP1A	1.0052	2.9720	1.7486	4.1954	1.5615	10.3383	0.0000	0.0000	9.1009
NDUFS2	1.1225	2.5687	1.8871	3.2503	1.5616	10.3562	0.0000	0.0000	8.9773
BIN1	1.0367	2.0638	0.3435	3.7842	0.8919	9.8663	0.0000	0.0000	8.2842
DPP7	1.2650	2.5026	2.1157	2.8896	1.3627	9.8948	0.0000	0.0000	8.2460
SMIM26	1.2521	4.2236	3.4661	4.9811	3.9252	9.9032	0.0000	0.0000	8.2253
DENR	1.0747	2.7557	2.4626	3.0487	1.4071	9.7461	0.0000	0.0000	8.0016

TMEM209	1.0916	2.1129	1.3942	2.8315	0.9281	9.5170	0.0000	0.0000	7.6467
DNAJC2	1.3551	2.8495	2.1280	3.5710	1.5294	9.3583	0.0000	0.0000	7.2368
DUOX2	1.1469	-3.2100	-4.2797	-2.1402	2.0205	-9.3447	0.0000	0.0000	7.2127
FAM120AOS	1.1979	2.8048	0.9542	4.6554	1.5312	8.8976	0.0000	0.0000	6.4036
NAA60	1.3420	2.2744	1.8916	2.6572	0.9091	8.6304	0.0000	0.0000	5.9885
WASL	1.0811	3.0124	1.7752	4.2496	1.9088	8.6789	0.0000	0.0000	5.9800
DHRS11	1.2850	3.4634	1.2053	5.7215	2.3606	8.5751	0.0000	0.0000	5.7885
NAAA	1.1887	2.6248	1.8186	3.4311	1.7538	8.2361	0.0000	0.0000	5.1256
IDH3G	1.0923	3.0976	2.6169	3.5783	1.7145	8.0539	0.0000	0.0000	4.8727
TMEM170A	1.2127	2.5070	1.4686	3.5453	1.7231	8.1034	0.0000	0.0000	4.8678
ETFDH	1.0619	2.4540	1.3968	3.4818	1.3846	8.0281	0.0000	0.0000	4.7585
SDHAF3	1.2346	2.6456	2.2872	3.0041	1.1319	7.9110	0.0000	0.0000	4.6060
SURF1	1.0409	3.1509	2.6493	3.6525	2.8415	7.3862	0.0000	0.0000	3.4214
AAMDC	1.1706	3.0919	2.8419	3.3419	1.5161	7.3153	0.0000	0.0000	3.3438
VPS28	1.0197	3.3980	3.1347	3.6613	2.9162	7.3140	0.0000	0.0000	3.3013
TOR1AIP1	1.1553	2.3812	0.9649	3.7975	1.4060	7.2974	0.0000	0.0000	3.2673
OSBPL1A	1.2142	2.2439	0.0747	4.4132	1.1594	7.2723	0.0000	0.0000	3.1991
HSD17B2	1.0391	3.5545	2.3474	4.7617	2.0504	7.2038	0.0000	0.0000	3.0880
SLC38A1	1.0512	2.0269	1.5812	2.4727	1.6565	7.1897	0.0000	0.0000	3.0144
CUTA	1.1430	3.2145	2.7636	3.6655	3.3172	7.0416	0.0000	0.0000	2.7274
PCGF5	1.1740	2.3039	0.1561	4.4517	1.4253	6.8617	0.0000	0.0000	2.3388
SNX2	1.0539	2.0389	1.5566	2.5213	1.4644	6.6796	0.0000	0.0001	1.9545
CREG1	1.0627	2.3530	-0.3660	5.0720	1.3357	6.6326	0.0000	0.0001	1.8776
RGS10	1.1943	3.0957	3.0744	3.1170	1.5377	6.5683	0.0000	0.0001	1.7545
CNOT1	1.2493	2.0469	1.2221	2.8717	1.4190	6.5284	0.0000	0.0001	1.6030
AIP	1.0640	2.7929	1.8062	3.7796	1.1427	6.4782	0.0000	0.0001	1.5996
LCN2	1.1999	-4.2918	-4.8056	-3.7780	4.7525	-6.4988	0.0000	0.0001	1.5885
TLK1	1.1708	2.2638	1.3867	3.1410	1.6290	6.4256	0.0000	0.0001	1.4067
SMIM31	1.0672	2.9542	1.1073	4.8012	2.0235	6.4142	0.0000	0.0001	1.3950
MT1G	1.3051	4.5469	4.2089	4.8850	4.6498	6.4193	0.0000	0.0001	1.3782
MT1F	1.3225	4.2595	3.7539	4.7651	2.2089	6.4065	0.0000	0.0001	1.3698
C1orf115	1.3646	2.3083	1.7434	2.8732	1.4543	6.2509	0.0000	0.0001	1.0220
PABPN1	1.3307	2.4463	1.9672	2.9255	1.8991	6.2391	0.0000	0.0001	0.9665
FRA10AC1	1.0910	2.4987	1.7821	3.2152	1.8903	5.9706	0.0000	0.0002	0.3792
RAB11B	1.3986	3.1120	1.3116	4.9125	2.1656	5.9233	0.0000	0.0002	0.2675
PLIN3	1.3445	2.9826	2.2671	3.6981	2.4740	5.9201	0.0000	0.0002	0.2596
SFT2D1	1.1878	3.6605	3.5308	3.7903	3.2930	5.9009	0.0000	0.0002	0.2409
GRPEL1	1.1027	2.9930	2.6054	3.3806	2.3347	5.7248	0.0000	0.0003	-0.1583
NFKBIZ	1.2384	-2.7780	-3.4394	-2.1167	1.5072	-5.5964	0.0000	0.0004	-0.4498
RAB10	1.1116	2.0675	-0.1711	4.3061	3.1027	5.5671	0.0000	0.0005	-0.4948
HSD11B2	1.0725	2.4535	0.9718	3.9352	1.5715	5.4830	0.0000	0.0005	-0.6921
PPP1R2	1.0489	2.4129	0.4242	4.4016	1.6878	5.3745	0.0000	0.0007	-0.9414
DUOXA2	1.2098	-3.0830	-4.1102	-2.0557	2.2453	-5.2429	0.0000	0.0009	-1.2422

THYN1	1.0156	3.0352	3.0297	3.0407	2.2036	5.1892	0.0001	0.0010	-1.3650
GSN	1.1628	-2.4056	-3.2804	-1.5308	2.4534	-5.1948	0.0001	0.0010	-1.3715
FUCA2	1.0090	2.5719	1.9303	3.2135	1.7523	5.1808	0.0001	0.0010	-1.3802
ALDH3A2	1.0687	2.4176	1.7136	3.1216	1.9924	5.0776	0.0001	0.0012	-1.6213
CFTR	1.2096	2.2837	1.8260	2.7414	2.0353	5.0299	0.0001	0.0013	-1.7587
ARCN1	1.0583	2.4454	1.7879	3.1028	1.7451	4.9369	0.0001	0.0016	-1.9551
MISP	1.2641	2.8242	2.4721	3.1763	2.3163	4.9398	0.0001	0.0016	-1.9688
JUN	1.1337	-2.3037	-2.6510	-1.9564	2.7454	-4.8655	0.0001	0.0018	-2.1264
PDCD6	1.1284	2.5592	1.5396	3.5788	2.8315	4.8509	0.0001	0.0019	-2.1637
SERINC3	1.3812	2.7648	2.3241	3.2056	2.0722	4.8413	0.0001	0.0019	-2.1984
MTIF3	1.2038	2.5977	1.9645	3.2310	2.0853	4.5842	0.0002	0.0033	-2.7857
CAT	1.2661	3.0692	2.6045	3.5339	2.6787	4.5266	0.0002	0.0037	-2.9249
MKRN1	1.1319	2.4524	1.5158	3.3890	1.9920	4.4154	0.0003	0.0047	-3.1772
RIOK3	1.2594	2.5707	1.9929	3.1485	2.5190	4.0103	0.0007	0.0107	-4.1333
GINM1	1.2567	2.7076	1.2419	4.1733	2.2207	3.9711	0.0008	0.0116	-4.2207
CS	1.0507	2.2078	2.0467	2.3689	1.7359	3.8992	0.0009	0.0135	-4.3839
PRKACB	1.0531	2.1111	1.6229	2.5993	2.1290	3.7879	0.0012	0.0171	-4.6352
UBL3	1.1677	2.2203	0.2425	4.1981	1.7130	3.7465	0.0013	0.0184	-4.7379
HADHB	1.3168	2.6766	2.1982	3.1549	2.4432	3.7438	0.0013	0.0185	-4.7513
MPST	1.2551	2.7293	2.3006	3.1581	2.8325	3.7011	0.0015	0.0202	-4.8448
PIM2	1.1566	-2.3799	-3.0119	-1.7479	3.1572	-3.6767	0.0015	0.0213	-4.8998
MT2A	1.1490	3.0011	0.8139	5.1884	4.3139	3.6596	0.0016	0.0220	-4.9271
NOP53	1.0608	2.4990	0.6576	4.3404	3.3111	3.6213	0.0018	0.0238	-5.0129
GUCA2A	1.1132	3.0834	2.2929	3.8739	3.8847	3.4515	0.0026	0.0336	-5.4113
ARL8B	1.1934	2.4567	1.7385	3.1750	2.1461	3.4236	0.0028	0.0355	-5.4753
MT1X	1.1662	2.0991	0.0392	4.1591	5.6005	3.3712	0.0031	0.0396	-5.5817
CXCL1	1.0137	-2.7494	-3.2856	-2.2133	2.8412	-3.2589	0.0040	0.0496	-5.8358

C) RHI

Sample	VIP scores	logFC	CI.L	CI.R	AveExpr	t	P.Value	adj.P.Val	B
TRPT1	1.5907	3.9412	3.6011	4.2813	1.7188	11.0813	0.0000	0.0000	8.8145
USP2	1.5163	3.0640	2.2829	3.8450	1.3222	68.2823	0.0000	0.0000	43.7965
CCZ1	1.4227	2.6629	2.2479	3.0779	1.0210	89.4685	0.0000	0.0000	48.9330
STAT1	1.3926	-2.8620	-4.8032	-0.9208	2.1033	-7.5876	0.0000	0.0000	2.7139
AXL	1.3758	2.8094	1.9010	3.7179	1.0431	94.1468	0.0000	0.0000	50.0536
DYNC1LI2	1.3519	2.7302	0.6836	4.7768	2.1059	4.4036	0.0003	0.0171	-4.1302
LUZP1	1.3187	2.3053	1.4627	3.1479	1.2686	8.2587	0.0000	0.0000	4.0372
FNTA	1.2371	3.7707	3.1198	4.4215	1.5439	37.6805	0.0000	0.0000	31.6508

PDZK1IP1	1.1948	-4.2771	-4.7010	-3.8533	4.0069	-6.1693	0.0000	0.0006	-0.1477
SBDS	1.1903	2.1934	1.3633	3.0235	3.6336	4.3920	0.0003	0.0174	-4.1210
ENPP4	1.1712	2.2027	1.1905	3.2150	1.0357	12.1122	0.0000	0.0000	10.4117
MRPL1	1.1541	2.4960	1.9205	3.0715	1.3047	7.0993	0.0000	0.0001	1.8465
COLGALT1	1.1511	2.4484	1.2877	3.6092	0.8548	133.8343	0.0000	0.0000	56.8397
SNORD47	1.1177	-3.7743	-5.0464	-2.5023	2.6893	-7.1462	0.0000	0.0001	1.8517
HEPACAM2	1.1101	2.7581	2.0725	3.4437	2.0458	5.8488	0.0000	0.0010	-0.8705
MRPS9	1.1017	3.2515	2.1059	4.3971	1.7237	9.9302	0.0000	0.0000	7.0174
POF1B	1.0954	-2.3661	-3.3663	-1.3660	2.1573	-3.9897	0.0008	0.0364	-5.0620
SLC52A2	1.0893	3.1790	0.7758	5.5822	1.3065	15.2243	0.0000	0.0000	14.5927
RNASET2	1.0773	3.7067	2.4058	5.0075	2.6784	9.2429	0.0000	0.0000	5.8394
CYP2B6	1.0750	2.4770	1.4332	3.5208	1.1614	67.5004	0.0000	0.0000	43.5798
PLEKHJ1	1.0671	3.0327	2.6685	3.3969	2.5893	4.1738	0.0005	0.0256	-4.6269
BZW2	1.0670	2.0479	-0.0811	4.1769	0.9947	4.7768	0.0001	0.0082	-3.1352
TGFBR2	1.0630	-2.2035	-2.6346	-1.7724	1.7201	-5.2029	0.0001	0.0035	-2.3021
FERMT1	1.0532	2.3751	1.9792	2.7710	2.1458	4.2555	0.0004	0.0225	-4.4332
ARRDC1	1.0499	2.6005	1.7567	3.4444	1.3426	12.0907	0.0000	0.0000	10.4709
ECHDC1	1.0441	2.8696	2.4387	3.3005	1.4219	20.3706	0.0000	0.0000	19.9600
ANP32A	1.0372	2.3211	1.9144	2.7278	2.9935	4.4302	0.0003	0.0163	-4.0404
TRNY	1.0179	3.7472	2.3381	5.1563	2.2501	17.3794	0.0000	0.0000	16.8581
CPEB4	1.0163	2.0411	1.8091	2.2731	1.5343	5.3280	0.0000	0.0027	-2.0079
RNPS1	1.0133	-2.6085	-2.8705	-2.3465	1.9714	-7.4011	0.0000	0.0001	2.3921
GSTM4	1.0080	2.0349	1.5851	2.4846	1.1422	7.5343	0.0000	0.0000	2.7489
MED31	1.0055	2.7576	2.1019	3.4133	1.2133	13.3427	0.0000	0.0000	12.1944

D) Nancy

Sample	VIP Scores	logFC	CI.L	CI.R	AveExpr	t	P.Value	adj.P.Val	B
PDZK1IP1	1.7273	-5.6081	-6.0322	-5.1840	4.0069	-20.0512	0.0000	0.0000	16.8621
DCAF6	1.6463	2.0701	1.4830	2.6571	0.5992	5.0758	0.0001	0.0012	0.9359
RNASET2	1.5755	4.2496	3.9138	4.5855	2.6784	20.5675	0.0000	0.0000	17.3105
USP2	1.5208	3.0637	0.4853	5.6421	1.3222	170.4111	0.0000	0.0000	58.9512

DNMBP	1.4582	2.3262	-1.0507	5.7032	0.5761	65.6334	0.0000	0.0000	39.6447
LCN2	1.4196	-4.8817	-6.8830	-2.8804	4.9245	-9.2096	0.0000	0.0000	3.3467
VSIG2	1.4127	3.5998	2.0043	5.1953	2.0074	5.6394	0.0000	0.0004	-3.7252
BTN2A1	1.4125	2.5898	2.2874	2.8922	0.9022	433.8996	0.0000	0.0000	77.1324
DHRSX_1	1.4121	3.2583	2.7756	3.7409	1.6589	10.5788	0.0000	0.0000	5.5019
TRPT1	1.3986	3.6472	1.7014	5.5929	1.7188	7.6402	0.0000	0.0000	0.4020
PDE8A	1.3969	2.2718	0.9767	3.5669	0.8967	11.1635	0.0000	0.0000	6.5355
MAFG	1.3923	2.2282	1.8197	2.6367	0.5986	42.2439	0.0000	0.0000	34.2991
YOD1	1.3890	2.2517	1.4000	3.1034	0.6303	22.0838	0.0000	0.0000	23.7258
DUOX2	1.3704	-3.3303	-3.6837	-2.9768	2.1215	-11.6090	0.0000	0.0000	7.0808
MED31	1.3430	3.3156	1.3360	5.2952	1.2133	242.3434	0.0000	0.0000	65.6884
C7orf55-LUC7L2	1.3348	2.9734	2.6027	3.3440	0.8535	973.1416	0.0000	0.0000	92.4368
FERMT1	1.3336	2.5667	1.9339	3.1995	2.1458	3.4229	0.0030	0.0356	-8.7017
CCZ1	1.3321	2.6837	0.4160	4.9513	1.0210	245.9757	0.0000	0.0000	66.2126
VSIG10	1.3314	2.3641	1.9811	2.7471	1.2704	10.5877	0.0000	0.0000	5.5838
OXSR1	1.3221	2.5389	0.2924	4.7853	1.1617	8.8911	0.0000	0.0000	2.7419
EDN3	1.3203	2.8884	1.7019	4.0749	0.7464	205.1310	0.0000	0.0000	64.4679
FNTA	1.2957	3.8008	3.1889	4.4127	1.5439	27.9498	0.0000	0.0000	23.2208
CPTP	1.2920	2.9198	1.7178	4.1219	0.9375	123.0577	0.0000	0.0000	53.8137
PIM2	1.2917	-2.7106	-3.3766	-2.0445	3.2792	-4.0906	0.0007	0.0092	-7.2086
RCOR1	1.2846	2.2074	0.7661	3.6488	0.6954	22.0685	0.0000	0.0000	18.8777
TCEANC2	1.2825	2.1141	1.5361	2.6921	0.6407	30.3227	0.0000	0.0000	24.8894
GLRX5	1.2808	4.2810	3.7582	4.8038	1.9266	10.8255	0.0000	0.0000	5.9636
ASL	1.2786	3.5881	3.2051	3.9711	1.6101	9.2534	0.0000	0.0000	3.3591
FRA10AC1	1.2648	2.5976	1.9326	3.2625	1.7842	4.4900	0.0003	0.0040	-6.2912
TUFM	1.2525	3.0342	1.7396	4.3288	2.1252	8.2238	0.0000	0.0000	1.4875
MRPL1	1.2511	2.7599	1.4640	4.0558	1.3047	5.7850	0.0000	0.0003	-3.3383
RMDN2	1.2339	2.4089	1.4345	3.3834	0.8619	58.3242	0.0000	0.0000	37.2470
CPEB4	1.2293	2.1705	1.5902	2.7507	1.5343	4.4071	0.0003	0.0048	-6.4857
AKAP1	1.2229	2.9960	2.4916	3.5004	1.4370	9.7392	0.0000	0.0000	4.2017
MCU	1.2143	2.7294	1.4821	3.9768	1.1960	48.0224	0.0000	0.0000	33.7099
MT1H	1.2122	3.6958	2.1956	5.1960	1.7380	5.0774	0.0001	0.0012	-4.8910
SFXN4	1.2023	2.1668	1.6619	2.6718	1.2492	6.0160	0.0000	0.0002	-2.8250
PCK1	1.1902	2.6055	-0.8055	6.0164	1.4977	8.1662	0.0000	0.0000	1.3720
PET117	1.1881	2.9599	1.9481	3.9718	1.8581	6.0789	0.0000	0.0002	-2.7876
PSMF1	1.1853	2.1150	1.6125	2.6176	1.1005	13.8186	0.0000	0.0000	10.1487
RNF11	1.1828	2.3324	1.6673	2.9975	1.0627	7.5281	0.0000	0.0000	0.4924
DHRS11	1.1751	2.8325	-0.0615	5.7264	2.2325	3.7041	0.0016	0.0201	-8.0580
SRSF2	1.1684	2.0035	2.0032	2.0038	0.9675	5.6974	0.0000	0.0003	-3.3664
ELAVL1	1.1626	2.1872	1.5955	2.7789	0.7991	16.4870	0.0000	0.0000	13.4132
S100P	1.1576	-2.4065	-4.4701	-0.3430	5.3617	-4.0870	0.0007	0.0093	-7.1751

ENPP4	1.1559	2.1792	-0.1053	4.4638	1.0357	16.1586	0.0000	0.0000	13.0023
SLC35B1	1.1437	2.7321	1.0386	4.4255	0.9902	22.5417	0.0000	0.0000	22.5916
FZD5	1.1430	2.0749	1.6609	2.4890	1.3060	4.8795	0.0001	0.0018	-5.3951
MGAT4B	1.1420	2.0966	1.6437	2.5495	0.8185	13.6821	0.0000	0.0000	10.0646
CAPN7	1.1338	2.3411	2.0617	2.6205	1.0918	13.3302	0.0000	0.0000	9.7921
PLA2G2A	1.1283	-2.4030	-2.6788	-2.1272	5.4456	-4.4796	0.0003	0.0041	-6.2619
RNF4	1.1275	2.7052	1.9709	3.4394	0.9076	120.0257	0.0000	0.0000	53.4486
EPS8L3	1.1234	2.8500	2.2538	3.4462	1.2794	11.7250	0.0000	0.0000	7.3538
RCN2	1.1145	3.0969	1.7046	4.4892	1.4137	10.2254	0.0000	0.0000	5.1056
GTF3A	1.1042	3.1816	3.1790	3.1843	2.8585	3.6357	0.0018	0.0231	-8.2211
ANGEL2	1.1009	2.3204	1.7472	2.8936	0.8542	16.9447	0.0000	0.0000	18.0816
PSMD7	1.1007	-2.7661	-3.0955	-2.4367	3.9742	-3.8827	0.0011	0.0141	-7.6131
FUCA2	1.0923	2.7280	2.2636	3.1925	1.6312	5.6010	0.0000	0.0004	-3.7895
SURF2	1.0907	2.7833	2.2766	3.2900	0.8689	14.2580	0.0000	0.0000	15.2276
CCDC124	1.0863	3.4047	2.9852	3.8243	2.0379	5.1584	0.0001	0.0010	-4.7620
HSPA14	1.0843	2.5854	1.5400	3.6308	0.8538	5.8036	0.0000	0.0003	2.0626
MMP24OS	1.0780	3.5300	2.7514	4.3085	1.9620	6.3654	0.0000	0.0001	-2.1263
FIS1	1.0705	3.1597	2.6769	3.6426	3.3136	4.1786	0.0005	0.0077	-6.9897
ZFYVE21	1.0694	2.9724	2.9719	2.9728	1.3176	8.6943	0.0000	0.0000	2.4335
MRPS9	1.0665	3.0449	2.4187	3.6710	1.7237	7.1945	0.0000	0.0000	-0.4149
CRACR2B	1.0648	2.2826	0.1856	4.3795	0.6627	57.3027	0.0000	0.0000	41.2849
PKP3	1.0641	2.2427	1.9489	2.5366	1.6579	3.9663	0.0009	0.0118	-7.4773
ESCO1	1.0636	2.4109	1.5899	3.2319	0.9892	21.2240	0.0000	0.0000	18.1209
MYO1B	1.0571	2.0618	1.4702	2.6534	1.2126	5.0523	0.0001	0.0013	-4.9247
SULT1A1	1.0555	2.0167	0.3630	3.6704	0.8165	4.8906	0.0001	0.0017	0.1893
KNOP1	1.0508	3.5551	0.2299	6.8802	1.0753	29.3189	0.0000	0.0000	27.2852
QTRT1	1.0506	3.4430	1.8883	4.9977	1.9778	6.8593	0.0000	0.0000	-1.1261
VAMP3	1.0426	2.2302	1.6028	2.8576	1.2424	5.7398	0.0000	0.0003	-3.4606
SCYL2	1.0392	2.1886	2.1880	2.1893	1.2277	5.7712	0.0000	0.0003	-3.3441
EHHADH	1.0338	2.2234	1.5675	2.8793	0.7636	53.9918	0.0000	0.0000	35.8960
CRYL1	1.0257	2.6429	2.0176	3.2683	1.4027	8.4477	0.0000	0.0000	2.0003
RSBN1L	1.0215	2.4241	2.1042	2.7439	1.3204	7.8273	0.0000	0.0000	0.8242
TMEM97	1.0201	3.3062	1.5581	5.0543	1.0319	95.0503	0.0000	0.0000	48.8580
SDHAF3	1.0184	2.4746	0.1704	4.7788	0.9237	7.0288	0.0000	0.0000	-0.6088
CARNMT1	1.0178	2.3958	1.6011	3.1906	0.8824	24.6258	0.0000	0.0000	20.8106
TTC19	1.0143	2.0101	1.5575	2.4626	1.3947	3.3870	0.0032	0.0383	-8.7494
HOXB9	1.0109	2.6825	2.0006	3.3644	1.3291	56.5326	0.0000	0.0000	36.9611
SLAIN2	1.0045	2.5033	0.5176	4.4890	1.6550	4.6920	0.0002	0.0026	-5.7723

Supplementary Table 4: AUC values of the 60 genes and corresponding p values for healing vs. non healing defined by ECCS

ECCS Genes	AUC	Pval
VSIG2	0,928571	0,000225
PRDM1	0,916667	0,00233
CPEB4	0,904762	0,000749
EDEM1	0,892857	0,002211
GTF3A	0,892857	0,002261
TGFBR2	0,886905	0,008169
FZD5	0,880952	0,002984
TTC38	0,869048	0,003706
YIPF6	0,869048	0,005096
ATPAF1	0,863095	0,004702
ZMAT2	0,857143	0,005699
HECA	0,857143	0,00128
TRPT1	0,857143	0,019488
MPP7	0,85119	0,002742
AKAP1	0,845238	0,003885
FBLN1	0,845238	0,007347
MMP24OS	0,833333	0,001962
B4GALT5	0,833333	0,002807
UMAD1	0,833333	0,005254
PCLAF	0,833333	0,009656
DHRSX_1	0,833333	0,011492
PDZK1IP1	0,827381	0,004077
CCDC124	0,827381	0,005782
LCN2	0,821429	0,002072
KIAA1522	0,821429	0,012356
GCNT3	0,821429	0,018105
ENPP4	0,809524	0,007145
TXNL4A	0,809524	0,008488
RCN2	0,809524	0,015965
TUFM	0,809524	0,022864
AKIRIN2	0,809524	0,023535
CCT8	0,803571	0,017613
DHX8	0,803571	0,019591
GLRX5	0,803571	0,024659
COMMD4	0,797619	0,010609
PKP3	0,797619	0,011982
USP2	0,797619	0,013124
VSIG10	0,797619	0,014492
CSE1L	0,791667	0,025922
RNF4	0,785714	0,009087
RNASET2	0,785714	0,02173
RNASE6	0,785714	0,023538
CRYZL1	0,779762	0,018313

UBFD1	0,77381	0,009904
TMEM208	0,77381	0,018783
LSM14A	0,77381	0,021151
DAAM1	0,77381	0,023186
NKLE2	0,77381	0,024759
PPP2R3C	0,77381	0,025761
SCYL2	0,77381	0,027757
ANGEL2	0,761905	0,011278
LACTB2	0,75	0,026535
CCZ1	0,75	0,028245
RAB32	0,738095	0,024325
FSIP2-AS1	0,714286	0,031755
RCC1L	0,696429	0,005987
STAT6	0,684524	0,02774
BIN3	0,678571	0,005545
DENND2A	0,678571	0,019398
SDHAF3	0,642857	0,031501

Supplementary Table 5: KEGG pathway enrichment analysis of the differentially expressed genes defined by A) ECSS, B) Mayo, C) RHI and D) Nancy scores. Genes in pathways for which p<0.05 are listed.

A) ECSS

Pathway	**P-value**	**Adjusted P-value**	**Genes**
Glyoxylate and dicarboxylate metabolism	9.58E-04	0.295123447	PCCB;ACO2;ACAT1
Spliceosome	0.001837	0.282872521	DHX8;ZMAT2;PLRG1;TXNL4A;PQBP1
Terpenoid backbone biosynthesis	0.008895	0.913199567	FNTA;ACAT1
Citrate cycle (TCA cycle)	0.016193	1	ACO2;PCK1
Mucin type O-glycan biosynthesis	0.017237	1	GCNT3;B4GALT5
Propanoate metabolism	0.018309	0.939864758	PCCB;ACAT1
Pyruvate metabolism	0.02656	1	PCK1;ACAT1
Th17 cell differentiation	0.032663	1	STAT6;AHR;TGFBR2
Valine, leucine and isoleucine degradation	0.038936	1	PCCB;ACAT1
N-Glycan biosynthesis	0.041932	1	DPM2;ALG3

B) Mayo

Pathway	P-value	Adjusted P-value	Genes

Mineral absorption	1.84E-05	0.005673	MT2A;MT1F;MT1G;MT1X;MT1H
Steroid hormone biosynthesis	5.92E-04	0.091101	HSD11B2;DHRS11;HSD17B2;COMT
Citrate cycle (TCA cycle)	9.16E-04	0.094059	CS;IDH3G;PCK1
Endocytosis	9.99E-04	0.076891	RAB10;SNX2;BIN1;VPS4A;WASL;VPS28;RAB11B
AMPK signaling pathway	0.001051	0.06477	RAB10;PCK1;ELAVL1;CFTR;RAB11B
Tryptophan metabolism	0.00245	0.125754	ALDH3A2;EHHADH;CAT
Fatty acid degradation	0.0028	0.123202	HADHB;ALDH3A2;EHHADH
IL-17 signaling pathway	0.003012	0.11597	JUN;LCN2;CXCL1;ELAVL1
Valine, leucine and isoleucine degradation	0.003589	0.122838	HADHB;ALDH3A2;EHHADH
Bile secretion	0.011077	0.341178	PRKACB;CFTR;ABCG2
Thyroid hormone synthesis	0.01193	0.334031	DUOXA2;PRKACB;DUOX2
Glyoxylate and dicarboxylate metabolism	0.015726	0.403633	CS;CAT
beta-Alanine metabolism	0.016741	0.39663	ALDH3A2;EHHADH
Salmonella infection	0.017823	0.392115	JUN;CXCL1;WASL
Fc gamma R-mediated phagocytosis	0.020678	0.424597	GSN;BIN1;WASL
Tight junction	0.023838	0.458886	JUN;WASL;PRKACB;CFTR
Pyruvate metabolism	0.025808	0.467583	ALDH3A2;PCK1
Vasopressin-regulated water reabsorption	0.032275	0.552264	PRKACB;RAB11B
ABC transporters	0.033637	0.545281	CFTR;ABCG2
Cocaine addiction	0.039305	0.605296	JUN;PRKACB
Ovarian steroidogenesis	0.039305	0.576472	HSD17B2;PRKACB
Viral carcinogenesis	0.040367	0.565131	JUN;GSN;GTF2B;PRKACB
Vibrio cholerae infection	0.040775	0.546026	PRKACB;CFTR

C) RHI

Pathways	P-value	Adjusted P-value	Genes
Vasopressin-regulated water reabsorption	0.014379	1	DCTN6;DYNC1LI2
Purine metabolism	0.016561	1	AK2;ENPP4;NUDT16
Metabolism of xenobiotics by cytochrome P450	0.037909	1	GSTM4;CYP2B6
NOD-like receptor signaling pathway	0.037942	1	CASP5;STAT1;MCU
Pancreatic cancer	0.038845	1	STAT1;TGFBR2

D) Nancy

Pathway	**P-value**	**Adjusted P-value**	**Genes**
N-Glycan biosynthesis	0.001421	0.437816	DPM2;MGAT4B;ALG3;MGAT1
RNA polymerase	0.003355	0.516732	POLR3GL;POLR1C;POLR2G
Propanoate metabolism	0.003676	0.377422	EHHADH;ECHDC1;ACAT1
Arginine biosynthesis	0.017584	1	GOT1;ASL
Terpenoid backbone biosynthesis	0.01922	1	FNTA;ACAT1

Other types of O-glycan biosynthesis	0.01922	0.986635	POGLUT1;COLGALT1
Lysine degradation	0.019899	0.875552	EHHADH;COLGALT1;ACAT1
Butanoate metabolism	0.030277	1	EHHADH;ACAT1
Citrate cycle (TCA cycle)	0.034405	1	ACO2;PCK1
Glyoxylate and dicarboxylate metabolism	0.034405	1	ACO2;ACAT1
Metabolism of xenobiotics by cytochrome P450	0.035718	1	GSTM4;CYP2B6;UGT2A3
PPAR signaling pathway	0.035718	0.916754	EHHADH;PCK1;SLC27A2
Spliceosome	0.042342	1	DHX8;SRSF2;TXNL4A;PQBP1
Pentose and glucuronate interconversions	0.043266	0.951852	UGT2A3;CRYL1
Alanine, aspartate and glutamate metabolism	0.0456	0.936329	GOT1;ASL
Chemical carcinogenesis	0.04615	0.888382	SULT1A1;GSTM4;UGT2A3
Phenylalanine, tyrosine and tryptophan biosynthesis	0.047813	0.86626	GOT1

Supplementary Table 6: Go Biological process enrichment analysis of the differentially expressed genes defined by A) ECSS, B) Mayo, C) RHI and D) Nancy scores. Genes in pathways for which p<0.05 are listed.

A) ECSS

Biological Process	P-value	Adjusted P-value	Genes
positive regulation of type I interferon production (GO:0032481)	7.10E-04	1	POLR3GL;FLOT1;STAT6;PQBP1
short-chain fatty acid catabolic process (GO:0019626)	0.001144232	1	PCCB;PCK1
response to sterol (GO:0036314)	0.002219058	1	INSIG1;TGFBR2
negative regulation of substrate adhesion-dependent cell spreading (GO:1900025)	0.002651561	1	AP1AR;FBLN1
cellular response to exogenous dsRNA (GO:0071360)	0.003120361	1	FLOT1;PQBP1
endosome to lysosome transport (GO:0008333)	0.00374914	1	SNAPIN;BIN1;SCYL2
RNA splicing, via transesterification reactions with bulged adenosine as nucleophile (GO:0000377)	0.004484009	1	DHX8;ZMAT2;GEMIN6;PLRG1;TXNL4A;PQBP1
cellular response to dsRNA (GO:0071359)	0.00473974	1	FLOT1;PQBP1
protein O-linked glycosylation (GO:0006493)	0.006761228	1	DPM2;POGLUT1;GCNT3;B4GALT5
mRNA splicing, via spliceosome (GO:0000398)	0.00724515	1	DHX8;ZMAT2;GEMIN6;PLRG1;TXNL4A;PQBP1
melanosome organization (GO:0032438)	0.009700777	1	RAB32;SNAPIN
protein glycosylation (GO:0006486)	0.010315151	1	POGLUT1;ALG3;GCNT3;SIRT6
mRNA processing (GO:0006397)	0.010547371	1	DHX8;ZMAT2;GEMIN6;PLRG1;TXNL4A;PQBP1
lysosomal transport (GO:0007041)	0.011549909	1	SNAPIN;BIN1;SCYL2
canonical Wnt signaling pathway (GO:0060070)	0.011988693	1	HOXB9;FZD5;SCYL2
transcription from RNA polymerase III promoter (GO:0006383)	0.013232733	1	POLR3GL;GTF3A
cellular response to ketone (GO:1901655)	0.014190598	1	AHR;PCK1
RNA phosphodiester bond hydrolysis (GO:0090501)	0.014190598	1	LACTB2;RNASE6
regulation of receptor internalization (GO:0002090)	0.014190598	1	FLOT1;SCYL2
positive regulation of cytokine production (GO:0001819)	0.014542657	1	FZD5;POLR3GL;FLOT1;STAT6;PQBP1
regulation of embryonic development (GO:0045995)	0.015177573	1	POGLUT1;RBM19
negative regulation of cell morphogenesis involved in differentiation (GO:0010771)	0.016193246	1	FBLN1;AP1AR

protein stabilization (GO:0050821)	0.017417574	1	TNIP2;USP2;FLOT1;CCT8
regulation of type I interferon production (GO:0032479)	0.01800139	1	POLR3GL;STAT6;PQBP1
response to exogenous dsRNA (GO:0043330)	0.019408383	1	FLOT1;PQBP1
Wnt signaling pathway, planar cell polarity pathway (GO:0060071)	0.019722525	1	DAAM1;FZD5;PSMD3
regulation of establishment of planar polarity (GO:0090175)	0.020315749	1	DAAM1;FZD5;PSMD3
regulation of interleukin-1 beta secretion (GO:0050706)	0.020534799	1	FZD5;CPTP
negative regulation of cell-substrate adhesion (GO:0010812)	0.021687909	1	FBLN1;AP1AR
positive regulation of cellular metabolic process (GO:0031325)	0.022154034	1	APOC1;SCYL2;TGFBR2
regulation of mitotic cell cycle (GO:0007346)	0.022763	1	ANGEL2;USP2;HECA;OXSR1
regulation of receptor-mediated endocytosis (GO:0048259)	0.022867323	1	APOC1;FLOT1
cellular response to organonitrogen compound (GO:0071417)	0.025413301	1	DHX8;AHR;CPEB4
response to cAMP (GO:0051591)	0.027840386	1	AHR;DUOX2
tRNA aminoacylation (GO:0043039)	0.027840386	1	AIMP2;EEF1E1
regulation of substrate adhesion-dependent cell spreading (GO:1900024)	0.029145624	1	FBLN1;AP1AR
RNA catabolic process (GO:0006401)	0.031827893	1	RNASET2;RNASE6
nucleobase-containing compound catabolic process (GO:0034655)	0.031827893	1	RNASET2;RNASE6
negative regulation of protein modification by small protein conjugation or removal (GO:1903321)	0.036025388	1	SVBP;RNF4
tRNA aminoacylation for protein translation (GO:0006418)	0.036025388	1	AIMP2;EEF1E1
positive regulation of tumor necrosis factor production (GO:0032760)	0.037469567	1	FZD5;LY96
negative regulation of mRNA catabolic process (GO:1902373)	0.038376226	1	PKP3
arginine biosynthetic process (GO:0006526)	0.038376226	1	ASL
protein geranylgeranylation (GO:0018344)	0.038376226	1	FNTA
positive regulation of deacetylase activity (GO:0090045)	0.038376226	1	FNTA
positive regulation of toll-like receptor 3 signaling pathway (GO:0034141)	0.038376226	1	FLOT1
ribonucleoside biosynthetic process (GO:0042455)	0.038376226	1	QTRT2
negative regulation of cytoplasmic translation (GO:2000766)	0.038376226	1	CPEB4
viral release from host cell (GO:0019076)	0.038376226	1	PPID

regulation of T cell tolerance induction (GO:0002664)	0.038376226	1	TGFBR2
adenylate cyclase-inhibiting G-protein coupled acetylcholine receptor signaling pathway (GO:0007197)	0.038376226	1	DHX8
SREBP signaling pathway (GO:0032933)	0.038376226	1	INSIG1
ceramide transport (GO:0035627)	0.038376226	1	CPTP
muscle tissue development (GO:0060537)	0.038376226	1	POGLUT1
positive regulation of clathrin-dependent endocytosis (GO:2000370)	0.038376226	1	SCYL2
negative regulation of sterol transport (GO:0032372)	0.038376226	1	APOC1
negative regulation of phospholipid metabolic process (GO:1903726)	0.038376226	1	APOC1
queuosine biosynthetic process (GO:0008616)	0.038376226	1	QTRT2
exit from host cell (GO:0035891)	0.038376226	1	PPID
regulation of epithelial to mesenchymal transition involved in endocardial cushion formation (GO:1905005)	0.038376226	1	TGFBR2
queuosine metabolic process (GO:0046116)	0.038376226	1	QTRT2
membrane raft assembly (GO:0001765)	0.038376226	1	FLOT1
citrate metabolic process (GO:0006101)	0.038376226	1	ACO2
response to UV-A (GO:0070141)	0.038376226	1	PPID
acetyl-CoA biosynthetic process (GO:0006085)	0.038376226	1	ACAT1
negative regulation of mitotic cell cycle (GO:0045930)	0.038935675	1	ANGEL2;HECA
cellular macromolecule catabolic process (GO:0044265)	0.038935675	1	RNASET2;RNASE6
cellular lipid biosynthetic process (GO:0097384)	0.044628639	1	ACAT1
positive regulation of inositol phosphate biosynthetic process (GO:0060732)	0.044628639	1	DHX8
coenzyme A biosynthetic process (GO:0015937)	0.044628639	1	ACAT1
regulation of alpha-beta T cell differentiation (GO:0046637)	0.044628639	1	PRDM1
negative regulation of MyD88-independent toll-like receptor signaling pathway (GO:0034128)	0.044628639	1	LY96
ribonucleoside bisphosphate biosynthetic process (GO:0034030)	0.044628639	1	ACAT1
positive regulation of cellular senescence (GO:2000774)	0.044628639	1	EEF1E1
regulation of toll-like receptor 3 signaling pathway (GO:0034139)	0.044628639	1	FLOT1
cellular response to histamine (GO:0071420)	0.044628639	1	DHX8

cellular response to sterol depletion (GO:0071501)	0.044628639	1	INSIG1
regulation of sterol transport (GO:0032371)	0.044628639	1	APOC1
purine nucleoside bisphosphate biosynthetic process (GO:0034033)	0.044628639	1	ACAT1
positive regulation of B cell differentiation (GO:0045579)	0.044628639	1	PPP2R3C
chylomicron remnant clearance (GO:0034382)	0.044628639	1	APOC1
detection of molecule of bacterial origin (GO:0032490)	0.044628639	1	LY96
positive regulation of CD4-positive, alpha-beta T cell activation (GO:2000516)	0.044628639	1	TGFBR2
negative regulation of nitrogen compound metabolic process (GO:0051172)	0.044628639	1	APOC1

B) Mayo

Biological Process	P-value	Adjusted P-value	Genes
cellular response to cadmium ion (GO:0071276)	2.57E-08	1.31E-04	MT2A;JUN;MT1F;MT1G;MT1X;MT1H
response to cadmium ion (GO:0046686)	3.94E-08	1.01E-04	MT2A;JUN;MT1F;MT1G;MT1X;MT1H
cellular response to zinc ion (GO:0071294)	1.07E-07	1.83E-04	MT2A;MT1F;MT1G;MT1X;MT1H
cellular response to copper ion (GO:0071280)	1.86E-07	2.37E-04	MT2A;MT1F;MT1G;MT1X;MT1H
response to copper ion (GO:0046688)	4.76E-07	4.86E-04	MT2A;MT1F;MT1G;MT1X;MT1H
cellular zinc ion homeostasis (GO:0006882)	1.48E-06	0.001255118	MT2A;MT1F;MT1G;MT1X;MT1H
zinc ion homeostasis (GO:0055069)	1.48E-06	0.001075816	MT2A;MT1F;MT1G;MT1X;MT1H
response to zinc ion (GO:0010043)	1.74E-06	0.00110996	MT2A;MT1F;MT1G;MT1X;MT1H
cellular transition metal ion homeostasis (GO:0046916)	2.24E-06	0.001268639	MT2A;MT1F;LCN2;MT1G;MT1X;MT1H;ABCG2
vesicle-mediated transport (GO:0016192)	1.31E-05	0.006675874	RAB10;TMEM87B;SNX2;BIN1;VPS4A;PLIN3;WASL;OSBPL1A;SFT2D1;PICALM;STX10;RAB11B
endosomal transport (GO:0016197)	1.69E-05	0.007851896	RAB10;TMEM87B;SNX2;BIN1;VPS4A;VPS28;PICALM;STX10;RAB11B
cellular response to metal ion (GO:0071248)	4.45E-05	0.01893684	MT2A;JUN;MT1F;MT1G;MT1X;MT1H
protein acetylation (GO:0006473)	5.67E-05	0.022264506	NAA60;GTF2B;EHHADH;PCK1
positive regulation of viral transcription (GO:0050434)	1.35E-04	0.049180572	JUN;DHX9;POLR2B;GTF2B

positive regulation of viral process (GO:0048524)	1.78E-04	0.060625607	DHX9;POLR2B;GTF2B;VPS4A
neutrophil degranulation (GO:0043312)	2.60E-04	0.082997743	RAB10;DPP7;GSN;JUP;RNASET2;CREG1;FUCA2;CAT;LCN2;HBB;CXCL1
neutrophil activation involved in immune response (GO:0002283)	2.79E-04	0.083857365	RAB10;DPP7;GSN;JUP;RNASET2;CREG1;FUCA2;CAT;LCN2;HBB;CXCL1
neutrophil mediated immunity (GO:0002446)	3.00E-04	0.084954686	RAB10;DPP7;GSN;JUP;RNASET2;CREG1;FUCA2;CAT;LCN2;HBB;CXCL1
cellular divalent inorganic cation homeostasis (GO:0072503)	4.81E-04	0.129259793	MT2A;MT1F;MT1G;MT1X;MT1H
positive regulation of clathrin-dependent endocytosis (GO:2000370)	5.99E-04	0.152947999	WASL;PICALM
regulation of mRNA processing (GO:0050684)	7.46E-04	0.181320552	PABPN1;DHX9;SAFB2
negative regulation of growth (GO:0045926)	0.001051464	0.243891878	MT2A;MT1F;MT1G;MT1X;MT1H
ribosome disassembly (GO:0032790)	0.001109606	0.246187762	DENR;MTIF3
regulation of aspartic-type endopeptidase activity involved in amyloid precursor protein catabolic process (GO:1902959)	0.001109606	0.235929938	BIN1;PICALM
vesicle organization (GO:0016050)	0.001353759	0.276329201	SNX2;VPS4A;WASL;PICALM;STX10
steroid biosynthetic process (GO:0006694)	0.001660179	0.325842034	HSD11B2;DHRS11;HSD17B2;OSBPL1A
regulation of viral transcription (GO:0046782)	0.002128021	0.402196027	DHX9;POLR2B;GTF2B
response to cAMP (GO:0051591)	0.002128021	0.387831883	JUN;DUOX2;CFTR
regulation of stem cell population maintenance (GO:2000036)	0.002152335	0.378736702	CNOT1;ELAVL1
internal protein amino acid acetylation (GO:0006475)	0.002152335	0.366112145	EHHADH;PCK1
negative regulation of amyloid precursor protein catabolic process (GO:1902992)	0.002152335	0.354302076	BIN1;PICALM
transcytosis (GO:0045056)	0.002152335	0.343230136	PICALM;RAB11B
regulation of protein localization (GO:0032880)	0.002285372	0.353401558	VPS4A;STX10;PICALM
vesicle budding from membrane (GO:0006900)	0.002572003	0.386027459	VPS4A;WASL
peptidyl-methionine modification (GO:0018206)	0.002572003	0.374998103	NAA60;METAP1
cholesterol transport (GO:0030301)	0.002800039	0.396905549	VPS4A;APOC1;ABCG2
nucleus organization (GO:0006997)	0.002986141	0.411845297	BIN1;VPS4A;TMEM170A
renal absorption (GO:0070293)	0.003026938	0.406485935	GSN;HBB
endoplasmic reticulum tubular network organization (GO:0071786)	0.003026938	0.396063218	RAB10;TMEM170A
positive regulation of actin nucleation (GO:0051127)	0.003026938	0.386161638	GSN;WASL

ribonucleoprotein complex disassembly (GO:0032988)	0.003026938	0.376743061	DENR;MTIF3
negative regulation of receptor-mediated endocytosis (GO:0048261)	0.003516678	0.427276317	APOC1;PICALM
hydrogen peroxide catabolic process (GO:0042744)	0.003516678	0.417339659	CAT;HBB
fatty acid oxidation (GO:0019395)	0.004030023	0.467391037	HADHB;ALDH3A2;EHHADH
fatty acid beta-oxidation (GO:0006635)	0.004030023	0.45700457	HADHB;EHHADH;ETFDH
regulation of mRNA metabolic process (GO:1903311)	0.004040764	0.448261319	DHX9;SAFB2
regulation of clathrin-dependent endocytosis (GO:2000369)	0.004040764	0.438723844	WASL;PICALM
regulation of actin nucleation (GO:0051125)	0.004598746	0.488904196	GSN;WASL
cellular response to dsRNA (GO:0071359)	0.004598746	0.47892656	DHX9;RIOK3
positive regulation of DNA-templated transcription, initiation (GO:2000144)	0.004598746	0.469348028	JUN;GTF2B
regulation of protein localization to membrane (GO:1905475)	0.005190174	0.519322731	GSN;VPS4A
response to purine-containing compound (GO:0014074)	0.005190174	0.509335755	JUN;DUOX2
N-terminal protein amino acid modification (GO:0031365)	0.005190174	0.499725647	NAA60;METAP1
positive regulation by host of viral transcription (GO:0043923)	0.005190174	0.490471468	JUN;GTF2B
regulation of amyloid-beta formation (GO:1902003)	0.005814605	0.539489598	BIN1;PICALM
ubiquitin-dependent protein catabolic process via the multivesicular body sorting pathway (GO:0043162)	0.005814605	0.529855855	VPS4A;VPS28
response to organophosphorus (GO:0046683)	0.005814605	0.520560138	JUN;DUOX2
response to reactive oxygen species (GO:0000302)	0.006717739	0.591045216	JUN;CAT;HBB
intracellular protein transport (GO:0006886)	0.007039025	0.608816038	RAB10;PDCD6;TLK1;VPS28;STX10;RAB11B;ARCN1
hydrogen peroxide metabolic process (GO:0042743)	0.007160717	0.609018991	CAT;HBB
viral budding via host ESCRT complex (GO:0039702)	0.007160717	0.599035073	VPS4A;VPS28
organelle disassembly (GO:1903008)	0.007160717	0.589373217	DENR;MTIF3
iron ion homeostasis (GO:0055072)	0.007688351	0.622756393	LCN2;ABCG2;PICALM
fatty acid catabolic process (GO:0009062)	0.008379038	0.668097356	HADHB;ALDH3A2;EHHADH
regulation of gene silencing by miRNA (GO:0060964)	0.009105084	0.71481917	DHX9;POLR2B;ELAVL1
cholesterol efflux (GO:0033344)	0.009416541	0.728069855	APOC1;ABCG2
viral budding (GO:0046755)	0.009416541	0.71720314	VPS4A;VPS28
response to metal ion (GO:0010038)	0.011077212	0.831279583	MT2A;PDCD6;MT1X
positive regulation of defense response (GO:0031349)	0.011929681	0.882277675	DHX9;DDT;RIOK3
positive regulation of interferon-beta production (GO:0032728)	0.011946217	0.870879207	DHX9;RIOK3

regulation of translation (GO:0006417)	0.012032518	0.864816016	DHX9;CNOT1;POLR2B;ELAVL1;METAP1
response to lipid (GO:0033993)	0.012578438	0.891496795	JUN;HSD17B2;CXCL1;PCK1
modulation by host of viral transcription (GO:0043921)	0.012848369	0.898153825	JUN;GTF2B
regulation of protein localization to cell surface (GO:2000008)	0.012848369	0.886016611	RAB11B;PICALM
cellular response to glucose stimulus (GO:0071333)	0.012848369	0.874203056	PCK1;RAB11B
negative regulation of endocytosis (GO:0045806)	0.01377931	0.925208162	APOC1;PICALM
cellular response to ketone (GO:1901655)	0.01377931	0.913192472	PCK1;CFTR
retrograde transport, endosome to Golgi (GO:0042147)	0.015709267	1	TMEM87B;SNX2;STX10
regulation of leukocyte chemotaxis (GO:0002688)	0.015725963	1	CXCL1;IL6R
nuclear envelope organization (GO:0006998)	0.015725963	1	VPS4A;TMEM170A
multivesicular body assembly (GO:0036258)	0.015725963	0.990735657	VPS4A;VPS28
multivesicular body organization (GO:0036257)	0.016740887	1	VPS4A;VPS28
vesicle-mediated transport to the plasma membrane (GO:0098876)	0.016740887	1	RAB10;RAB11B
protein transport (GO:0015031)	0.018547406	1	RAB10;PDCD6;TLK1;STX10;RAB11B;ARCN1
cellular protein localization (GO:0034613)	0.01879808	1	RAB10;PDCD6;TLK1;STX10;RAB11B;ARCN1
positive regulation of nucleocytoplasmic transport (GO:0046824)	0.018851993	1	JUP;DHX9
platelet aggregation (GO:0070527)	0.018851993	1	HBB;METAP1
mRNA stabilization (GO:0048255)	0.018851993	1	DHX9;ELAVL1
positive regulation of leukocyte migration (GO:0002687)	0.019947409	1	CXCL1;IL6R
positive regulation of exocytosis (GO:0045921)	0.019947409	1	VPS4A;CFTR
endoplasmic reticulum organization (GO:0007029)	0.019947409	1	RAB10;TMEM170A
cellular macromolecular complex assembly (GO:0034622)	0.019947409	1	BIN1;PICALM
negative regulation of protein kinase B signaling (GO:0051898)	0.021068897	1	PDCD6;NOP53
negative regulation of protein complex assembly (GO:0031333)	0.021068897	1	CPTP;NOP53
positive regulation of ATPase activity (GO:0032781)	0.021068897	1	DHX9;TOR1AIP1
actin polymerization or depolymerization (GO:0008154)	0.022216085	1	GSN;WASL
regulation of receptor-mediated endocytosis (GO:0048259)	0.022216085	1	APOC1;PICALM
positive regulation of smooth muscle cell proliferation (GO:0048661)	0.023388603	1	JUN;IL6R
regulation of cell death (GO:0010941)	0.023770051	1	JUN;HBB;PDE8A
mitochondrial respiratory chain complex assembly (GO:0033108)	0.0244168	1	SURF1;SDHAF3;NDUFS2
homotypic cell-cell adhesion (GO:0034109)	0.024586084	1	HBB;METAP1

positive regulation of innate immune response (GO:0045089)	0.024586084	1	DHX9;RIOK3
endocytosis (GO:0006897)	0.027156365	1	SNX2;BIN1;HBB;WASL;PICALM
cellular response to cytokine stimulus (GO:0071345)	0.027484921	1	MT2A;DHX9;LCN2;MT1X;CXCL1;IL6R;DUOX2
bicarbonate transport (GO:0015701)	0.028324708	1	HBB;CFTR
positive regulation of receptor-mediated endocytosis (GO:0048260)	0.028324708	1	WASL;PICALM
response to hydrogen peroxide (GO:0042542)	0.030935397	1	CAT;HBB
positive regulation of interleukin-6 production (GO:0032755)	0.030935397	1	DHX9;IL6R
viral life cycle (GO:0019058)	0.031403905	1	VPS4A;UBP1;VPS28
hexose metabolic process (GO:0019318)	0.033637462	1	FUCA2;PCK1
cellular response to peptide hormone stimulus (GO:0071375)	0.033683321	1	RAB10;PCK1;PRKACB
RNA metabolic process (GO:0016070)	0.034473437	1	PABPN1;DHX9;POLR2B;RNASET2
positive regulation of tumor necrosis factor production (GO:0032760)	0.036428186	1	DHX9;DDT
positive regulation of nucleobase-containing compound transport (GO:0032241)	0.037795259	1	DHX9
arginine biosynthetic process (GO:0006526)	0.037795259	1	ASL
regulation of keratinocyte apoptotic process (GO:1902172)	0.037795259	1	GSN
intracellular pH elevation (GO:0051454)	0.037795259	1	CFTR
dosage compensation by inactivation of X chromosome (GO:0009048)	0.037795259	1	PCGF5
positive regulation of aspartic-type peptidase activity (GO:1905247)	0.037795259	1	PICALM
viral release from host cell (GO:0019076)	0.037795259	1	VPS4A
N-terminal peptidyl-methionine acetylation (GO:0017196)	0.037795259	1	NAA60
positive regulation of amyloid-beta clearance (GO:1900223)	0.037795259	1	PICALM
glycosyl compound catabolic process (GO:1901658)	0.037795259	1	FUCA2
negative regulation of lymphocyte migration (GO:2000402)	0.037795259	1	WASL
negative regulation of cytokinesis (GO:0032466)	0.037795259	1	VPS4A
bundle of His cell-Purkinje myocyte adhesion involved in cell communication (GO:0086073)	0.037795259	1	JUP
ceramide transport (GO:0035627)	0.037795259	1	CPTP
cardiolipin acyl-chain remodeling (GO:0035965)	0.037795259	1	HADHB

positive regulation of interferon-alpha secretion (GO:1902741)	0.037795259	1	DHX9
cellular nitrogen compound catabolic process (GO:0044270)	0.037795259	1	MPST
iron ion import (GO:0097286)	0.037795259	1	PICALM
negative regulation of sterol transport (GO:0032372)	0.037795259	1	APOC1
negative regulation of phospholipid metabolic process (GO:1903726)	0.037795259	1	APOC1
iron ion import across plasma membrane (GO:0098711)	0.037795259	1	PICALM
exit from host cell (GO:0035891)	0.037795259	1	VPS4A
insulin secretion involved in cellular response to glucose stimulus (GO:0035773)	0.037795259	1	RAB11B
regulation of interferon-alpha secretion (GO:1902739)	0.037795259	1	DHX9
positive regulation of aspartic-type endopeptidase activity involved in amyloid precursor protein catabolic process (GO:1902961)	0.037795259	1	PICALM
positive regulation of RNA export from nucleus (GO:0046833)	0.037795259	1	DHX9
positive regulation of chemotaxis (GO:0050921)	0.03785596	1	CXCL1;IL6R
establishment of protein localization to mitochondrion (GO:0072655)	0.039304905	1	GRPEL1;AIP
cytosolic transport (GO:0016482)	0.040170351	1	TMEM87B;SNX2;STX10
regulation of exocytosis (GO:0017157)	0.042265007	1	RAB10;CFTR
positive regulation of actin filament polymerization (GO:0030838)	0.042265007	1	GSN;WASL
protein localization to basolateral plasma membrane (GO:1903361)	0.0439552	1	RAB10
cardiac muscle cell-cardiac muscle cell adhesion (GO:0086042)	0.0439552	1	JUP
protein localization to cytoplasmic stress granule (GO:1903608)	0.0439552	1	DHX9
intracellular sterol transport (GO:0032366)	0.0439552	1	VPS4A
regulation of entry of bacterium into host cell (GO:2000535)	0.0439552	1	FUCA2
negative regulation of leukocyte migration (GO:0002686)	0.0439552	1	WASL
regulation of chromatin assembly or disassembly (GO:0001672)	0.0439552	1	TLK1
regulation of endocytic recycling (GO:2001135)	0.0439552	1	RAB11B
regulation of MDA-5 signaling pathway (GO:0039533)	0.0439552	1	RIOK3
oxygen transport (GO:0015671)	0.0439552	1	HBB

regulation of lymphocyte migration (GO:2000401)	0.0439552	1	WASL
glycoside catabolic process (GO:0016139)	0.0439552	1	FUCA2
vesicle transport along actin filament (GO:0030050)	0.0439552	1	WASL
regulation of anion transport (GO:0044070)	0.0439552	1	RAB11B
G-quadruplex DNA unwinding (GO:0044806)	0.0439552	1	DHX9
regulation of sterol transport (GO:0032371)	0.0439552	1	APOC1
positive regulation of isomerase activity (GO:0010912)	0.0439552	1	DHX9
formation of translation preinitiation complex (GO:0001731)	0.0439552	1	DENR
regulation of interleukin-18 production (GO:0032661)	0.0439552	1	DHX9
negative regulation of retinoic acid receptor signaling pathway (GO:0048387)	0.0439552	1	CNOT1
positive regulation of protein deubiquitination (GO:1903003)	0.0439552	1	NOP53
chylomicron remnant clearance (GO:0034382)	0.0439552	1	APOC1
morphogenesis of a polarized epithelium (GO:0001738)	0.0439552	1	RAB10
negative regulation of nitrogen compound metabolic process (GO:0051172)	0.0439552	1	APOC1
protein targeting to mitochondrion (GO:0006626)	0.046855918	1	GRPEL1;AIP
negative regulation of cellular component organization (GO:0051129)	0.046855918	1	WASL;NOP53
positive regulation of immune response (GO:0050778)	0.046855918	1	DHX9;RIOK3
positive regulation of response to stimulus (GO:0048584)	0.046855918	1	DHX9;CFTR

C) RHI

Biological Process	**P-value**	**Adjusted P-value**	**Genes**
positive regulation of mitochondrial calcium ion concentration (GO:0051561)	4.69E-04	1	FIS1;MCU
mitochondrial translational elongation (GO:0070125)	4.72E-04	1	MRPS9;MRPL1;MRPL54;TUFM
positive regulation of mesenchymal cell proliferation (GO:0002053)	9.13E-04	1	STAT1;TGFBR2
translational elongation (GO:0006414)	9.59E-04	1	MRPS9;MRPL1;MRPL54;TUFM
mitochondrial translation (GO:0032543)	0.001028594	1	MRPS9;MRPL1;MRPL54;TUFM

regulation of mesenchymal cell proliferation (GO:0010464)	0.001093102	0.929683261	STAT1;TGFBR2
response to purine-containing compound (GO:0014074)	0.002222324	1	STAT1;DUOX2
viral entry into host cell (GO:0046718)	0.002222324	1	AXL;WWP1
response to organophosphorus (GO:0046683)	0.002493396	1	STAT1;DUOX2
release of cytochrome c from mitochondria (GO:0001836)	0.002493396	1	FIS1;IFI6
endoplasmic reticulum calcium ion homeostasis (GO:0032469)	0.002493396	1	FIS1;HERPUD1
mitochondrial calcium ion homeostasis (GO:0051560)	0.002779249	1	FIS1;MCU
dendritic cell differentiation (GO:0097028)	0.003394807	1	AXL;TGFBR2
negative regulation of response to endoplasmic reticulum stress (GO:1903573)	0.003724263	1	UBXN1;HERPUD1
STAT cascade (GO:0097696)	0.003724263	1	STAT1;NMI
outflow tract septum morphogenesis (GO:0003148)	0.003724263	1	GATA6;TGFBR2
mitochondrial translational termination (GO:0070126)	0.006055414	1	MRPS9;MRPL1;MRPL54
translational termination (GO:0006415)	0.00746237	1	MRPS9;MRPL1;MRPL54
antigen processing and presentation of exogenous peptide antigen (GO:0002478)	0.007677789	1	DCTN6;DYNC1LI2;DCTN3
antigen processing and presentation of exogenous peptide antigen via MHC class II (GO:0019886)	0.007677789	1	DCTN6;DYNC1LI2;DCTN3
antigen processing and presentation of peptide antigen via MHC class II (GO:0002495)	0.007896859	1	DCTN6;DYNC1LI2;DCTN3
entry into host cell (GO:0030260)	0.00826504	1	AXL;WWP1
apoptotic mitochondrial changes (GO:0008637)	0.008758118	1	FIS1;IFI6
viral life cycle (GO:0019058)	0.010034976	1	AXL;UBP1;WWP1
response to cAMP (GO:0051591)	0.011983166	1	STAT1;DUOX2
JAK-STAT cascade (GO:0007259)	0.011983166	1	STAT1;NMI
nucleobase-containing compound catabolic process (GO:0034655)	0.01376208	1	RNASET2;NUDT16
RNA catabolic process (GO:0006401)	0.01376208	1	RNASET2;NUDT16
apoptotic process (GO:0006915)	0.015660188	1	FIS1;CASP5;CDK11B;TGFBR2
regulation of intrinsic apoptotic signaling pathway (GO:2001242)	0.01629995	1	FIS1;HERPUD1
macrophage derived foam cell differentiation (GO:0010742)	0.024645968	1	STAT1
mesenchymal cell differentiation involved in kidney development (GO:0072161)	0.024645968	1	STAT1

regulation of epithelial to mesenchymal transition involved in endocardial cushion formation (GO:1905005)	0.024645968	1	TGFBR2
arginine biosynthetic process (GO:0006526)	0.024645968	1	ASL
negative regulation of transforming growth factor beta production (GO:0071635)	0.024645968	1	GATA6
protein geranylgeranylation (GO:0018344)	0.024645968	1	FNTA
positive regulation of deacetylase activity (GO:0090045)	0.024645968	1	FNTA
regulation of transforming growth factor beta2 production (GO:0032909)	0.024645968	1	GATA6
negative regulation of cytoplasmic translation (GO:2000766)	0.024645968	1	CPEB4
citrate metabolic process (GO:0006101)	0.024645968	1	ACO2
vascular smooth muscle cell differentiation (GO:0035886)	0.024645968	1	GATA6
regulation of T cell tolerance induction (GO:0002664)	0.024645968	1	TGFBR2
snRNA modification (GO:0040031)	0.024645968	1	MRPL1
negative regulation of endoplasmic reticulum calcium ion concentration (GO:0032471)	0.024645968	1	FIS1
coronary vasculature development (GO:0060976)	0.024645968	1	GATA6
positive regulation of clathrin-dependent endocytosis (GO:2000370)	0.024645968	1	SCYL2
foam cell differentiation (GO:0090077)	0.024645968	1	STAT1
Golgi vesicle transport (GO:0048193)	0.026323541	1	DCTN6;DYNC1LI2;DCTN3;NUDT19
xenobiotic catabolic process (GO:0042178)	0.028694887	1	GSTM4
positive regulation of mitotic sister chromatid separation (GO:1901970)	0.028694887	1	ANAPC5
regulation by virus of viral protein levels in host cell (GO:0046719)	0.028694887	1	STAT1
cellular response to interferon-alpha (GO:0035457)	0.028694887	1	AXL
flavin-containing compound metabolic process (GO:0042726)	0.028694887	1	SLC52A2
positive regulation of metaphase/anaphase transition of cell cycle (GO:1902101)	0.028694887	1	ANAPC5
regulation of pinocytosis (GO:0048548)	0.028694887	1	AXL
positive regulation of ER-associated ubiquitin-dependent protein catabolic process (GO:1903071)	0.028694887	1	HERPUD1

riboflavin metabolic process (GO:0006771)	0.028694887	1	SLC52A2
positive regulation of CD4-positive, alpha-beta T cell activation (GO:2000516)	0.028694887	1	TGFBR2
negative regulation of dendritic cell apoptotic process (GO:2000669)	0.028694887	1	AXL
cellular response to decreased oxygen levels (GO:0036294)	0.029054566	1	GATA6;CPEB4
cellular response to type I interferon (GO:0071357)	0.029897537	1	STAT1;IFI6
type I interferon signaling pathway (GO:0060337)	0.029897537	1	STAT1;IFI6
fatty acid catabolic process (GO:0009062)	0.029897537	1	NUDT19;ECHDC1
protein lipoylation (GO:0009249)	0.032727202	1	GLRX5
cellular response to interleukin-21 (GO:0098757)	0.032727202	1	STAT1
galactose catabolic process (GO:0019388)	0.032727202	1	GALE
rRNA pseudouridine synthesis (GO:0031118)	0.032727202	1	MRPL1
positive regulation of alpha-beta T cell differentiation (GO:0046638)	0.032727202	1	TGFBR2
positive regulation of mitotic metaphase/anaphase transition (GO:0045842)	0.032727202	1	ANAPC5
interleukin-21-mediated signaling pathway (GO:0038114)	0.032727202	1	STAT1
regulation of ERAD pathway (GO:1904292)	0.032727202	1	UBXN1
calcium-mediated signaling (GO:0019722)	0.034255935	1	FIS1;MCU
positive regulation of proteasomal ubiquitin-dependent protein catabolic process (GO:0032436)	0.034255935	1	RNF114;HERPUD1
hexose catabolic process (GO:0019320)	0.036742978	1	GALE
production of siRNA involved in RNA interference (GO:0030422)	0.036742978	1	TSNAX
ornithine metabolic process (GO:0006591)	0.036742978	1	ASL
atrioventricular valve development (GO:0003171)	0.036742978	1	TGFBR2
positive regulation of hemostasis (GO:1900048)	0.036742978	1	ENPP4
positive regulation of coagulation (GO:0050820)	0.036742978	1	ENPP4
peroxisome fission (GO:0016559)	0.036742978	1	FIS1
mitochondrial fragmentation involved in apoptotic process (GO:0043653)	0.036742978	1	FIS1
columnar/cuboidal epithelial cell differentiation (GO:0002065)	0.036742978	1	GATA6
mitochondrial calcium uptake (GO:0036444)	0.036742978	1	MCU

regulation of ER-associated ubiquitin-dependent protein catabolic process (GO:1903069)	0.036742978	1	HERPUD1
cellular response to oxygen levels (GO:0071453)	0.036742978	1	CPEB4
ionotropic glutamate receptor signaling pathway (GO:0035235)	0.036742978	1	CPEB4
mitochondrion morphogenesis (GO:0070584)	0.036742978	1	FIS1
receptor recycling (GO:0001881)	0.036742978	1	PLEKHJ1
ER to Golgi vesicle-mediated transport (GO:0006888)	0.039014654	1	DCTN6;DYNC1LI2;DCTN3
transforming growth factor beta receptor signaling pathway (GO:0007179)	0.039789801	1	FNTA;TGFBR2
hemopoiesis (GO:0030097)	0.039789801	1	GLRX5;TGFBR2
protein-cofactor linkage (GO:0018065)	0.040742283	1	GLRX5
cell differentiation involved in metanephros development (GO:0072202)	0.040742283	1	STAT1
positive regulation of natural killer cell activation (GO:0032816)	0.040742283	1	AXL
regulation of dendritic cell apoptotic process (GO:2000668)	0.040742283	1	AXL
galactose metabolic process (GO:0006012)	0.040742283	1	GALE
regulation of cytoplasmic translation (GO:2000765)	0.040742283	1	CPEB4
smooth muscle cell differentiation (GO:0051145)	0.040742283	1	GATA6
regulation of mitochondrial depolarization (GO:0051900)	0.040742283	1	IFI6
protein prenylation (GO:0018342)	0.040742283	1	FNTA
myeloid dendritic cell differentiation (GO:0043011)	0.040742283	1	TGFBR2
thyroid hormone generation (GO:0006590)	0.040742283	1	DUOX2
epithelial cell morphogenesis (GO:0003382)	0.040742283	1	POF1B
RNA transport (GO:0050658)	0.04365429	1	RNPS1;TGFBR2
cellular response to interferon-beta (GO:0035458)	0.044725183	1	STAT1
negative regulation of morphogenesis of an epithelium (GO:1905331)	0.044725183	1	STAT1
interleukin-27-mediated signaling pathway (GO:0070106)	0.044725183	1	STAT1
cell part morphogenesis (GO:0032990)	0.044725183	1	FIS1
embryonic hemopoiesis (GO:0035162)	0.044725183	1	TGFBR2
positive regulation of extracellular matrix organization (GO:1903055)	0.044725183	1	COLGALT1
metanephric mesenchyme development (GO:0072075)	0.044725183	1	STAT1

interleukin-35-mediated signaling pathway (GO:0070757)	0.044725183	1	STAT1
positive regulation of protein deacetylation (GO:0090312)	0.044725183	1	FNTA
urea cycle (GO:0000050)	0.044725183	1	ASL
response to sterol (GO:0036314)	0.044725183	1	TGFBR2
positive regulation of cell cycle (GO:0045787)	0.045637037	1	USP2;NUDT16
PERK-mediated unfolded protein response (GO:0036499)	0.048691746	1	HERPUD1
negative regulation of ERAD pathway (GO:1904293)	0.048691746	1	UBXN1
regulation of sister chromatid cohesion (GO:0007063)	0.048691746	1	CTCF
negative regulation of leukocyte apoptotic process (GO:2000107)	0.048691746	1	AXL
regulation of rRNA processing (GO:2000232)	0.048691746	1	NUDT16

D) Nancy

Biological Process	**P-value**	**Adjusted P-value**	**Genes**
regulation of mitotic cell cycle (GO:0007346)	2.20E-04	1	DUSP3;ANGEL2;USP2;CDK1;PIM2;OXSR1;CDK11B;THAP1
protein acetylation (GO:0006473)	2.87E-04	0.733157139	ESCO1;GTF2B;EHHADH;PCK1
negative regulation of ubiquitin-protein ligase activity involved in mitotic cell cycle (GO:0051436)	6.47E-04	1	PSMD7;CDK1;UBE2D1;ANAPC5;PSMF1
regulation of ubiquitin-protein ligase activity involved in mitotic cell cycle (GO:0051439)	6.90E-04	0.880181796	PSMD7;CDK1;UBE2D1;ANAPC5;PSMF1
positive regulation of ubiquitin-protein ligase activity involved in regulation of mitotic cell cycle transition (GO:0051437)	8.83E-04	0.901066525	PSMD7;CDK1;UBE2D1;ANAPC5;PSMF1
negative regulation of ubiquitin protein ligase activity (GO:1904667)	9.37E-04	0.796765559	PSMD7;CDK1;UBE2D1;ANAPC5;PSMF1
anaphase-promoting complex-dependent catabolic process (GO:0031145)	0.001052008	0.766913782	PSMD7;CDK1;UBE2D1;ANAPC5;PSMF1
positive regulation of ubiquitin protein ligase activity (GO:1904668)	0.00124406	0.793554918	PSMD7;CDK1;UBE2D1;ANAPC5;PSMF1
regulation of cell cycle (GO:0051726)	0.001262447	0.71580734	RNF167;WEE1;ZNF703;CDK1;PIM2;OXSR1;CDK11B;THAP1

blood vessel endothelial cell proliferation involved in sprouting angiogenesis (GO:0002043)	0.001382548	0.705514009	ITGB1BP1;NRARP
fatty acid oxidation (GO:0019395)	0.001421481	0.659437897	EHHADH;ECHDC1;SLC27A2;ACAT1
fatty acid beta-oxidation (GO:0006635)	0.001421481	0.604484739	EHHADH;ECHDC1;SLC27A2;ACAT1
positive regulation of protein ubiquitination involved in ubiquitin-dependent protein catabolic process (GO:2000060)	0.001620088	0.635946661	PSMD7;CDK1;UBE2D1;ANAPC5;PSMF1
adherens junction assembly (GO:0034333)	0.001923155	0.700990161	RAMP2;ZNF703
positive regulation of mitochondrial calcium ion concentration (GO:0051561)	0.002547777	0.866753771	FIS1;MCU
regulation of embryonic development (GO:0045995)	0.002766843	0.88244988	POGLUT1;RBM19;CDK1
positive regulation of type I interferon production (GO:0032481)	0.00314481	0.94399795	POLR3GL;POLR1C;FLOT1;PQBP1
fatty acid catabolic process (GO:0009062)	0.003731445	1	EHHADH;ECHDC1;SLC27A2;ACAT1
DNA-templated transcription, elongation (GO:0006354)	0.004149045	1	GTF2B;POLR1C;POLR2G;NELFCD;SSRP1
internal protein amino acid acetylation (GO:0006475)	0.004909119	1	EHHADH;PCK1
regulation of ubiquitin protein ligase activity (GO:1904666)	0.005143232	1	CDK1;UBE2D1;ANAPC5
negative regulation of substrate adhesion-dependent cell spreading (GO:1900025)	0.00585331	1	AP1AR;ITGB1BP1
cellular response to exogenous dsRNA (GO:0071360)	0.006873392	1	FLOT1;PQBP1
regulation of viral transcription (GO:0046782)	0.006917351	1	GTF2B;POLR2G;NELFCD
positive regulation of viral transcription (GO:0050434)	0.007410629	1	GTF2B;POLR2G;NELFCD
neutrophil degranulation (GO:0043312)	0.007529424	1	CTSA;PSMD7;ACTR1B;RNASET2;FUCA2;LCN2;ENPP4;S100P;RHOF;CCT8;SLC27A2
proteasome-mediated ubiquitin-dependent protein catabolic process (GO:0043161)	0.007905834	1	RNF11;PSMD7;CDK1;UBE2D1;YOD1;ANAPC5;PSMF1;RNF4
neutrophil activation involved in immune response (GO:0002283)	0.007988109	1	CTSA;PSMD7;ACTR1B;RNASET2;FUCA2;LCN2;ENPP4;S100P;RHOF;CCT8;SLC27A2
neutrophil mediated immunity (GO:0002446)	0.008468287	1	CTSA;PSMD7;ACTR1B;RNASET2;FUCA2;LCN2;ENPP4;S100P;RHOF;CCT8;SLC27A2
proteasomal protein catabolic process (GO:0010498)	0.008767529	1	RNF11;PSMD7;CDK1;UBE2D1;ANAPC5;PSMF1;RNF4
sprouting angiogenesis (GO:0002040)	0.009013032	1	RAMP2;NRARP;ITGB1BP1
positive regulation of viral process (GO:0048524)	0.009013032	1	GTF2B;POLR2G;NELFCD
regulation of mitotic cell cycle phase transition (GO:1901990)	0.009454292	1	PSMD7;CEP70;CDK1;UBE2D1;ANAPC5;PSMF1

DNA-templated transcription, initiation (GO:0006352)	0.009938443	1	GTF2B;MED31;POLR1C;CDK1;POLR2G;NR3C2
cellular response to dsRNA (GO:0071359)	0.010373554	1	FLOT1;PQBP1
mitochondrial translational elongation (GO:0070125)	0.010400666	1	MRPS9;MRPL1;MRPL54;TUFM
3'-UTR-mediated mRNA stabilization (GO:0070935)	0.011681883	1	ANGEL2;ELAVL1
regulation of receptor recycling (GO:0001919)	0.011681883	1	AP1AR;VAMP3
protein deubiquitination (GO:0016579)	0.013257767	1	PSMD7;TNIP2;USP2;CDK1;UBE2D1;YOD1;PSMF1
transcription elongation from RNA polymerase II promoter (GO:0006368)	0.014012754	1	GTF2B;POLR2G;NELFCD;SSRP1
positive regulation of mitotic cell cycle (GO:0045931)	0.014211962	1	DUSP3;EDN3;USP2
protein modification by small protein removal (GO:0070646)	0.014323582	1	PSMD7;TNIP2;USP2;CDK1;UBE2D1;YOD1;PSMF1
mitochondrial calcium ion homeostasis (GO:0051560)	0.014502135	1	FIS1;MCU
mitochondrial respiratory chain complex assembly (GO:0033108)	0.01502522	1	SDHAF3;ECSIT;TTC19;PET117
inositol phosphate-mediated signaling (GO:0048016)	0.016011193	1	EDN3;DHX8
steroid metabolic process (GO:0008202)	0.01608275	1	SULT1A1;CYP2B6;DHRS11;MSMO1
protein stabilization (GO:0050821)	0.016752939	1	TNIP2;USP2;FLOT1;PIM2;CCT8
ubiquitin-dependent protein catabolic process (GO:0006511)	0.019000844	1	RNF11;PSMD7;CDK1;UBE2D1;ANAPC5;PSMF1;NTAN1;RNF4
positive regulation of protein targeting to membrane (GO:0090314)	0.019220169	1	FIS1;ITGB1BP1
translational elongation (GO:0006414)	0.019531351	1	MRPS9;MRPL1;MRPL54;TUFM
protein localization to membrane (GO:0072657)	0.020427695	1	RAB32;RAMP2;FLOT1;ITGB1BP1;PKP3
transcription initiation from RNA polymerase II promoter (GO:0006367)	0.020427695	1	GTF2B;MED31;CDK1;POLR2G;NR3C2
mitochondrial translation (GO:0032543)	0.020774585	1	MRPS9;MRPL1;MRPL54;TUFM
regulation of cytokine production (GO:0001817)	0.02141403	1	TWSG1;BTN3A1;BTN2A1;FLOT1
T cell receptor signaling pathway (GO:0050852)	0.021931319	1	PSMD7;BTN3A1;BTN2A1;UBE2D1;PSMF1
second-messenger-mediated signaling (GO:0019932)	0.022666445	1	EDN3;DHX8;MCU
negative regulation of endothelial cell apoptotic process (GO:2000352)	0.022674533	1	RAMP2;TNIP2
transcription, DNA-templated (GO:0006351)	0.023834234	1	POLR3GL;GTF2B;POLR1C;GTF3A;POLR2G;NELFCD;SSRP1;THAP1
cellular response to vascular endothelial growth factor stimulus (GO:0035924)	0.024490401	1	RAMP2;ITGB1BP1

positive regulation of developmental process (GO:0051094)	0.024791527	1	FIS1;EDN3;ZNF703;RBM19
glycolipid metabolic process (GO:0006664)	0.025632723	1	CTSA;POGLUT1;CPTP
regulation of protein targeting to membrane (GO:0090313)	0.028293013	1	FIS1;ITGB1BP1
transcription from RNA polymerase III promoter (GO:0006383)	0.028293013	1	POLR3GL;GTF3A
RNA splicing, via transesterification reactions with bulged adenosine as nucleophile (GO:0000377)	0.028471594	1	DHX8;SRSF2;POLR2G;TXNL4A;ELAVL1;PQBP1
RNA phosphodiester bond hydrolysis (GO:0090501)	0.030277218	1	MRPL1;NOB1
regulation of receptor internalization (GO:0002090)	0.030277218	1	FLOT1;SCYL2
protein K11-linked ubiquitination (GO:0070979)	0.030277218	1	ANAPC5;RNF4
regulation of Notch signaling pathway (GO:0008593)	0.031016916	1	POGLUT1;NRARP;ITGB1BP1
negative regulation of epithelial cell apoptotic process (GO:1904036)	0.032315028	1	RAMP2;TNIP2
negative regulation of cell morphogenesis involved in differentiation (GO:0010771)	0.03440522	1	AP1AR;ITGB1BP1
canonical Wnt signaling pathway (GO:0060070)	0.034509941	1	HOXB9;FZD5;SCYL2
antigen processing and presentation of exogenous peptide antigen via MHC class I, TAP-dependent (GO:0002479)	0.036947033	1	PSMD7;PSMF1;VAMP3
regulation of macromolecule metabolic process (GO:0060255)	0.037664023	1	EDN3;CDK1;FLOT1;CDK11B
antigen processing and presentation of exogenous peptide antigen via MHC class I (GO:0042590)	0.040763777	1	PSMD7;PSMF1;VAMP3
regulation of transcription from RNA polymerase II promoter in response to hypoxia (GO:0061418)	0.040763777	1	PSMD7;UBE2D1;PSMF1
positive regulation of Notch signaling pathway (GO:0045747)	0.040978145	1	POGLUT1;ITGB1BP1
response to exogenous dsRNA (GO:0043330)	0.040978145	1	FLOT1;PQBP1
mRNA stabilization (GO:0048255)	0.040978145	1	ANGEL2;ELAVL1
steroid biosynthetic process (GO:0006694)	0.042078641	1	DHRS11;MSMO1;SLC27A2
mRNA splicing, via spliceosome (GO:0000398)	0.043123662	1	DHX8;SRSF2;POLR2G;TXNL4A;ELAVL1;PQBP1
regulation of interleukin-1 beta secretion (GO:0050706)	0.04326601	1	FZD5;CPTP
negative regulation of cell-substrate adhesion (GO:0010812)	0.04560042	1	AP1AR;ITGB1BP1
regulation of endothelial cell apoptotic process (GO:2000351)	0.04560042	1	RAMP2;TNIP2
actin filament bundle organization (GO:0061572)	0.04560042	1	MYO1B;RHOF
regulation of receptor-mediated endocytosis (GO:0048259)	0.047980258	1	APOC1;FLOT1
epithelial cell migration (GO:0010631)	0.047980258	1	FERMT1;S100P

positive regulation of signaling (GO:0023056)	0.047980258	1	EDN3;VAMP3
secondary alcohol biosynthetic process (GO:1902653)	0.047980258	1	MSMO1;ACAT1
cellular response to molecule of bacterial origin (GO:0071219)	0.048968135	1	FZD5;TNIP2;AXL
modification-dependent protein catabolic process (GO:0019941)	0.049418585	1	RNF11;UBE2D1;PSMF1;NTAN1

Supplementary Table 7: KEGG Pathway and GO Biological process enrichment analysis of genes commonly upregulated in healed mucosa defined by ECSS and RHI (A and B) and ECSS and Nancy (C and D) scores. The genes involved in each pathway are listed.

Pathway	**P-value**	**Adjusted P-value**	**Genes**
Arginine biosynthesis	0.025937	1	ASL
Terpenoid backbone biosynthesis	0.027156	1	FNTA
Glyoxylate and dicarboxylate metabolism	0.036854	1	ACO2
Citrate cycle (TCA cycle)	0.036854	1	ACO2
Alanine, aspartate and glutamate metabolism	0.042868	1	ASL
Arachidonic acid metabolism	0.075887	1	CYP2B6
Retinol metabolism	0.080514	1	CYP2B6
Metabolism of xenobiotics by cytochrome P450	0.088558	1	CYP2B6
Progesterone-mediated oocyte maturation	0.116736	1	CPEB4
Drug metabolism	0.126674	1	CYP2B6
Oocyte meiosis	0.145154	1	CPEB4
Purine metabolism	0.149448	1	ENPP4
Cellular senescence	0.182026	1	MCU
NOD-like receptor signaling pathway	0.200389	1	MCU
Calcium signaling pathway	0.210419	1	MCU

B: Go Biological Process Pathway analysis of the 25 common upregulated genes in healed vs non-healed mucosa defined by ECSS and RHI scores.

Biological process	**P-value**	**Adjusted P-value**	**Genes**
protein geranylgeranylation (GO:0018344)	0.007477	1	FNTA
positive regulation of deacetylase activity (GO:0090045)	0.007477	1	FNTA
negative regulation of cytoplasmic translation (GO:2000766)	0.007477	1	CPEB4

positive regulation of clathrin-dependent endocytosis (GO:2000370)	0.007477	1	SCYL2
citrate metabolic process (GO:0006101)	0.007477	1	ACO2
arginine biosynthetic process (GO:0006526)	0.007477	1	ASL
protein lipoylation (GO:0009249)	0.009958	1	GLRX5
positive regulation of mitochondrial calcium ion concentration (GO:0051561)	0.009958	1	MCU
production of siRNA involved in RNA interference (GO:0030422)	0.011196	1	TSNAX
ionotropic glutamate receptor signaling pathway (GO:0035235)	0.011196	1	CPEB4
positive regulation of hemostasis (GO:1900048)	0.011196	1	ENPP4
mitochondrial calcium uptake (GO:0036444)	0.011196	1	MCU
cellular response to oxygen levels (GO:0071453)	0.011196	1	CPEB4
positive regulation of coagulation (GO:0050820)	0.011196	1	ENPP4
ornithine metabolic process (GO:0006591)	0.011196	1	ASL
regulation of cytoplasmic translation (GO:2000765)	0.012433	1	CPEB4
protein-cofactor linkage (GO:0018065)	0.012433	1	GLRX5
protein prenylation (GO:0018342)	0.012433	1	FNTA
positive regulation of protein deacetylation (GO:0090312)	0.013668	1	FNTA
urea cycle (GO:0000050)	0.013668	1	ASL
tricarboxylic acid metabolic process (GO:0072350)	0.016133	1	ACO2
RNA interference (GO:0016246)	0.016133	1	TSNAX
regulation of clathrin-dependent endocytosis (GO:2000369)	0.018593	1	SCYL2
mitochondrial calcium ion homeostasis (GO:0051560)	0.023495	1	MCU
production of small RNA involved in gene silencing by RNA (GO:0070918)	0.023495	1	TSNAX

positive regulation of blood coagulation (GO:0030194)	0.023495	1	ENPP4
entrainment of circadian clock by photoperiod (GO:0043153)	0.024717	1	USP2
photoperiodism (GO:0009648)	0.025937	1	USP2
mitochondrial calcium ion transmembrane transport (GO:0006851)	0.025937	1	MCU
epoxygenase P450 pathway (GO:0019373)	0.025937	1	CYP2B6
positive regulation of receptor internalization (GO:0002092)	0.025937	1	SCYL2
cytosolic calcium ion transport (GO:0060401)	0.027156	1	MCU
exogenous drug catabolic process (GO:0042738)	0.028373	1	CYP2B6
drug catabolic process (GO:0042737)	0.029589	1	CYP2B6
regulation of rhodopsin mediated signaling pathway (GO:0022400)	0.032017	1	FNTA
positive regulation of wound healing (GO:0090303)	0.032017	1	ENPP4
regulation of receptor internalization (GO:0002090)	0.034438	1	SCYL2
calcium ion import (GO:0070509)	0.034438	1	MCU
regulation of blood coagulation (GO:0030193)	0.036854	1	ENPP4
positive regulation of insulin secretion (GO:0032024)	0.03806	1	MCU
mitochondrial transmembrane transport (GO:1990542)	0.039264	1	MCU
cellular response to amino acid stimulus (GO:0071230)	0.039264	1	CPEB4
cellular response to glucose starvation (GO:0042149)	0.040467	1	CPEB4
response to amino acid (GO:0043200)	0.041668	1	CPEB4
glutamate receptor signaling pathway (GO:0007215)	0.044067	1	CPEB4

positive regulation of peptide hormone secretion (GO:0090277)	0.047654	1	MCU

C: KEGG Pathway analysis of the 79 common upregulated genes in healed vs non-healed mucosa defined by ECSS and Nancy scores.

Pathways	P-value	Adjusted P-value	Genes
Terpenoid backbone biosynthesis	0.003381	1	FNTA;ACAT1
Citrate cycle (TCA cycle)	0.006238	0.960625185	ACO2;PCK1
Glyoxylate and dicarboxylate metabolism	0.006238	0.64041679	ACO2;ACAT1
Pyruvate metabolism	0.010385	0.799650795	PCK1;ACAT1
Spliceosome	0.016063	0.989479356	DHX8;TXNL4A;PQBP1
N-Glycan biosynthesis	0.016695	0.857034519	DPM2;ALG3
Synthesis and degradation of ketone bodies	0.038814	1	ACAT1

D) Go Biological Process Pathway analysis of the 79 common upregulated genes in healed vs non-healed mucosa defined by ECSS and Nancy scores.

Biological Process	P-value	Adjusted P-value	Genes
cellular response to exogenous dsRNA (GO:0071360)	0.001168	1	FLOT1;PQBP1
cellular response to dsRNA (GO:0071359)	0.001783	1	FLOT1;PQBP1
positive regulation of type I interferon production (GO:0032481)	0.001897	1	POLR3GL;FLOT1;PQBP1
canonical Wnt signaling pathway (GO:0060070)	0.003024	1	HOXB9;FZD5;SCYL2
protein stabilization (GO:0050821)	0.003098	1	TNIP2;USP2;FLOT1;CCT8
transcription from RNA polymerase III promoter (GO:0006383)	0.005072	1	POLR3GL;GTF3A
regulation of receptor internalization (GO:0002090)	0.005448	1	FLOT1;SCYL2
regulation of embryonic development (GO:0045995)	0.005837	1	POGLUT1;RBM19

response to exogenous dsRNA (GO:0043330)	0.007514	1	FLOT1;PQBP1
regulation of interleukin-1 beta secretion (GO:0050706)	0.007963	1	FZD5;CPTP
regulation of receptor-mediated endocytosis (GO:0048259)	0.008897	1	APOC1;FLOT1
positive regulation of cytokine production (GO:0001819)	0.011258	1	FZD5;POLR3GL;FLOT1;PQBP1
endosome to lysosome transport (GO:0008333)	0.015452	1	BIN1;SCYL2
negative regulation of cellular catabolic process (GO:0031330)	0.020672	1	CPTP;APOC1
phospholipid transport (GO:0015914)	0.022077	1	CPTP;APOC1
negative regulation of phospholipid metabolic process (GO:1903726)	0.02347	1	APOC1
exit from host cell (GO:0035891)	0.02347	1	PPID
negative regulation of mRNA catabolic process (GO:1902373)	0.02347	1	PKP3
arginine biosynthetic process (GO:0006526)	0.02347	1	ASL
protein geranylgeranylation (GO:0018344)	0.02347	1	FNTA
positive regulation of deacetylase activity (GO:0090045)	0.02347	1	FNTA
membrane raft assembly (GO:0001765)	0.02347	1	FLOT1
positive regulation of toll-like receptor 3 signaling pathway (GO:0034141)	0.02347	1	FLOT1
negative regulation of cytoplasmic translation (GO:2000766)	0.02347	1	CPEB4
citrate metabolic process (GO:0006101)	0.02347	1	ACO2

viral release from host cell (GO:0019076)	0.02347	1	PPID
adenylate cyclase-inhibiting G-protein coupled acetylcholine receptor signaling pathway (GO:0007197)	0.02347	1	DHX8
ceramide transport (GO:0035627)	0.02347	1	CPTP
muscle tissue development (GO:0060537)	0.02347	1	POGLUT1
positive regulation of clathrin-dependent endocytosis (GO:2000370)	0.02347	1	SCYL2
response to UV-A (GO:0070141)	0.02347	1	PPID
acetyl-CoA biosynthetic process (GO:0006085)	0.02347	1	ACAT1
negative regulation of sterol transport (GO:0032372)	0.02347	1	APOC1
second-messenger-mediated signaling (GO:0019932)	0.025002	1	DHX8;MCU
protein localization to membrane (GO:0072657)	0.025526	1	RAB32;FLOT1;PKP3
carbohydrate homeostasis (GO:0033500)	0.025756	1	PCK1;MCU
glycolipid metabolic process (GO:0006664)	0.027293	1	POGLUT1;CPTP
regulation of sterol transport (GO:0032371)	0.027328	1	APOC1
cellular lipid biosynthetic process (GO:0097384)	0.027328	1	ACAT1
purine nucleoside bisphosphate biosynthetic process (GO:0034033)	0.027328	1	ACAT1
positive regulation of inositol phosphate biosynthetic process (GO:0060732)	0.027328	1	DHX8

coenzyme A biosynthetic process (GO:0015937)	0.027328	1	ACAT1
ribonucleoside bisphosphate biosynthetic process (GO:0034030)	0.027328	1	ACAT1
chylomicron remnant clearance (GO:0034382)	0.027328	1	APOC1
regulation of toll-like receptor 3 signaling pathway (GO:0034139)	0.027328	1	FLOT1
cellular response to histamine (GO:0071420)	0.027328	1	DHX8
negative regulation of nitrogen compound metabolic process (GO:0051172)	0.027328	1	APOC1
regulation of mitotic cell cycle (GO:0007346)	0.027624	1	ANGEL2;USP2;OXSR1
regulation of synaptic transmission, dopaminergic (GO:0032225)	0.031172	1	FLOT1
positive regulation of mitochondrial calcium ion concentration (GO:0051561)	0.031172	1	MCU
ketone body biosynthetic process (GO:0046951)	0.031172	1	ACAT1
protein lipoylation (GO:0009249)	0.031172	1	GLRX5
positive regulation of protein localization to Cajal body (GO:1904871)	0.031172	1	CCT8
negative regulation of lipase activity (GO:0060192)	0.031172	1	APOC1
short-chain fatty acid catabolic process (GO:0019626)	0.031172	1	PCK1
desmosome organization (GO:0002934)	0.031172	1	PKP3
protein K6-linked ubiquitination (GO:0085020)	0.031172	1	RNF4

succinate metabolic process (GO:0006105)	0.031172	1	SDHAF3
regulation of aspartic-type endopeptidase activity involved in amyloid precursor protein catabolic process (GO:1902959)	0.031172	1	BIN1
regulation of protein localization to Cajal body (GO:1904869)	0.031172	1	CCT8
stress-activated protein kinase signaling cascade (GO:0031098)	0.031292	1	TNIP2;OXSR1
lysosomal transport (GO:0007041)	0.032952	1	BIN1;SCYL2
glucose homeostasis (GO:0042593)	0.034647	1	PCK1;MCU
positive regulation of establishment of protein localization to telomere (GO:1904851)	0.035	1	CCT8
production of siRNA involved in RNA interference (GO:0030422)	0.035	1	TSNAX
negative regulation of protein sumoylation (GO:0033234)	0.035	1	RNF4
ornithine metabolic process (GO:0006591)	0.035	1	ASL
endosome to melanosome transport (GO:0035646)	0.035	1	RAB32
positive regulation of hemostasis (GO:1900048)	0.035	1	ENPP4
endosome to pigment granule transport (GO:0043485)	0.035	1	RAB32
negative regulation of amyloid-beta formation (GO:1902430)	0.035	1	BIN1
positive regulation of coagulation (GO:0050820)	0.035	1	ENPP4
toll-like receptor 3 signaling pathway (GO:0034138)	0.035	1	TNIP2

regulation of cell-cell adhesion mediated by cadherin (GO:2000047)	0.035	1	FLOT1
mitochondrial calcium uptake (GO:0036444)	0.035	1	MCU
cellular response to oxygen levels (GO:0071453)	0.035	1	CPEB4
positive regulation of astrocyte differentiation (GO:0048711)	0.035	1	BIN1
ionotropic glutamate receptor signaling pathway (GO:0035235)	0.035	1	CPEB4
positive regulation of cholesterol esterification (GO:0010873)	0.035	1	APOC1
regulation of astrocyte differentiation (GO:0048710)	0.038814	1	BIN1
protein-cofactor linkage (GO:0018065)	0.038814	1	GLRX5
membrane raft organization (GO:0031579)	0.038814	1	FLOT1
negative regulation of cholesterol transport (GO:0032375)	0.038814	1	APOC1
dorsal/ventral axis specification (GO:0009950)	0.038814	1	FZD5
very-low-density lipoprotein particle assembly (GO:0034379)	0.038814	1	APOC1
positive regulation of steroid metabolic process (GO:0045940)	0.038814	1	APOC1
response to histamine (GO:0034776)	0.038814	1	DHX8
mitotic nuclear envelope reassembly (GO:0007084)	0.038814	1	ANKLE2
negative regulation of interleukin-1 beta secretion (GO:0050713)	0.038814	1	CPTP
coenzyme A metabolic process (GO:0015936)	0.038814	1	ACAT1

regulation of establishment of protein localization to telomere (GO:0070203)	0.038814	1	CCT8
ketone body metabolic process (GO:1902224)	0.038814	1	ACAT1
regulation of cytoplasmic translation (GO:2000765)	0.038814	1	CPEB4
regulation of NLRP3 inflammasome complex assembly (GO:1900225)	0.038814	1	CPTP
positive regulation of glial cell differentiation (GO:0045687)	0.038814	1	BIN1
protein prenylation (GO:0018342)	0.038814	1	FNTA
positive regulation of protein secretion (GO:0050714)	0.041752	1	PPID;MCU
protein kinase C signaling (GO:0070528)	0.042612	1	FLOT1
regulation of cholesterol esterification (GO:0010872)	0.042612	1	APOC1
protein O-linked mannosylation (GO:0035269)	0.042612	1	DPM2
positive regulation of heterotypic cell-cell adhesion (GO:0034116)	0.042612	1	FLOT1
negative regulation of amyloid precursor protein catabolic process (GO:1902992)	0.042612	1	BIN1
positive regulation of protein localization to chromosome, telomeric region (GO:1904816)	0.042612	1	CCT8
T cell proliferation (GO:0042098)	0.042612	1	BTN3A1
negative regulation of fatty acid biosynthetic process (GO:0045717)	0.042612	1	APOC1
positive regulation of tumor necrosis factor secretion (GO:1904469)	0.042612	1	FZD5

positive regulation of protein deacetylation (GO:0090312)	0.042612	1	FNTA
urea cycle (GO:0000050)	0.042612	1	ASL
internal protein amino acid acetylation (GO:0006475)	0.042612	1	PCK1
positive regulation of myoblast fusion (GO:1901741)	0.042612	1	FLOT1
cellular response to molecule of bacterial origin (GO:0071219)	0.043607	1	FZD5;TNIP2
regulation of type I interferon production (GO:0032479)	0.044546	1	POLR3GL;PQBP1
regulation of myoblast fusion (GO:1901739)	0.046396	1	FLOT1
regulation of skeletal muscle tissue development (GO:0048641)	0.046396	1	FLOT1
alternative mRNA splicing, via spliceosome (GO:0000380)	0.046396	1	PQBP1
negative regulation of substrate adhesion-dependent cell spreading (GO:1900025)	0.046396	1	AP1AR
positive regulation of establishment of protein localization (GO:1904951)	0.046396	1	CCT8
negative regulation of metabolic process (GO:0009892)	0.046396	1	APOC1
positive regulation of skeletal muscle tissue development (GO:0048643)	0.046396	1	FLOT1
negative regulation of interleukin-1 secretion (GO:0050711)	0.046396	1	CPTP
phospholipid efflux (GO:0033700)	0.046396	1	APOC1
positive regulation of T cell cytokine production (GO:0002726)	0.046396	1	FZD5
negative regulation of fatty acid metabolic process (GO:0045922)	0.046396	1	APOC1