Bioinformatic applications in psoriasis: genetics, transcriptomics, and microbiomics

Jason E Parad, MPH, MBE[1] and Wilson Liao, MD[2]

■ **Abstract**

Bioinformatics uses computationally intensive approaches to make sense of complex biological data sets. Here we review the role of bioinformatics in 3 areas of biology: genetics, transcriptomics, and microbiomics. Examples of bioinformatics in each area are given with respect to psoriasis and psoriatic arthritis, related inflammatory disorders at the forefront of bioinformatic research in dermatology. While bioinformatic technologies and analyses have traditionally been developed and deployed in siloes, the field of integrative omics is on the horizon. Powered by the advent of machine learning, bioinformatic integration of large data sets has the potential to dramatically revolutionize our knowledge of pathogenetic mechanisms and therapeutic targets.

Semin Cutan Med Surg 38:E3-E11 © 2019 Frontline Medical Communications

Bioinformatics promises to dramatically advance our understanding of human health and disease. Integrating the fields of mathematics, statistics, and computer science, bioinformatics utilizes computational methods to analyze and interpret large biological data sets. The past 3 decades of research in bioinformatics have largely focused on the analysis of genetic, transcriptomic, and microbiomic data. In more recent years, analyses of proteomics[1] and metabolomics[2] have also become of increasing interest. This article seeks to review bioinformatic techniques in genetics, transcriptomics, and microbiomics (Table) and offer examples of these techniques as applied to psoriasis and psoriatic arthritis.

Psoriasis is a chronic, autoimmune inflammatory skin disease that affects about 3% of the world population.[3] Multiple phenotypes have been described, including plaque, guttate, inverse, pustular, palmoplantar, scalp, and erythrodermic psoriasis. Psoriasis has also been associated with numerous comorbidities, including psoriatic arthritis in up to 30% of affected individuals.[4] While the etiologies of psoriasis and psoriatic arthritis remain poorly understood, they are thought to arise from the complex interplay of genetic, immunologic, and environmental factors. Microbial factors have also long been implicated in psoriatic pathogenesis. While a number of treatments are available for psoriasis and psoriatic arthritis, none is effective in all cases. As such, there is great interest in understanding psoriatic heterogeneity in an effort to stratify patients for more personalized therapy (Figure).

[1]School of Medicine, University of California, San Francisco, CA.
[2]Department of Dermatology, University of California, San Francisco, CA.
Disclosures: The authors have nothing to disclose.
Correspondence: Jason E Parad, MPH, MBE; jason.parad@ucsf.edu

Here we review the role of bioinformatics in 3 areas of biology as applied to psoriatic disease: (1) genetics, the study of DNA variation and its relation to disease; (2) transcriptomics, the study of RNA transcripts and their variation across biological states; and (3) microbiomics, the study of bacterial, viral, and fungal genomes present in a particular environment such as the human host.

Genetics

Linkage analysis

Historically, the primary method of studying single-gene disorders was linkage analysis, which queries a set of genetic markers (typically dozens to several hundred) in affected and unaffected members of multigenerational families in order to map heritable traits to their chromosomal locations.[5] Linkage analysis can be conducted using parametric or nonparametric methods. Parametric analyses calculate a logarithm of odds score based on an explicit genetic model and display superior performance when the model sufficiently approximates the true mode of inheritance.[6] Nonparametric methods evaluate allele sharing among affected individuals without particular model assumptions and are necessary for analyzing diseases of complex genetic origin.[7] In either case, linkage analysis has demonstrated the greatest utility in detecting alleles or variants of large effect size.[8]

Linkage analyses have been used in psoriasis research to identify 9 susceptibility loci, referred to as PSORS1-9. Among these, PSORS1 and PSORS2 have received the greatest attention. Located within the major histocompatibility complex (MHC), PSORS1 on 6p21.3 accounts for 35%-50% of the total genetic contribution to disease.[9] PSORS2 was identified in a linkage analysis of a large family of European ancestry with plaque psoriasis, in whom 30% had developed psoriatic arthritis.[10] PSORS2 was further implicated in a genome-wide linkage scan of a Taiwanese family with psoriasis across 5 generations[11] as well as in a linkage study of 224 affected sibling pairs.[12] Underscoring the polygenic inheritance of psoriasis, early linkage analyses eventually motivated larger-scale approaches for gene identification such as genome-wide association studies (GWAS).

Genome-wide association studies

Gene locus identification

GWAS typically use a case-control design (comparing unrelated subjects who are affected and unaffected) to identify an association between a genetic marker and a phenotype of interest. In some instances, GWAS do not examine case controls and instead examine the association of genetic markers with a continuous or quantitative trait. In either situation, loci are identified by examining hundreds of thousands of single-nucleotide polymorphisms (SNPs) interspersed throughout the genome, typically using DNA microarray technology.[13] Loci that harbor SNP variants that are

1085-5629/13$-see front matter © 2019 Frontline Medical Communications
DOI: 10.12788/j.sder.2019.003

TABLE. Major biological domains of psoriasis research with their relevant technologies and bioinformatic analyses.

Biological domain	Relevant technologies	Bioinformatic analyses
Genetics	· DNA microarray · Whole genome sequencing · Exome sequencing	· Linkage analysis · Genome-wide association studies · Fine-mapping causal variants
Transcriptomics	· Microarray · RNA-seq – *Bulk tissue RNA-Seq* – *FACS-seq* – *Single-cell RNA-Seq*	· Differential expression analysis · Network analysis · Pathway analysis
Microbiomics	· rRNA gene phylotyping · Whole-genome shotgun sequencing	· Taxa detection · Diversity analysis – *Alpha diversity* – *Beta diversity* · Functional analysis

more frequently observed in individuals with, rather than without, the disease are deemed to be associated. Owing to the phenomenon of linkage disequilibrium, scrutiny of these loci can then guide the discovery of pathogenic variants.

Bioinformatic pipelines that analyze GWAS data utilize several steps. First, the DNA microarray data are subjected to quality control checks to ensure that low-quality DNA samples are removed, that poorly performing SNP assays are removed, that subjects related to each other are removed, and that the cases and controls are generally matched in terms of their genetic ancestry. Next, association testing between SNPs and disease is performed with various statistical tests, many of which can adjust for covariates such as demographic features, disease features, and subtle differences in ancestry. SNPs that are identified as statistically significant are often tested in independent replication cohorts, with a final meta-analysis performed.

Well-suited to the study of plaque psoriasis given its polygenic inheritance, GWAS have dramatically expanded the number of loci associated with psoriasis susceptibility. Large-scale GWAS and meta-analyses have convincingly identified 63 loci contributing to psoriasis susceptibility in European populations.[14] Many large intercontinental consortia have further pooled hundreds of thousands of samples, allowing for the identification of susceptibility loci with very mild effect sizes.[15,16] For instance, a large trans-ethnic genome-wide meta-analysis of psoriasis gathered roughly 15,000 psoriasis cases across Caucasian and Chinese ancestries to identify a handful of novel associations.[17]

GWAS have also been used to investigate psoriatic arthritis, with the results underscoring the role of the MHC, confirming associations with IL-23 and IL-12B, and identifying a novel locus known to harbor genes associated with other autoimmune diseases.[15] Despite these increasing number of associations, there remains a lack of comprehensive analysis of each individual risk allele with psoriatic clinical phenotypes.[16]

Fine-mapping causal variants

The association signals identified through GWAS can contain hundreds of variants spanning large regions of numerous genes. Fine-mapping is a bioinformatic process to identify true causal variants among all the associated variants. Statistical selection of causal variants can be based on association *P* values such as $P < 5 \times 10^{-8}$ or on Bayesian methods that assign to each variant a posterior probability of causality. Bayesian methods are useful in that they allow for the incorporation of prior biological knowledge from pathway analyses or functional annotations.[18] Fine-mapping requires a sufficiently large sample size to separate out the most highly correlated signals and rigorous genotyping or imputation of the variants therein.[19]

Fine-mapping studies in psoriasis have largely focused on the analysis of PSORS1. Initial studies using this bioinformatic approach sought to localize the primary risk locus, narrowing PSORS1 to an approximately 300-kb region with multiple biologically plausible candidate genes. This effort was followed by a study in a Caucasian sample that identified HLA-C*06:02 as the PSORS1 risk allele.[20] A follow-up study in a Chinese population confirmed that while HLA-C*06:02 was a major risk allele, it could not completely account for the full linkage evidence of PSORS1.[9] Fine-mapping with conditional analysis has further been used to identify additional psoriasis susceptibility alleles distributed across the MHC.[21,22] For instance, a large-scale fine-mapping analysis in individuals of European ancestry used a combination of genotyping and imputation to examine the genetic variation in each of 8 psoriasis susceptibility regions, confirming, among other findings, the presence of multiple psoriasis effectors in the MHC.[23]

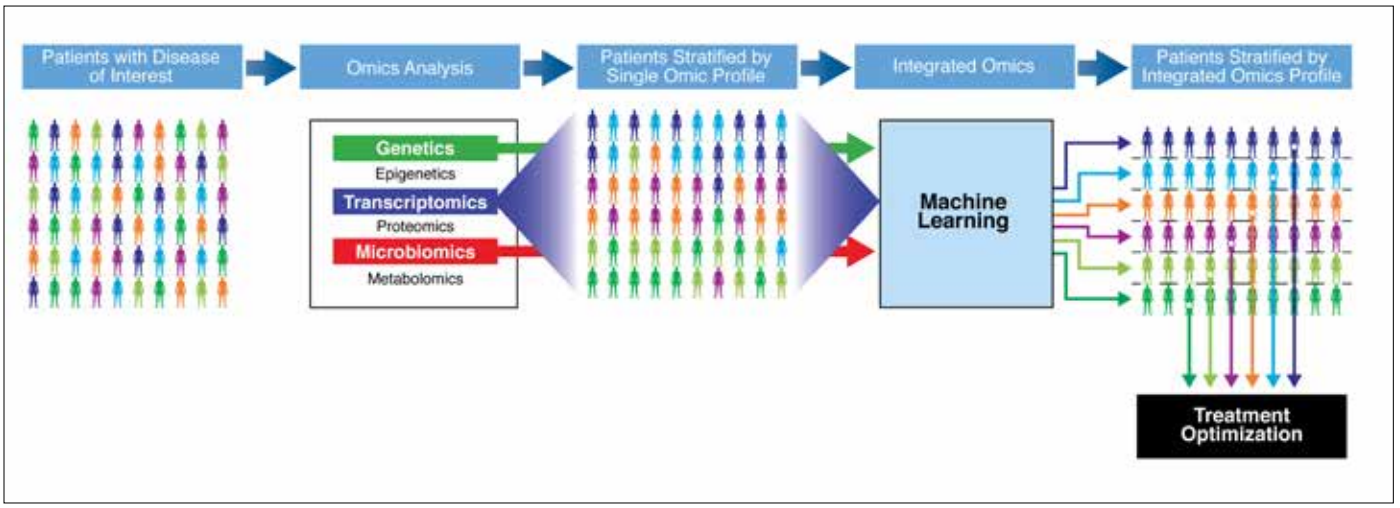

FIGURE. Integrated omics analysis of a heterogeneous disease allows for patient stratification and treatment optimization.

Exome sequencing

Exome sequencing is a genomic technique that involves sequencing only the exons, or protein-coding genes, in a genome. The human exome contains about 180,000 exons, which total about 30 million base pairs and 1% of the human genome. Sequencing of the exome is performed using high-throughput DNA sequencing technology. The goal is to identify the genetic variants responsible for disease phenotypes, and to do so at a lower cost than whole-genome sequencing. Whereas GWAS studies focus on identifying common variants (minor allele frequency >1% in a population) associated with a disease, exome sequencing studies focus on identifying infrequent or rare variants (minor allele frequency <1%) associated with a disease.

Exome sequencing has been used in psoriasis to identify causal variants in families and populations. For instance, exome sequencing of the affected European and Taiwanese families noted above, as well as of a child with severe pustular psoriasis, concluded the 17-year search for PSORS2 by identifying mutations in CARD14, a gene implicated in the recruitment of inflammatory cells by keratinocytes.[24] A follow-up study used exome sequencing to identify 15 additional rare missense variants in CARD14 across 7 psoriasis cohorts.[25] Studies looking at generalized pustular psoriasis in Japanese,[26] Tunisian,[27] and European[28] individuals have also been successful in identifying mutations in IL36RN, which has been shown to antagonize cytokines of the IL-1 family.[29]

Transcriptomics

Our knowledge of psoriasis has also benefited from characterization of the transcriptome. The transcriptome comprises the total cellular complement of coding and noncoding RNA.[30] Given the diverse roles of RNA as messenger, regulator, and housekeeper, transcriptomic analysis can shed light on the dynamic state of one or more cells in a particular environment. Characterizing transcriptomic differences between a disease tissue and its healthy counterpart can therefore help elucidate the pathogenesis, mechanisms, and therapeutic targets of disease.

Transcriptomic technologies

The principal technologies used in transcriptomic analysis are microarray and RNA sequencing (RNA-seq). Both rely on purifying an RNA sample of interest and then converting it cDNA for further bioinformatic processing.

Microarray

Microarray was the initial bioinformatic technology deployed in transcriptomic analysis. It involves a chip with an array of ever-updated probes designed to hybridize the RNA-derived cDNA of interest. As such, it relies on previous knowledge of the genome to detect and quantify known transcripts or isoforms.[30] Relative to RNA-seq, pre-processing and low-level analyses of the results are relatively straightforward. New microarray datasets can also be readily combined with those available in public databases without introducing platform-specific heterogeneity.[31,32] Within the field of psoriasis, microarrays remain popular for profiling gene expression in certain tissues such as peripheral blood.[33,34]

RNA sequencing

RNA-seq has emerged as a powerful discovery-based tool for characterizing the psoriatic transcriptome. It utilizes next-generation sequencing technology to sequence the RNA-derived cDNA of interest. Relative to microarray, RNA-seq offers notable advantages, including greater sensitivity and dynamic range of detection.[35] RNA-seq also allows for the characterization of splice variants, gene isoforms, and novel gene fusions.[32] While RNA-seq in some cases complements the results of microarray-based studies,[31] it is increasingly viewed as a replacement technology. Thus far, RNA-seq has been utilized in psoriasis research to characterize the coding transcriptome,[36,37] miRNAome,[38] and lncRNAome,[39] along with the lncRNAome of psoriatic arthritis.[34]

Fluorescence-activated cell sorting sequencing. While RNA-seq has been traditionally performed on bulk tissue samples or cell populations expanded in cell culture, there are emerging isolation techniques compatible with downstream RNA-seq analysis.[40] Fluorescence-activated cell sorting (FACS) is one such technology that

utilizes multiparametric flow cytometry to sort a heterogeneous mixture of cells uniquely labeled with fluorescent antibodies.[40] FACS can thereby enrich for expression signals from relatively rare cells while avoiding cell culture amplification methods that may significantly alter gene expression profiles.[41] The technology also benefits from the availability of robust, low-cost commercial platforms with user-friendly interfaces and efficient data visualization tools.[40] Researchers of psoriasis have effectively used FACS-seq to sort and sequence nonuniformly distributed populations of keratinocytes, dendritic cells, CD4+ T effector cells, and CD8+ T effector cells.[41]

Single-cell RNA sequencing. Unlike FACS-seq which enriches for distinct populations of cells, single-cell RNA sequencing (scRNA-seq) allows for transcriptomic analysis of individual cells. Utilizing high-throughput microfluidic cell capture or other microwell plate-based technology, scRNA-seq can enrich for relatively low-abundance cell types and detect previously undetectable gene expression signals.[42] Yet as a relatively new technology, scRNA-seq faces significant computational and analytical challenges.[43] Within psoriasis research, FACS-seq remains favorable to scRNA-seq given the greater ease of cell capture and library preparation.[41]

Bioinformatic analyses

The profiling technologies of microarray and RNA-seq have allowed for 3 main types of transcriptomic analysis: differential expression analysis, co-expression network analysis, and pathway analysis.

Differential expression analysis

Differential expression analysis entails characterizing the genes that are differentially up- or downregulated between experimental and reference tissues with the goal of gaining pathogenetic, mechanistic, or therapeutic insights. Microarray and RNA-seq have both been used for such analysis, with the latter now being the more widely employed approach. Still, appropriate consensus protocols for identifying and reconciling differentially expressed genes (DEGs) elucidated through RNA-seq alone or in combination with microarray data remain an active area of research.[44]

Research in psoriasis has made use of differential expression analysis for nearly 2 decades. Early microarray-based studies yielded hundreds of DEGs, and the advent of RNA-seq has expanded that number into the thousands.[36,37] Thus far, studies have profiled DEGs of lesional versus uninvolved psoriatic skin;[45-48] psoriatic versus normal,[49] atopic,[50] and squamous cell carcinomatous skin;[51] pre- versus post-tumor necrosis factor inhibitor–treated psoriatic blood and lesional skin;[33] psoriatic arthritic blood versus normal blood;[34] and psoriatic arthritic synovial biopsy and blood versus healthy controls.[52]

Direct insights from differential expression analyses are manifold, ranging from the implication of core psoriatic genes, to the analysis of therapeutic response, to the identification of disease biomarkers. For instance, one recent study using RNA-seq demonstrated a core set of 763 DEGs across psoriatic phenotypes as well as hundreds of DEGs unique to scalp, palmoplantar, and conventional plaque psoriasis.[48] A second study using this technology illuminated a unique lncRNA signature between psoriatic and healthy skin as well as between psoriatic skin before and after treatment with adalimumab.[39] A third, microarray-based study demonstrated the upregulation of osteoactivin in the peripheral blood and synovial biopsies of individuals with psoriatic arthritis, along with higher serum levels of osteoactivin in psoriatic arthritis but not other arthritides, suggesting the potential utility of this glycosylated protein as a biomarker of disease.[52]

Network analysis

In addition to looking at DEGs individually, there has been interest in detecting their involvement in coordinated expression. Genes, on estimate, interact with 6 other genes and possess 10 biological functions.[53] Network analysis among DEGs can thus dramatically expand the genetic and functional knowledge of disease. A popular systems biology approach for constructing gene networks is weighted gene co-expression network analysis (WGCNA). Building on previously unweighted methods (eg, pairwise correlations, Bayesian models, and linear regression), WGCNA uses a correlation-based soft-thresholding weight to prioritize strong pairwise correlations.[54] It can also reveal densely clustered subnetworks known as "gene modules," along with their most influential "hub genes," which have been shown to orchestrate module behavior.[55] WGCNA has been successful in revealing candidate genes and molecular targets in various autoimmune conditions, including Sjögren's syndrome, inflammatory bowel disease, and chronic fatigue syndrome.[54]

WGCNA has also been pivotal in psoriasis research, with the earliest such study serving as the initial application of this technique to RNA-seq data of human skin.[36] The chief use of WGCNA in the field has been to assemble inputs for pathway analysis, as outlined below. Modular analysis in WGCNA has assisted in this regard by at once reducing the number of inputs and increasing their explanatory power. Still, network analysis in its own right has revealed interesting findings pertaining to both psoriasis and psoriatic arthritis. For instance, one study demonstrated that lncRNAs constitute the majority of genes in modules significantly correlated with psoriasis. Furthermore, as most of these lncRNAs were not identified through differential expression analysis, network analysis was hypothesized to more robustly include low-abundance transcripts.[54] A subsequent WGCNA study of several psoriatic phenotypes additionally demonstrated that the majority of hub genes are not differentially expressed.[48] Network analysis has similarly underscored the importance of lncRNAs in the transcriptome of psoriatic arthritis.[34]

Pathway analysis

Much of the utility in identifying DEGs and gene co-expression networks lies in the ability to subsequently enrich for specific biological pathways and functions. The most popular bioinformatic tools for pathway analysis and functional enrichment in psoriasis research are Ingenuity Pathway Analysis (IPA) and Gene Ontology (GO), respectively.[47] The Molecular Signatures Database and Kyoto Encyclopedia of Genes and Genomes (KEGG) have also been commonly used for pathway analysis.[54] Mapping genes and gene networks onto biological processes and functions contained

within constantly updated omics repositories has led to a number of mechanistic conclusions.

Indeed, work in psoriasis has applied pathway analysis to differential expression and network analyses to yield confirmatory and novel insights. As one example, IPA of core DEGs across psoriatic phenotypes has demonstrated enrichment for endothelin-1 signaling, confirming previous work showing higher serum plasma levels of this biomarker.[48] As another example, IPA of WGCNA data elucidated a module of coordinately expressed genes that was both related to keratinocyte differentiation and IL-17 responsive, suggesting a role for IL-17 in innate host defense through signaling to the epidermal barrier.[36]

Functional enrichment analysis with GO has been similarly illustrative. For instance, a study of psoriatic uninvolved skin using this technology found enrichment for defense response among upregulated transcripts and for lipid metabolism among downregulated transcripts.[47] Of note, such enrichment for lipid metabolism is thought to be consistent with psoriatic pathogenesis through the promotion of either defects in the epidermal lipid barrier[47] or fatty acid–mediated differentiation of T cells into T_{reg} cells, the latter being critical players in the suppression of the inflammatory response.[54] Use of GO in psoriatic arthritis has also demonstrated enrichment for processes of suspected pathogenetic importance, including immune response and glycolipid metabolism.[34] Intriguingly, a study of psoriatic lesional skin using the Molecular Signatures Database went on to demonstrate enrichment for olfactory receptor signaling, a pathway not previously identified through differential expression analysis and of particular interest given recent data suggesting a role for olfactory receptors in cutaneous wound healing.[54]

Microbiomics

The human microbiome comprises the totality of bacteria, fungi, archaea, viruses, and arthropods that reside in and on our bodies. Among these diverse organisms, bacteria have been increasingly recognized for their role in maintaining important physiologic processes such as synthesizing essential compounds and preserving the skin barrier. Indeed, dysbiosis of the microbiome has been implicated in a variety of diseases, including obesity,[56] inflammatory bowel disease,[57] cardiovascular disease,[58] cirrhosis,[59] and autism.[60] The hope is that understanding the complex interplay between microbes and disease will reveal critical insights into pathogenesis and treatment.

Linking the microbiome to psoriasis

The importance of microbes in psoriatic disease has long been appreciated. Infection of the upper respiratory tract with streptococcal bacteria was linked to psoriasis in the 1950s[61] and has since been implicated in its initiation[62] and exacerbation.[63] Topical application of the fungus *Malassezia* has similarly been shown to induce[64] and worsen[65] psoriatic plaques in the skin of psoriatic individuals. In addition to the clear role of external pathogens, research on the imiquimod-induced mouse model of psoriasis has suggested that commensal gut bacteria control the inflammatory response associated with the disease.[66] The hypothesis that gut bacteria similarly mediate psoriatic arthritis remains under active investigation.[67]

Sampling the microbiome

Characterizing microbial-host interactions begins with sampling the microbial community of interest. The intestinal microbiome is typically sampled through collection of a stool specimen. Sampling the skin is accomplished by biopsy, curette, or skin swab and entails more complex considerations given site-specific differences in pH, moisture, sebum content, and topography that influence microbial community architecture.[68] Work in psoriasis has also more recently begun profiling the blood microbiome through samples of peripheral blood.[69] Whereas early research required culturing samples for subsequent analysis, culture-independent methods are now in near-exclusive use and facilitate analysis of the 99% of the microbiome incapable of being cultivated.[68]

Microbiomic technologies

After collecting a sample, microbial DNA can be extracted to identify the organisms present and quantify their relative abundances. Two main technologies for characterizing the microbiome are used: ribosomal RNA (rRNA) gene phylotyping and whole-genome shotgun (WGS) sequencing/shotgun metagenomics.[70]

rRNA gene phylotyping

rRNA gene phylotyping was the initial culture-independent method for microbial detection. All bacteria contain the 16S rRNA gene, comprising several regions that are highly conserved and 9 regions that are hypervariable. The hypervariable regions, denoted V1-V9, themselves contain both semi-conserved regions that allow for polymerase chain reaction (PCR)-based sequencing and variable regions that enable bacterial classification. While hypervariable regions are not as accurate in classification as is the whole 16S rRNA gene, they reliably predict taxonomic levels at a fraction of the cost. For this reason, semi-conserved sequences in hypervariable regions are widely used in large-scale studies aiming to characterize entire microbial communities.[71] Specifically, the V4 region has been useful in classifying enteric microbes, V1-V3 has worked well for cutaneous microbes in general,[72] and V3-V5 may be useful for identifying microbes of diagnostic relevance to psoriasis.[73] Mycological identification is often analogously performed by sequencing the eukaryotic 18S rRNA gene with *Malassezia*-specific PCR primers.[74] Despite its limited taxonomic resolution and inability to offer any direct genomic or functional assessment of a microbial community, rRNA gene phylotyping remains a powerful and widespread tool for taxonomic classification.[75]

Whole-genome shotgun sequencing

Whole-genome shotgun (WGS) sequencing offers a more global picture of a microbial community. It involves shearing the genomes contained within a microbial sample and then sequencing random fragments. The fragments can then be aligned, assembled, and compared to a reference database for taxonomic identification. WGS overcomes many limitations of PCR-based surveys by, for instance, detecting microbes lacking a universal gene such as 16S,[76] enhancing identification of taxa at the species level,[77] and profiling the functional potential of a community.[78] Shotgun metagenomic research on skin microbiota has emerged only over the past decade, with psoriasis research representing the first appli-

cation of this technology to skin disease.[75] While WGS remains the more expensive and computationally intensive approach, its cost is expected to decrease with advancement of the technology.

Bioinformatic analyses

Detection of Taxa

With these sequences in hand, the next step is taxonomic classification. Classification of 16S sequence data begins with clustering sequences into operational taxonomic units (OTUs), a working name for groups of related bacteria.[79] OTU clusters can be based on the similarity of sequences to each other or to those available in an annotated database, approaches known as "de novo" and "closed-reference" OTU picking, respectively. "Open-reference" OTU picking is an increasingly recommended third strategy that employs a closed-reference strategy followed by de novo picking among unsuccessfully mapped reads.[79] Similarity thresholds of 95% and 97-99% are generally regarded as appropriate proxies for OTU classification at the genus and species level, respectively.[79] Robust bioinformatic approaches have also been developed for taxonomic analysis of shotgun data. One popular method, which was used by the first WGS study of psoriasis, classifies shotgun reads by mapping them to a pre-computed catalog of unique clade-specific marker genes.[80] An alternative method makes use of lowest common ancestor positioning to hierarchically classify pre-aligned sequences on a taxonomy tree, with sequences failing to meet a similarity threshold being assigned to progressively higher taxonomic levels.[70]

The above bioinformatic tools for taxonomic classification have been widely used in studies of the psoriatic microbiome. A review of studies that employed predominantly 16S rRNA phylotyping to characterize psoriatic cutaneotypes found a trend toward a higher relative abundance of *Streptococcus* and a lower relative abundance of *Propionibacterium* in psoriasis patients versus controls.[72] A more recent study using this technology elucidated a psoriatic core intestinal microbiome as well as 3 enterotypes, with patients belonging to the enterotype marked by a predominance of *Prevotella* being more likely to have bacteria detected in their peripheral blood as well as a higher inflammatory status.[81] In the sole shotgun metagenomic study on psoriasis noted above, use of MetaPhlAn 2, a tool mapping shotgun reads to a database of clade-specific marker genes, revealed increased *Staphylococcus* in psoriatic versus unaffected skin but few discriminative features at the species level.[75] More recent 16S rRNA research using a high sequencing depth showed a relative enrichment of *Staphylococcus aureus* in particular and further validated strong Th17 polarization in mice colonized with this bacterium.[82] Of note, 16S rRNA research on psoriatic arthritis has thus far demonstrated a gut microbial profile similar to that observed in inflammatory bowel disease.[83]

Diversity analysis

The field of bacterial ecology has developed 2 sets of bioinformatic tools for analyzing the diversity of microbial communities.

Alpha diversity. Alpha diversity refers to the diversity of species within an individual community. In studies of the microbiome, these communities are often well-defined ecological niches such as distinct areas of the skin or intestine.[84] Alpha diversity can be assessed in terms of evenness, or the distribution of species, as well as richness, or the number of species present in a sample. Common indices of alpha diversity that combine these 2 metrics include the Shannon and Simpson indices. The Shannon index involves summing the proportion of each species relative to the total number of species in a given community.[85] The Simpson index is a similar measure that gives more weight to dominant species.

Studies of psoriatic skin lesions have generated conflicting conclusions about alpha diversity.[72] The earliest study to assess alpha diversity demonstrated with skin swabs that psoriatic lesional skin was associated with a greater Simpson diversity index than nonlesional or control skin.[86] A subsequent study comparing biopsied psoriatic lesional skin to normal skin with lesions removed by wide excision, however, revealed no difference in mean Shannon indices but a narrower distribution of indices among cases versus controls.[86] The largest microbiomic study of psoriasis to date demonstrated a trend towards a lower Shannon index at the phylum, class, order, family, and genus levels in lesional psoriatic skin compared to nonlesional skin and healthy skin. It also showed that systemic treatment with methotrexate or tumor necrosis factor inhibitors led to a persistent decrease in richness in lesional but not unaffected skin.[87] Conflicting results are thought to be due to differences in sampling technique and the use of site-matched and not site-matched sampling.[72]

Beta diversity. Beta diversity considers the dissimilarity of bacterial composition between communities.[87] It can be quantified through either a phylogenetic or taxon-based approach. Phylogenetic methods take evolutionary history into account, assigning lower weights to differences in abundance of closely related species.[70] UniFrac is a popular phylogenetic method that measures the amount of unique evolution of one community relative to others[88] and has been shown to align with meaningful biological patterns.[89] Taxon-based methods characterize the dissimilarity between samples based only on counts, without use of a phylogenetic tree. In this way, they are less adept in suppressing noise but are more sensitive to differences in OTUs with high sequence similarity that may nonetheless be of distinct biological significance. Bray-Curtis dissimilarity is a popular taxon-based method that is robust to count matrices filled with zeros, which is common in microbial community data.[70] Dissimilarity matrices can then be further visualized with methods such as principal coordinate analysis, which transforms the matrices into a new set of orthogonal axes that explain their maximum amount of variation.[90]

Within the field of psoriasis, studies of beta diversity have yielded similarly conflicting results.[72] For instance, one study using UniFrac and principal coordinate analysis demonstrated lower beta diversity among psoriasis lesions relative to controls, implying reduced variation in OTU composition of psoriatic microbial communities.[91] In contrast, the largest microbiomic study referenced above used intragroup UniFrac analysis to demonstrate that beta diversity increased from control to unaffected to lesional skin, indicating the uniqueness of psoriatic microbial communities.[87] However, longitudinal analysis in a small subset of these patients and controls demonstrated that differences in beta diversity were no longer observed at a 12- and 36-week follow-up.[87]

Functional analysis

Bioinformatic tools also allow for profiling the function of a microbial community in relation to its host.[70] Functional inference of 16S data is commonly accomplished with PICRUSt software. By mapping representative OTU sequences to phylogenetic gene markers in a reference database, PICRUSt is able to predict and quantify functional genes likely to be associated with the OTUs. Counts of functional genes can then be further analyzed by pathway analysis (eg, KEGG) to determine key biological functions. However, shotgun metagenomics data offer a more reliable functional assessment. Software programs such as MEGAN, MG-RAST, and HUMAnN directly map sequence data to gene databases and organize the data into biological pathways using tools such as KEGG pathways or the SEED hierarchy.[92] Ideally, metabolic inferences from microbiomic data are to be compared and reconciled with transcriptomic analyses.[92]

Functional study of the psoriatic microbiome has thus far yielded only limited or conflicting conclusions. For instance, application of PICRUSt to swabs of healthy and psoriatic skin found both samples to be enriched with bacteria capable of amino acid and carbohydrate metabolism, merely suggesting a general role for bacterial metabolism in host-microbe interaction.[93] In contrast, a recent fecal microbiota study using PICRUSt found an overrepresentation of pathways involving bacterial chemotaxis and carbohydrate transport.[94] As for the shotgun metagenomics study referenced above, HUMAnN was utilized to investigate microbial communities of the ear and elbow.[75] The ears of psoriatic individuals compared to those of controls showed a decreased prevalence of pathways involved in the metabolism of vitamins and cofactors—a result that aligns with transcriptomic pathway analyses suggesting a reduced role of lipid metabolism in psoriatic skin. At the elbow, however, biological functions between diseased and unaffected metagenomes were more uniform.

Conclusion

Omics generally concerns the collective characterization of biological disciplines ending in *-omics*. In addition to the fields of genetics, transcriptomics, and microbiomics reviewed above, omics includes epigenomics, proteomics, and metabolomics, among others, which have overall received less attention to date in psoriasis research. While these disciplines have traditionally operated in siloes, work in omics increasingly seeks to integrate data across disciplines to achieve high-level insights. Already, a pilot study in psoriasis has begun to combine approaches in genomics, transcriptomics, and proteomics to predict treatment response.[95] Indeed, the hope is that integration of multi-level omic data will overcome the limitations of individual biomarker analysis to effectively stratify patients for targeted therapy.[96] Coupled with advances in machine learning and an increase in cross-disciplinary collaboration, bioinformatics holds the potential to revolutionize our understanding and treatment of human disease.

References

1. Williamson JC, Scheipers P, Schwämmle V, Zilbert JR, Beck HC, Jensen ON. A proteomics approach to the identification of biomarkers for psoriasis utilising keratome biopsy. *J Proteomics*. 2013;94:176-85. doi:10.1016/j.jprot.2013.09.010.
2. Yan D, Afifi L, Jeon C, et al. The metabolomics of psoriatic disease. *Psoriasis* (Auckl). 2017;7:1-15. doi:10.2147/PTT.S118348.
3. Lebwohl M. Psoriasis. *Lancet*. 2003;361(9364):1197-1204. doi:10.1016/S0140-6736(03)12954-6.
4. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. *N Engl J Med*. 2017;376(10):957-970. doi:10.1056/NEJMra1505557.
5. Ott J, Wang J, Leal SM. Genetic linkage analysis in the age of whole-genome sequencing. *Nat Rev Genet*. 2015;16(5):275-284. doi:10.1038/nrg3908.
6. Strauch K, Fimmers R, Kurz T, Deichmann KA, Wienker TF, Baur MP. Parametric and nonparametric multipoint linkage analysis with imprinting and two-locus-trait models: application to mite sensitization. *Am J Hum Genet*. 2000;66(6):1945-1957. doi:10.1086/302911.
7. Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES. Parametric and nonparametric linkage analysis: a unified multipoint approach. *Am J Hum Genet*. 1996;58(6):1347-1363.
8. Bailey-Wilson JE, Wilson AF. Linkage analysis in the next-generation sequencing era. *Hum Hered*. 2011;72(4):228-236. doi:10.1159/000334381.
9. Fan X, Yang S, Huang W, et al. Fine mapping of the psoriasis susceptibility locus PSORS1 supports HLA-C as the susceptibility gene in the Han Chinese population. *PLoS Genet*. 2008;4(3):e1000038. doi:10.1371/journal.pgen.1000038.
10. Tomfohrde J, Silverman A, Barnes R, et al. Gene for familial psoriasis susceptibility mapped to the distal end of human chromosome 17q. *Science*. 1994;264(5162):114-1145.
11. Hwu WL, Yang CF, Fann CS, et al. Mapping of psoriasis to 17q terminus. *J Med Genet*. 2005;42(2):152-158. doi:10.1136/jmg.2004.018564.
12. Nair RP, Henseler T, Jenisch S, et al. Evidence for two psoriasis susceptibility loci (HLA and 17q) and two novel candidate regions (16q and 20p) by genome-wide scan. Hum Mol Genet. 1997;6(8):1349-1356.
13. Spain SL, Barrett JC. Strategies for fine-mapping complex traits. Hum Mol Genet. 2015;24(R1):R111-R119. doi:10.1093/hmg/ddv260.
14. Tsoi LC, Stuart PE, Tian C, et al. Large scale meta-analysis characterizes genetic architecture for common psoriasis associated variants. *Nat Commun*. 2017;8:15382. doi:10.1038/ncomms15382.
15. Liu Y, Helms C, Liao W, et al. A genome-wide association study of psoriasis and psoriatic arthritis identifies new disease loci. *PLoS Genet*. 2008;4(3):e1000041. doi:10.1371/journal.pgen.1000041.
16. Julià A, Tortosa R, Hernanz JM, et al. Risk variants for psoriasis vulgaris in a large case-control collection and association with clinical subphenotypes. *Hum Mol Genet*. 2012;21(20):4549-4557. doi:10.1093/hmg/dds295.
17. Yin X, Low HQ, Wang L, et al. Genome-wide meta-analysis identifies multiple novel associations and ethnic heterogeneity of psoriasis susceptibility. *Nat Commun*. 2015;6:6916. doi:10.1038/ncomms7916.
18. Zhang X, Cupples LA, Liu CT. A fine-mapping study of central obesity loci incorporating functional annotation and imputation. *Eur J Hum Genet*. 2018;26(9):1369-1377. doi:10.1038/s41431-018-0168-5.
19. Marchini J, Howie B. Genotype imputation for genome-wide association studies. *Nat Rev Genet*. 2010;11(7):499-511. doi:10.1038/nrg2796.
20. Nair RP, Stuart PE, Nistor I, et al. Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. *Am J Hum Genet*. 2006;78(5):827-851. doi:10.1086/503821.
21. Knight J, Spain SL, Capon F, et al. Conditional analysis identifies three novel major histocompatibility complex loci associated with psoriasis. *Hum Mol Genet*. 2012;21(23):5185-5192. doi:10.1093/hmg/dds344.
22. Feng BJ, Sun LD, Soltani-Arabshahi R, et al. Multiple loci within the major histocompatibility complex confer risk of psoriasis. *PLoS Genet*. 2009;5(8):e1000606. doi:10.1371/journal.pgen.1000606.
23. Das S, Stuart PE, Ding J, et al. Fine mapping of eight psoriasis susceptibility loci. *Eur J Hum Genet*. 2015;23(6):844-853. doi:10.1038/ejhg.2014.172.
24. Jordan CT, Cao L, Roberson ED, et al. PSORS2 is due to mutations in CARD14. *Am J Hum Genet*. 2012;90(5):784-795. doi:10.1016/j.ajhg.2012.03.012.
25. Jordan CT, Cao L, Roberson ED, et al. Rare and common variants in CARD14, encoding an epidermal regulator of NF-kappaB, in psoriasis. *Am J Hum Genet*. 2012;90(5):796-808. doi:10.1016/j.ajhg.2012.03.013.
26. Farooq M, Nakai H, Fujimoto A, et al. Mutation analysis of the IL36RN gene in 14 Japanese patients with generalized pustular psoriasis. *Hum Mutat*. 2013;34(1):176-183. doi:10.1002/humu.22203.
27. Marrakchi S, Guigue P, Renshaw BR, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N Engl J Med*. 2011;365(7):620-628. doi:10.1056/NEJMoa1013068.
28. Onoufriadis A, Simpson MA, Pink AE, et al. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. *Am J Hum Genet*. 2011;89(3):432-437. doi:10.1016/j.ajhg.2011.07.022.

29. Blumberg H, Dinh H, Dean C Jr, et al. IL-1RL2 and its ligands contribute to the cytokine network in psoriasis. *J Immunol*. 2010;185(7):4354-4362. doi:10.4049/jimmunol.1000313.
30. Manzoni C, Kia DA, Vandrovcova J, et al. Genome, transcriptome and proteome: The rise of omics data and their integration in biomedical sciences. *Brief Bioinform*. 2018;19(2):286-302. doi:10.1093/bib/bbw114.
31. Swindell WR, Xing X, Voorhees JJ, Elder JT, Johnston A, Gudjonsson JE. Integrative RNA-seq and microarray data analysis reveals GC content and gene length biases in the psoriasis transcriptome. *Physiol Genomics*. 2014;46(15):533-546. doi:10.1152/physiolgenomics.00022.2014.
32. Chavan SS, Bauer MA, Peterson EA, Heuck CJ, Johann DJ Jr. Towards the integration, annotation and association of historical microarray experiments with RNA-seq. *BMC Bioinformatics*. 2013;14(Suppl 14):S4. doi:10.1186/1471-2105-14-S14-S4.
33. Chow M, Lai K, Ahn R, Gupta R, Arron S, Liao W. Effect of adalimumab on gene expression profiles of psoriatic skin and blood. *J Drugs Dermatol*. 2016;15(8):988-994.
34. Dolcino M, Pelosi A, Fiore PF, et al. Long non-coding RNAs play a role in the pathogenesis of psoriatic arthritis by regulating MicroRNAs and genes involved in inflammation and metabolic syndrome. *Front Immunol*. 2018;9:1533. doi:10.3389/fimmu.2018.01533.
35. 't Hoen PA, Ariyurek Y, Thygesen HH, et al. Deep sequencing-based expression analysis shows major advances in robustness, resolution and inter-lab portability over five microarray platforms. *Nucleic Acids Res*. 2008;36(21):e141. doi:10.1093/nar/gkn705.
36. Li B, Tsoi LC, Swindell WR, et al. Transcriptome analysis of psoriasis in a large case-control sample: RNA-seq provides insights into disease mechanisms. *J Invest Dermatol*. 2014;134(7):1828-1838. doi:10.1038/jid.2014.28.
37. Jabbari A, Suárez-Fariñas M, Dewell S, Krueger JG. Transcriptional profiling of psoriasis using RNA-seq reveals previously unidentified differentially expressed genes. *J Invest Dermatol*. 2012;132(1):246-249. doi:10.1038/jid.2011.267.
38. Joyce CE, Zhou X, Xia J, et al. Deep sequencing of small RNAs from human skin reveals major alterations in the psoriasis miRNAome. *Hum Mol Genet*. 2011;20(20):4025-4040. doi:10.1093/hmg/ddr331.
39. Gupta R, Ahn R, Lai K, et al. Landscape of long noncoding RNAs in psoriatic and healthy skin. *J Invest Dermatol*. 2016;136(3):603-609. doi:10.1016/j.jid.2015.12.009.
40. Saliba A, Westermann AJ, Gorski SA, Vogel J. Single-cell RNA-seq: Advances and future challenges. *Nucleic Acids Res*. 2014;42(14):8845-8860. doi:10.1093/nar/gku555.
41. Ahn RS, Taravati K, Lai K, et al. Transcriptional landscape of epithelial and immune cell populations revealed through FACS-seq of healthy human skin. *Sci Rep*. 2017;7(1):1343. doi:10.1038/s41598-017-01468-y.
42. Tang F, Barbacioru C, Wang Y, et al. mRNA-seq whole-transcriptome analysis of a single cell. *Nat Methods*. 2009;6(5):377-382. doi:10.1038/nmeth.1315.
43. Stegle O, Teichmann SA, Marioni JC. Computational and analytical challenges in single-cell transcriptomics. *Nat Rev Genet*. 2015;16(3):133-145. doi:10.1038/nrg3833.
44. Costa-Silva J, Domingues D, Lopes FM. RNA-seq differential expression analysis: An extended review and a software tool. *PLoS One*. 2017;12(12):e0190152. doi:10.1371/journal.pone.0190152.
45. Oestreicher JL, Walters IB, Kikuchi T, et al. Molecular classification of psoriasis disease-associated genes through pharmacogenomic expression profiling. *Pharmacogenomics J*. 2001;1(4):272-287.
46. Zhou X, Krueger JG, Kao MC, et al. Novel mechanisms of T-cell and dendritic cell activation revealed by profiling of psoriasis on the 63,100-element oligonucleotide array. *Physiol Genomics*. 2003;13(1):69-78. doi:10.1152/physiolgenomics.00157.2002.
47. Gudjonsson JE, Ding J, Li X, et al. Global gene expression analysis reveals evidence for decreased lipid biosynthesis and increased innate immunity in uninvolved psoriatic skin. *J Invest Dermatol*. 2009;129(12):2795-2804. doi:10.1038/jid.2009.173.
48. Ahn R, Yan D, Chang HW, et al. RNA-seq and flow-cytometry of conventional, scalp, and palmoplantar psoriasis reveal shared and distinct molecular pathways. *Sci Rep*. 2018;8(1):11368. doi:10.1038/s41598-018-29472-w.
49. Bowcock AM, Shannon W, Du F, et al. Insights into psoriasis and other inflammatory diseases from large-scale gene expression studies. *Hum Mol Genet*. 2001;10(17):1793-1805.
50. Nomura I, Gao B, Boguniewicz M, Darst MA, Travers JB, Leung DY. Distinct patterns of gene expression in the skin lesions of atopic dermatitis and psoriasis: A gene microarray analysis. *J Allergy Clin Immunol*. 2003;112(6):1195-1202. doi:10.1016/j.jaci.2003.08.049.
51. Haider AS, Peters SB, Kaporis H, et al. Genomic analysis defines a cancer-specific gene expression signature for human squamous cell carcinoma and distinguishes malignant hyperproliferation from benign hyperplasia. *J Invest Dermatol*. 2006;126(4):869-881. doi:10.1038/sj.jid.5700157.
52. Dolcino M, Ottria A, Barbieri A, et al. Gene expression profiling in peripheral blood cells and synovial membranes of patients with psoriatic arthritis. *PLoS One*. 2015;10(6):e0128262. doi:10.1371/journal.pone.0128262.
53. Li J, Zhou D, Qiu W, et al. Application of weighted gene co-expression network analysis for data from paired design. *Sci Rep*. 2018;8(1):622. doi:10.1038/s41598-017-18705-z.
54. Ahn R, Gupta R, Lai K, Chopra N, Arron ST, Liao W. Network analysis of psoriasis reveals biological pathways and roles for coding and long non-coding RNAs. *BMC Genomics*. 2016;17(1):841. doi:10.1186/s12864-016-3188-y.
55. Horvath S, Zhang B, Carlson M, et al. Analysis of oncogenic signaling networks in glioblastoma identifies ASPM as a molecular target. *Proc Natl Acad Sci USA*. 2006;103(46):17402-17407. doi:0608396103.
56. Turnbaugh PJ, Gordon JI. The core gut microbiome, energy balance and obesity. *J Physiol*. 2009;587(Pt 17):4153-4158. doi:10.1113/jphysiol.2009.174136.
57. Knights D, Lassen KG, Xavier RJ. Advances in inflammatory bowel disease pathogenesis: Linking host genetics and the microbiome. *Gut*. 2013;62(10):1505-1510. doi:10.1136/gutjnl-2012-303954.
58. Amar J, Lange C, Payros G, et al. Blood microbiota dysbiosis is associated with the onset of cardiovascular events in a large general population: The D.E.S.I.R. study. *PLoS One*. 2013;8(1):e54461. doi:10.1371/journal.pone.0054461.
59. Ahluwalia V, Betrapally NS, Hylemon PB, et al. Impaired gut-liver-brain axis in patients with cirrhosis. *Sci Rep*. 2016;6:26800. doi:10.1038/srep26800.
60. Kang DW, Park JG, Ilhan ZE, et al. Reduced incidence of Prevotella and other fermenters in intestinal microflora of autistic children. *PLoS One*. 2013;8(7):e68322. doi:10.1371/journal.pone.0068322.
61. Norrlind R. Psoriasis following infections with hemolytic streptococci. *Acta Derm Venereol*. 1950;30(1):64-72.
62. Telfer NR, Chalmers RJ, Whale K, Colman G. The role of streptococcal infection in the initiation of guttate psoriasis. *Arch Dermatol*. 1992;128(1):39-42.
63. Gudjonsson JE, Thorarinsson AM, Sigurgeirsson B, Kristinsson KG, Valdimarsson H. Streptococcal throat infections and exacerbation of chronic plaque psoriasis: A prospective study. *Br J Dermatol*. 2003;149(3):530-534. doi:10.1046/j.1365-2133.2003.05552.x.
64. Lober CW, Belew PW, Rosenberg EW, Bale G. Patch tests with killed sonicated microflora in patients with psoriasis. *Arch Dermatol*. 1982;118(5):322-325.
65. Gomez-Moyano E, Crespo-Erchiga V, Martinez-Pilar L, et al. Do Malassezia species play a role in exacerbation of scalp psoriasis? *J Mycol Med*. 2014;24(2):87-92. doi:10.1016/j.mycmed.2013.10.007.
66. Zákostelska Z, Málkova J, Klimešová K, et al. Intestinal microbiota promotes psoriasis-like skin inflammation by enhancing Th17 response. *PLoS One*. 2016;11(7):e0159539. doi:10.1371/journal.pone.0159539.
67. Eppinga H, Konstantinov S, Peppelenbosch M, Thio H. The microbiome and psoriatic arthritis. *Curr Rheumatol Rep*. 2014;16(3):407. doi:10.1007/s11926-013-0407-2.
68. Grice EA, Segre JA. The skin microbiome. *Nat Rev Microbiol*. 2011;9(4):244-253. doi:10.1038/nrmicro2537.
69. Munz OH, Sela S, Baker BS, Griffiths CE, Powles AV, Fry L. Evidence for the presence of bacteria in the blood of psoriasis patients. *Arch Dermatol Res*. 2010;302(7):495-498. doi:10.1007/s00403-010-1065-0.
70. Jovel J, Patterson J, Wang W, et al. Characterization of the gut microbiome using 16S or shotgun metagenomics. *Front Microbiol*. 2016;7:459. doi:10.3389/fmicb.2016.00459.
71. Yang B, Wang Y, Qian PY. Sensitivity and correlation of hypervariable regions in 16S rRNA genes in phylogenetic analysis. *BMC Bioinformatics*. 2016;17:135. doi:10.1186/s12859-016-0992-y.
72. Yan D, Issa N, Afifi L, Jeon C, Chang HW, Liao W. The role of the skin and gut microbiome in psoriatic disease. *Curr Dermatol Rep*. 2017;6(2):94-103. doi:10.1007/s13671-017-0178-5.
73. Statnikov A, Alekseyenko AV, Li Z, et al. Microbiomic signatures of psoriasis: Feasibility and methodology comparison. *Sci Rep*. 2013;3(1):2620. doi:10.1038/srep02620.
74. Paulino LC, Tseng CH, Strober BE, Blaser MJ. Molecular analysis of fungal microbiota in samples from healthy human skin and psoriatic lesions. *J Clin Microbiol*. 2006;44(8):2933-2941. doi:10.1128/JCM.00785-06.
75. Tett A, Pasolli E, Farina S, et al. Unexplored diversity and strain-level structure of the skin microbiome associated with psoriasis. *NPJ Biofilms Microbiomes*. 2017;3:14. doi:10.1038/s41522-017-0022-5.
76. Chen K, Pachter L. Bioinformatics for whole-genome shotgun sequencing of microbial communities. *PLoS Comput Biol*. 2005;1(2):106-112. doi:10.1371/journal.pcbi.0010024.

77. Meisel JS, Hannigan GD, Tyldsley AS, et al. Skin microbiome surveys are strongly influenced by experimental design. *J Invest Dermatol*. 2016;136(5):947-956. doi:10.1016/j.jid.2016.01.016.
78. Kuczynski J, Lauber CL, Walters WA, et al. Experimental and analytical tools for studying the human microbiome. *Nat Rev Genet*. 2011;13(1):47-58. doi:10.1038/nrg3129.
79. Goodrich JK, Di Rienzi SC, Poole AC, et al. Conducting a microbiome study. *Cell*. 2014;158(2):250-262. doi:10.1016/j.cell.2014.06.037.
80. Segata N, Waldron L, Ballarini A, Narasimhan V, Jousson O, Huttenhower C. Metagenomic microbial community profiling using unique clade-specific marker genes. *Nat Methods*. 2012;9(8):811-814. doi:10.1038/nmeth.2066.
81. Codoñer FM, Ramírez-Bosca A, Climent E, et al. Gut microbial composition in patients with psoriasis. *Sci Rep*. 2018;8(1):3812. doi:10.1038/s41598-018-22125-y.
82. Chang HW, Yan D, Singh R, et al. Alteration of the cutaneous microbiome in psoriasis and potential role in Th17 polarization. *Microbiome*. 2018;6(1):154. doi:10.1186/s40168-018-0533-1.
83. Scher JU, Ubeda C, Artacho A, et al. Decreased bacterial diversity characterizes the altered gut microbiota in patients with psoriatic arthritis, resembling dysbiosis in inflammatory bowel disease. *Arthritis Rheumatol*. 2015;67(1):128-139. doi:10.1002/art.38892.
84. Lozupone CA, Knight R. Species divergence and the measurement of microbial diversity. *FEMS Microbiol Rev*. 2008;32(4):557-578. doi:10.1111/j.1574-6976.2008.00111.x.
85. Shannon CE. A mathematical theory of communication. *Bell System Technical Journal*. 1948;27(3):379-423. doi:10.1002/j.1538-7305.1948.tb01338.x.
86. Gao Z, Tseng CH, Strober BE, Pei Z, Blaser MJ. Substantial alterations of the cutaneous bacterial biota in psoriatic lesions. *PLoS One*. 2008;3(7):e2719. doi:10.1371/journal.pone.0002719.
87. Alekseyenko AV, Perez-Perez GI, De Souza A, et al. Community differentiation of the cutaneous microbiota in psoriasis. *Microbiome*. 2013;1(1):31. doi:10.1186/2049-2618-1-31.
88. Lozupone C, Hamady M, Knight R. UniFrac--an online tool for comparing microbial community diversity in a phylogenetic context. *BMC bioinformatics*. 2006;7(1):371. doi:10.1186/1471-2105-7-371.
89. Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. *Proc Natl Acad Sci USA*. 2005;102(31):11070-11075. doi:10.1073/pnas.0504978102.
90. Navas-Molina JA, Peralta-Sánchez JM, González A, et al. Advancing our understanding of the human microbiome using QIIME. *Methods Enzymol*. 2013;531:371-444. doi:10.1016/B978-0-12-407863-5.00019-8.
91. Fahlén A, Engstrand L, Baker BS, Powles A, Fry L. Comparison of bacterial microbiota in skin biopsies from normal and psoriatic skin. *Arch Dermatol Res*. 2012;304(1):15-22. doi:10.1007/s00403-011-1189-x.
92. Mitra S, Rupek P, Richter DC, et al. Functional analysis of metagenomes and metatranscriptomes using SEED and KEGG. *BMC Bioinformatics*. 2011;12 Suppl 1:S21. doi:10.1186/1471-2105-12-S1-S21.
93. Yan D, Chang HW, Singh R, et al. 2296: Functional analysis of the cutaneous microbiome in psoriatic disease. *J Clin Transl Sci*. 2017;1 (suppl 1):15. doi:10.1017/cts.2017.68.
94. Chen YJ, Ho HJ, Tseng CH, Lai ZL, Shieh JJ, Wu CY. Intestinal microbiota profiling and predicted metabolic dysregulation in psoriasis patients. *Exp Dermatol*. 2018;27(12):1336-1343. doi:10.1111/exd.13786
95. Foulkes AC, Watson DS, Carr DF, et al. A framework for multi-omic prediction of treatment response to biologic therapy for psoriasis. *J Invest Dermatol*. 2019;139(1):100-107. doi:10.1016/j.jid.2018.04.041.
96. Johnston A, Sarkar MK, Vrana A, Tsoi LC, Gudjonsson JE. The molecular revolution in cutaneous biology: The era of global transcriptional analysis. *J Invest Dermatol*. 2017;137(5):e87-e91. doi:10.1016/j.jid.2016.02.817.