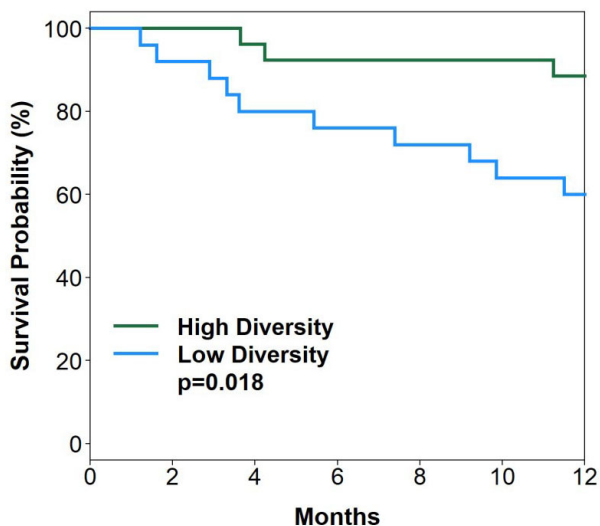


Figure 2. One-year overall survival of patients with high (>2.77) versus low (<2.77) diversity defined by median Shannon-Index.

Conclusion. We have shown a significant correlation between engraftment microbiome diversity and 1-year OS. Early antibiotic exposure was detrimental to microbiome diversity. Approaches to preserve microbiome diversity and prevent BSI are likely to improve HCT outcomes. Our ongoing trial using rifaximin will provide preliminary data regarding this approach.



Number at Risk		Months						
		0	2	4	6	8	10	12
High	26	26	25	24	24	24	24	23
Low	25	23	20	19	18	16	15	

Disclosures. All Authors: No reported disclosures

42. Common Population Variants Cause Susceptibility to Disseminated Coccidioidomycosis

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Session: O-9. Basic and Translational Science

Background. *Coccidioides* are endemic, dimorphic fungi found in soils of southwestern United States, Mexico and Central America. Infection occurs via inhalation of arthroconidia which swell, differentiate into spherules and rupture releasing endospores. While the majority of infected individuals will never report illness, roughly 1/3 seek medical attention for fungal pneumonia and ~1% of those present with disseminated coccidioidomycosis (DCM). IL12-IFN γ pathway mutations have

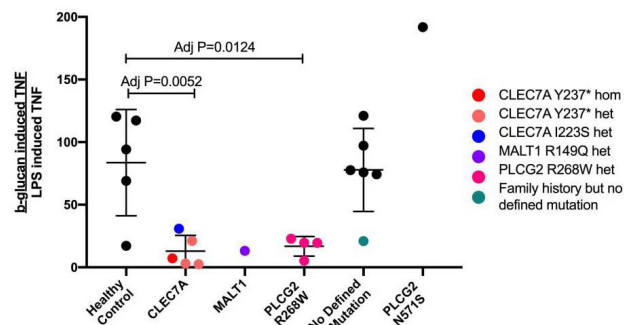
been reported in DCM but are exceedingly rare and cannot account for the ~500–600 cases of DCM/year.

Methods. We performed whole exome sequencing on 66 individuals with DCM, retaining variants predicted damaging (CADD >15) with a population frequency < 10%.

Results. Homozygous *CLEC7A* c.714T >G; p.Y238* causing a truncated Dectin-1 receptor was overrepresented (OR=9.8449, 95% CI 3.0841 to 31.4260, P=0.0001). Dectin-1 signaling pathway variants included 3 homozygous and 11 heterozygous *CLEC7A* p.Y238* individuals, one each *CLEC7A* p.I223S and *MALT1* p.R149Q and five *PLCG2* p.R268W. Since Dectin-1 is the receptor for β -glucan, a major *Coccidioides* cell-wall component, we hypothesized that Dectin-1 pathway variants could affect fungal recognition and cellular response. Healthy control PBMCs stimulated with purified β -glucan or heat-killed *Candida albicans* induced 6-fold more TNF α than patients with homozygous or heterozygous *CLEC7A*, *PLCG2* or *MALT1* variants (P=0.0022, Ordinary one-way ANOVA). Additionally, one patient with a family history of DCM but lacking a defined mutation also failed to up-regulate TNF α after stimulation.

Normalized TNF production from healthy control and DCM patient's peripheral blood mononuclear cells

Conclusion.



These data are consonant with increased dissemination in *Clec7a*^{-/-} mice as well as in patients receiving anti-TNF biologics. These gene variants accounted for 31% of our DCM cohort (21/66 patients). This is the first demonstration of variants outside the IL12-IFN γ pathway impairing fungal recognition and cellular response in coccidioidomycosis. Common heterozygous variants may be sufficient for disease susceptibility to highly pathogenic organisms.

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43. The Capsule and Beyond: Genetic Determinants of Pediatric streptococcus Pneumoniae empyema

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Session: O-9. Basic and Translational Science

Background. *Streptococcus pneumoniae* is the most common cause of pneumonia in children, including empyema, a severe complication with increasing incidence in the post-pneumococcal vaccine era. Only a subset of > 90 serotypes cause empyema. Virulence determinants of empyema remain largely unknown.

Methods. We performed Illumina sequencing of invasive Pneumococcal isolates from pediatric patients at Primary Children's Hospital (Salt Lake City, UT) isolated between 1996–2018, *de novo* genome assembly (SPADES), annotation (PROKKA), serotyping (Quelling and SeroBA), and pan-genome assembly (ROARY). SCOARY and pyseer were used for microbial GWAS. Maximum likelihood phylogeny was calculated using RAxML/Gubbins.

Results. 366 pneumococcal isolates were analyzed from 39 serotypes and multiple phenotypes including pneumonia (n=76), empyema (n=63), CNS infection (n=54), and isolated bacteremia (n=79). Serotypes and empyema phenotype clustered roughly by phylogeny. Most analyzed empyema isolates after 2010 were serotype 3 (19/25); prior to PCV-13 introduction serotypes 1 (8/38), 7F (7/38), and 19A (11/38) were more highly represented. Genes implicated in capsule synthesis, transposases, and metabolism were statistically correlated with the empyema phenotype.

Conclusion. Specific capsular or metabolic genes may confer optimal fitness for pleural disease. Further characterization of these genetic associations is needed and will inform future treatment and prevention.

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44. In-host Infection Dynamics Of Pseudomonas Aeruginosa Pneumonia

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