Results. A total of 80 patients were included. 45 patients (56%) were immunocompromised, and 14 (18%) had prothestic hardware or grafts. The most common clinical syndrome was pneumonia/respiratory failure (31%), followed by sepsis/septic shock (15%) and endocarditis (13%). 72% of patients received antibiotics prior to sending the Karius assay. The most common reason for sending the assay was pneumonia/respiratory failure (31%), followed by sepsis/septic shock (14%), and PJP (14); the most common co-pathogens were Aspergillus sp (49), followed by an Mucorales sp (17) and PJP (14). There were 17 samples with the detection of Aspergillus sp than 7 days prior to Karius testing (i.e., 61.8%, p=0.004) (Table 3).

2). A positive impact was observed in solid organ transplant recipients (SOTR, 71.4%, p=0.004) (Table 3). The most common reason for sending the Karius assay was unknown clinical syndrome was pneumonia/respiratory failure (31%), followed by sepsis/septic shock (14%) and PJP (14%).

Table 1: Patient Demographics and Characteristics of the Karius® Assay

| Total patients | No (%) |
|----------------|--------|
| Gender | Male | Female |
| Age (years), median (IQR) | 54.5 (35-59) | 54.5 (35-59) |
| Race | Black | White | Other |
| Type of Clinical Impact, (n=25) | 3 | 2 | 0 |
| Uncertain or No Impact | 9 (4) | 9 (4) | 0 |

Table 2: Patient Characteristics and Laboratory Data

| Comorbidity | n (%) | Unexplained or No Impact | Positive Impact |
|-------------|-------|--------------------------|-----------------|
| Diabetes    | 13 (61) | 5 (22) | 8 (36) |
| Cancer      | 20 (91) | 5 (22) | 15 (68) |
| Heart failure | 20 (91) | 5 (22) | 15 (68) |
| Four or more comorbidities | 20 (91) | 5 (22) | 15 (68) |

Conclusion. In our cohort, clinical utility of Karius testing was highest in SOTR and in patients with sepsis. Prolonged antimicrobial use (> 7 days) prior to Karius testing limited the utility of the assay. Prospective studies evaluating the utility of mNGS mcDNA assays should be performed to further clarify its role in clinical management.

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662. Using Machine Learning to Aid in the Diagnosis of Multisystem Inflammatory Syndrome in Children

Maulin Sonje1, MD; John Tan, PhD; Emily Wong, MD; Loma Linda University, Loma Linda, California

Session: P-30: Diagnostics: Typing/sequencing

Background. Multisystem inflammatory syndrome in children (MIS-C) is a newly recognized inflammatory syndrome that occurs post Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) infection. It affects multiple organ systems - particularly cardiac, gastrointestinal, dermatologic and neurologic. Clinicians may have difficulty diagnosing MIS-C due to its novelty and similarity to Kawasaki disease. Our goal was to use machine learning to predict whether children would have MIS-C based on symptoms and laboratory values.

Methods. A retrospective review was conducted of patients admitted to Loma Linda University Children's Hospital who were suspected of having MIS-C. Demographic, symptom (such as fever, abdominal pain, diarrhea, shock, etc), and laboratory data were collected from the electronic medical record. The model was trained on 115 patients and 20 laboratory variables, there was a total of 130 missing values (5.7%). Missing laboratory values were imputed using the median value based on the presence or absence of MIS-C. The data were split into a training (93 patients, 80%) and test (22 patients, 20%) set. The training set was used to train a random forest model and the testing set was used to evaluate model performance. R 4.0.2 was used for modeling with the following packages: tidymodels and randomForest.

Results. There were 115 patients of which 49 were females, and 77 were diagnosed with MIS-C. The median age of the patients with MIS-C was 115 months and 79 months for those without MIS-C. In the testing set, all 15 patients with MIS-C were classified correctly but of the 7 without MIS-C, the model predicted 4 of the patients correctly. This gives a sensitivity of 100% and specificity of 57%. When changing the seed and testing set, the sensitivity remained 100% but the specificity improved to 86%. The random forest algorithm showed that the most important features were pro-calcitonin, ferritin, pro-BNP, and CRP.

Conclusion. During the height of the SARS-CoV-2 pandemic, many children were being admitted with suspected MIS-C, but clinicians struggled to confirm the diagnosis. We have found a model predicting which of these patients had MIS-C with high sensitivity. This model is a first step of many toward creating the foundation of personalized medicine for children.

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663. Two (Plus) Birds, One Stone: The Rapid, Comprehensive, Non-invasive Detection of Co-Pathogens of Critical Importance Using A Plasma-based Microbial Cell-free DNA Next-generation Sequencing Test

Matthew Smollin, PharmD1; Martin S. Lindner, PhD2; Nicholas R. Degner, MD, MPH1, MS2; Ricardo Castillo-Galvan, MD MPH1; Jose Alexander, MD, D(ABMM), FCCM, CIC, SM, MB(ASCP), BCMAS1; Christiana R. de Vries, MD, PhD1; Ann Macintyre, DO1; Bradley Perkins, MD1; Aism A. Ahmed, MD1; Aparna Arun, MD1; 1Karius, Inc., Atlanta, Georgia; 2Karius Inc., San Francisco, California; 3Karius, Redwood City, California; 4Karius, Inc, Redwood City, CA

Session: P-30: Diagnostics: Typing/sequencing

Background. Immunocompromised (IC) patients are at risk for infections by a spectrum of invasive pathogens. The overlap in presentation makes it challenging to differentiate among infectious etiologies and critical co-infections (CI) may remain undiagnosed. Open-ended, comprehensive assessment of infection through microbial cell-free DNA (mcDNA) next-generation sequencing (NGS) of plasma offers the potential for the rapid identification of multiple co-infecting pathogens of critical importance (CI-POCI) with one test.

Methods. Karius Test1 (KT) results from patients who underwent clinical testing from December 2016 to April 2021 were reviewed for detections of two or more CI-POCI including parasitic, fungi (Pneumocystis jiroveci, Trichosporon sp, endemic mycoses, Aspergillus sp., Mucorales, Non-Aspergillus/Non-Mucorales molds), mycobacteria, Legionella sp., Nocardia sp. and Listeria. KT, developed and validated in Karius' CLIA certified/CAP accredited lab, detects mcDNA from plasma. McDNA is extracted, NGS performed, human sequences removed and remaining sequences aligned to a curated pathogen database of > 1500 organisms. Organisms present above a statistical threshold are reported and quantified. For > 85% of tests the time to result reporting is the next day from sample receipt.

Results. KT detected CI of two or more POCI in 59 samples (75% adults, 25% children). The most common partnering co-pathogens of critical importance were Aspergillus sp (38), Mucorales (17) and PIP (14); the most common combinations were two or more distinct Aspergillus sp (14) followed by an Aspergillus sp and a Mucorales (12). There were 17 samples with the detection of three or more CI-POCI (29%).

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Abstracts • OFID 2021:8 (Suppl 1) • 5433
The outer circle sections represent Karius Test detections belonging to different taxonomic groups. The length of each circle section is proportional to the total number of detections of a taxon belonging to that group. The chords connecting a pair of circle sections are proportional to the number of times two taxa from those groups were observed together, weighted by the total number of taxa detected.

**Conclusion.** Plasma cell-free mNGS offers a rapid, comprehensive non-invasive means of detecting CI-POCI in IC patients with one test. Although rare, co-infections with POCI can greatly increase mortality. The KT can provide important insights into pathogen-pathogen interactions in complex hosts and help optimize therapy.

**Disclosures.** Matthew Smollin, PharmD, Karius, Inc. (Employee) Martin S. Lindner, PhD, Karius, Inc. (Consultant) Nicholas R. Degner, MD, MPH, MS, Karius Inc. (Employee, Shareholder) Ricardo Castillo-Galvan, MD MPH, Karius Inc. (Consultant) Jose Alexander, MD, D(ABMM), FCCM, CIC, SM, MB(AACPM), BCMAS, Karius (Employee) Ann Macintyre, DO, Karius, Inc. (Employee) Bradley Perkins, MD, Karius, Inc. (Employee) Asim A. Ahmed, MD, Karius, Inc. (Employee) Aparna Arum, MD, Karius, Inc. (Employee)

**Clinical Impact of mNGS Testing**

| Characteristic | Total (n=25) | mNGS testing ordered after completion of routine microbiological testing, n (%) |
|---------------|-------------|--------------------------------------------------------------------------------|
| Age (years (median and range)) | 51 (28-76) | 11 (44) |
| Male, n (%) | 14 (58) | 7 (28) |
| Underlying condition | | |
| Hematopoietic cell transplant, n (%) | 5 (20) | 3 (12) |
| Acute malignancy, n (%) | 6 (24) | 3 (12) |
| Primary immunodeficiency, n (%) | 2 (8) | 2 (8) |
| Rheumatologic disease, n (%) | 0 | 0 |
| Other immunocompromised state, n (%) | 1 (4) | 1 (4) |
| Congestive heart disease, n (%) | 4 (16) | 3 (12) |
| None | 1 (4) | 1 (4) |
| Admitted to ICU at time of testing, n (%) | | |
| mNGS testing ordered after completion of routine microbiological testing, n (%) | 17 (71) | 9 (36) |
| Computed Test | 2 (8) | 2 (8) |
| Positive Test Results | 15 (60) | 12 (48) |
| Patient ultimately died, n (%) | 1 (4) | 1 (4) |

**Table 1. Clinical characteristics of patients who underwent mNGS testing and test results**

**Conclusion.** In this study, the majority of plasma cell-free mNGS tests had no impact on clinical care. mNGS testing did positively impact care in 2 patients, but did not have a negative impact on care in 2 instances, leading to further testing and unnecessary treatment. Further investigation is needed to determine the ideal population or clinical condition for testing and the ideal time of sending plasma cell-free mNGS tests.

**Disclosures.** All Authors: No reported disclosures

665. Clinical and Financial Impact of Next Generation Sequencing (NGS) in addition to Conventional Microbiology Testing in our Urban Referral Health Center

**Session:** P-30. Diagnostics: Typing/sequencing

**Background.** Metagenomic next-generation sequencing (mNGS) of plasma cell-free DNA has significant potential to improve infectious diseases diagnostics through unbiased detection of pathogens. However, the optimal patient population or clinical condition for this testing has not been determined.

**Methods.** We performed a retrospective review of all orders for plasma cell-free DNA mNGS using the Karius test (Karius, Redwood City, CA) from The Children's Hospital of Philadelphia from 7/1/19-3/30/21. Chart review was determined if the test had a positive, negative, or no clinical impact.

**Results.** 25 mNGS tests were ordered on 24 unique patients. The majority of tests were ordered on immunocompromised patients (Table 1). Most mNGS tests were ordered after completion of routine microbiological testing (17/25, 71%). Three tests were not completed as ordered. Most completed tests (18/22, 82%) had no impact on clinical care as they confirmed the known diagnosis or were not acted upon (Figure 1). mNGS testing had a positive impact in 2 cases. For one patient with congenital heart disease presented with persistent fever and concern for endocarditis despite negative infectious workup, a negative mNGS result allowed for continued monitoring without therapy. Another patient with a lymphomas disorder had mNGS performed due to persistent clinical instability; testing was positive for Candida parapsilosis, allowing for early initiation of antifungal therapy. However, test results had a negative clinical impact in 2 other patients. In a patient with congenital heart disease and fever, identification of two organisms led to prolonged antibiotic therapy for endocarditis without resolution of symptoms. In a patient with leukemia, report of a dematiaceous mold led to further diagnostic testing, including a lumbar puncture, as well as treatment with antifungal therapy despite no clear diagnosis.

**Table 1. Clinical characteristics of patients who underwent mNGS testing and test results**

| Characteristic | Total (n=25) | mNGS testing ordered after completion of routine microbiological testing, n (%) |
|---------------|-------------|--------------------------------------------------------------------------------|
| Age (years (median and range)) | 51 (28-76) | 11 (44) |
| Male, n (%) | 14 (58) | 7 (28) |
| Underlying condition | | |
| Hematopoietic cell transplant, n (%) | 5 (20) | 3 (12) |
| Acute malignancy, n (%) | 6 (24) | 3 (12) |
| Primary immunodeficiency, n (%) | 2 (8) | 2 (8) |
| Rheumatologic disease, n (%) | 0 | 0 |
| Other immunocompromised state, n (%) | 1 (4) | 1 (4) |
| Congestive heart disease, n (%) | 4 (16) | 3 (12) |
| None | 1 (4) | 1 (4) |
| Admitted to ICU at time of testing, n (%) | | |
| mNGS testing ordered after completion of routine microbiological testing, n (%) | 17 (71) | 9 (36) |
| Computed Test | 2 (8) | 2 (8) |
| Positive Test Results | 15 (60) | 12 (48) |
| Patient ultimately died, n (%) | 1 (4) | 1 (4) |

**Conclusion.** In this study, the majority of plasma cell-free mNGS tests had no impact on clinical care. mNGS testing did positively impact care in 2 patients, but did not have a negative impact on care in 2 instances, leading to further testing and unnecessary treatment. Further investigation is needed to determine the ideal population or clinical condition for testing and the ideal time of sending plasma cell-free mNGS tests.

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