PROPOSAL TITLE: Targeting Plasma Metagenomic Sequencing to Improve Patient Care and Reduce Waste
PROJECT LEAD(S): Natasha Spottiswoode, Monica Fung, Rama Yakubu
EXECUTIVE SPONSOR(S): Charles Chiu (UCSF Microbiology Director)

ABSTRACT. Plasma metagenomic sequencing (pmNGS) is an infectious disease diagnostic tool that detects microbial DNA from patient plasma[1]. Due to its unbiased nature, pmNGS can identify bacteria, fungi, parasites and DNA viruses, including those clinicians have not considered in their differential diagnosis or that are difficult to identify[2]. The diagnostic power of pmNGS can circumvent invasive, expensive diagnostic procedures[3] and potentially shorten patient stays. However, the per-syndrome utility of pmNGS is not well established, and its cost is high compared to other infectious disease diagnostics. Absent institutional or national guidelines for use, UCSF has seen skyrocketing volumes of pmNGS, with an increase from 18 tests in 2018 to 616 in 2024, with an estimated annual cost >$1 million. Here we propose a multipronged approach to define clinical indications for which pmNGS has highest impact, reduce unnecessary testing costs, analyze hospital days saved, avoid costs related to preventable procedures, and promote equity and excellence. We have created an Infectious Disease/Clinical Microbiology Consensus guidance statement to structure use of pmNGS testing (Appendices 1-2). We will update the APeX lab order for pmNGS to align with this guidance. Next, we will estimate pmNGS effects on patient antimicrobial management, length of stay, and need for procedures, stratified by clinical syndrome (Appendix 3). This approach will enable assessment of pmNGS utility, improve care, and reduce waste.

TEAM
Project Lead: Natasha Spottiswoode MD DPhil *(Assistant Professor of Infectious Disease)*
Project Lead: Monica Fung MD MPH (*Associate Professor of Infectious Disease, Clinical Director of Transplant/Immunocompromised ID, Director of ID Inpatient Services)*
Project Lead: Rama Yakubu MD PhD *(Co-Director, UCSF Microbiology)*
Antimicrobial Stewardship: William Simmons MD *(Assistant Professor of Infectious Disease, Director of Antimicrobial Stewardship)*
Scientific Guidance: Charles Langelier MD PhD *(Associate Professor of Infectious Diseases)*
Infectious Disease Fellow: Emily Lydon MD
Infectious Disease Fellow: Julieta Rodriguez MD
Infectious Disease Fellow: Nathan Radakovich MD
Clinical Research Coordinator: Hannah Teal
Executive Sponsor: Charles Chiu MD PhD (*Professor of Laboratory Medicine, Co-Director, UCSF Microbiology)*

PROBLEM: The use of pmNGS has dramatically increased at UCSF over the last few years. Yet, studies of its effectiveness in diagnosis are limited. Single-center retrospective analyses of pmNGS have been small (all <200 patients) and have had extremely disparate estimations of clinical utility, ranging from 7%[4], to 30.4%[5], to 46%[6]. This variability is explained at least in part by the fact that pmNGS is ordered on different patient populations and for different clinical syndromes. The few clinical indications which have been studied for pmNGS utility are lower respiratory infection (LRTI) in immunocompromised patients[7], febrile neutropenia (FN)[8,9] and sepsis[10]. Prospective, real-time assessment of pmNGS impact by clinical syndrome is needed to

understand clinical utility and promote appropriate use. UCSF is poised to lead the nation in this area. Much of the foundational mNGS basic research was performed by UCSF-affiliated scientists, leading to deep scientific and clinical expertise in our institution[11-13]. Moreover, UCSF is a marked outlier in use of pmNGS compared to peer institutions, which order this test far less frequently (West Coast Transplant Infectious Disease Society; 10/2/24). Lacking more robust data, it is unclear if practice patterns at UCSF represent an over-use of laboratory resources and significant extra cost outlay; or, conversely, we are under-using this test and creating an equity gap between patients who receive this test, and those who do not.

This is a logical moment to pursue by-syndrome clinical effectiveness analyses. Firstly, the UCSF health center usage, already higher than comparator institutions, is increasing markedly. 164 pmNGS tests were sent in 2022, 255 in 2023, and 614 in 2024 (Figure 1), leading to a total cost in 2024 estimated >$1 million at approximately $2,200/test (Figure 1; Appendix 3). 34 tests have been sent in just the first two weeks of 2025, a rate triple that of the equivalent period in 2024. This increase in use suggests increasing clinician awareness of this diagnostic technique, but likely also some percent of overuse. Finally, there is active consideration of implementing pmNGS for diagnosis in common critical illness syndromes, such as sepsis[10]. Assessing utility of current clinical use for pmNGS is essential before extending the scope of its use.

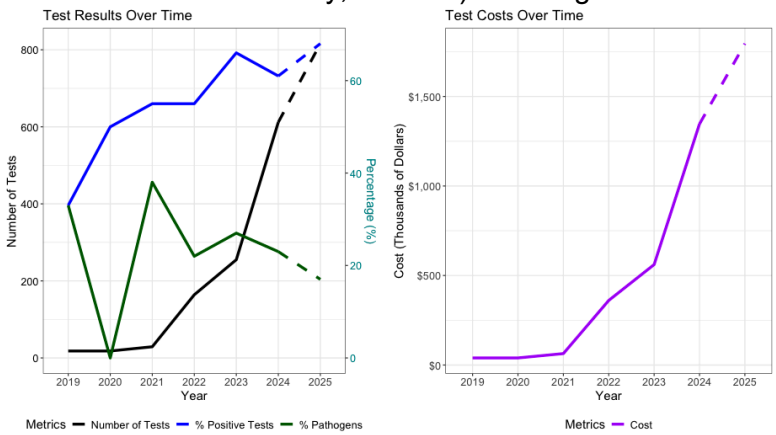

Figure 1. **pmNGS volume and cost at UCSF are increasing sharply**. Left panel: Volume of pmNGS tests sent at UCSF since the test introduction (black line), % of tests with at least one microbe detected (blue line) and % of tests with high-pathogenicity organisms detected (green). Right panel: estimated cost of pmNGS testing per year. 2025 is projected by # tests sent from 1/1/25-1/17/25 and 2024 per-test cost.

TARGET: The *overarching* goal of this proposal is (1) define the proportion of pmNGS tests that change length of stay and/or procedure need when sent for assessment of each of the syndromes in Appendix 1, and (2) leverage that information to standardize diagnostic use; promote early deployment of test in high-impact scenarios; and reduce use in the clinical scenarios expected to have lowest impact. We *specifically* aim to attenuate the rising rate of testing per year, by avoiding 10-15% of inappropriate tests from 2024 testing levels (5-6 tests per month). Secondly, we aim to ensure that all patients with a given syndrome receive the same guideline-directed care, rather than the current testing landscape in which test use is highly dependent on specific provider practices rather than policy. These efforts are *measurable* by means of clinician surveys coupled with retrospective review (Appendices 2-3). Given high test volume and faculty enthusiasm and engagement, especially from highest-utilizing groups, we expect our goals to be eminently *achievable.* This work is exceptionally *relevant* from a patient care and cost control perspective, given the dramatic yearly increase in pmNGS testing and associated direct costs, as well as the potential anticipated benefit to patient care and cost decrease if this test is deployed to its fullest promise (Appendix 4). This is a *timebound* project, with tracking of outcomes for 1 year, after which the pmNGS use guidelines and APeX order will be iterated to promote care, equity, and cost control. Finally, this project is *equitable* and *inclusive* in its goals, as it seeks to standardize care and ensure all patients are getting timely diagnostic care, while avoiding resource over-use.

GAPS:

Gap 1: Disconnect between stakeholders. The growing capacity for novel diagnostics such as pmNGS is outstripping the robust evaluation of how they should be deployed. Traditional research funds do not support quality improvement/stewardship projects, and personnel with clinical and scientific expertise are siloed from teams focusing on quality improvement and cost control.
Gap 2: Overuse. At UCSF, test volume has increased 20x from 2021 to 2024, with associated increased costs. The utility of this test is not established in different scenarios, with other centers estimating ~50-90% of tests do not change management[4-6]. Overuse is a gap.
Gap 3. No tracking of current use. At the moment, there is not robust assessment of what pmNGS is used for at UCSF. Therefore, we do not know which services and indications are driving the uptick in test volume and associated costs.
Gap 4: No coordinated guidance. Absent coordinated guidance on when to use this test, test use at UCSF is dependent on the diagnostic familiarity or particular prior experiences of an individual provider, leading to inequities and inconsistencies in which patients receive this test and at what points in their diagnostic journey.

INTERVENTIONS

- Alter the order format for pmNGS to integrate the indication options in the APeX order with the Infectious Disease/Clinical Microbiology Consensus Molecular Testing Guidance (Appendix 1) such that clinicians must indicate the guideline-concordant reason they are ordering this test.
- Leverage the daily Micro Reports of pmNGS and survey clinicians about patient outcomes (antimicrobial changes, days of stay changes, and procedures avoided or pursued) by clinical syndrome.
    - Publish internal quarterly reports summarizing results by syndrome and ordering service, and disseminate to key stakeholders.
- Promote effective test use by:
    - Iterating test order format in APeX to restrict to higher-yield clinical scenarios.
    - Establish and maintain a weekly clinical microbial sequencing board[12] to review pmNGS cases in real time between microbiologists and clinicians, and promote effective use by regular discussions with high-use clinical services.

PRACTICE SETTING AND TARGET POPULATION: This project will focus specifically on the inpatient use of pmNGS testing with a focus on the infectious disease and immunocompromised transplant services that guide either the use or interpretation of the majority of pmNGS tests at this time. However, we anticipate that lessons learned will be applicable to all clinicians using pmNGS within UCSF, and will also directly impact practices of other peer institutions.
BARRIERS: Key to this project is the iterative assessment of test utility by the ordering or recommending clinicians. This requires short-term follow up of results, which in the first year of this project will be labor-intensive. Thus, we have requested dedicated time for a clinical research coordinator (Hannah Teal) and for a supervising clinician (Dr. Spottiswoode).
ADVERSE EVENTS: pmNGS results have the potential to drastically improve patient care, but false negatives or false positives have the potential to cause harm by causing under- or over-treatment. The iterative nature of this project, in which indications for future years will be based on this funded year, will help to minimize these potential unwanted consequences. Moreover, the identification of low-yield clinical scenarios for which pmNGS should be avoided will not only help to reduce overall costs, but also reduce adverse events.

RETURN ON INVESTMENT (ROI) – We estimated the ROI of this proposed project as between **$172,074-245,385.** Appendix 4 contains all baseline costs and per-month estimations.

- **Estimated costs saved by avoiding testing in low-yield scenarios (est: $132,000-$158,400)** Other centers have estimated 54-94% pmNGS tests did not change management.

Conservatively, we extrapolated that 10-15% of UCSF tests in lowest-yield clinical scenarios could be avoided. Projected ROI for the next year is therefore based on costs from 10-15% of tests sent in 2024 (Figure 2, L panel, burgundy lines).

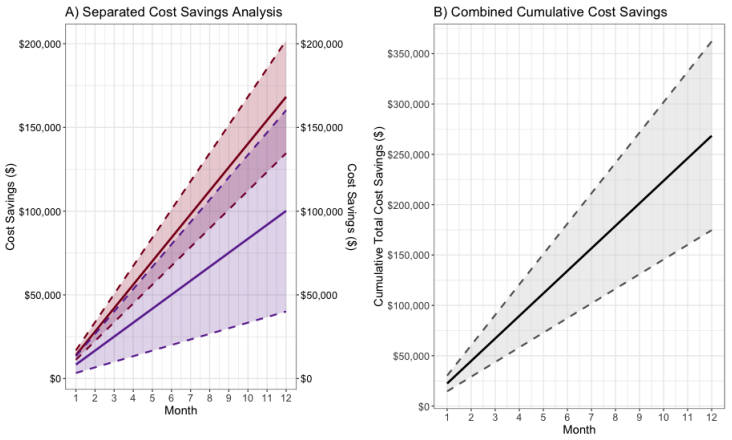

Figure 2. **Panel A** shows the estimated costs saved by reducing unnecessary testing (burgundy lines; solid is estimated saved costs while dotted lines are upper and lower bounds) and the costs saved by avoiding unneeded bronchoscopies (purple lines; dotted lines are upper and lower bounds). **Panel B** shows the estimated total cost saved over the next year, with upper and lower bounds shown in dotted lines.

- **Costs saved by avoiding invasive procedures (est: $40,074-$160,296).** Early studies have suggested that in hematological malignancy patients who underwent bronchoscopies for diagnosis of LRTI, 25% might have avoided bronchoscopy if pmNGS results were available[3]. At UCSF, experience supports bronchoscopies avoided if non-culturable organisms are detected (*Pneumocystis jirovecii; Toxoplasma gondii,* etc.) or if pre-test probability of an infectious LRTI was low. We will prospectively ask clinicians to fill out a survey stating if any procedures were obviated as a result of pmNGS testing. We estimated ROI by conservatively estimating 0.5-2 additional bronchoscopies and associated diagnostic testing might be avoided per month, and omitted other procedures (biopsies, etc.) (Figure 2, L panel, red lines).
- **Total costs saved.** We only included cost savings from reducing unnecessary test use and specifically preventing bronchoscopies, though we will also assess effects of these tests on length of stay by clinician estimation (Appendix 3). Estimated savings are shown in Figure 2.
- **Other considerations.** pmNGS results may revolutionize a patient's care, change therapeutic management, and/or lead to epidemiologic investigations. These hard-to-predict benefits are not included in our ROI estimations, but should be considered as part of the global consequences of standardizing test uptake. Two recent examples:
    - **Example 1:** Heart transplant patient with cavitary pneumonia receives pmNGS that reveals *Rhizopus*, leading to lobectomy performed same day.
    - **Example 2:** Bone marrow transplant patient with fevers and lymphadenopathy receives pmNGS that shows *Mycobacterium tuberculosis*, leading to isolation and public health investigation.
- **SUSTAINABILITY** – After this year, we will be able to iterate the Infectious Disease/Clinical Microbiology Consensus Molecular Testing Guidance to promote highest-yield testing and avoid of pmNGS test ordering in low -impact clinical scenarios. We will integrate new testing guidelines into the APeX ordering system workflow. In parallel, we will actively communicate our findings to Infectious Disease groups and other major users of this diagnostic test.

BUDGET

NAME	ROLE ON PROJECT	Cal. Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
Natasha Spottiswoode	Project Lead	1.2	232,063	23,063 (10%)	NA	23,206
Hannah Teal	Clinical Research Coordinator	4	77,552	26,794 (34.5%)	NA	26,794
Monica Fung	Project Lead	As-needed				
Rama Yakubu	Project Lead	As-needed				
Total Estimated Budget						**50,000**

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