Background

- Urinary Tract Infections (UTI) are among the most common community-acquired infections. Routine diagnosis of UTI typically includes urine culture performed by phenotypic antimicrobial susceptibility testing (AST).
- More than 1 in 5 women experience clinical treatment failure with appropriate antimicrobial management.
- Current guidelines are informed by urine culture, which favors the detection of microorganisms that grow rapidly in the presence of oxygen. Pre-analytical factors, e.g. prior antimicrobial exposure of the patient, sample storage conditions, and time to plate inoculation can also influence the sensitivity of urine culture.

Methods

- Precision Metagenomic (PM) sequencing is culture independent and offers the potential to broadly detect uropathogens and associated genetic markers of antimicrobial resistance (AMR) directly from urine, with analytical sensitivity approaching that of PCR.
- Reduction in the time to pathogen + AMR characterization is expected, with a potential to improve upon suboptimal antibiotic stewardship practices.
- The observed microbiology in the study cohort encompassed a broad spectrum of clinical etiologies, including those associated with sexually transmitted infection.

Study Samples Represented the Population at Risk of UTI

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Females</th>
<th>≥ 50 years</th>
<th>≥ 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean Catch</td>
<td>524</td>
<td>307</td>
<td>156</td>
</tr>
<tr>
<td>Catheter</td>
<td>490</td>
<td>290</td>
<td>100</td>
</tr>
<tr>
<td>Not Specified</td>
<td>26</td>
<td>17</td>
<td>4</td>
</tr>
</tbody>
</table>

The majority of PM targets had some analytical factors, e.g. prior antibiotic exposure of the patient, sample storage conditions, and time to plate inoculation can also influence the sensitivity of urine culture. The observed microbiology in the study cohort encompassed a broad spectrum of clinical etiologies, including those associated with sexually transmitted infection.

Results

- PM sequencing was performed on 524 urine samples from women, ≥ 50 years, and ≥ 65 years of age.
- The majority of PM targets had some analytical factors, e.g. prior antibiotic exposure of the patient, sample storage conditions, and time to plate inoculation can also influence the sensitivity of urine culture.
- The observed microbiology in the study cohort encompassed a broad spectrum of clinical etiologies, including those associated with sexually transmitted infection.

Detection of AMR markers by PM is concordant with observed AST phenotypes.

PM was non-inferior to culture for the detection of the most common uropathogens in residual clinical samples from adults symptomatic of urinary tract infection.

Limitations

- Sub-group analysis based on clinical metadata was outside the scope of this study.
- Sample size by PM was exposed to unique preanalytical variables via shipping and storage.

Discussion

- A clinically useful novel UTI solution must be able to identify the causative agent and characterize the antimicrobial susceptibility of potential uropathogens in a sample. In addition to the PM method was non-inferior to culture for the detection of common uropathogens in clinical samples, and PM enhanced diagnostic yield for potential pathogens that were missed by culture.
- PM identified AMR markers from urine in agreement with reported resistance phenotypes of isolates.
- PM-based quantification from urine correlated with bacterial culture-based quantification of isolates.
- The observed results support the feasibility of a PM-based test for the diagnosis of UTI in symptomatic individuals and demonstrate the potential for enhanced sensitivity, yield and utility of PM for this indication.

Future Directions

- Orthogonal testing by shotgun DNA-sequencing and targeted PCR assays will be performed to confirm additional detections by PM.
- Thresholding and QC/QA approaches will be defined.
- The negative and positive predictive values of AMR markers generated by PM will be determined.
- The clinical utility of PM testing to improve clinical outcomes and inform new stewardship strategies will be evaluated in prospective, interventional studies.

References