Forum for
Collaborative HIV Research

FORUM NGS PROJECT

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Facilitating collaborative research in drug development and health policy

Purpose: to advance the regulatory pathway for NGS applied to viral pathogens by collaborating with multiple industry, academic and regulatory laboratories in developing proficiency panels.

Objectives:

1. Characterize the nature and extent of inter and intra lab variation in different settings and under different conditions through a pilot proficiency panel consisting of patient derived isolates and HIV PCR products.
2. Identify and address data workflows, pipelines, and analyses issues through the project generated database (in collaboration with the Bioinformatics working group).

Proficiency Panel Project – Participating Labs

1. The laboratory aspect of the project involves five industry labs, five academic labs and CBER/FDA.

	Roche 454	MiSeQ	PacBio RS
CBER/FDA - Viswanath Ragupathy		X	
CFE/VC - Richard Harrigan		X	
Harvard/BWH - Jon Li		X	
Monogram - Chris Petropoulos		X	
Pacific Biosciences - Ellen Paxinos			X
Pacific Biosciences - Roche			X
Quest Diagnostics - Ron Kagan	GS JR		
Siemens - AJ Chmura		X	
UCSD - Davey Smith	FLX		X
UCSF - Teri Liegler		X	
UNC - Shuntai Zhou		X	

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Summary

- Successful consensus recovery and good agreement
- Mixtures captured in most cases
- Tropism prediction largely in agreement with the expectation
- DRAMs successfully recovered
- Fairly robust recovery of minor DRAMs
- Rare cases of possible contamination/mislabeling

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Conclusions

- Analysis of raw NGS sequence data allowed DAVP to observe:
  - Low frequency treatment-emergent substitutions of unknown clinical significance
  - Cross-contamination of clinical trial samples
  - RT-PCR artifacts that confounded interpretation of NGS resistance data
- NGS may prove useful in identifying minor populations of resistant viruses present at baseline that could lead to treatment failure if the wrong regimen is prescribed
- Structural bioinformatics provided insight into the mechanism of resistance for substitutions that arose during treatment with SOF
- Access to NGS data and analysis software allowed CDER reviewers to make better informed decisions during review

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E Donaldson, March 12, 2015 www.hivforum.org