INSTITUTE FOR COMPUTATIONAL BIOLOGY

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CHARACTERIZING IMMUNE PROFILES OF CLEVELANDERS: THE METROHEALTH/INSTITUTE FOR COMPUTATIONAL BIOLOGY PILOT STUDY (MIPS)

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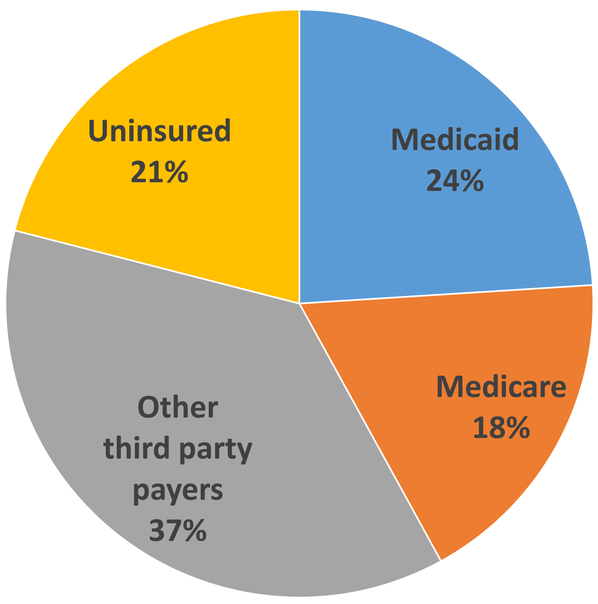
INTRODUCTION

- Precision medicine aims to deliver the right drug or treatment the first time to the patient.
- Successful precision medicine strategies will require longitudinal health, lifestyle, exposure, and 'omic data.
- Electronic health records (EHRs) are potential sources of individual-level longitudinal data for health, lifestyle, and exposures.
- The Cleveland area boasts three major hospital systems with EHRs: University Hospitals, the Cleveland Clinic, and the MetroHealth System.
- The Case Western Reserve University (CWRU) Institute for Computational Biology (ICB) was founded in 2013 to establish an EHR data warehouse and secure research environment for precision medicine research.
- The MetroHealth System and CWRU's ICB are collaborating in a pilot study to generate 'omic data using biospecimens from consented patients with EHRs.
- We describe here a sub-aim of MIPs: the characterization of patient immune profiles and its correlation with kidney function and disease.

STUDY POPULATION

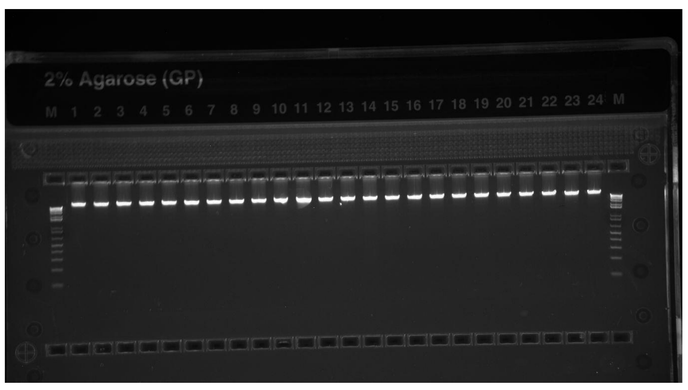
- We are ascertaining patients visiting the nephrology clinic at the MetroHealth System.
- The MetroHealth System's EHR (Epic) was installed in 1999.
- The MetroHealth System had approximately 1.03 million outpatient visits and 500,000 patient lives covered in 2015.
- The MetroHealth System payer mix is diverse (Figure 1).



- Since late February 2016, we have ascertained 83 patients for MIPs.
- Approximately half of MIPs participants are self-described African American (48%) and female (58%). The average age of MIPs participants is 61 years.

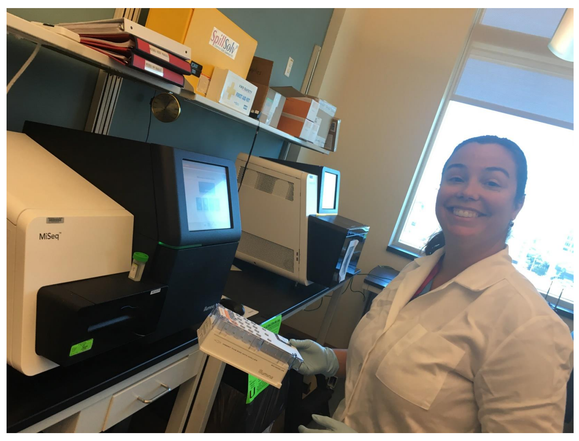
METHODS

- We are collecting three EDTA-coated vaccutainers of whole blood at the time of the clinic visit. Genomic DNA is extracted from one vacutainer (Figure 2), and the others are spun to save the plasmas and buffy coat for future studies.
- Figure 2. Genomic DNA integrity and quality in MIPs is high. DNA samples are checked for quality using a 2% agarose gel. The average yield is ~50 micrograms. Photo credit: Dr. Kristy Miskimen.



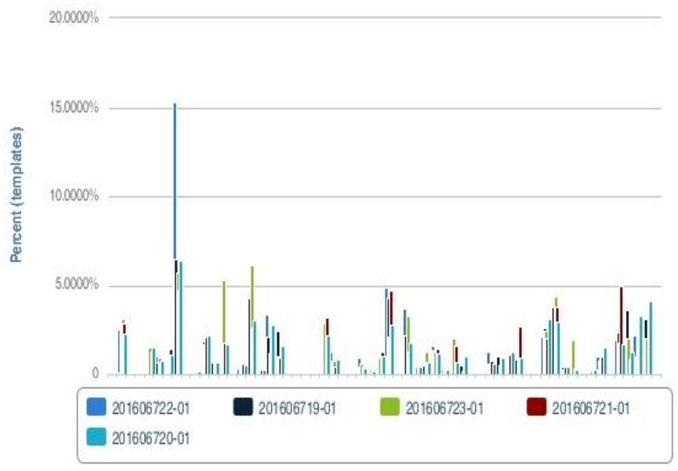
- Genome-wide genotyping using the Illumina Mega^{EX} is on-going at the University of Miami Hussman Institute for Human Genomics Center for Genome Technology Genotyping Core (Figure 3).

- The Illumina MEGA^{EX}, also known as the Illumina Multi-ethnic Global Beadchip, is a consortium-built array of >2 million markers designed for maximized imputation accuracy of diverse populations.
- Immune profiles are being characterized using Adaptive Biotechnologies ImmunoSeq.
- ImmunoSeq targets the beta chain of the T-cell receptor in alpha/beta T cells. PCR amplification using validated primer sets is followed by library preparation and MiSeq sequencing for each of the six genomic DNA replicates (Figure 4).



RESULTS

- The first five genomic DNA samples have been processed using ImmunoSeq. The data were further processed by Adaptive Biotechnolgoies ANALYZER bioinformatics pipeline, which provides individual sample-level measures of T-cell receptor diversity including the number of rearrangements, number of porudctive rearrangements, and productive clonality (ranging from 0 to 1 representing the range from polyclonal to monoclonal).
- In the first five genomic DNA samples from MIPs, productive clonality ranged from 0.0151 to 0.1632.
- The distribution of the most common clones for the first five genomic DNA samples from MIPs is given in Figure 5. The distribution differed across the five samples. V genes detected are displayed on the X-axis and the percent (template) on the y-axis. The detected V genes are color-coded by MIPs participant.



FUTURE DIRECTIONS

- We intend to process all MIPs samples to generate genome-wide genotype data and T-cell receptor diversity data as 'omic datatypes.
- 'Omic data will be combined with data from MetroHealth's EHR in the CWRU ICB's secure research environment (SRE). The SRE was developed by CWRU's ICB and Information Technology Services with the goals of managing and maintaining a secure research environment for computing, governed by a risk-based security program that includes implementation of controls which meet recommendations or requirements of regulatory and information security standards. The SRE is hosted in a HIPAA-compliant and professionally managed Tier III datacenter.
- We will characterize T-cell diversity by basic demographics and compare these distributions with those available in the Adaptive Biotechnologies public database. We will perform a cross-sectional study of health status and T-cell diversity to establish associations with various biomarkers of kidney function and disease.
- Should T-cell diversity correlate with kidney function (defined as estimated glomerular filtration rate or eGFR), we plan to explore its usefulness in prediction modeling for chronic kidney disease (CKD).
- CKD is the gradual loss of kidney function over time. CKD progression is non-linear and highly variable. Several non-modifiable and modifiable risk factors such as race/ethnicity (African-descent) and hypertension have been identified. Novel biomarkers such as 'omic immune profiles may be needed to more accurately identify patients at risk for CKD progressing to end stage disease.

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