BloodPAC: Establishing Standards to Accelerate Development and Approval of Liquid Biopsy Technology

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Executive Director
In President Obama’s final State of the Union address on January 12, 2016, the President asked then Vice President Joe Biden to head up a new national effort to end cancer as we know it.
Joe Biden announces major new steps in his fight for better cancer research

“Cancer is not a national problem. It is not an international problem. It is a humanitarian problem”

https://tinyurl.com/zr955sr
The Cancer Moonshot Mission

Make a **decade’s** worth of progress in half the time, in the areas of **cancer prevention, diagnosis, treatment, and care.**

How do we engage **EVERYONE**?

• Cancer patients and their caregivers
  • Clinicians
  • Health organizations
  • Advocacy groups
  • Researchers
  • Technologists
  • Industry leaders
• **Individuals and organizations throughout the private sector**
Partnerships & The Cancer Moonshot

Can we form new partnerships to defy the bounds of innovation?
White House Cancer Moonshot Partnerships

Announced over 70 public-private partnerships in less than 1 year

• NCI Cloud Collaborations with Amazon Web Services and Microsoft
• Lyft and Uber expand their support of affordable, reliable transportation for cancer patients
• Bristol-Myers Squibb Foundation commitment of $25 million over two-years to alleviate cancer inequities
BloodPAC GOAL

To cut assay development times in half through the creation of an open database for liquid biopsies, accelerating the development of safe and effective blood profiling diagnostic technologies for patient benefit.
QUESTION: How can we accelerate progress?

ANSWER: Through a collaborative group of over 30 organizations representing academia, government, pharma, biotech, regulatory and professional societies, and individuals with unparalleled enthusiasm, focus and commitment.
THE BLOOD PROFILING ATLAS IN CANCER IS BORN

- Memorandum sent to Vice President on Liquid Biopsies and Blood Profiling: 9/8/16
- Initial Group Meeting at White House: 9/28/16
- First Full Blood PAC Meeting: 10/18/16
- BCRF and PCF announce pilot projects with Blood PAC: 12/20/16
- Pre-Analytical Minimal Technical Data Elements Established and Supported by FDA & CAP: Q4 2017 & Q1 2018
- BloodPAC Data Train 1 Meeting at White House: 12/20/16
- BloodPAC Generic Analytic Protocol Pre-Sub & Discussion: Q4 2018 & Q1 2019
- BloodPAC Established as an Independent Organization: 2/2017

Timeline:
- August 31, 2016
- December 20, 2016
- TODAY
TO BEGIN

Launch a pilot to aggregate, make freely available, and harmonize for further analyses:

• Raw datasets from circulating tumor cells, circulating tumor DNA, and exosome assays
• Relevant clinical data (e.g. clinical diagnosis, treatment history and outcomes)
• Sample preparation and handling protocols from different studies.
Questions to start us off

Can we: Replace the old status quo of one tube, one technology with the new world of multiple technologies per tube/draw?

And: Rather than trying to find one right answer in silo, we share what needle one technology found, and perhaps didn’t find, without benchmarking?

Finally: Rather than only sharing the binary outcome of the test with the physician, we share all the raw data from each technology in a publically accessible portal for scientific interpretation.
Why is this so hard?

Because it requires close collaboration and a shift in the way we see, develop and execute research.
THE BLOODPAC DATA COMMONS

1. Define variables

2. Collaborate and develop standards

3. Submit data to the BloodPAC Data Commons

4. Organize & analyze data

Courtesy of Thermo Fisher Scientific
A Range of Assays are in Development for Different Tumor Products in Blood and Other Fluids

BloodPAC Data Contributing Members

cfDNA  cfRNA  cfProtein  Exosomes  CTC  Future Analytes

Aggregation of Existing Data and New Data Generation

Contribution to BloodPAC Data Commons
Technology Development Process

Pre-Analytics
- Analyte
- Sample Collection
- Patient Factors

Analytics
- Sample Storage and Processing
- Assay SOP

Clinical Validation
- Assay Results
- Patient Data
Pre-Analytic Minimal Technical Data Elements (MTDEs)

Minimal Technical Data Elements — Variables that are required for submission of samples to the BloodPAC Data Commons.

Pre-Analytical MTDEs — Pre-analytic variables that would affect assay performance, and are required for submission of samples to the Data Commons.
Pre-Analytic MTDE Progress

- BloodPAC Member Review
  - 26 Pre-Analytical Variables
  - FDA Consultation Meeting 1
    - MTDEs
    - BloodPAC Data Commons
    - FDA Consultation Meeting 2
    - Additional Pre-Analytical Variables
  - 11 Pre-Analytical MTDEs
# BloodPAC Pre-Analytic cfDNA 11 MTDEs

<table>
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<th>cfDNA MTDEs</th>
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<tr>
<td>Blood collection tube type</td>
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<tr>
<td>Blood fractionation approach</td>
</tr>
<tr>
<td>Time to fractionation</td>
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<tr>
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<tr>
<td>Storage temperature</td>
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<td>Shipment temperature</td>
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<td>DNA isolation method name</td>
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<td>DNA quantification method</td>
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<tr>
<td>Sample type</td>
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<td>Time to assay</td>
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cfDNA MTDE Definitions

1. **Blood Collection Tube** - The type of tube used to collect the sample(s) taken from a biological entity for testing, diagnostic, propagation, treatment or research purposes.

2. **Blood Fractionation Approach** - The name or description of the method used to obtain the blood fraction sample.

3. **Time to Fractionation** – From blood draw to completion of fractionation.

4. **Time to Freezer** – From completion of fractionation to freezing.

5. **Storage Temperature** - The temperature, in centigrade, at which the sample was stored.

BloodPAC
6. **Shipment Temperature** - The average temperature at which the sample was kept during transportation.

7. **DNA Isolation Method Name** - The name or general description of the method used to isolate the analyte.

8. **DNA Quantification Method** - The name or general description of the method used to quantify the analyte yield or concentration of the aliquot.

9. **DNA Yield** - The total amount of DNA that was isolated from the sample.

10. **Sample Type** - Characterization of the sample as either clinical or contrived.

11. **Time to Assay** - Time from draw to analysis.
Technology Development Process

Pre-Analytics
- Analyte
- Sample Collection
- Patient Factors

Analytics
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Clinical Validation
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Patient Context Variables
Where We Started

Question posed to
FDA’s Center for Devices and Radiological Health (CDRH):

If we develop standardized protocols and methods for assessing analytical variables, can we accelerate the development and approval of NGS-based cfDNA assays?
Anaytical Variable Project Objective

The objective for the BloodPAC’s Generic Analytical Validation Protocols for Cell Free Assay Performance Verification is to provide a complete set of generic protocols designed to provide test developers/manufacturers with a core baseline of standardized analytical validation protocols with which to document a cell free assay’s analytical performance.

Revision 1 is intended for use by developers/manufacturers of NGS-based ctDNA in vitro diagnostic tests for oncology, regulatory bodies and clinical laboratories.
**Project Strategy**

**Develop a list of 11 generic analytical validation protocols**

1. Protocols for the Evaluation of a Reference Interval
2. Protocols for Evaluation of Limit of Blank (LoB)
3. Protocols for Evaluation of Limit of Detection (LoD)
4. Protocols for Evaluation of Contrived Sample Functional Characterization
5. Protocols for Determining Analytical Accuracy
6. Protocols for Evaluation of Linearity
7. Protocols for Evaluation of Limit of Quantitation (LoQ)
8. Protocols for Evaluation of Reportable Range
9. Protocols for Evaluation of Repeatability, Precision, and Reproducibility
10. Protocols for Interfering Substance
11. Protocols or Guardbanding Class III Medical Devices
Project Strategy

Develop a list of 5 standard methods

5. Standard Method: Preparation of Patient Sample Pools
Analytical Variables Working Group Process (AV WG)

- FDA Meeting
  - Nov, 2017
- Gather key Blood PAC members to form the “AV WG”
- Kickoff AV WG at Blood PAC Q4 Meeting in Dec, 2017
- State objectives and key assumptions
- Develop standard protocols and methods

- Consult with statisticians to refine analysis methods
- FDA Consult Meeting 1
  - May 15, 2018
- Revisions
- FDA Consult Meeting 2
  - Jun, 2018
- Revisions

- Submit protocol as Pre-Sub Submitted to CDRH
  - Aug, 2018
- FDA Face-to-Face Meeting Dec, 2018
- Revisions
- Resubmit to CDRH as supplement to Pre-Sub
  - 18 Feb, 2019

Next Steps:
- White paper, FDA workshop, how to implement?
BloodPAC
JFDI Challenge
Question: How do the same liquid biopsy cfDNA-like samples function across different labs and on different analysis platforms?

Answer: Through a collaborative research effort from Blood PAC members....we will run the experiments and make the results available to you all!

Goal:
• Establish some reference standards that can be evaluated across multiple platforms
• Provide Analysis tools that can query this data and demonstrate the capabilities of the data commons
• Provide benefit to the larger community (beyond BloodPAC)
What’s the Plan?

1. Provide four (4) sets of contrived cfDNA control samples to all participants
2. Each participant tests the control material as input into their liquid biopsy NGS sequencing system for rare variant detection
3. Review findings with BloodPAC members and FDA
4. Draft a paper
5. Make data accessible to BloodPAC members and the public
Summary
Synergy is Fostered thru BloodPAC Data Commons & Working Groups

Contrived Sample
(Thermo AcroMetrix® Oncology Hotspot Control)
Delivered to BloodPAC “Just Do It” Group Labs

Different NGS Assay Approaches by Group Labs
- Sample Prep Methodologies
- Sequencing Instrument/Platform
- Bioinformatics Pipeline & Analyses

BloodPAC Working Groups (WG)
- MTDE Preanalytical WG
- Data Modeling WG
- BloodPAC Working Groups (WG)
- Analytical Variables WG
- Patient Context Variable WG

BloodPAC Data Commons
- Sample Prep Details
- NGS Data
Aggregate & Additional Analyses, Planning

Lab 2
Lab N
Lab N
Experiment #1
Blood PAC Co-Chairs

Darya Chudova
Guardant Health

Ryan Dittamore
Epic Sciences

Jim Godsey, PhD
Thermo Fisher Scientific

Robert L. Grossman, PhD
OCC and University of Chicago

Peter Kuhn, PhD
University of Southern California

Jerry Lee, PhD
University of Southern California

Anne-Marie Martin, PhD
Novartis

Howard Scher, MD
MSKCC

John Simmons, PhD
PGDx

Jake Vinson
PCCTC
BloodPAC Members

The Arkansas Bioinformatics Consortium (AR-BIC), AstraZeneca, Biodesix, Breast Cancer Research Foundation (BCRF), Celgene, CHOP, College of American Pathologists (CAP), CytoLumina, Department of Defense (DOD), Epic Sciences, FDA, Foundation Medicine, Genomic Health, Guardant Health, Memorial Sloan Kettering Cancer Center, National Cancer Institute (NCI), Novartis, Open Commons Consortium (OCC), PCCTC, Personal Genome Diagnostics, Pfizer, Prostate Cancer Foundation (PCF), Provista, Seven Bridges, Streck, Sysmex Inostics, Thermo Fisher Scientific, University of Chicago, University of Michigan, University of Southern California, Weill Cornell Medicine.
What BloodPAC Offers its Members

1. Allows approved researchers access to member contributed datasets in a scalable, reproducible, privacy and security protected manner as part of the Consortium’s collaborative effort.

2. Access to samples while working in collaboration with the Department of Defense and Applied Proteogenomics Organizational Learning and Outcomes (APOLLO) network.

3. The ability to mold and influence the development of assays through a collaborative relationship with the FDA Oncology Center of Excellence, and the leadership of the Associate Director, Office of Hematology Oncology FDA and the CDRH Director.

4. The opportunity to establish best practices and principles to incorporate into operating procedures and eliminate duplication of efforts.

5. Foster the development and enhancement of relationships across all stakeholders in the field – pharmaceutical companies, technology companies, academic institutions, foundations, patient advocacy groups, physicians and government agencies.
Questions and Discussion

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