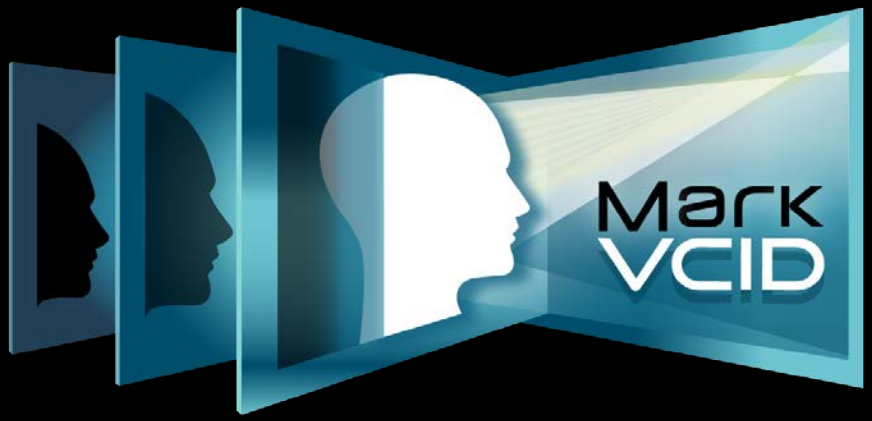

NIH Biomarkers Consortium for
Vascular Contributions to Cognitive Impairment and Dementia

Developing Best Practices and Biomarker Harmonization

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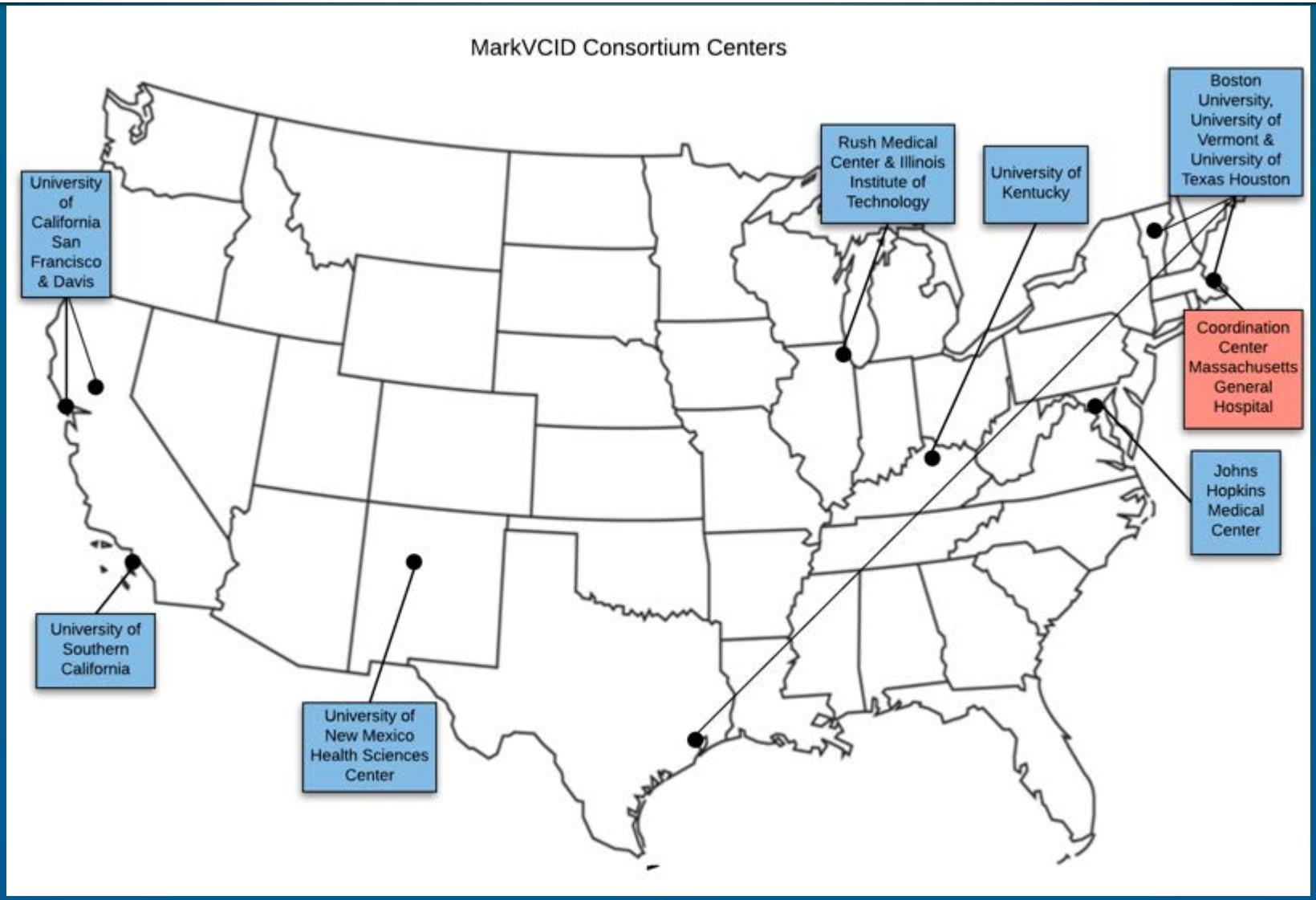
Outline

1. Opportunities and challenges in fluid biomarkers.
2. Current approaches by MarkVCID to address the challenges.
3. The path forward.
4. Discussion.

What is MarkVCID?

- NINDS/NIA funded consortium to discover and validate biomarkers for small vessel disease type VCID.
- UH2/UH3 mechanism with 2 year UH2 discovery phase and 3 year UH3 validation phase.
- Currently developing transition plans with UH3 due to start August 2018.
- Program is managed by Dr. Rod Corriveau and Dr. Linda McGavern.

MarkVCID sites

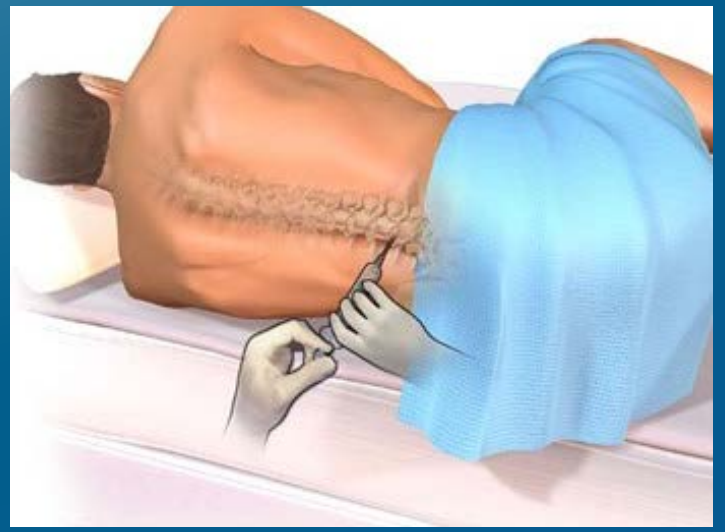


MarkVCID - A unique opportunity for us to evaluate biomarkers in a rigorous, reproducible manner

- There is **NO** wholly validated biomarker for cerebral small vessel disease.
- There are many single-site, single-cohort studies that report a novel biomarker. These have yet to be validated and reported as proven.
- This consortium aims to produce a battery of biomarkers that are validated across sites, across cohorts, and across platforms, that are useful for diagnosis, clinical trials, and tracking of disease.
- Sites are focusing on neuroimaging and fluid biomarkers.

The utility of fluid biomarkers

- Fluid biomarkers are easily obtained at a low cost and without the need of a site having specific equipment.
- A single fluid sample gives sufficient volume for the assessment of multiple analytes.
- Fluids can be shipped between institutions, or from rural health care facilities to centers for analysis and interpretation.



The challenges of fluid biomarkers

- As opposed to direct imaging of vessels / brain tissue in MRI, fluid biomarkers will be surrogates of pathologic processes.
- Sample preparation, storage methods, tube type, time of day, fasting state, unrelated illnesses, and medications, can all affect assay results.

Overcoming the challenges

- Implement best practices that all sites will be required to follow for the collection and storage of samples.
- Highlights of this document include requirements for:
  - Fasting, morning sample collection.
  - Standard needle size and type.
  - Standard tube types for collection and storage.
  - Standard aliquot size.
  - Standard temperature requirements for storage.

What samples are being collected?

- All MarkVCID sites are collecting longitudinal plasma samples from their cohorts.
- Four of the seven sites are collecting longitudinal CSF samples.
- Analysis equipment available for fluid samples are:
  - Meso-Scale Discoveries.
  - Luminex.
  - Quanterix (SiMoA)
  - Standard colorimetric ELISA.

Expectations of Individual Sites.

- Sites collecting fluid biospecimens will comply with best practices, beginning as early as possible but by the start of the UH3 phase.
- Sites will maintain samples at the required temperatures, de-identified using the MarkVCID coding system.
- Sites will aliquot and store a minimum volume of 5ml plasma and CSF that will be designated specifically to MarkVCID.
- Requests for samples will be reviewed and approved by the fluid biomarker subcommittee, for final approval by the steering committee.
- The sample shipping SOP will be followed when samples are to be shipped out.

Harmonization Processes

- Finalization of harmonization protocols is expected in the next few months.
- We have agreed that the best process for harmonization is the distribution of a standard sample (for both CSF and plasma) to sites with sufficient aliquots to complete the UH3 process.
- These standard samples will be included when batches of samples are being analyzed at each site.
- We will be generating pooled, diseased samples. Diseased is necessary for some biomarkers as some biomarkers are not expressed at all in non-demented controls.

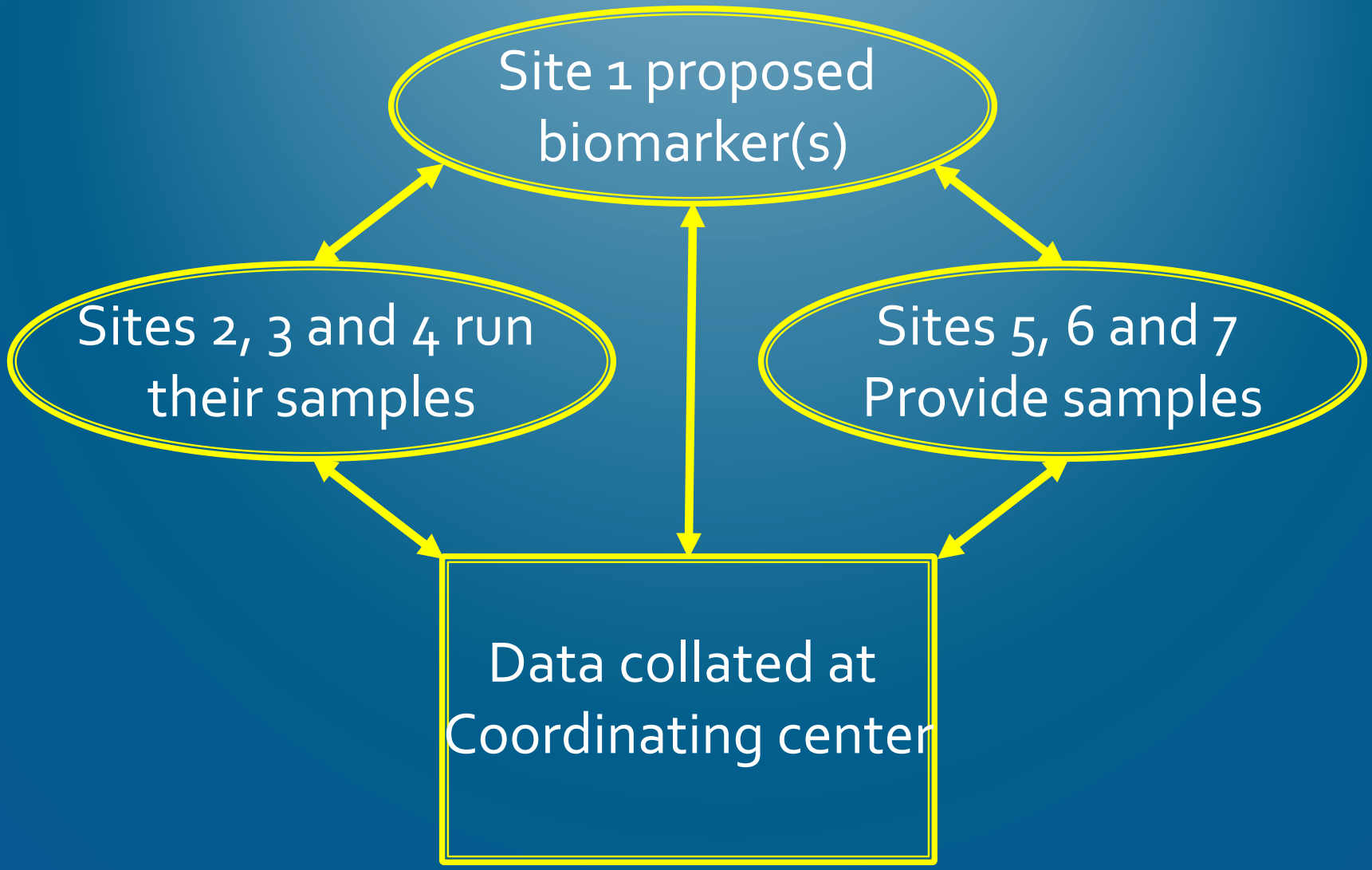
Improving Sharing

- A specific sharing subcommittee worked extensively on language of MTAs and consent forms.
- IRBs were updated to include common language.
- Now, these sharing forms are in place so that prospective collection of samples in UH3 will allow full sharing of samples between all of the consortium sites.
- Decision was made to maintain samples as a "virtual biorepository" but with centralized sample inventories.

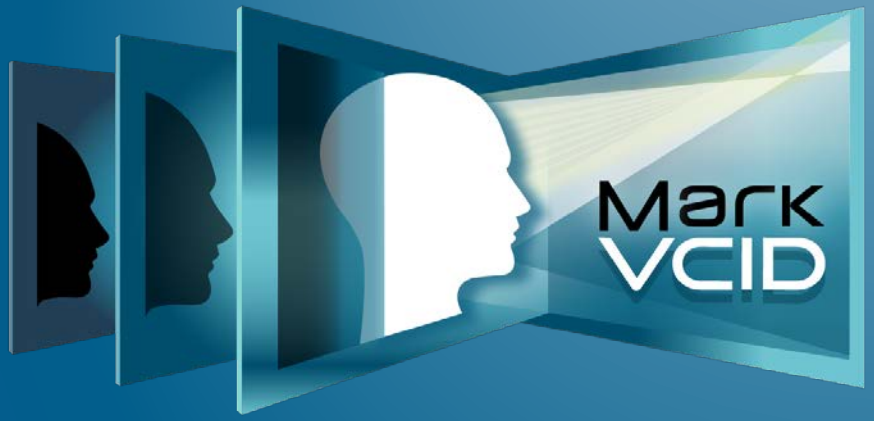
Next Steps

- The biomarkers will be proposed by each site to be cross-site tested.
- Biomarkers will be tested at different sites, on different platforms, and on different cohorts, to ensure reproducibility and consistency.
- Biomarkers will likely be categorized as diagnostic, or modifiable to indicate target engagement.
- Clinical trials will propose these fluid biomarkers as outcome measures (secondary).

Workflow


Site 1 proposed biomarker(s)
Sites 2, 3 and 4 run their samples
Sites 5, 6 and 7 Provide samples
Data collated at Coordinating center

Thanks to all



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