EVIDENTIARY CONSIDERATIONS FOR INTEGRATION OF BIOMARKERS IN DRUG DEVELOPMENT

A Symposium Co-Sponsored by FDA, M-CERSI and C-Path
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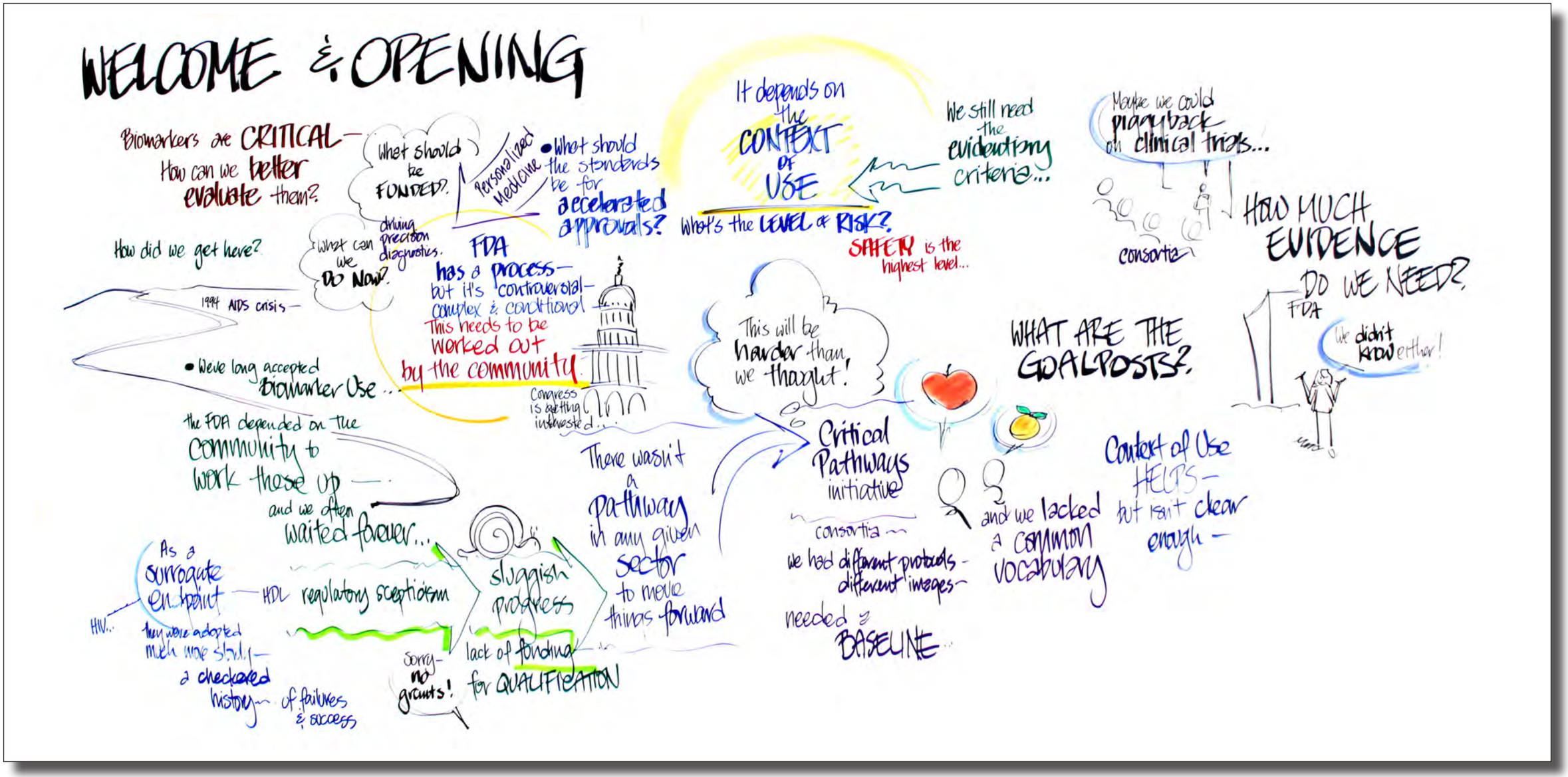
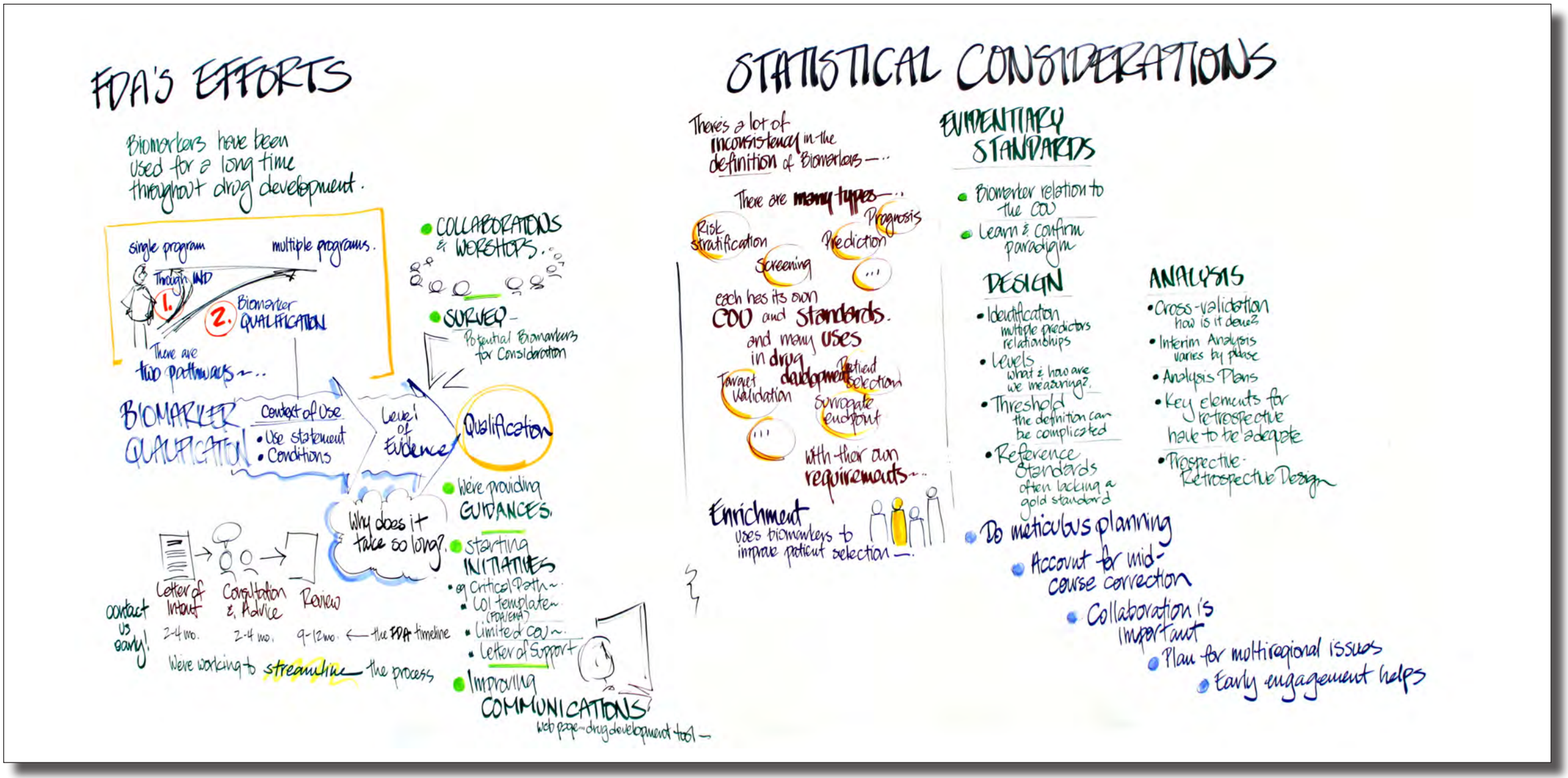
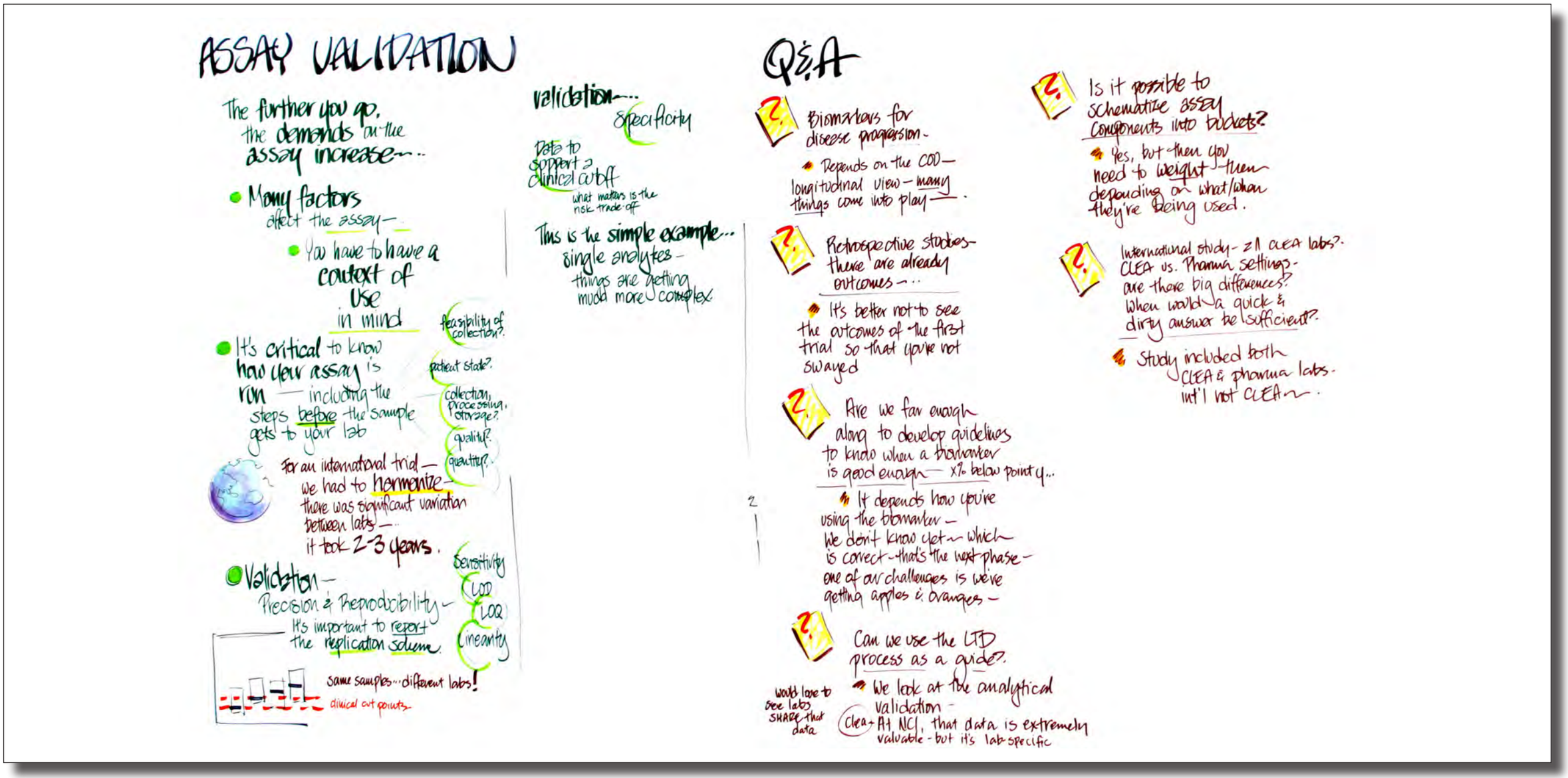
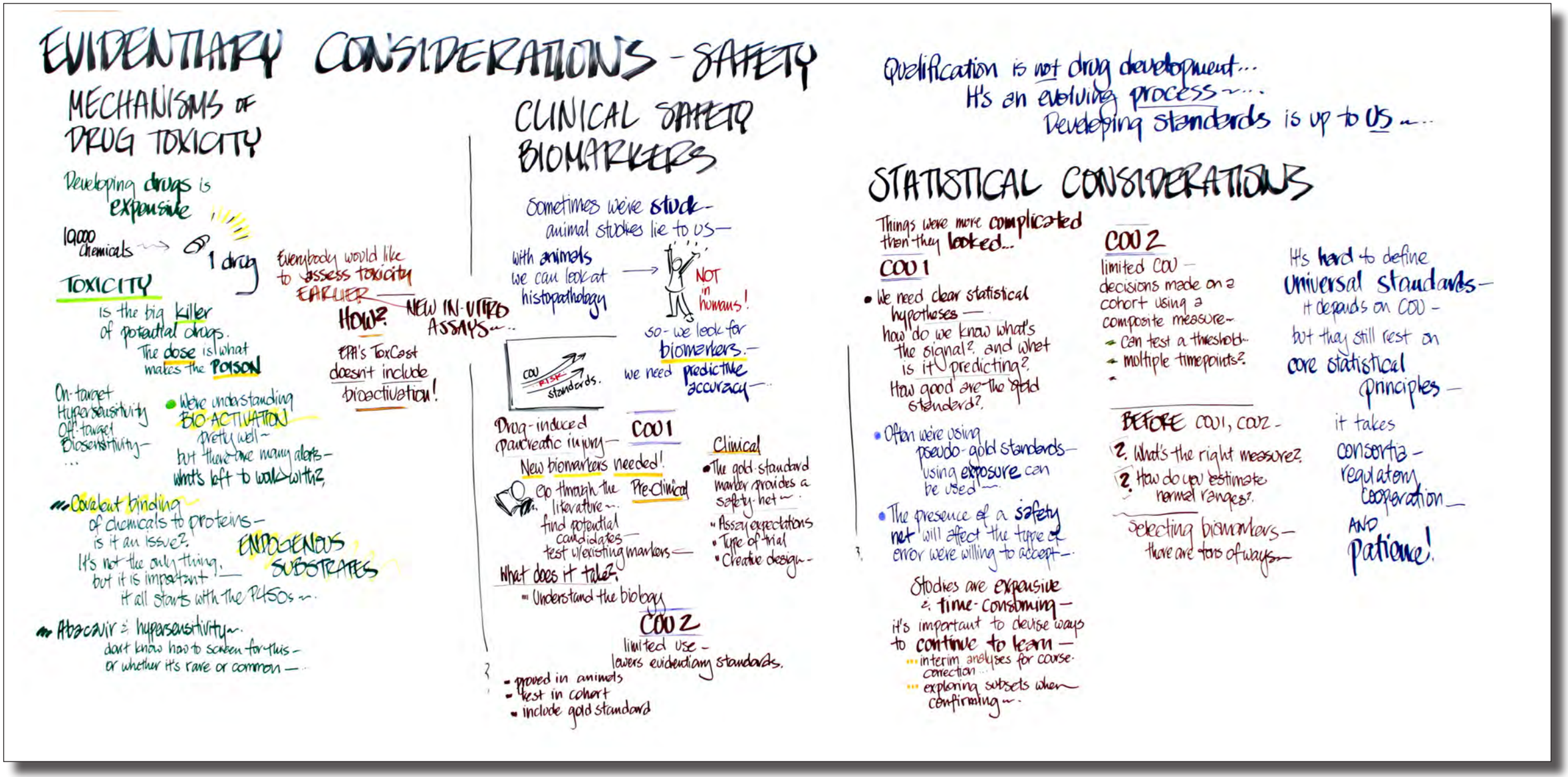
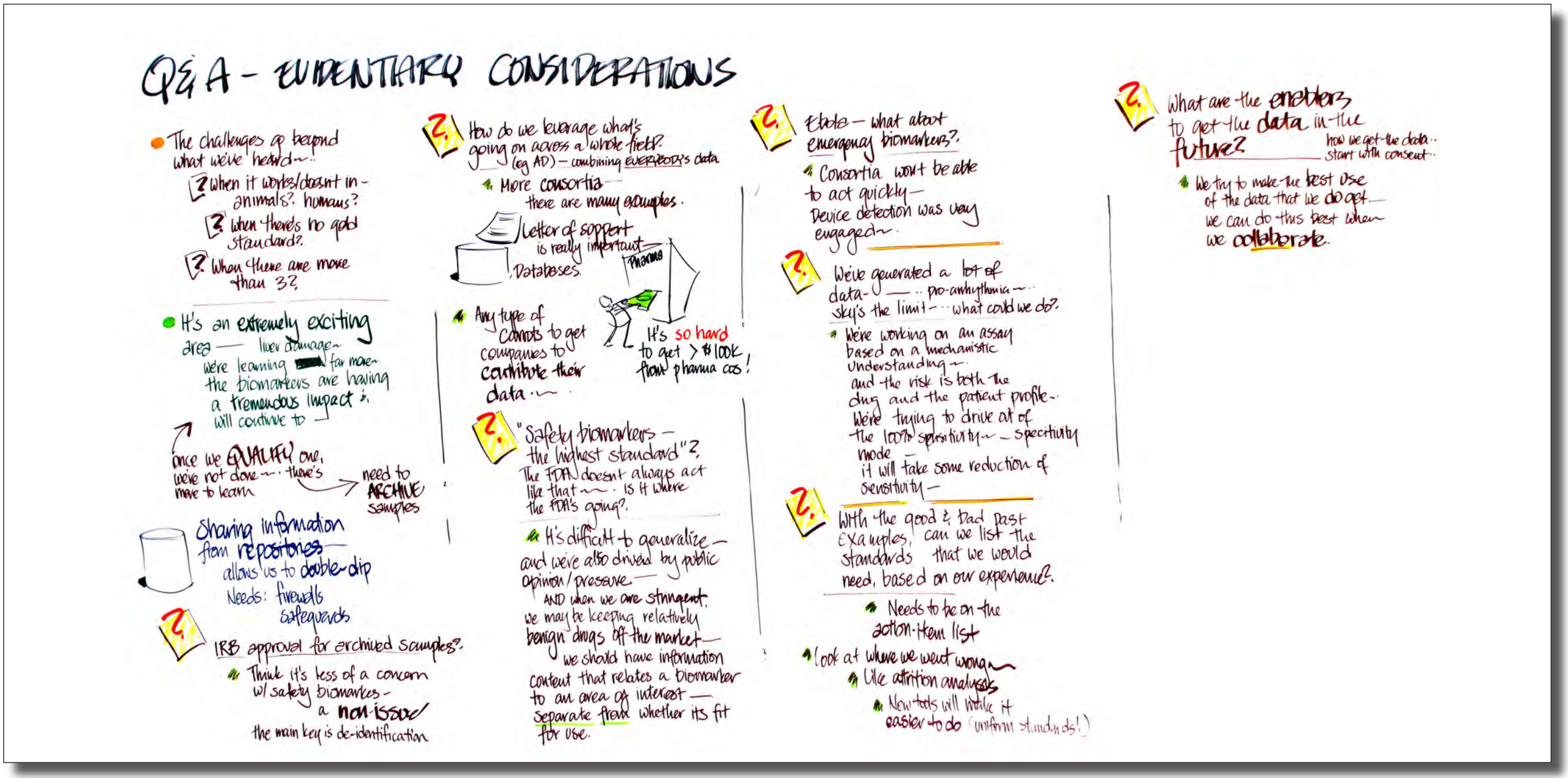

WELCOME & OPENING
Biomarkers are CRITICAL — How can we better evaluate them?
What should be FUNDED?
Personalized Medicine
driving precision diagnostics.
What should the standards be for accelerated approvals?
It depends on the CONTEXT of USE
What's the LEVEL of RISK?
SAFETY is the highest level...
We still need the evidentiary criteria...
Maybe we could piggyback on clinical trials...
consortia
HOW MUCH EVIDENCE DO WE NEED?
FDA
We didn't know either!
How did we get here?
What can we DO NOW?
1994 AIDS crisis —
FDA has a process — but it's controversial — complex & conditional
This needs to be worked out by the community
Congress is getting interested...
• We've long accepted Biomarker Use...
the FDA depended on the community to work these up — and we often waited forever...
This will be harder than we thought!
WHAT ARE THE GOALPOSTS?
Critical Pathways initiative
consortia
we had different protocols — different images — needed a BASELINE...
and we lacked a common vocabulary
Context of Use HELPS — but isn't clear enough —
There wasn't a pathway in any given sector to move things forward
As a surrogate endpoint — HDL
HIV...
they were adopted much more slowly — a checkered history — of failures & success
regulatory skepticism
sluggish progress
lack of funding for QUALIFICATION
sorry — no grants!

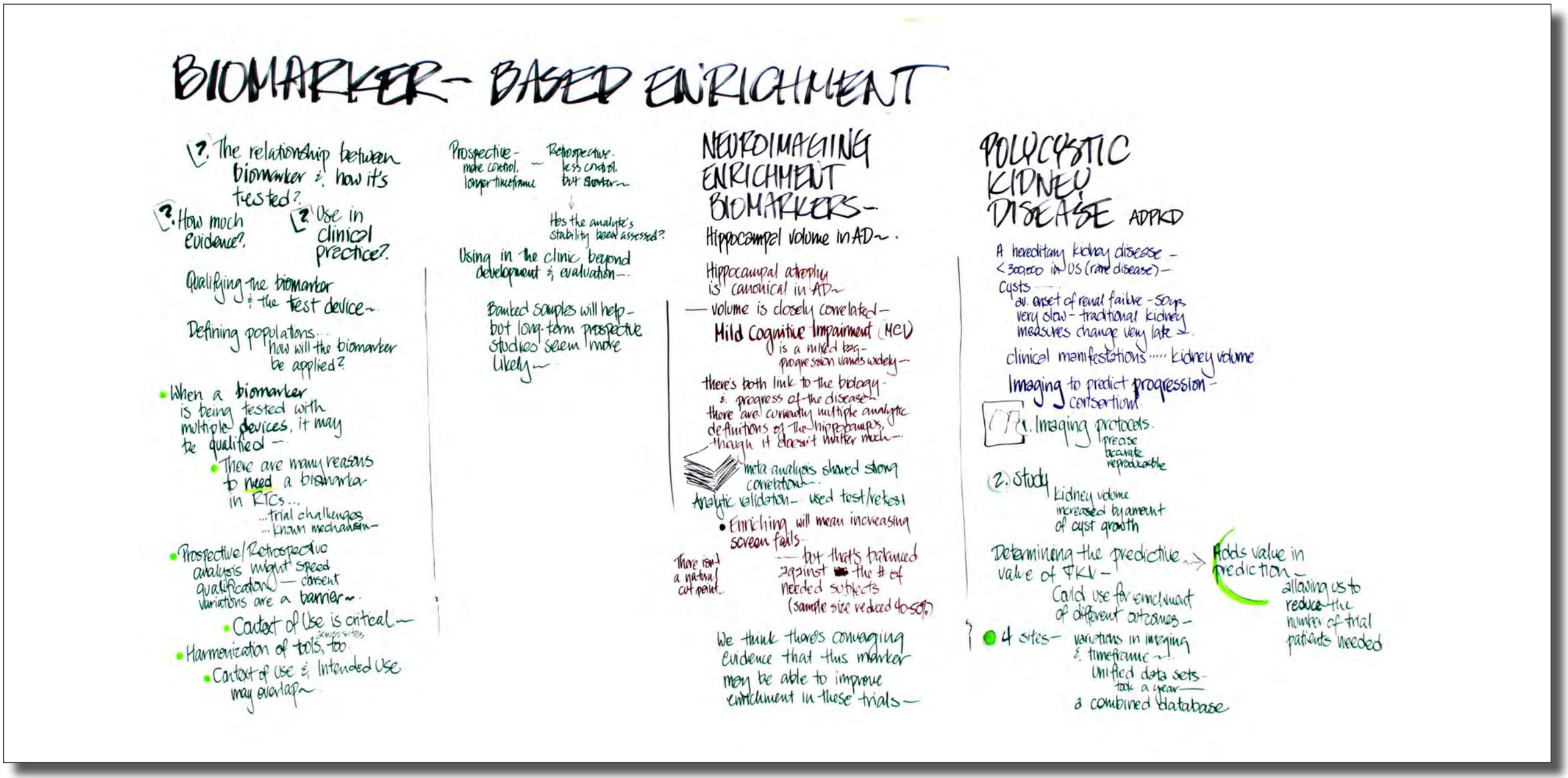

FDA'S EFFORTS
Biomarkers have been used for a long time throughout drug development.
single program
multiple programs.
Through IND
1.
2. Biomarker QUALIFICATION
There are two pathways...
BIOMARKER QUALIFICATION
Context of Use
• Use statement
• Conditions
Level of Evidence
Qualification
COLLABORATIONS & WORKSHOPS...
SURVEY - Potential Biomarkers for Consideration
We're providing GUIDANCES.
Starting INITIATIVES
• eg Critical Path...
• LOI template... (FDA/EMA)
• Limited COU...
• Letter of Support
Improving COMMUNICATIONS
Web page... drug development tool...
Why does it take so long?
Letter of Intent
Consultation & Advice
Review
2-4 mo.
2-4 mo.
9-12 mo. ← the FDA timeline
contact us early!
We're working to streamline the process
STATISTICAL CONSIDERATIONS
There's a lot of inconsistency in the definition of Biomarkers...
There are many types...
Risk stratification
Screening
Prediction
Prognosis
...
each has its own COU and standards.
and many uses in drug development
Target validation
Patient selection
Surrogate endpoint
...
with their own requirements...
Enrichment
Uses biomarkers to improve patient selection...
EVIDENTIARY STANDARDS
• Biomarker relation to the COU
• Learn & confirm paradigm
DESIGN
• Identification multiple predictors relationships
• Levels what & how are we measuring?
• Threshold the definition can be complicated
• Reference Standards often lacking a gold standard
ANALYSIS
• Cross-validation how is it done?
• Interim Analysis varies by phase
• Analysis Plans
• Key elements for retrospective have to be adequate
• Prospective-Retrospective Design
Do meticulous planning
Account for mid-course correction
Collaboration is important
Plan for multiregional issues
Early engagement helps


ASSAY VALIDATION
The further you go, the demands on the assay increase...
Many factors affect the assay—
You have to have a context of use in mind
It's critical to know how your assay is run — including the steps before the sample gets to your lab
feasibility of collection?
patient state?
collection, processing, storage?
quality?
quantity?
for an international trial — we had to harmonize — there was significant variation between labs — it took 2-3 years.
Validation — Precision & Reproducibility — It's important to report the replication scheme.
Sensitivity
LOD
LOQ
Linearity
same samples... different labs!
clinical cut points
validation...
specificity
Data to support a clinical cutoff
what matters is the risk trade-off
This is the simple example... single analytes — things are getting much more complex
Q&A
Biomarkers for disease progression.
Depends on the COD — longitudinal view — many things come into play —.
Retrospective studies — there are already outcomes...
It's better not to see the outcomes of the first trial so that you're not swayed
Are we far enough along to develop guidelines to know when a biomarker is good enough — x% below point y...
It depends how you're using the biomarker — We don't know yet — which is correct — that's the next phase — one of our challenges is we're getting apples & oranges —
Can we use the LTD process as a guide?
We look at the analytical validation —
CLEA + At NCI, that data is extremely valuable - but it's lab-specific
would love to see labs SHARE that data
Is it possible to schematize assay components into buckets?
Yes, but then you need to weight them depending on what/when they're being used.
International study - all CLEA labs? CLEA vs. Pharma settings - are there big differences? When would a quick & dirty answer be sufficient?
Study included both CLEA & pharma labs. Int'l not CLEA —.


EVIDENTIARY CONSIDERATIONS - SAFETY
MECHANISMS OF DRUG TOXICITY
Developing drugs is expensive
10,000 chemicals → 1 drug
TOXICITY is the big killer of potential drugs. The dose is what makes the POISON
Everybody would like to assess toxicity EARLIER — HOW? NEW IN-VITRO ASSAYS...
EPA's ToxCast doesn't include bioactivation!
On-target Hypersensitivity Off-target Biosensitivity ...
We're understanding BIO-ACTIVATION pretty well — but there are many alerts — what's left to work with?
Covalent binding of chemicals to proteins — is it an issue? It's not the only thing, but it is important — it all starts with the P450s...
ENDOGENOUS SUBSTRATES
Abacavir ≈ hypersensitivity... don't know how to screen for this — or whether it's rare or common —
CLINICAL SAFETY BIOMARKERS
Sometimes we're stuck — animal studies lie to us —
With animals we can look at histopathology → NOT in humans!
so - we look for biomarkers — we need predictive accuracy...
COU vs RISK — standards.
Drug-induced pancreatic injury — New biomarkers needed!
COU 1
Go through the literature... find potential candidates — test w/existing markers —
Pre-Clinical
Clinical
• The gold-standard marker provides a safety-net...
" Assay expectations
" Type of trial
" Creative design...
What does it take?
" Understand the biology
COU 2
limited use — lowers evidentiary standards.
- proved in animals
- test in cohort
- include gold standard
Qualification is not drug development... It's an evolving process.... Developing standards is up to US...
STATISTICAL CONSIDERATIONS
Things were more complicated than they looked...
COU 1
• We need clear statistical hypotheses — how do we know what's the signal? and what is it predicting? How good are the gold standard?
• Often we're using pseudo-gold standards — using exposure can be used...
• The presence of a safety net will affect the type of error we're willing to accept...
Studies are expensive & time-consuming — it's important to devise ways to continue to learn —
... interim analyses for course-correction...
... exploring subsets when confirming...
COU 2
limited COU — decisions made on a cohort using a composite measure...
- can test a threshold...
- multiple timepoints?
BEFORE COU1, COU2 -
2. What's the right measure?
2. How do you estimate normal ranges?
Selecting biomarkers — there are tons of ways...
It's hard to define Universal standards — it depends on COU — but they still rest on core statistical principles —
it takes consortia — regulatory cooperation — AND patience!


Q&A - EVIDENTIARY CONSIDERATIONS
The challenges go beyond what we've heard—
? when it works/doesn't in animals? humans?
? when there's no gold standard?
? when there are more than 3?
It's an extremely exciting area — liver damage— were learning [redacted] far more— the biomarkers are having a tremendous impact & will continue to —
once we QUALIFY one, we're not done— there's more to learn
need to ARCHIVE samples
Sharing information from repositories— allows us to double-dip
Needs: firewalls safeguards
? IRB approval for archived samples?
Think it's less of a concern w/ safety biomarkers - a non-issue/ the main key is de-identification
? How do we leverage what's going on across a whole field? (eg AD) — combining everybody's data
More consortia— there are many examples.
Letter of support is really important—
Databases
Pharma
It's so hard to get > 1 LOR from pharma cos!
Any type of carrots to get companies to contribute their data—
? "Safety biomarkers — the highest standard"? The FDA doesn't always act like that— Is it where the FDA's going?
It's difficult to generalize— and we're also driven by public opinion / pressure—
AND when we are stringent we may be keeping relatively benign drugs off the market—
we should have information content that relates a biomarker to an area of interest— separate from whether its fit for use.
? Ebola — what about emergency biomarkers?
Consortia won't be able to act quickly— Device detection was very engaged—
? We've generated a lot of data— — .. pro-arrhythmia— .. sky's the limit— .. what could we do?
We're working on an assay based on a mechanistic understanding— and the risk is both the drug and the patient profile— We're trying to drive at of the 100% specificity— — specificity mode — it will take some reduction of sensitivity —
? With the good & bad past examples, can we list the standards that we would need, based on our experience?
Needs to be on the action-item list
Look at where we went wrong—
Like attrition analyses
New tools will make it easier to do (uniform standards!)
? What are the enablers to get the data in the future? how we get the data.. start with consent..
We try to make the best use of the data that we do get— we can do this best when we collaborate.

EVIDENTIARY CONSIDERATIONS FOR BIOMARKER-BASED ENRICHMENT OF CLINICAL STUDY POPLATIONS TO INCREASE EFFICACY OR SAFETY OF DRUGS



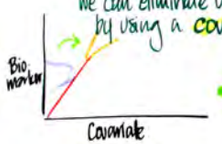
EVIDENTIARY CONSIDERATIONS FOR BIOMARKER-BASED ENRICHMENT OF CLINICAL STUDY POPULATIONS TO INCREASE EFFICACY OF SAFETY OF DRUGS

ENRICHMENT – STATISTICAL CONSIDERATIONS IN BQ

…Diagnosis…Prognosis…Prediction…

PRINCIPLES

- Sources of variation –
  were trying to change things – when the changes are small – before there's damage / illness
  We can eliminate variability by using a **covariate** –



- Random Error can result in misclassification
- The misclassification rate depends on disease **prevalence** – and the ratio of between to within patient ratio
- Sensitivity, Specificity & Predictive Value

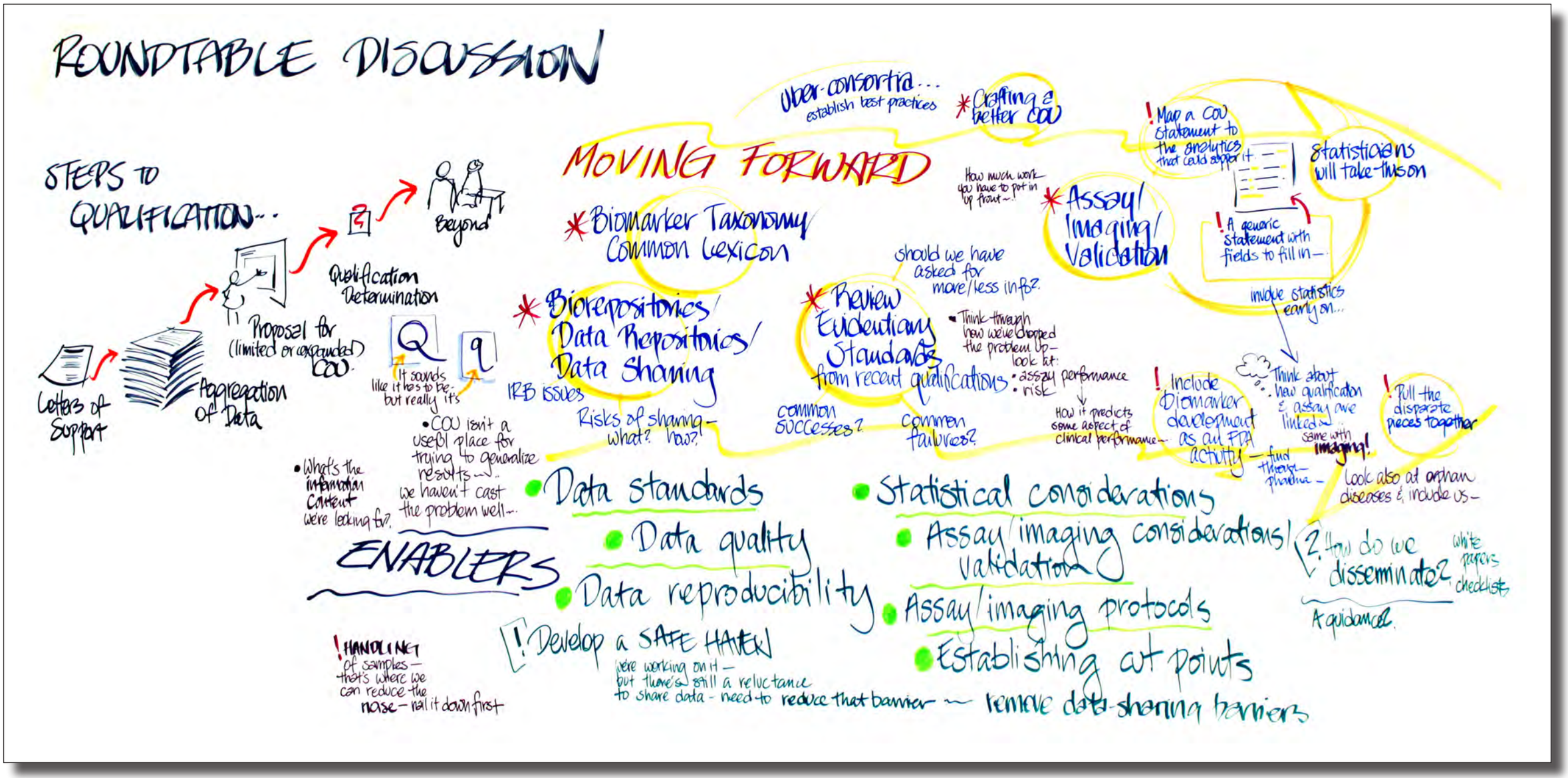
2. What if **slow progressors** respond **faster** to treatment?

If I can't see it, I'm not interested!

more **statistical methods** can help us measure in **smaller** but **accurate measurements** – to **predict earlier** & **intervene sooner**

PANEL

- Understanding the **progression** of a disease – we want to understand any signals in **variability** – . Being able to define **subsets** –
- Quantitate the descriptions of disease progression – easiest to take a **learning** sample & a **validation** sample. – We're not validating the **model**, rather the **biomarker**
- COU vs. **clinical** COU – Prognostic biomarkers usually have a clear COU – There's (1. biomarker does what it's supposed to do (2. what's the **utility** – implications for how many we'll need
- What if we use a biomarker for enrichment & it works – do we have to get an exclusion for the device as well? – The fear we shouldn't do biomarker enrichment is a false fear –
- It's putting the biomarker in the **context** of tools & understanding you have – Amyloidos, HIV – have different uses – using combinations looks at different aspects of the disease –
- Needing **prospective** data in addition to **retrospective** – retrospective will be key – including samples from the course of the trial – not just baseline –
- There can be issues – – is it truly a random sample? – are you salvaging from negative trials?
- Observational studies – can use – and registries – depends on the intended use of the biomarker –


ROUNDTABLE DISCUSSION
STEPS TO QUALIFICATION...
Letters of Support
Aggregation of Data
Proposal for (limited or expanded) COU
Qualification Determination
Beyond
MOVING FORWARD
Uber-consortia... establish best practices
*Crafting a better COU
*Biomarker Taxonomy/ Common Lexicon
*Biorepositories/ Data Repositories/ Data Sharing
IRB issues
Risks of sharing — what? how?
*Review Evidentiary Standards from recent qualifications
common successes?
common failures?
should we have asked for more/less info?
Think through how we've shaped the problem up — look at: assay performance, risk
How it predicts some aspect of clinical performance
*Assay/ Imaging/ Validation
How much work you have to put in up front...
! Map a COU statement to the analytics that could support it
! A generic statement with fields to fill in —
Statisticians will take this on
Involve statistics early on...
! Include Biomarker development as an FDA activity — fluid therapy — phantom
Think about how qualification & assay are linked... same with imaging!
! Pull the disparate pieces together
Look also at orphan diseases & include us —
Q
q
It sounds like it has to be; but really it's
• COU isn't a useful place for trying to generalize results — we haven't cast the problem well...
• What's the information content we're looking for?
ENABLERS
Data standards
Data quality
Data reproducibility
! Develop a SAFE HAVEN
we're working on it — but there's still a reluctance to share data - need to reduce that barrier
! HANDLING of samples — that's where we can reduce the noise — nail it down first
Statistical considerations
Assay/imaging considerations/ validation
Assay/imaging protocols
Establishing cut points
remove data-sharing barriers
2. How do we disseminate? white papers checklists
A guidance?