

DEVELOPING CLINICALLY IMPORTANT (AND USEFUL) ONCOLOGY BIOMARKERS: CHALLENGES AND SOLUTIONS

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Precision Medicine is Biomarker- Dependent - and Requires a New Generation of Clinical Trials!

Healthcare Realities

- Healthcare spending projected ~ \$3.0 trillion*
- Expected to continue to rise 4+%* per year for the foreseeable future
- through 2021 (~20% of economy)
- New cancer cases in the U.S. will increase by 30-40% due to the aging of our population in the next decade - unprecedented

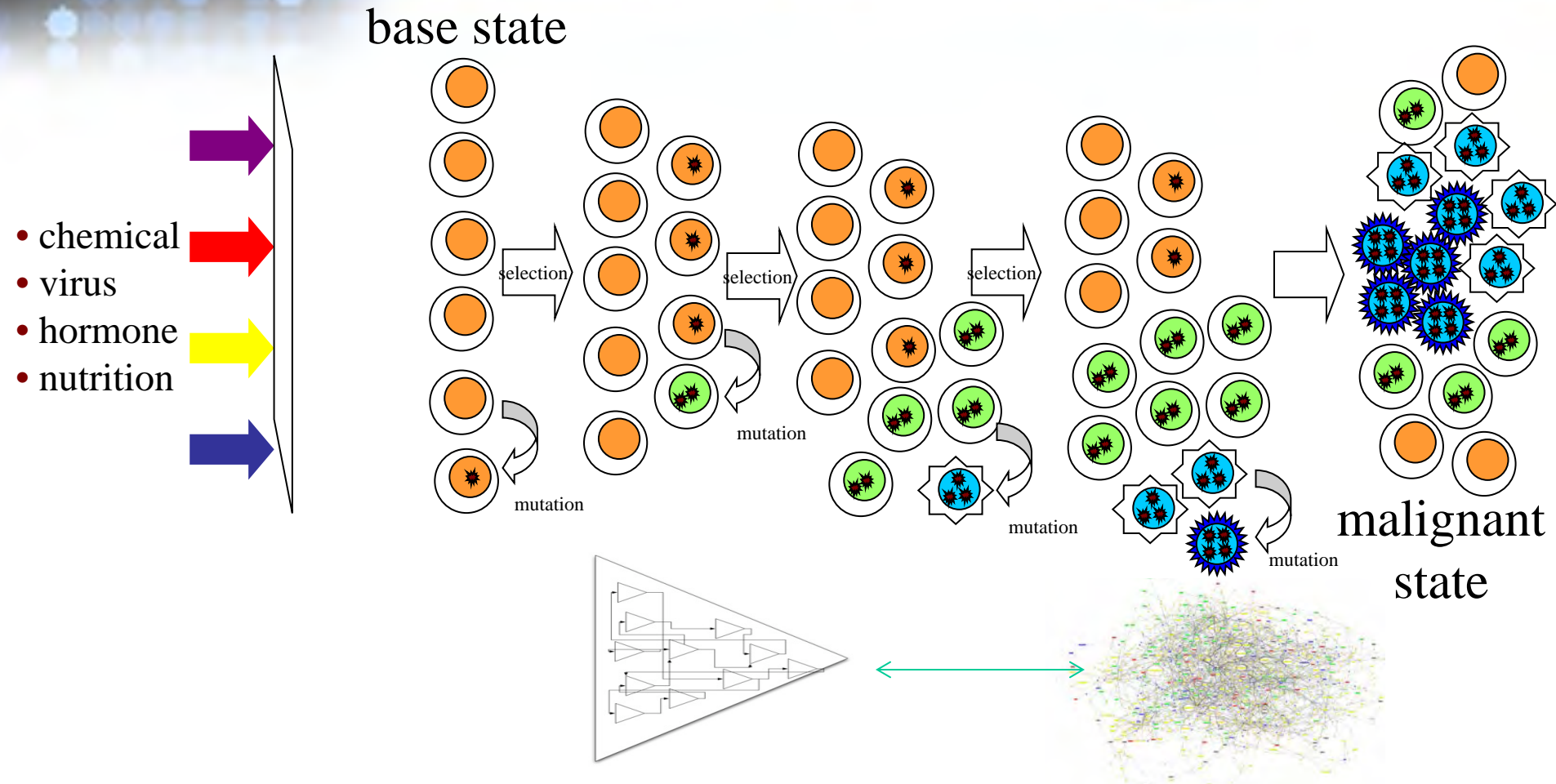
21st Century Medicine

- Early detection and Disease Risk based on molecular profiles (**Molecular Profiles from Patient Biospecimens**)
- Diagnosis based on molecular characterization of patients vs. pathologic analysis (**Biomarkers or signatures from Biospecimens**)
- Molecularly-based treatment using targeted agents (**Biomarker Driven Clinical trials (Biomarkers from Patient Biospecimens)**)
- Patient centric - connects research ➡ clinic ➡ in seamless **feedback loop (Biospecimens tie Research to Clinical Care)**

Precision (personalized) Medicine - Depends on Availability of High Quality HIGH QUALITY BIOMARKERS AND INNOVATIVE CLINICAL TRIALS)

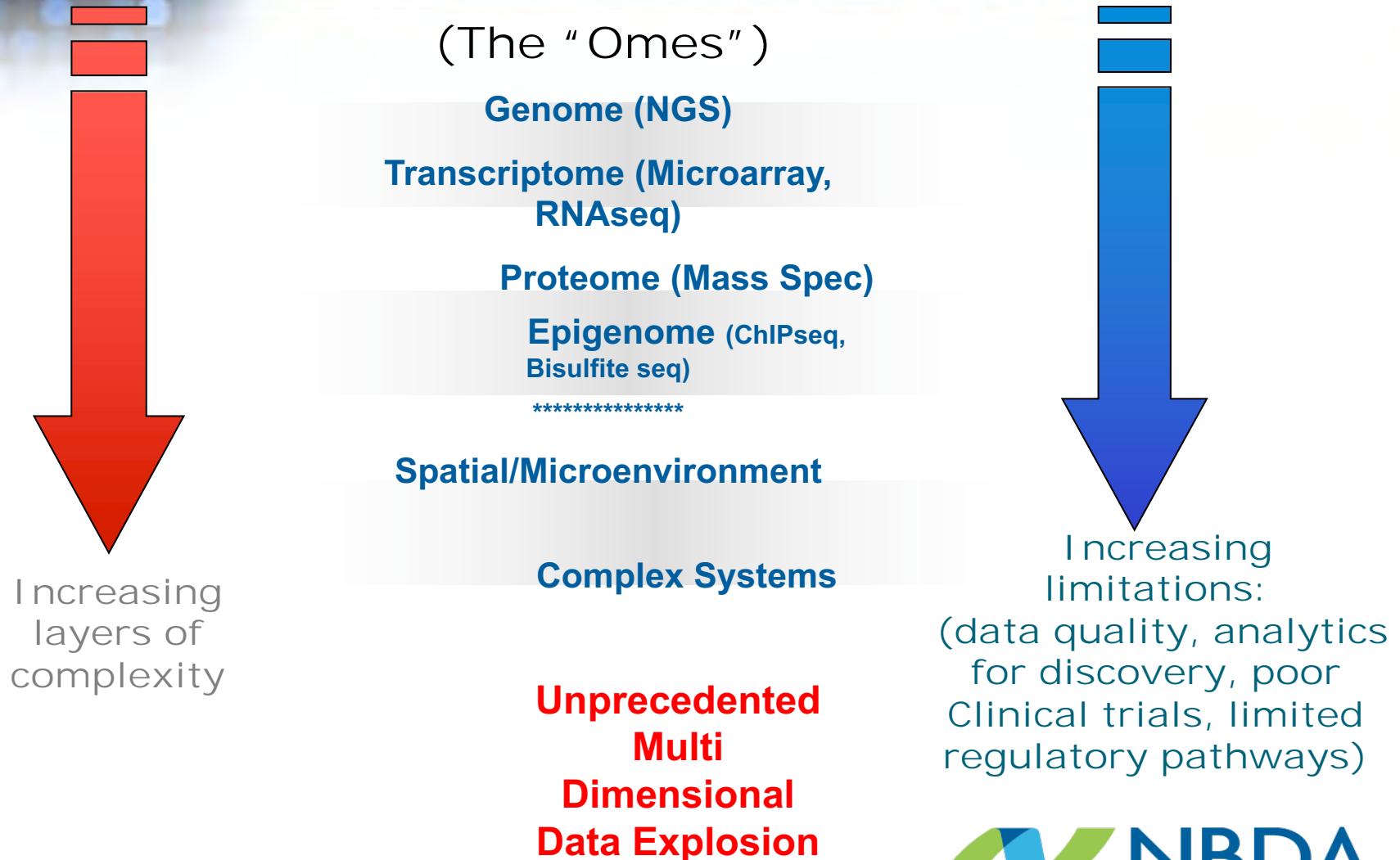
* CMS

Challenge: Cancer is a Complex Evolving System (composed of multiple subsystems)



Co-Evolution of Information-Driven Communication Between Cancer Cells/networks and their Environment (In Context) Across Scales

Challenge: Technology-Driven “Omics” Revolution= Increased Problems in Biomarker Discovery and Development



Challenge: The “Big Data” Explosion in Biomedicine

Adapted from
Laney: Gartner 2001, 2012 NSF/NIH 2012

Variety (Multidimensional
Genomic, Phenotypic,
Clinical Data)
(Complexity will increase)

Velocity
(Sheer rate of
data
generation in
genomics –
exceeding
Moore’s Law)

Major Data Types
Observational data
Experimental data
Simulation data

Volume
(Unprecedented
Amounts of omics
data –And it’s
early)

“ BIG DATA ”

FDA's Critical Path Opportunities Report (2006)

**“consensus
that the two most important areas for improving
medical product development are biomarker
development and streamlining clinical trials”**

<http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm>

Biomarker Definition

- **“A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”**

BIOMARKERS DEFINITIONS WORKING GROUP: BIOMARKERS AND SURROGATE ENDPOINTS: PREFERRED DEFINITIONS AND CONCEPTUAL FRAMEWORK. CLIN PHARMACOL THER 2001;69:89-95.

Clinical Endpoint Definition

- **“A characteristic or variable that reflects how a patient feels, functions or survives”**
- **Usually related to a desired effect, ie efficacy**
- **Clinical endpoints are preferred for use in efficacy trials and are usually acceptable as evidence of efficacy for regulatory purposes**

Janet Woodcock, FDA, 2015

Surrogate Endpoint Definition (The “holy grail of biomarkers – rarely achieved)

- **A biomarker intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm, or lack of benefit) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence**

(Janet Woodcock, FDA, 2015)

We are “awash” in Biomarkers – But few are FDA-approved for clinical use

Estimated number of papers
documenting thousands of claimed
biomarkers

150,000

100

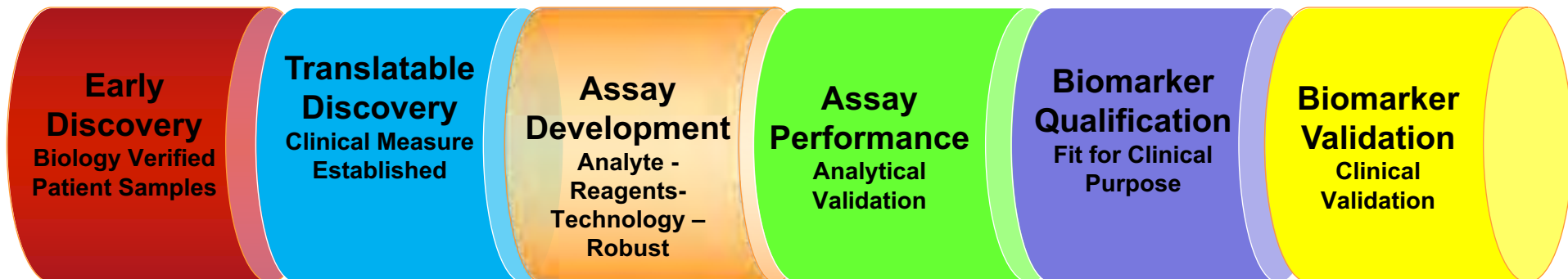


Estimated number of biomarkers
routinely used in the clinic

NBDA: A Biomarker and Clinical Trials “Think Tank”: Understanding and Addressing the Causes of Biomarker and Clinical Trial Failures



The NBDA Concept: End to End Standards-Based Systems for Biomarker Development



Failure begins in early discovery: wrong/irrelevant clinical question, poor samples, inadequate statistical design, no technology standards, poor quality data, lack of robust analysis and analytics

Standards/evidence required for each transition/decision point – failure in any module or system = overall failure!

Paralyzing Problems in Biomarkers Discovery

Biomarker discovery often isn't- most biomarkers should die here!!

Reproducibility of biomarker discoveries can be difficult and/or impossible because:

- ❖ Discoveries often start with irrelevant clinical questions (may address a biologically interesting questions) but not useful in clinical practice.
- ❖ Biomarker discoveries are often based on convenience samples
- ❖ Lack of a rigorous end-to-end appropriately powered statistical design (based on discovery and validation samples)
- ❖ Lack of (or ignore existing) technology standards
- ❖ Data and meta-data quality and provenance is often inadequate to poor
- ❖ Analysis and analytics are often inappropriate/inadequate for the sophistication of the clinical question and/or design

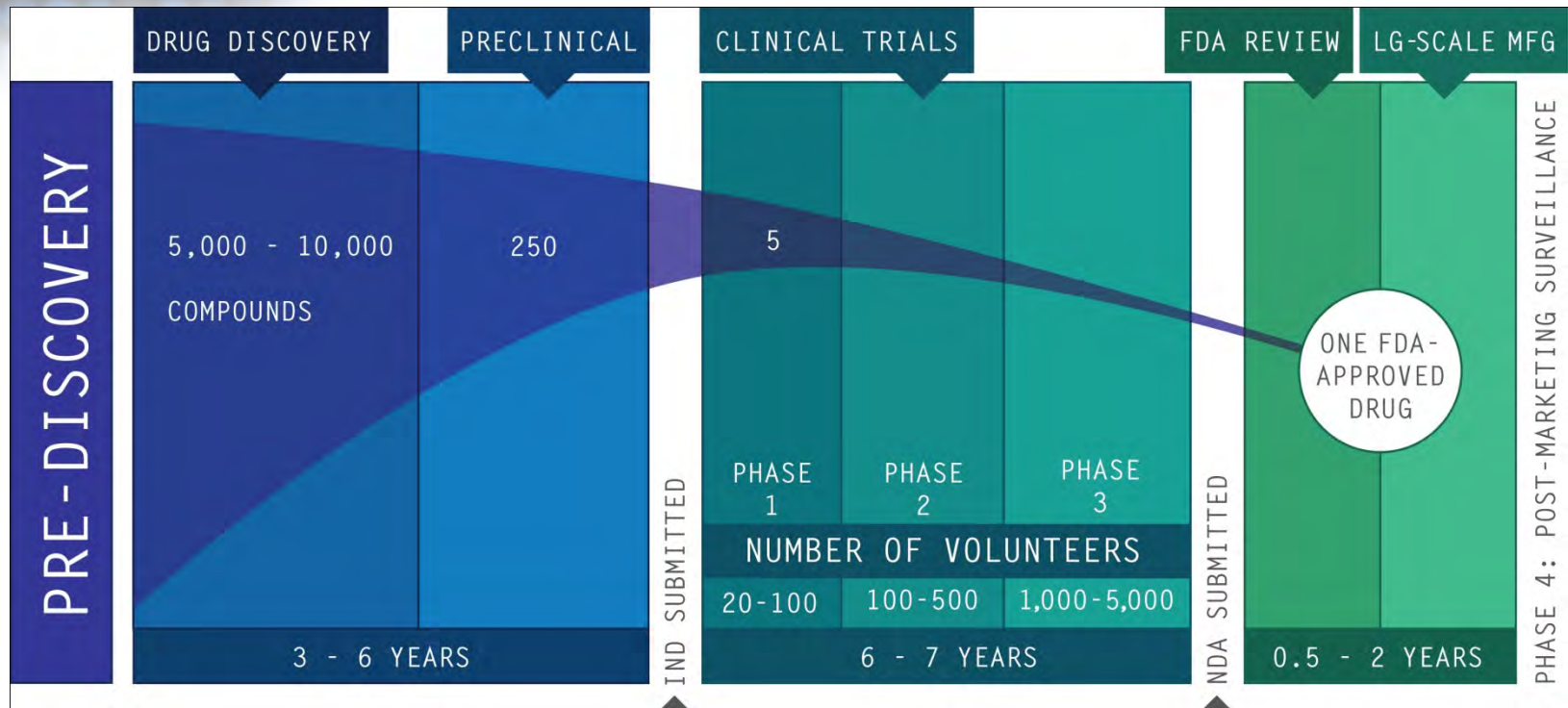
Biomarkers: Some Actions that We Should Take – and One Example of a Transformative Approach

The future of precision medicine will be driven in large measure by biomarkers (e.g., predictive, prognostic, surrogate endpoints, etc.)

- Biomarker discovery intended for serious clinical application must begin with a roadmap – end-to-end - what it will take to prove the specific context of use
- Standards must drive the biomarker discovery and development process
- Biospecimens will require extensive characterization (including pre-analytics)
- Controls will take on new meaning – test sets must be assessed and re-assessed against appropriate controls
- Quality data must become the norm –will need meta-data and provenance
- Sheer volume of data will require robust mathematical models and AI

Example: New clinical trials model that enable the validation and regulatory approval of clinically useful biomarkers

Biomarkers and Oncology Clinical Trials : Massive Attrition, Long Duration, High Costs

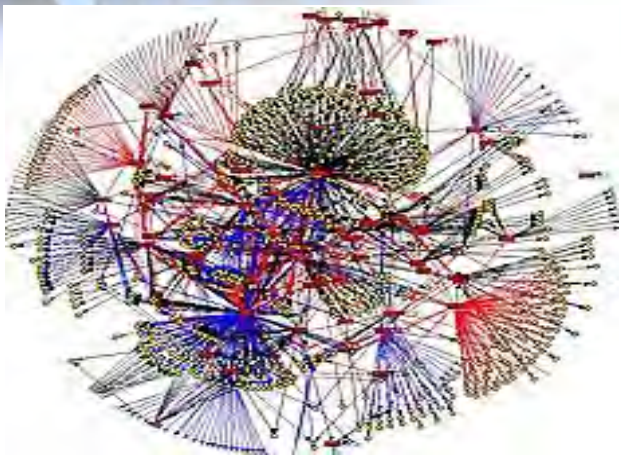


5-10,000:1 chance of success

12 Years

~ US\$ 2.0 B

Time and attrition are both directly related to lack of validated biomarkers of efficacy and toxicity



EXAMPLE: NEW CLINICAL TRIALS MODEL THAT ASSESS BOTH THE BIOMARKER(S) AND THE TEST AGENT(S) IN A FRAMEWORK THAT SUPPORTS THEIR REGULATORY APPROVAL(S)

Why a Community Designed and will Conduct the GBM AGILE? The Status Quo for GBM is “Unacceptable” *

- **Glioblastoma (GBM) is the most common adult brain tumor – no established causes**
- **There are ~14,000 cases diagnosed in the U.S., ~40,000 cases estimated for China annually**
- **The median survival for GBM patients is 14.6 month (less than 30% of patients will survive more than 2 years, 50% will die in the first year and 95% will be dead in 5 years)**
- **GBM cells are almost always “metastasized” within the brain, but rarely metastasize to the CNS**
- **Hundreds of clinical trials performed over several decades, with virtually no learning from these trials.**
- **Temozolomide (TMZ), a cytotoxic approved in 2004, increases average survival from 8.1 months to ~ 15 months**
- **Ironically, GBM is one of the best molecularly characterized cancer to date (via NCI’s TCGA project), but the knowledge has not enabled therapeutic successes**

* The GBM Global Team (~150 experts, survivors and advocates from the U.S., Australia, China and Europe to date) reached consensus in 2014 that GBM was “unacceptable” and undertook two years of work to design, re-design, fund and implement GBM AGILE. (The GBM AGILE collaboration is organized and managed through the non-profit National Biomarker Development Alliance , ASU Foundation)

GBM AGILE (Adaptive, Global, Innovative, Learning Environment)

GBM AGILE: A potentially transformative adaptive platform trial (performed under a Master protocol) where agents that are successful in “stage 1” can proceed seamlessly via algorithm to stage 2

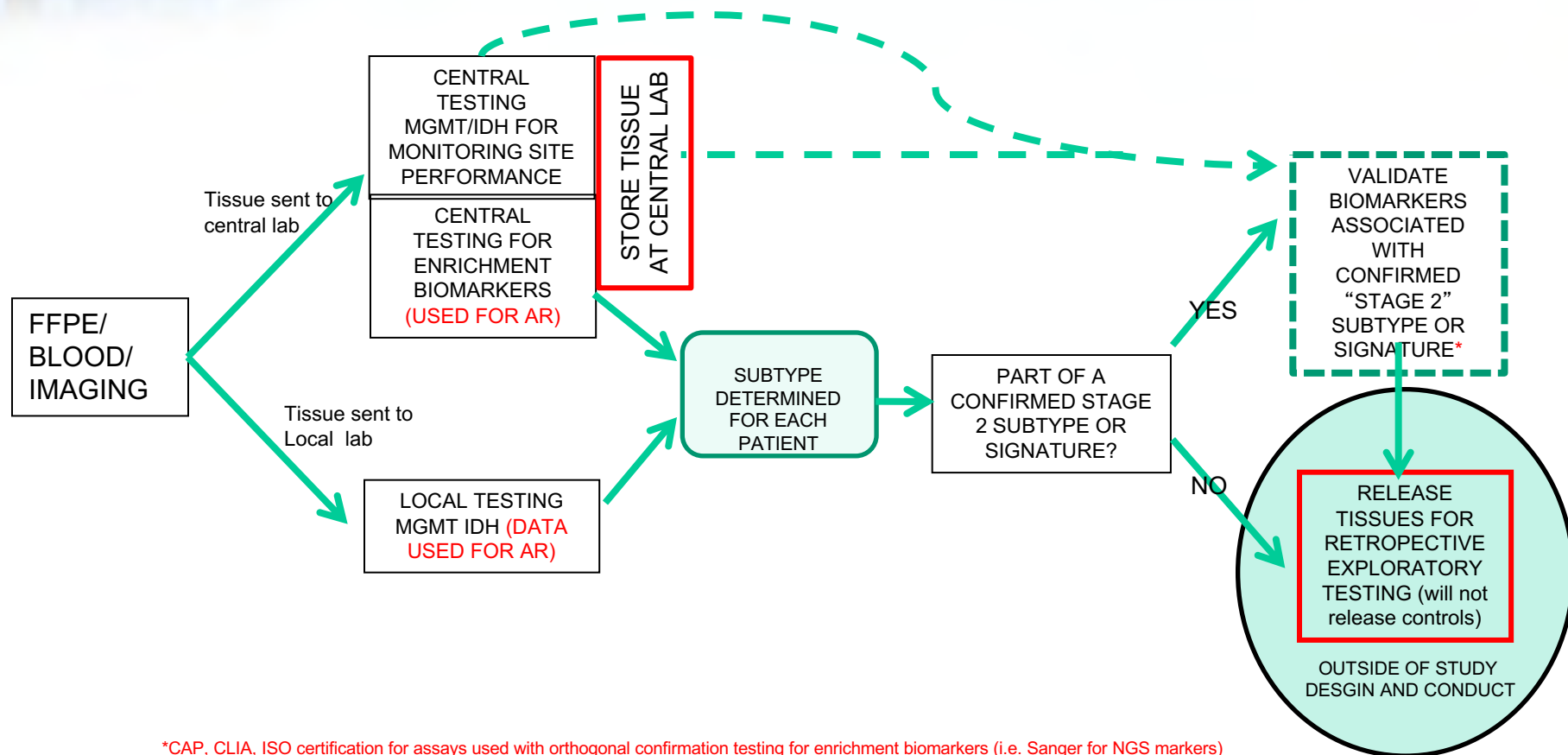
- **Focused on the disease – Likely the future for clinical trial (especially rare diseases)**
- **AGILE is not just any seamless transition – stage 1 (essentially a phase 2 screening trial via algorithm to stage 2 (essentially a phase 3 registration trial**
- **Biomarker strategy and regulatory approach could serve a model for how to develop biomarkers in a world that merges care and research**

Overview of GBM AGILE Biomarker Strategy

Biologically-based strategy:

- **Inclusion**—Defines biomarker inclusion into the trial
 - Isocitrate Dehydrogenase 1 (IDH1) (measured via IHC)*
 - IDH1 wild type GBM (95% of adult disease) focus for GBM AGILE
- **Stratification** – Defines patient “subtype” base upon line of therapy and biomarker predicting benefit of therapy.
 - 1st Line: O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation*
 - 2nd line: no biomarker predicting benefit of therapy
- **Enrichment** – Further defines patient “subtype” based upon pre-treatment biomarker hypothesized to be predictive of response to a specific experimental arm (One Per experimental arm, pretreatment tissue, FFPE, leverages TCGA)

Tissue Flow and Validation Process for Stratification and Enrichment Biomarkers in GBM AGILE



*CAP, CLIA, ISO certification for assays used with orthogonal confirmation testing for enrichment biomarkers (i.e. Sanger for NGS markers)

Achieving Clinically USEFUL Biomarkers in Oncology Requires Sweeping Change!



"It is not the strongest of the species that survives, nor the most intelligent, but the one most responsive to change."

Charles Darwin
(1809-1882)

The World Is Flat, Thomas L. Friedman,
Farrar, Straus & Giroux, publisher