The Power of Study Design

6th Semi-Annual Clinical Affairs & Regulatory Approvals For Diagnostics

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Key Points

Study design:

Things to consider

FDA regulation of LDTs:

Keep doing what you're doing well

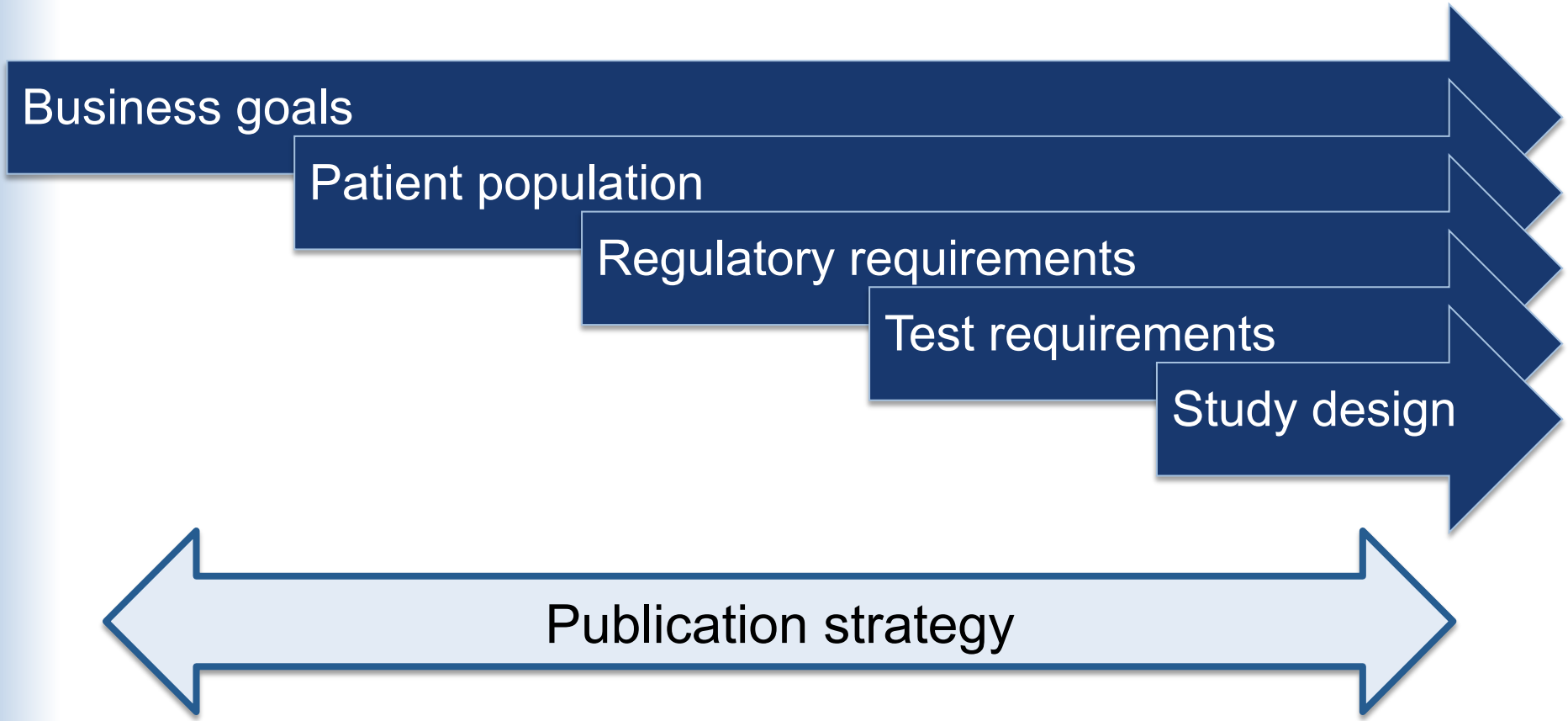
Publication → success

Case Study

Successes and lessons learned

Study goals = company goals

Start with the goal and work backward



Business goals

- Business strategy
- Unmet clinical need
- Target customer(s)
- Market and market size
- Messaging strategy
- Geography
  - States (CLIA)
  - US/global
- Reimbursement plan
- Revenue goals

Patient population

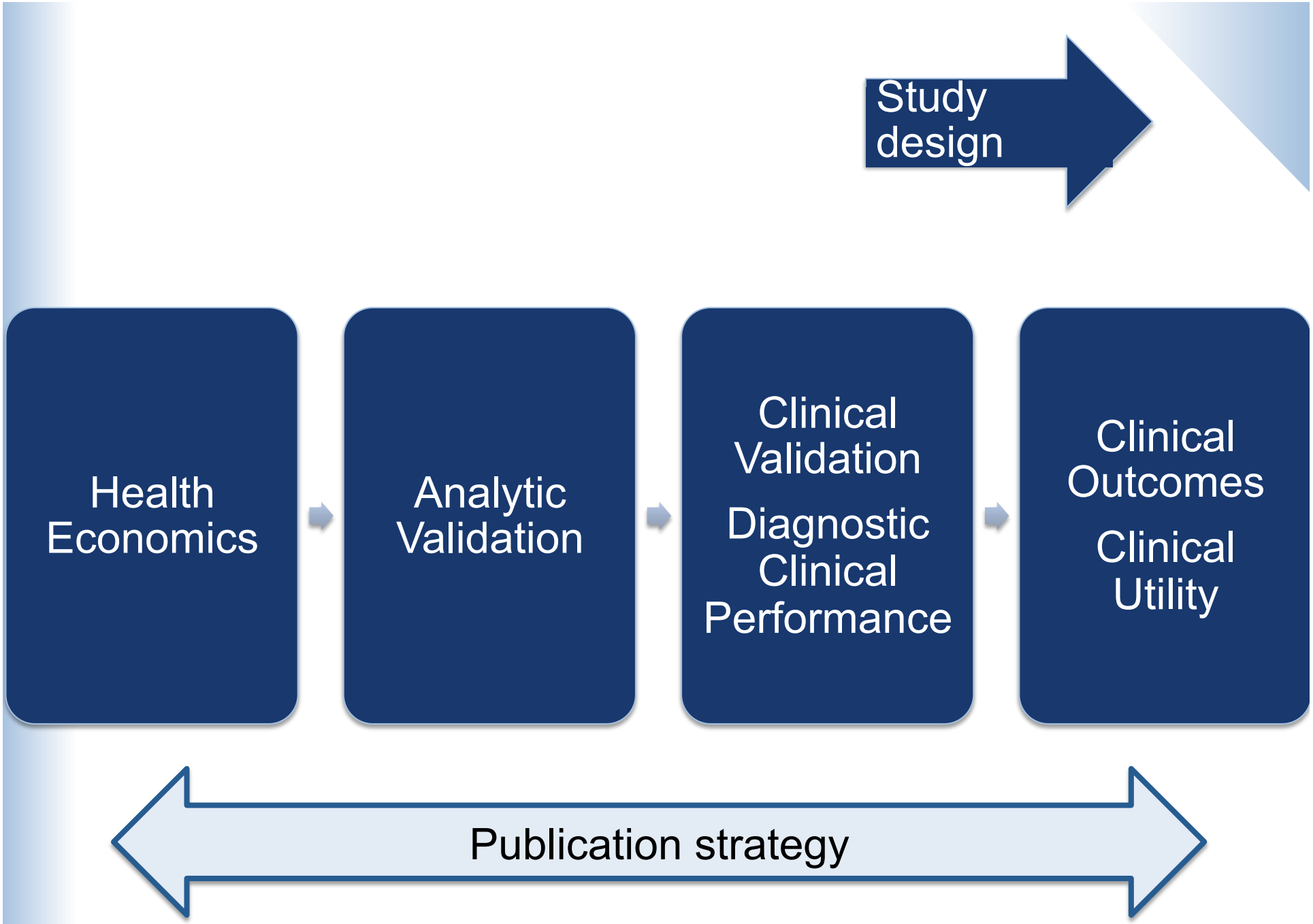
- Disease/health condition
- Unmet clinical need
- Gold standard
- Current landscape
  - Diagnostic tools
  - Best practices
  - Clinical guidelines

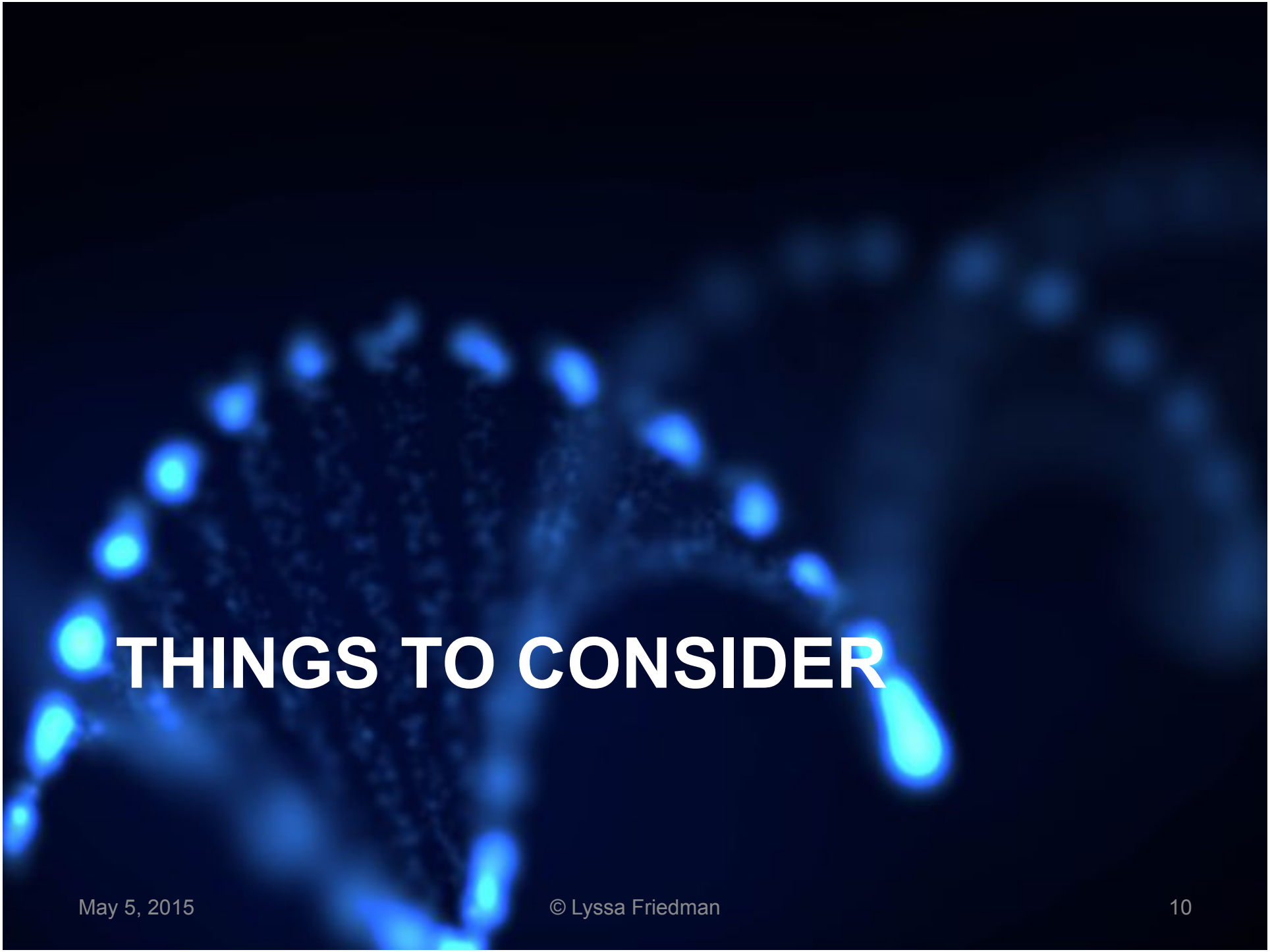
Regulatory requirements

- Risk classification
- LDT regulated by CLIA
- IVD
  - 510(k)
  - PMA
  - de novo
  - HDE
- Companion diagnostic
- Kit manufacturing

Test requirements

- Performance characteristics
  - Sensitivity
  - Specificity
  - Negative predictive value
  - Positive predictive value
- Test results
  - Continuous score
  - Discrete result
- Clinical significance





Study design

Health Economics

- Payer modeling
- Verify unmet need
- Verify market

Why commercialize? What business benefit?

Health Economics:
Consider the payer

- Market
- Payer landscape
- Target price
- Revenue targets
- Product positioning
- COGS

Study design

Analytic Validation

- Verify assay robustness
- Commercial readiness
- CLIA registration

Will the assay work? Is it submission-ready?

Analytic Validation
Consider the customer

Variability in handling at point of collection

Interruptions in current practice flow

Requisition form design

Patient report design

Study design

Clinical Validation

Diagnostic Clinical Performance

- Establish test performance
- Gold standard
- Intended use
- Support
  - FDA submission
  - CLIA registration (some states)
  - Publication plan
  - Physician adoption
  - Guideline acceptance
  - Payer adoption

Will the data be published? Will physicians order the test?
Will it withstand regulatory scrutiny? Will payers reimburse?

Clinical Validation/Diagnostic Performance
Consider the business and regulatory needs

Engage agency prior to initiating study

Clarify intended use

Identify a reference (gold) standard
- Consistent with practice
- Recognized by community/literature

Enroll subjects that represent target patients

Select sites that support intended use

Pre-specify
- Sample collection/handling procedures
- Analysis methods
- Use of archived samples (if needed)

Study design

Clinical Outcomes

Clinical Utility

- Patient outcome based on test use and results
- Randomized control trial
- Changes in physician behavior

What difference does it make to patient outcomes?
What difference does it make to healthcare costs?

Clinical Outcomes/Clinical Utility

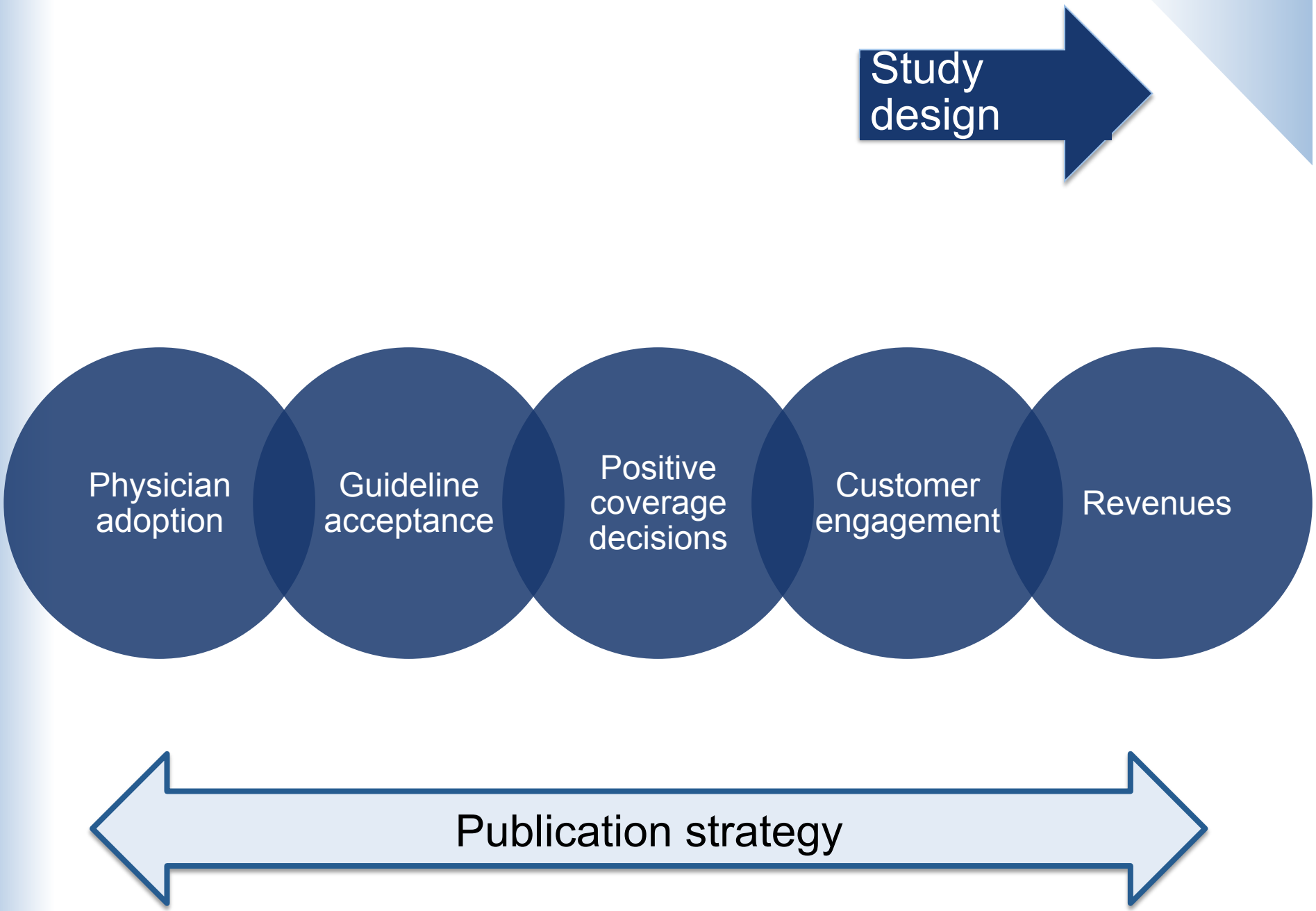
Consider the payer

Consider the patient

Effect on patient outcomes

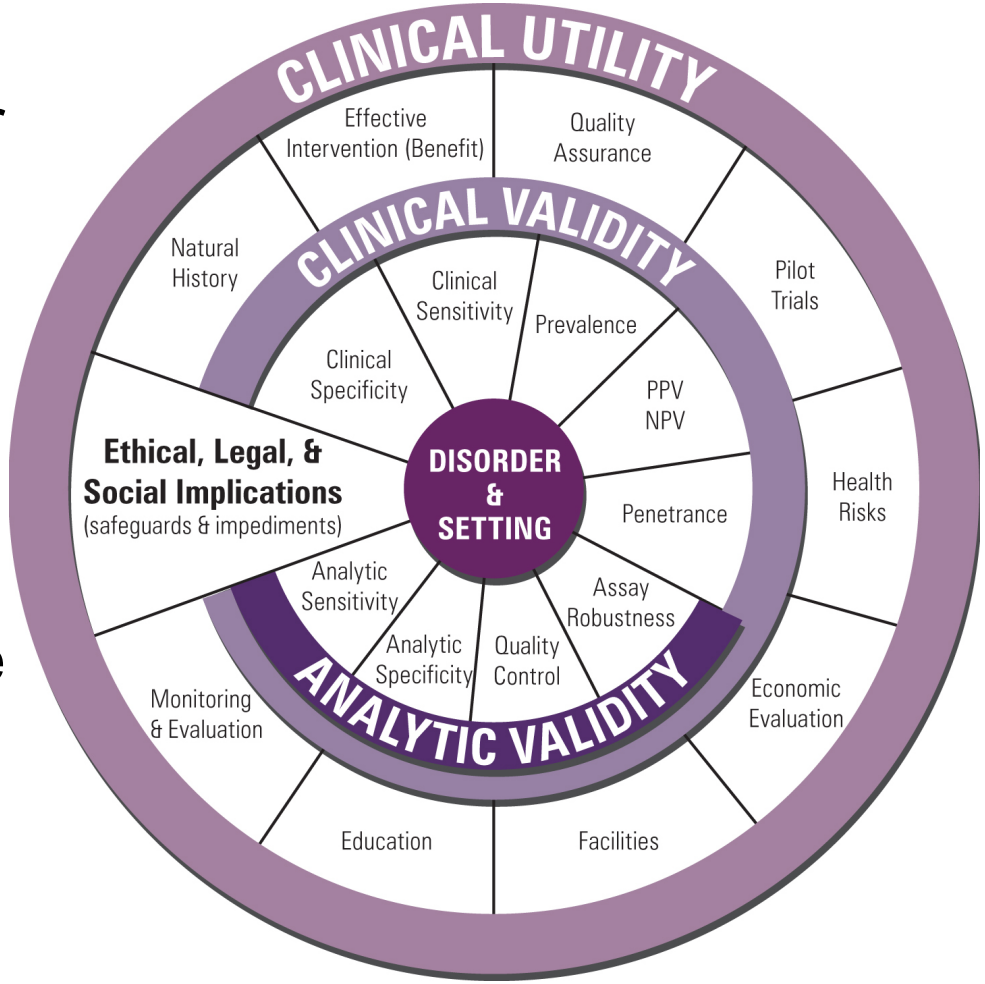
Ethics of randomized controlled trial when marketed test available

Effect on healthcare costs

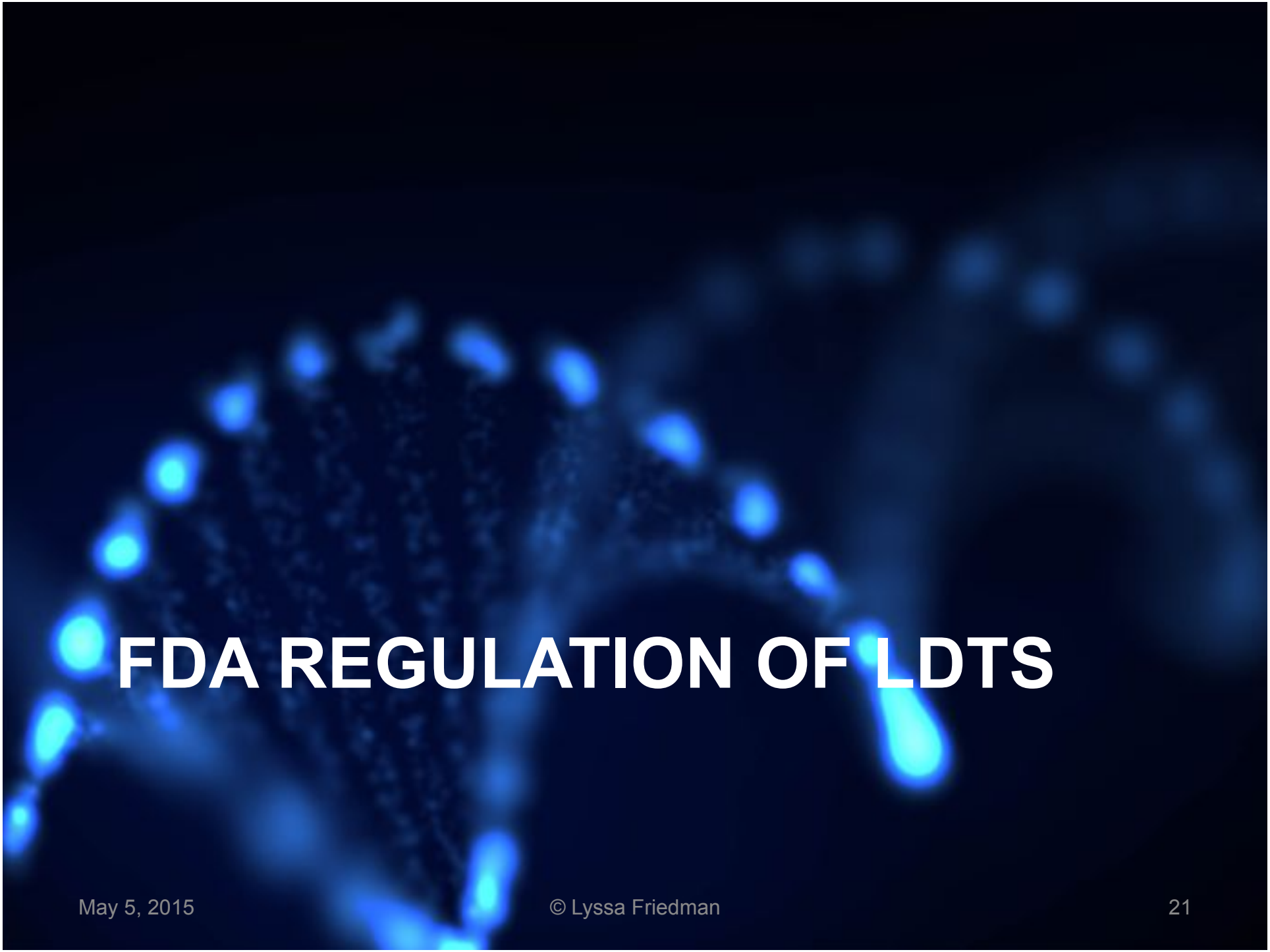


Publication strategy

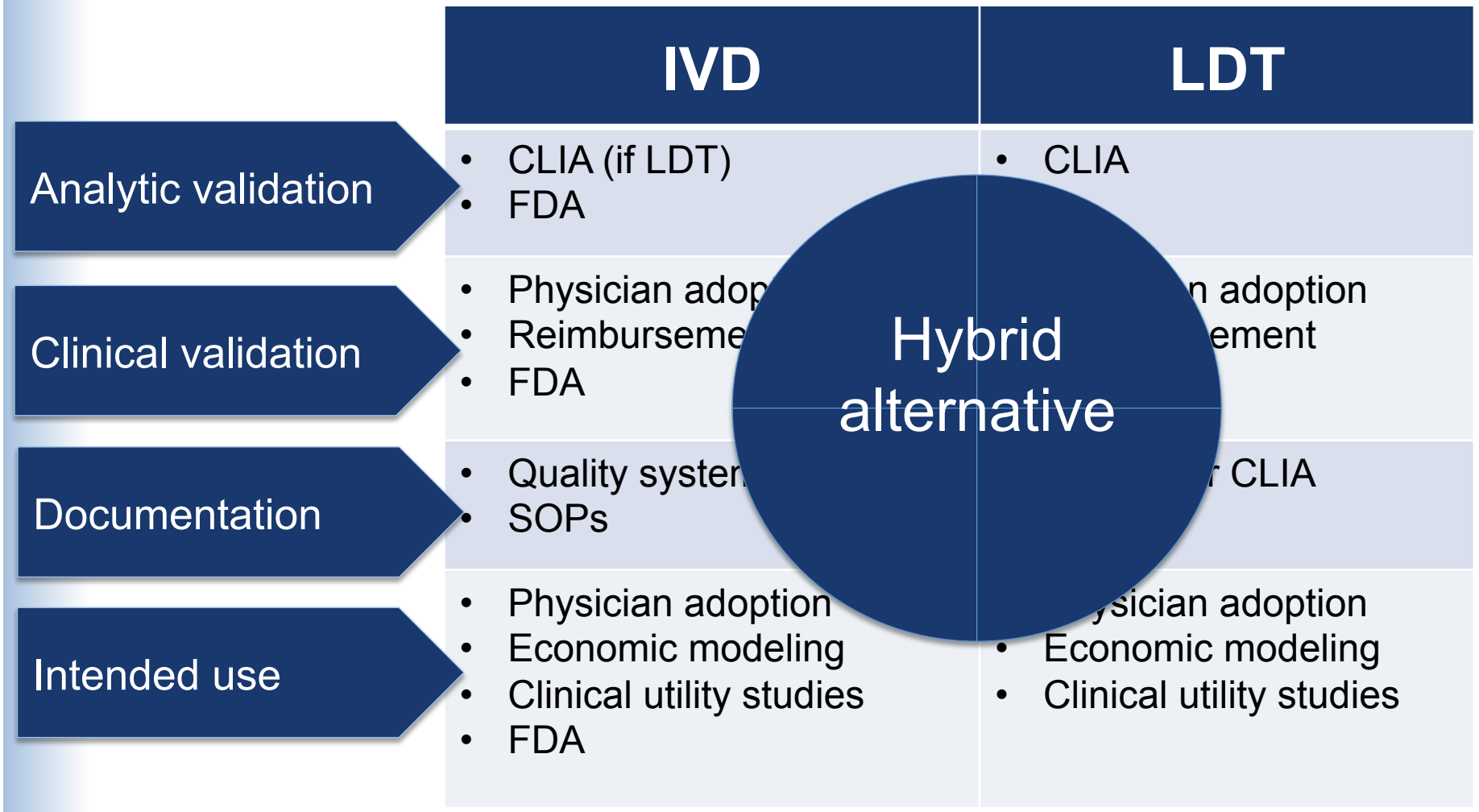
- ACCE Evaluation Process for Genetic Testing
  - **A**nalytic validity
  - **C**linical validity
  - **C**linical utility
  - **E**thical/legal/social
- Publications in these areas build the reimbursement case



Centers for Disease Control (CDC) Office of Public Health Genomics
Evaluation of Genomic Applications in Practice and Prevention (EGAPP™) Initiative



FDA regulation of LDTs

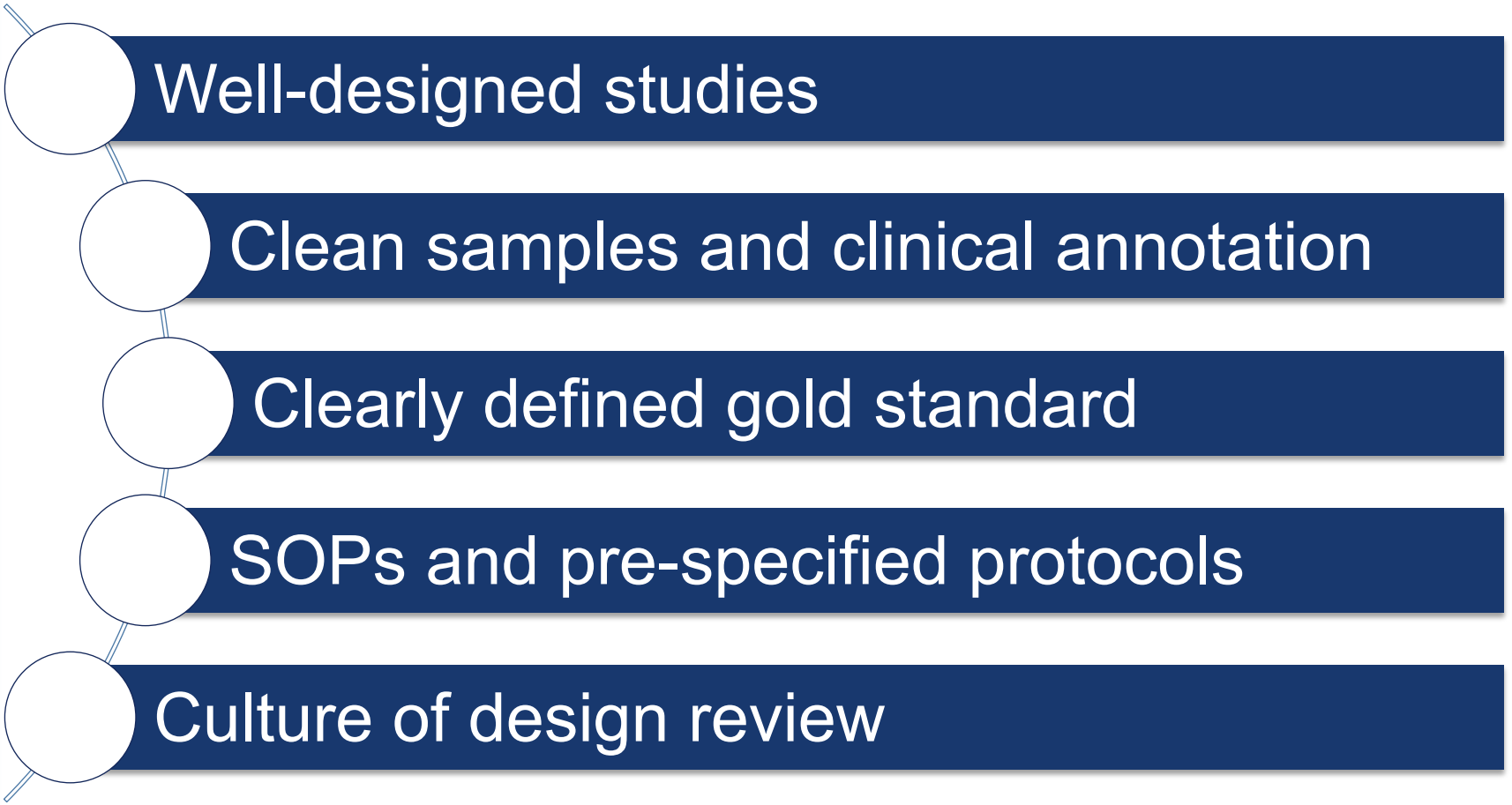


Diagnostic Test Working Group
An alternative to the FDA framework

- Would apply to all in vitro diagnostic tests
- Allocates IVD oversight responsibility across FDA, CMS and states
  - FDA: IVD development
  - CMS: lab operations
  - States: medical applications
- Sets criteria based on risk classification (high, moderate, low)
  - Can move from high to low when test and/or analyte becomes well characterized
  - Different premarket requirements based on risk
- Sets a new standard for IVDs: reasonable assurance of analytic validity and clinical validity for intended use
  - Includes published literature, guidelines in lieu of clinical trials for clinical validity
- Post-market quality system and recall reporting generally same as current FDA device requirements
- Proposed 3-4 year transition period for currently marketed LDTs and those entering market after proposal goes into effect
- Participating companies may include Becton Dickinson, Roche, Mayo Clinic, LabCorp, ARUP labs

http://www.fdalawblog.net
https://www.genomeweb.com

Keep doing what you're doing well



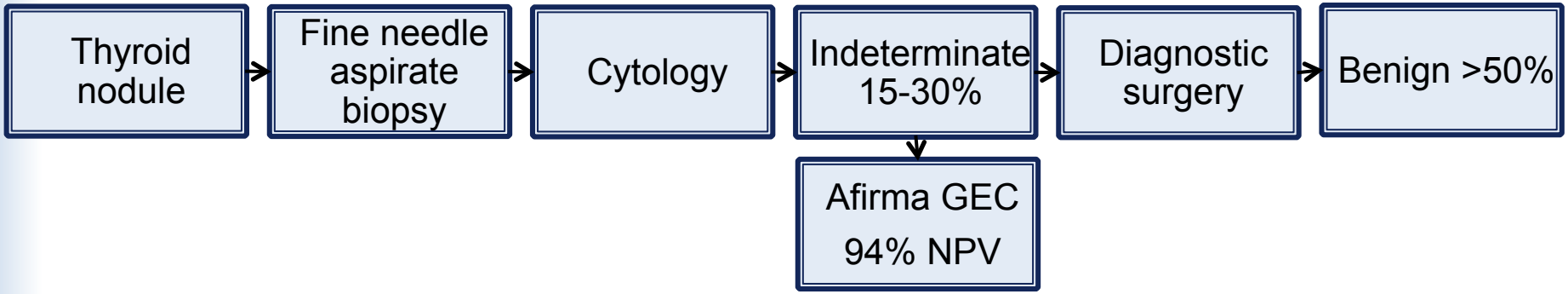
Site Selection
What are the goals?

- Study completion
- Accrual numbers
- Adherence to Good Clinical Practices
- Pristine samples
- Verifiable data
- Strategic relationship building

Key opinion leader | Collaborator | Influencer | Geographic significance

CASE STUDY AND LESSONS LEARNED

Case Study



- 142 genes, microarray
- Gold standard: histopathology (central panel)
- Optimized for sensitivity/NPV – safe to avoid surgery
- Company launched 2008 (IVDMIA) – design control implemented
- Product launched as LDT 2011
- Key publications
  - 2010: first clinical validation
  - 2011: economic model/cost effectiveness (replacement for surgery)
  - 2012: second clinical validation, clinical utility (change in recommendation for surgery)
  - 2013: second clinical utility, limits of gold standard

Case Study: Success/Challenges

Things that worked

- Funded on business plan – agnostic regarding clinical platform
- All-hands focus on rapid first product to market
- Aggressive publication plan – never missed an abstract deadline!
- Small niche market – close relationship with major KOLs and influencers, who were clinical sites, early customers, authors/speakers
- “Boutique” approach to managing clinical sites, even if challenging
- Two clinical validation studies using one amended clinical sample collection protocol
- IVDMIA era – design control

Lessons learned

- “Tarnished” gold standard required publication, customer education
- NPV as key message – refuted based on practice variations in malignancy prevalence significantly

What does success look like?

- Design a business plan that drives R&D and product development
- Build early relationships with KOLs and influencers
- Strategize cross-functionally from the beginning
- Stick to a long-term strategic publication plan
- Commit to a quality system (LDTs)
- Create a culture of design review with external reviewers (LDTs)
- Adhere to a milestone-based plan aligned with corporate goals
- Maintain relationships with strategic sites – even if challenging
- Never miss an abstract submission deadline
- Partner with marketing/sales group to transition sites to early customers

What are lessons learned?

Be willing to change thinking quickly and flexibly

Challenge market research assumptions when clinical operations offers counter-intel

Don’t underestimate the competition and the naysayers

Stress test the product messaging with regard to test performance