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FDA Regulation of Genomic Testing: Will Regulation Do More Harm Than Good?

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Changing Legal Environment

- Restructuring of genetic testing industry
  - *Ass'n for Molecular Pathology v Myriad* (2013)
  - *Mayo Collaborative Svcs v Prometheus* (2012)
  - HIPAA/HITECH data sales & pricing (2013)
- CLIA-HIPAA access rights (10/6/2014)
- Existing FDA research regulations
- FDA draft guidances (10/3/2014)
  - Regulatory oversight of LDTs
  - Notification and medical device reporting for LDTs
- FDA NGS discussion paper (12/29/2014)
- Precision Medicine Initiative (1/30/2015)

Calls for FDA to Regulate Genetic Tests

NIH-DOE Joint Task Force 1997:

Expressed concern about FDA's enforcement discretion for LDTs and called for advisory committee to help FDA assess options

SACGT 2000 recommendations:

"FDA should play a central role in serving as the ''gatekeeper'' for the introduction of new tests. … FDA's review will focus on assuring the analytical and clinical validity of a test."

65 Fed. Reg. 21107-08 (Apr. 9, 2000)

FDA vs. CLIA Regulation

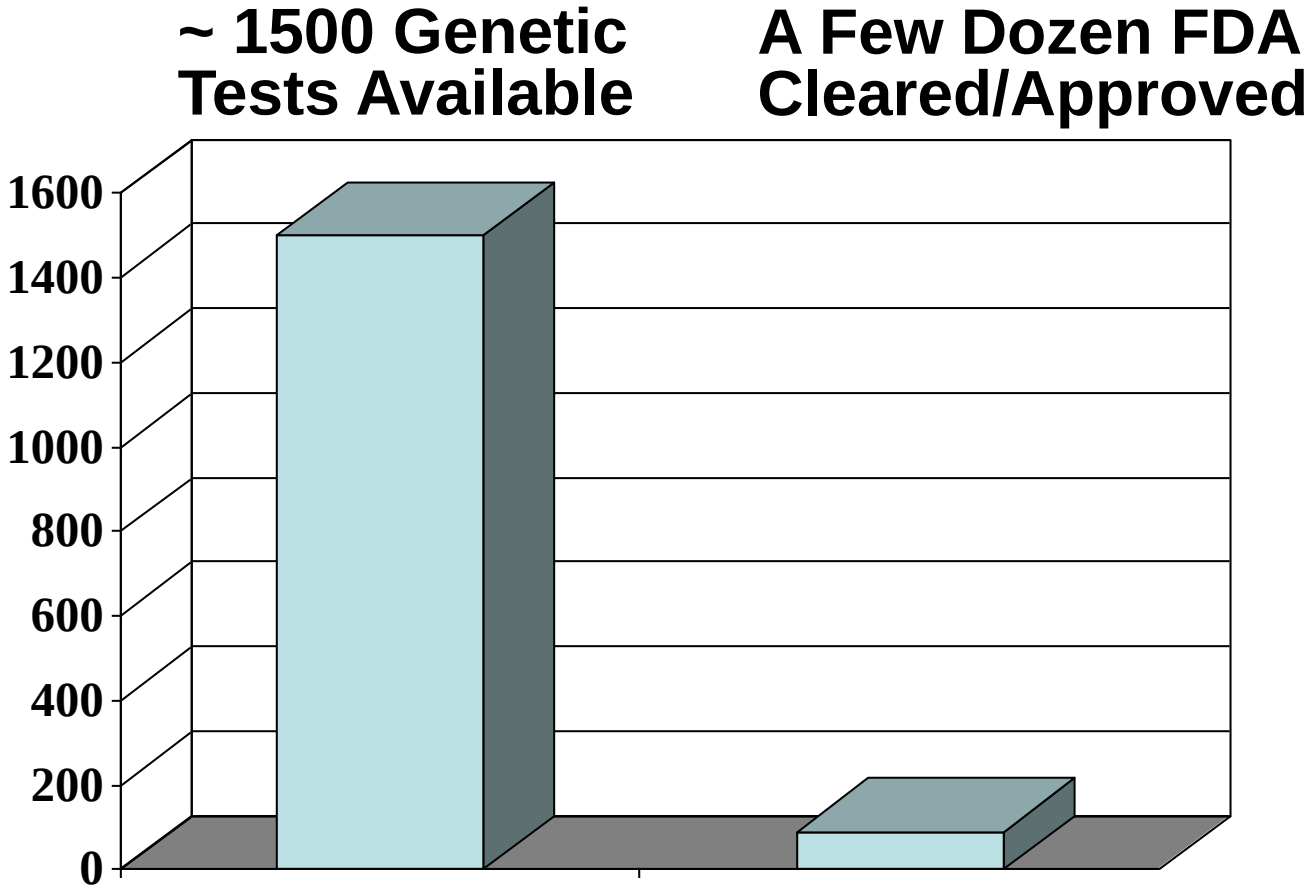
In vitro diagnostic product (IVD product)

- "Test kits" made by a device manufacturer
- Sold to labs for use in clinical testing
- Traditionally regulated by FDA

Lab-developed tests

- Made by labs for own use in testing patients
- Lab may make its own chemicals or buy them
- Bought chemicals can include FDA-regulated analyte-specific reagents (ASRs) made by device manufacturers
- Regulated by CMS
- FDA claims it has authority to regulate, but exercised enforcement discretion *until now.*

FDA Oversight of Genetic Tests



GeneTests, www.genetests.org; SACGHS "US System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of HHS" (2008).

Secretary's Advisory Cmte. for Genetic Testing: WHAT MAKES GENETIC TESTING "SAFE AND EFFECTIVE"?

1. Analytical Validity
2. Clinical Validity
3. Clinical Utility ["actionability"]
4. Social Consequences

SACGT, "Enhancing the Oversight of Genetic Tests" (2000)

Secretary's Advisory Council for Genetic Testing
CRITERIA TO ASSESS RISKS AND BENEFITS

1. Analytical validity. Does the test work? Does it identify the targeted genetic mutation? What are the rates of false positives and false negatives?

2. Clinical validity. Does the presence of the mutation shed light on whether the person's health will be affected?

Secretary's Advisory Council for Genetic Testing: CRITERIA TO ASSESS RISKS AND BENEFITS

3. Clinical Utility. Will knowing 1 & 2 actually improve health outcomes? Can anything be done in response to test results? Are there treatments, effective surveillance strategies, or risk-avoidance behaviors that will help?

4. Social Consequences. Stigmatization, discrimination, reproductive impact.

The question is not whether FDA can regulate genomic testing. The question is whether FDA can regulate genomic testing *well*.

"Under the FD&C Act, the FDA assures both the analytical validity and the clinical validity of diagnostic tests through its premarket clearance or approval process."

- FDA *LDT draft guidance*

Premarket review of genomic tests poses "certain challenges" that will require "novel approaches" to ensure analytical and clinical validity.

- FDA *NGS discussion paper*

Gene Sequencing Technology

≈ 3 billion base pairs per genome times two genomes per person

WGS reads essentially all of them

WES reads the 1.5% that codes proteins

≈ 22,000 human genes and many possible variants of each gene

WES: ≈ 10,000 variants per person

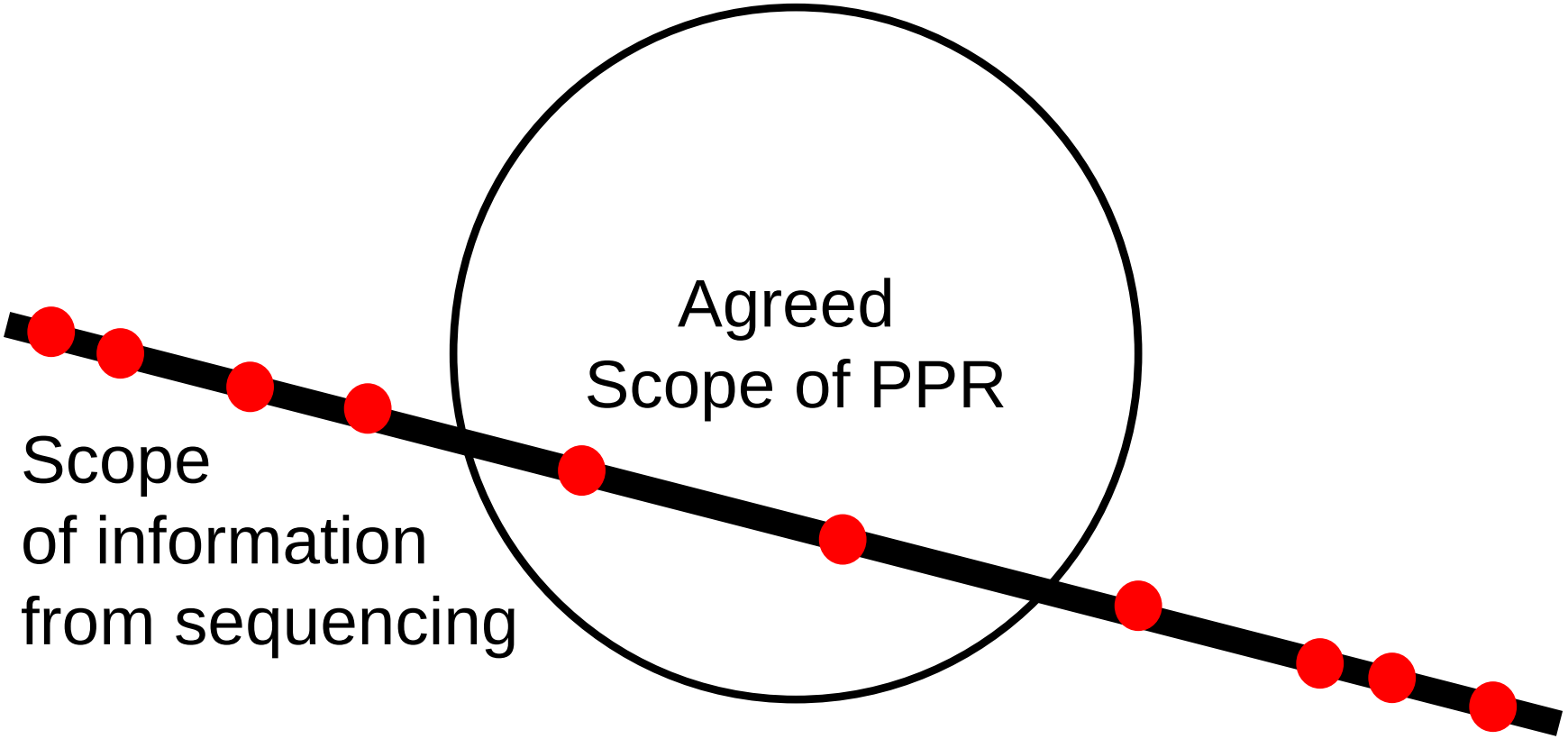
WGS: about 3 – 5 million per person

Variants of Unknown/Uncertain Significance (VUS): Clinical Validity and/or Utility Unknown

At least 90 – 125 variants merit further evaluation for clinical significance based on current knowledge *Dewey et al, JAMA 2014;311:1035*

57 variants (involving 56 genes) have enough clinical significance and clinical utility/actionability to warrant a deliberate search whenever clinical WGS or WES is performed *ACMG 2013*

Clinical Sequencing and the Physician-Patient Relationship



Problems with Premarket Review

Each human gene has many variants, just as one airline can have many aircraft

Different people “ride” on different variants of the same gene

FDA’s premarket review can clear or approve a genetic test based on evidence that one variant (or a subset of its variants) has clinical significance

Problems with Premarket Review

FDA's premarket review processes are analogous to an airline safety regulation that requires every airline to demonstrate that *one* of its planes is safe and effective to fly.

Establishing clinical validity of gene variants is inherently a postmarketing process.

FDA presently lacks a sufficient set of authorities for the required postmarketing regulation.

Genomic Regulatory Challenges

Privacy and Human Subject Protections

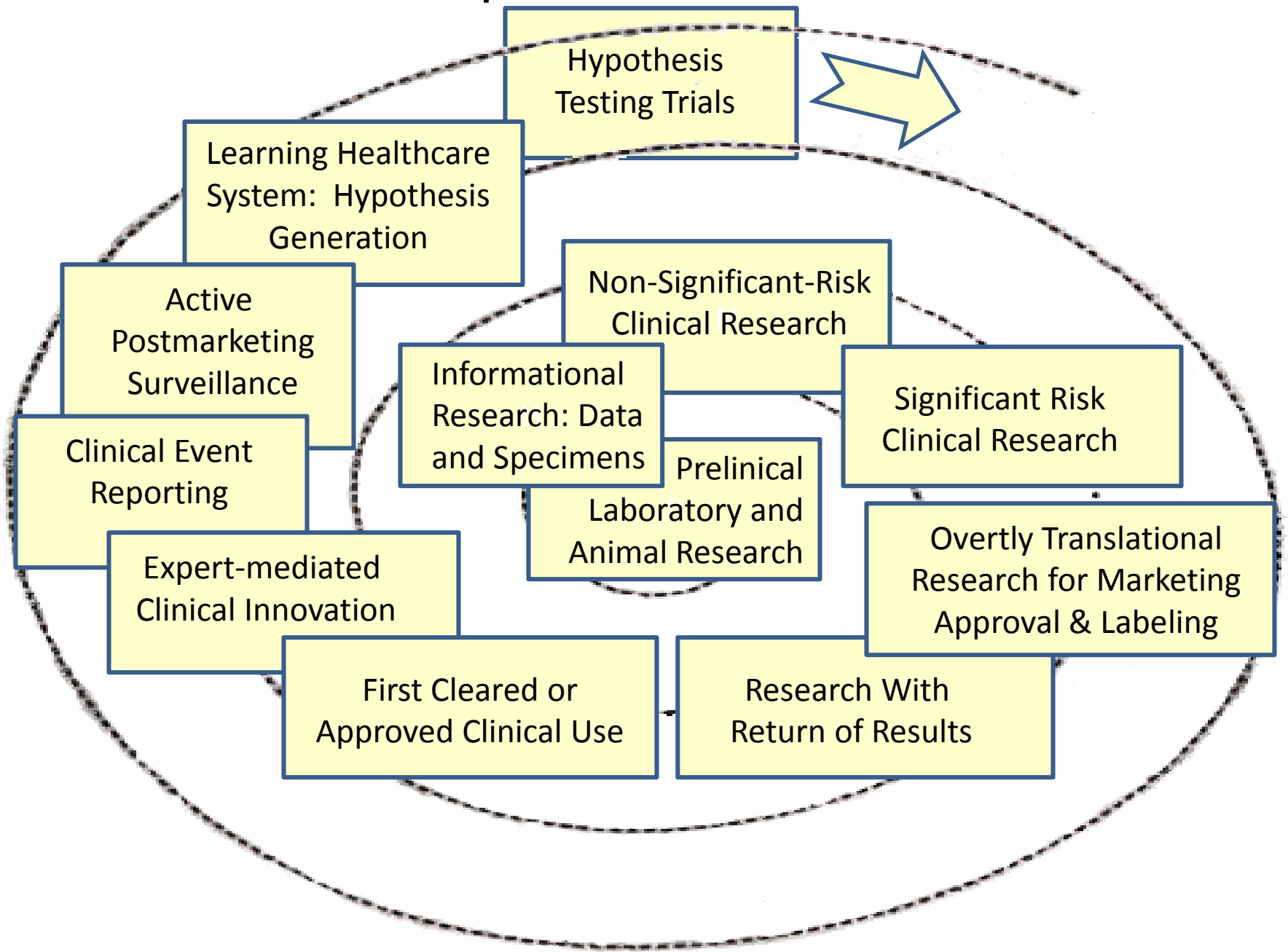
Consumer Health & Safety

Keep consumers—patients and research subjects—safe in the face of systemic ignorance about what genomic information implies about human health

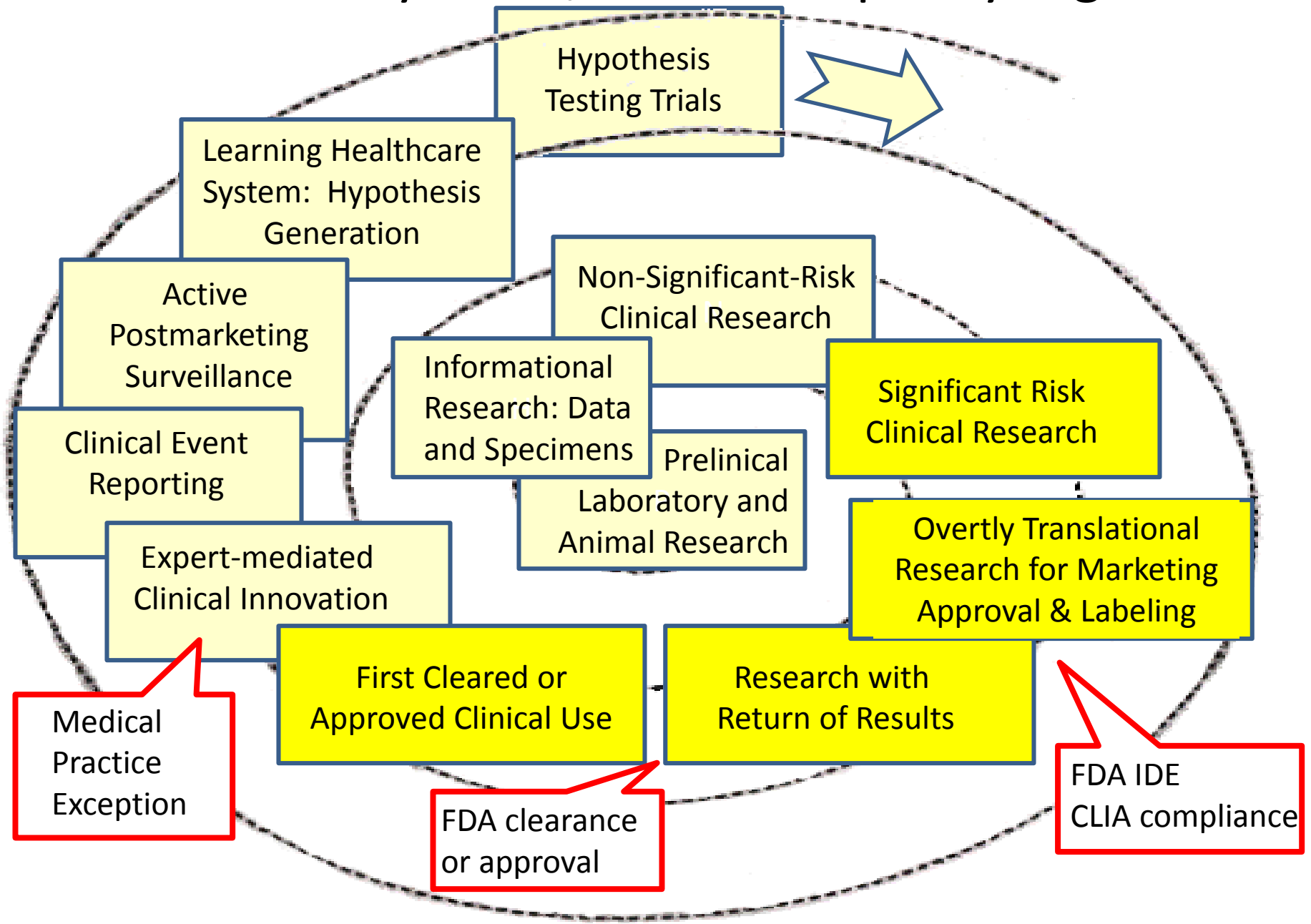
Continuous Learning

Reduce the ignorance as swiftly as possible

The Translational Spiral



Consumer safety - FDA/CLIA data quality regulation



Traditional FDA/CLIA consumer safety regulatory scheme

FDA vs. CLIA regulation

Prior data-driven review by an external regulator of analytical and clinical claims

- Low risk: exempt devices
- Moderate risk: 510(k) clearance
- Higher risk: premarket approval (PMA)

Test-specific quality systems and good manufacturing practices

Monitoring and reporting

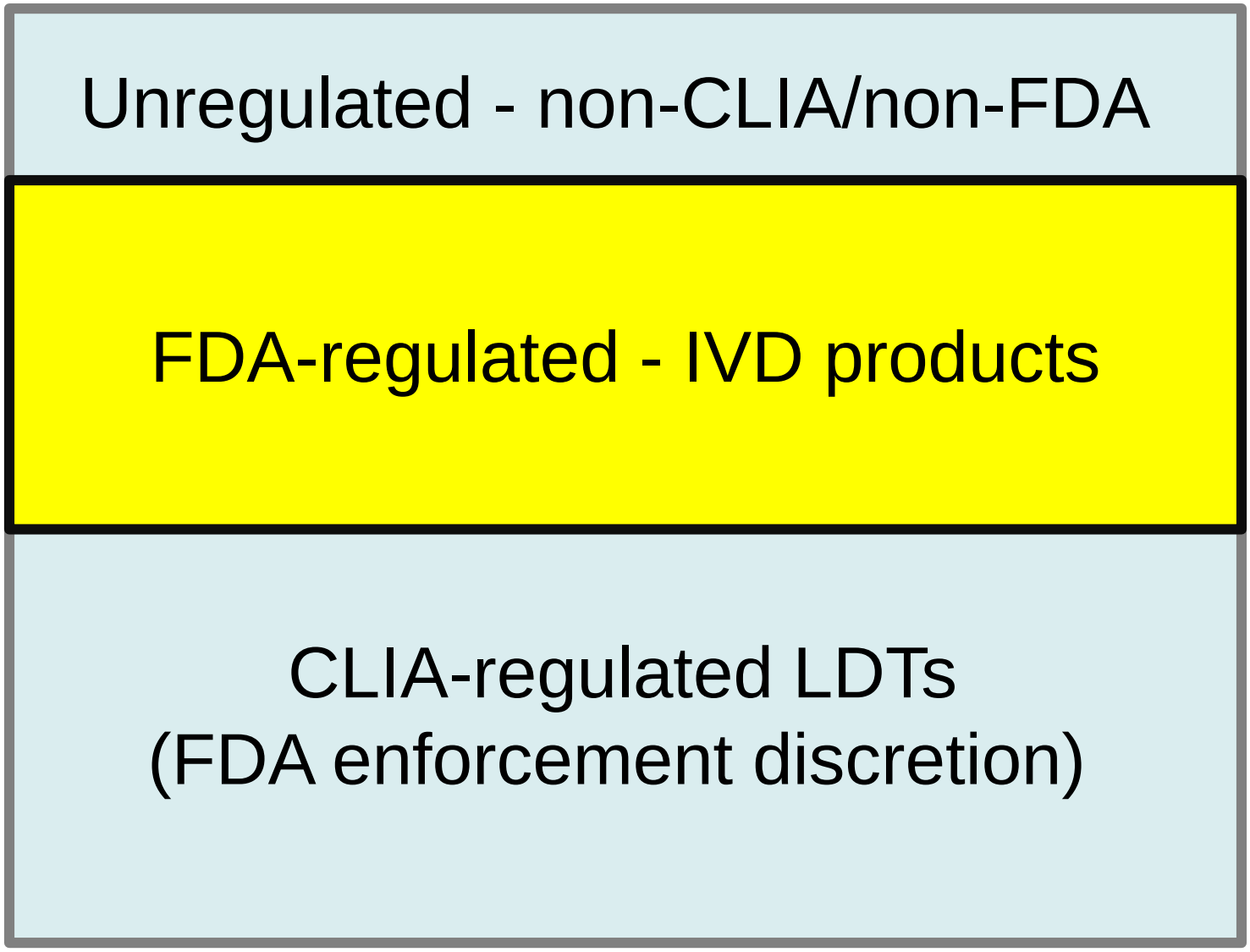
Recall authority

Traditional Premarket Review

	Analytical Claims	Claims of Clinical Validity	Claims of Clinical Utility
FDA IVD Products	√	√	?
CLIA Lab-Developed Tests	?	X	X

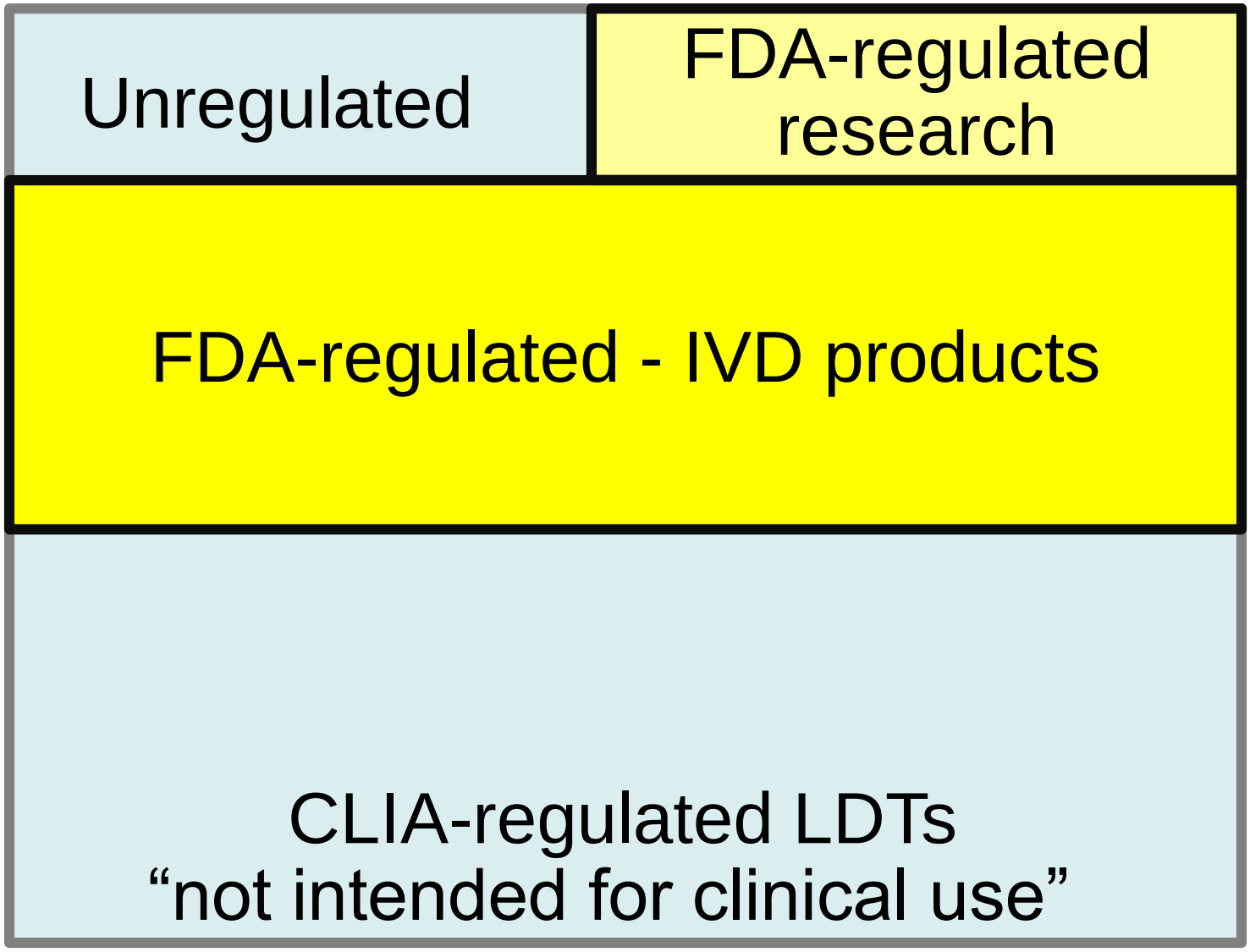
All *in vitro* diagnostics

Traditional Scheme



FDA regulation of research

FDA Regulation of Research



FDA's Medical Device Research Regulations

Informed consent	21 C.F.R. pt 50
IRB review	21 C.F.R. pt 56
Disclosure of COI	21 C.F.R. pt 54
Labeling, manufacturing, distribution of investigational devices	21 C.F.R. pt 809
IDE regulation	21 C.F.R. pt. 812

FDA vs. Common Rule

Regulating a product vs. an activity

- Product liability? Consumer protection laws?
- Scientific speech as promotional speech?

Governmental approval of research protocol

Scope of research that can be regulated

Different access to data and biospecimens

Different enforcement mechanisms

Part 812 IDE Requirements

Part 812 applies to studies *of* devices, not studies that merely *use* devices as tools to study other things *See 21 C.F.R. §§ 812.2(a), 812.3(h)*

IDE not required for “basic physiological research” that is “investigating a physiological principle” with “no intent to develop the device for marketing” or for “investigations to expand medical knowledge or conduct fundamental research”

But FDA can regulate:

- Broad scientific studies that incorporate a device study
- Significant-risk uses of investigational devices
- Sponsor-investigator studies (?)

Crucial Distinction

Sequencing a person's genome for general genetic and biomedical research purposes

- To study which variants appear in the human genome
- To study the medical significance of specific gene variants
- To study optimal procedures to communicate and use genetic information in clinical settings

Sequencing a person's genes to study the analytical or clinical performance characteristics of the sequencing technology

Design Principle #1

Studying a gene is not the same thing as studying a test that detects the gene

A-C-C-E framework frames safety and effectiveness of genetic testing in terms of:

- Analytical validity
- Clinical validity
- Clinical utility
- Ethical and social implications of testing

SACGT, “Enhancing the Oversight of Genetic Tests” (2000)

Design Principle #2

Genomic research may be exempt from FDA's IDE requirements if findings produced using investigational sequencing technologies can be—and are—confirmed using an established testing technology

- IDE exemption: 21 C.F.R. § 809.10(c)
- *But:* novel diagnostics for which no confirming technology exists won't be exempt

It is crucial to distinguish whether a study is using gene sequencing to make (implicit) analytical or clinical claims

Design Principle #3

FDA can regulate claims that laboratories and device manufacturers make about the clinical significance of gene variants, but it cannot regulate clinical claims that physicians make in the course of medical practice.

- Medical practice exception 21 U.S.C. § 396
- *But:* unlawful promotion (exception to the medical practice exception)

Return of results from genomic research
Impact of FDA's LDT draft guidance

Investigational genetic/genomic tests, including lab-developed tests, are subject to FDA's Investigational Device Exemption (IDE) regulation unless exempt.

No exemption—that is, IDE is required—"if test results are returned to the patients without confirmation by a medically accepted diagnostic product or procedure"

Potential impact on return of results

Labs can return uninterpreted data regarding which variants the individual has.

> HIPAA-covered labs may be *required* to return these data to individuals who request access, but are not required to provide counseling to clarify clinical significance. *2014 CLIA-HIPAA Amendments*

Discussing clinical significance triggers FDA's IDE requirements unless the clinical claims can be confirmed using a medically established test. *FDA LDT draft guidance*

> Individuals can explore clinical significance with their doctor in a physician-patient relationship.

Protecting genomic innovation

FDA's authority to regulate research is narrowly constrained by law:

- FD&C Act and FDA's own medical device regulations
- U.S. Constitution: First Amendment and federalism

Research activities can be structured to lighten the burdens associated with FDA's device regulations

Broader dialogue is needed to clarify roles of NIH and other funders, commercial suppliers of sequencing instruments, FDA, and investigators

Source: B. Evans, The Limits of FDA's Authority to Regulate Clinical Research Involving High-Throughput DNA Sequencing, http://ssrn.com/abstract=2484101

The proposed draft LDT guidances

What is a lab developed test for purposes of FDA's recent LDT draft guidance?

FDA is defining an LDT as an IVD product that is intended for clinical use and designed, manufactured, and used in a single laboratory.

Tests that are being marketed as LDTs but are not in fact LDTs are "out of compliance with the Food, Drug, and Cosmetic Act."

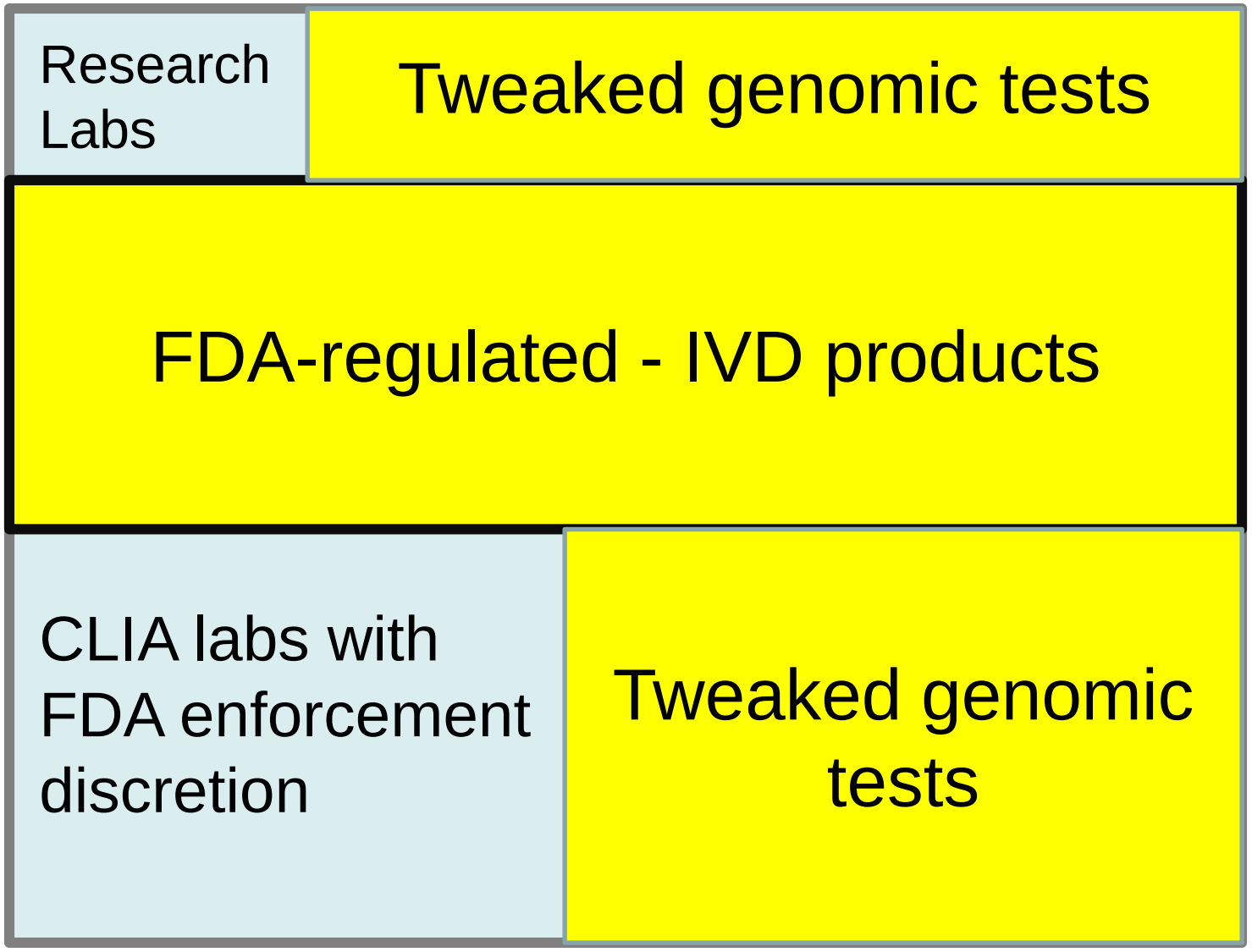
Draft LDT guidance at 5-6

Example. Laboratory A uses a commercial sequencing analyzer but tweaked its software or otherwise modified it to tailor it or improve its performance. The genomic testing:

1. Is *not* an LDT—not designed and manufactured in a single lab
2. never deserved FDA enforcement discretion in the first place, and is immediately out of compliance with the Food, Drug, and Cosmetic Act.

But to avoid disruption, FDA proposes to treat such non-LDTs as if they were LDTs during the LDT draft guidance's phase-in period.

FDA's implicit threat: Many genomic tests never deserved enforcement discretion in the first place.



The real question: What makes a test be an IVD product that FDA can regulate?

Intent for clinical use is the trigger for FDA regulation:

> "In vitro diagnostic products are reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae."

21 C.F.R. §809.3

How is intent for clinical use decided?

Objective intent of person legally responsible for labeling the device, based on such things as:

- Labeling claims
- Advertising
- Oral and written statements by the person or by his/her representatives
- Circumstances: if the device "is, with the knowledge of such persons or their representatives, offered or used for a purpose for which it is neither labeled nor advertised."

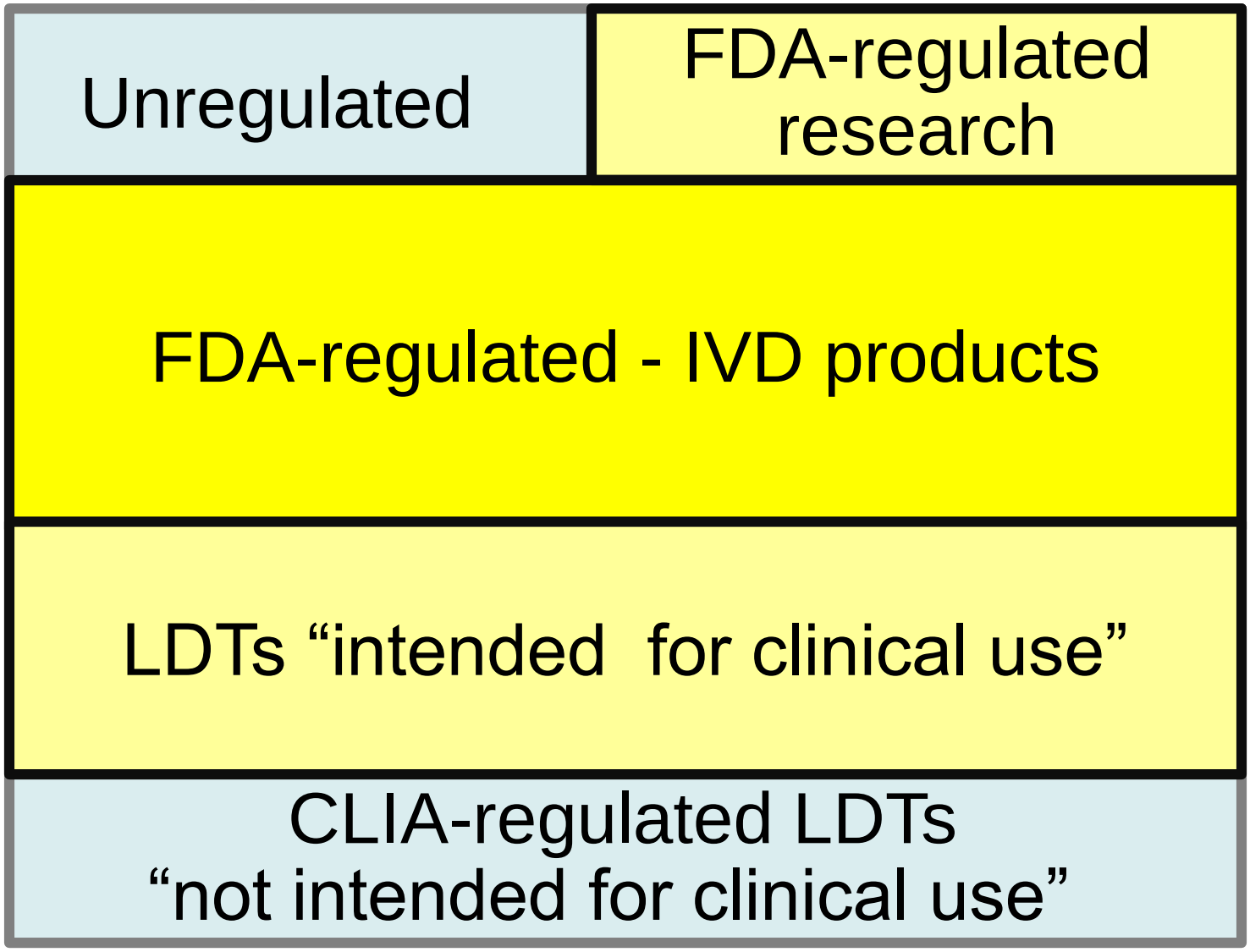
But: 21 C.F.R § 801.4 is more subtle than the LDT guidance suggests.

There are meaningful ethical and legal distinctions among:

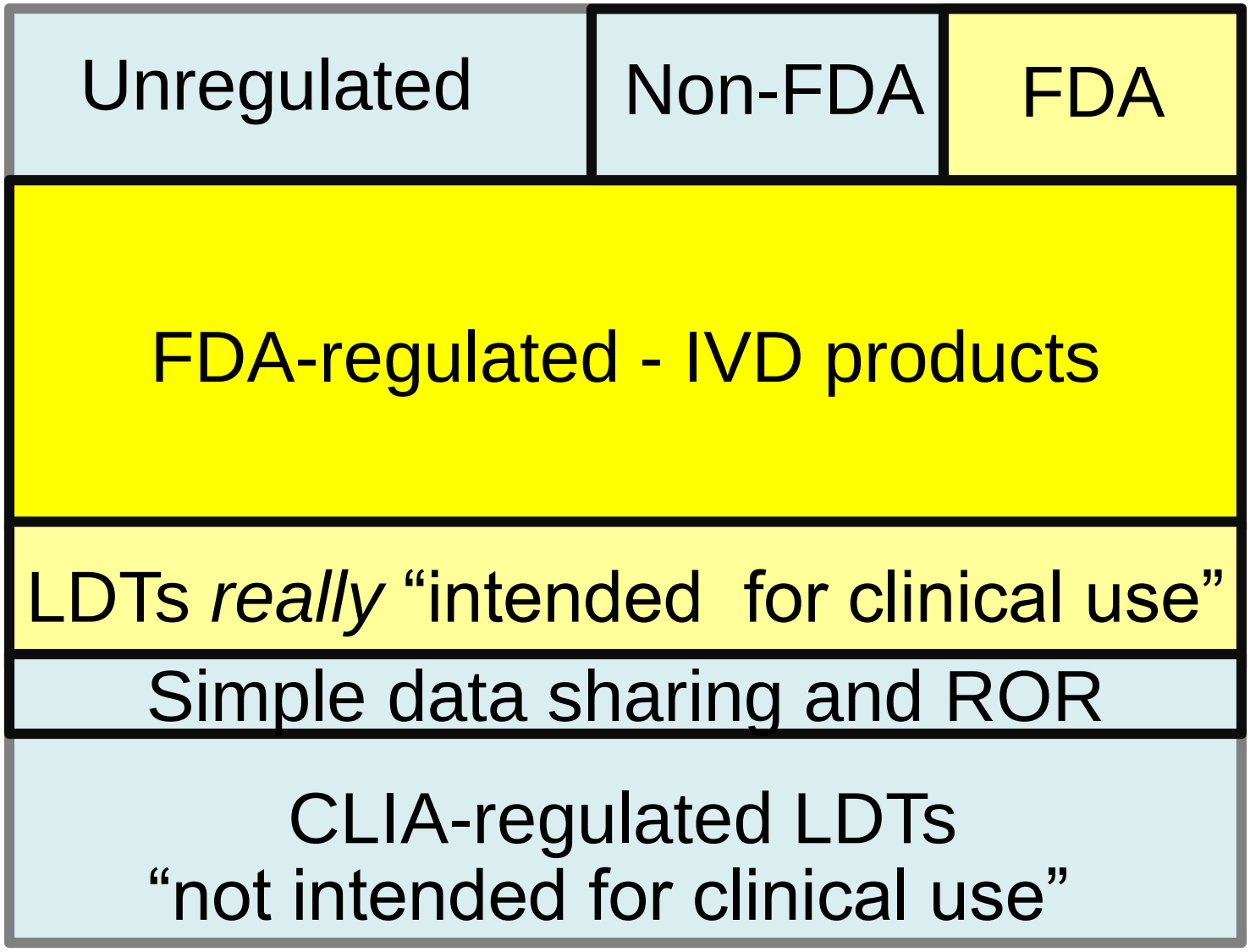
- Simple data-sharing
- Return of results/return of incidental findings
- Clinical care
- Research uses that don't make clinical claims or create significant risk
- Statements about the test and statements about the gene variants the test detects
- Statements made before a test is administered to a patient and statements made afterward

LDT guidance treats any return of results as showing intent for clinical use – needs further nuancing

Expanded FDA Regulation



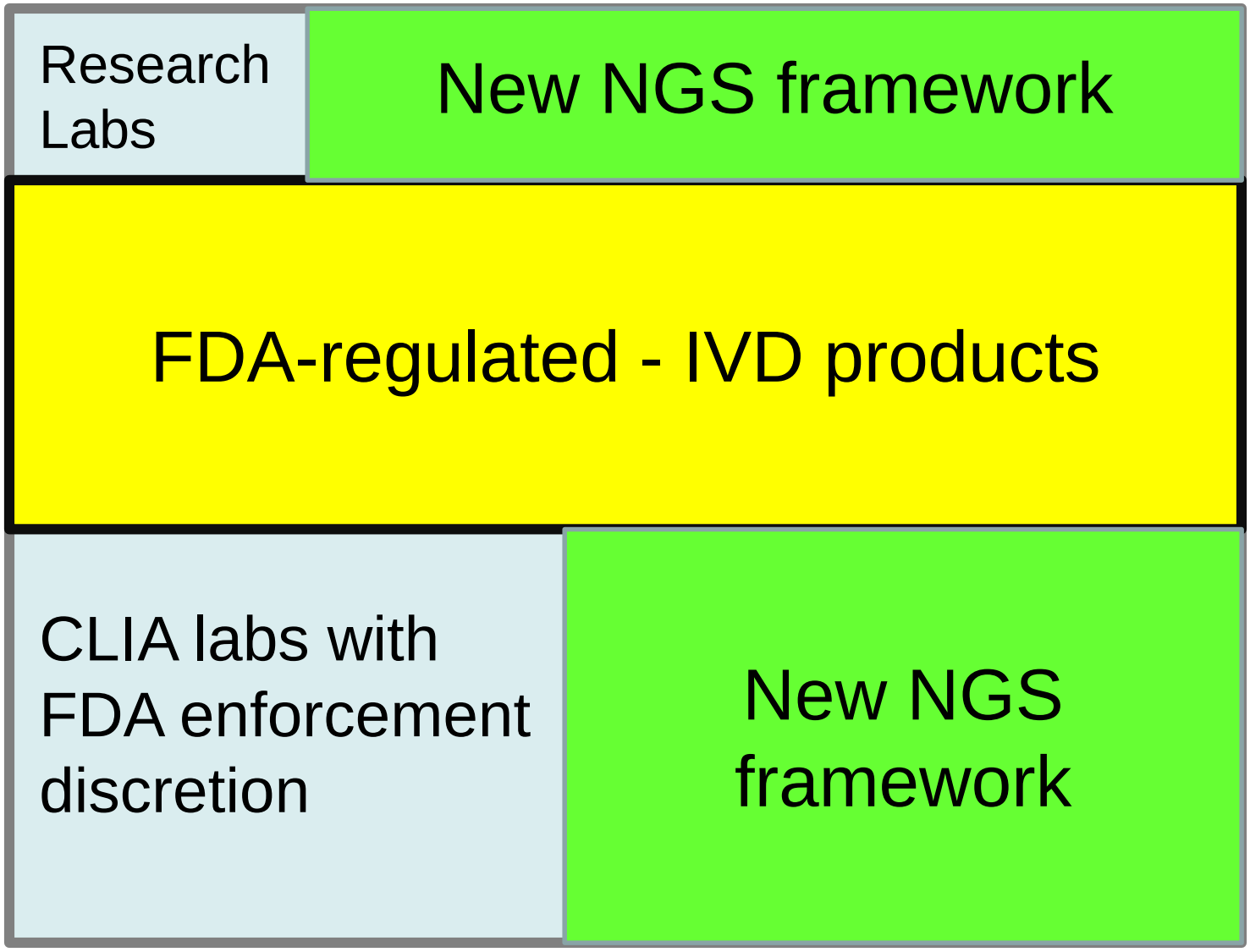
Nuanced FDA Regulation



This paradise is forever lost. Get over it.

All *in vitro* diagnostics

NGS needs its own regulatory framework



FDA's NGS discussion paper

FDA proposed definition of NGS:

"a human DNA sequencing assay performed on a particular NGS instrument (e.g., MiSeqDx) with a workflow defined by standard operating procedures that specify all materials and procedures" including "all steps from defining the patient sample type and method of DNA extraction to computational processing and sequencing data and, if offered, any portion of interpretation of the clinical meaning of individual variants identified in that patient that is performed within the test system (including software) rather than by a healthcare professional."

NGS discussion paper recognizes:

Premarket review of NGS “poses certain challenges”

FDA needs “new approaches to ensure analytical and clinical validity of NGS tests”

FDA asks for input on what those approaches should be.

FDA proposes to determine clinical validity based on literature review, ClinGen/ClinVar, and other “FDA-recognized evidence-based assessments”

FDA opens the door to allowing communication of less well-understood variants, possibly subject to warnings and disclaimers.

The looming data access problem

NIH and its international counterparts have fostered public genomic data commons

Problem: NIH's data-deposit requirements only apply to data generated using NIH funds

> Clinical translation ➡ future data will come largely from *clinical settings* (clinical labs with insurer funding) rather than *research settings* (NIH funding)

NIH data-deposit requirements don't apply to the proprietary datasets of clinical labs.

The Real Regulatory Problem

	Analytical Claims	Claims of Clinical Validity	Claims of Clinical Utility	Data Asset Quality & Access
FDA Device Regulation	√	√	?	
CLIA Lab-Developed Tests	?			

Policy Vacuum

Continuous learning and infrastructure creation