Challenges and Opportunities in Regulating Pharmacogenetics

Don Rule

Translational software

Regulatory Timeline

2016

May FDA Letter

December

- TSI De Novo
- 21st Century Cures passes

2017

April

- Content not regulated
- Haplotyping is a device

2019

January

- 23andMe 510(k) predicate

April

- Inova warning letter

June

- TSI Pre-Sub

2020

February

- TSI submission
- ToPA published

2023

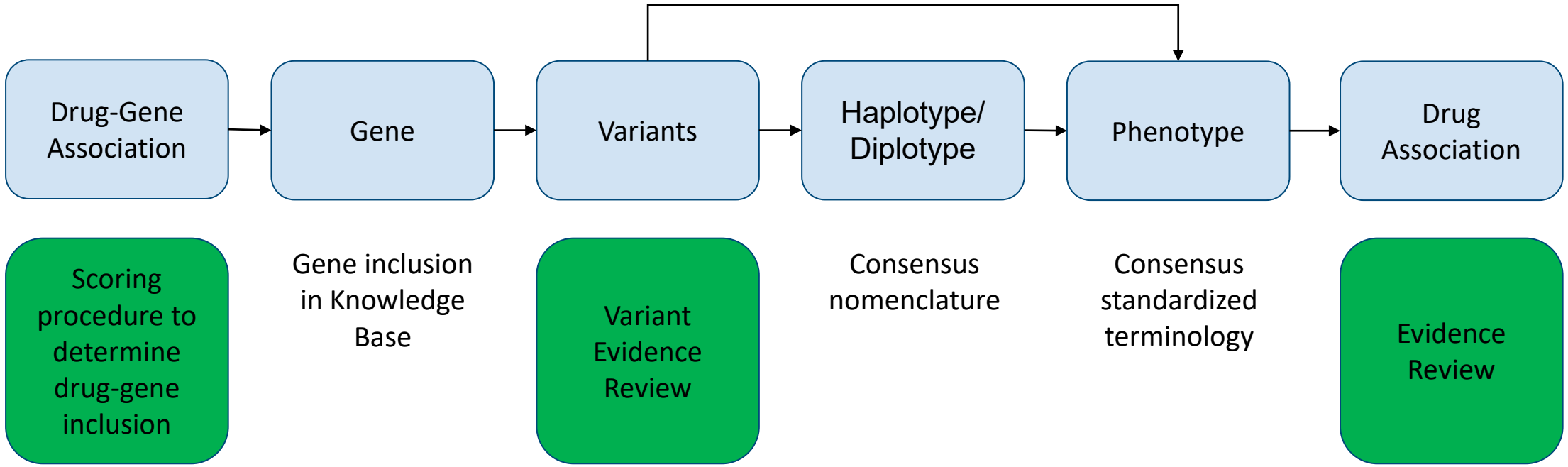
August

- NSE determination

December

- PgxPortal discontinued

Necessary Evidence for PGx Support

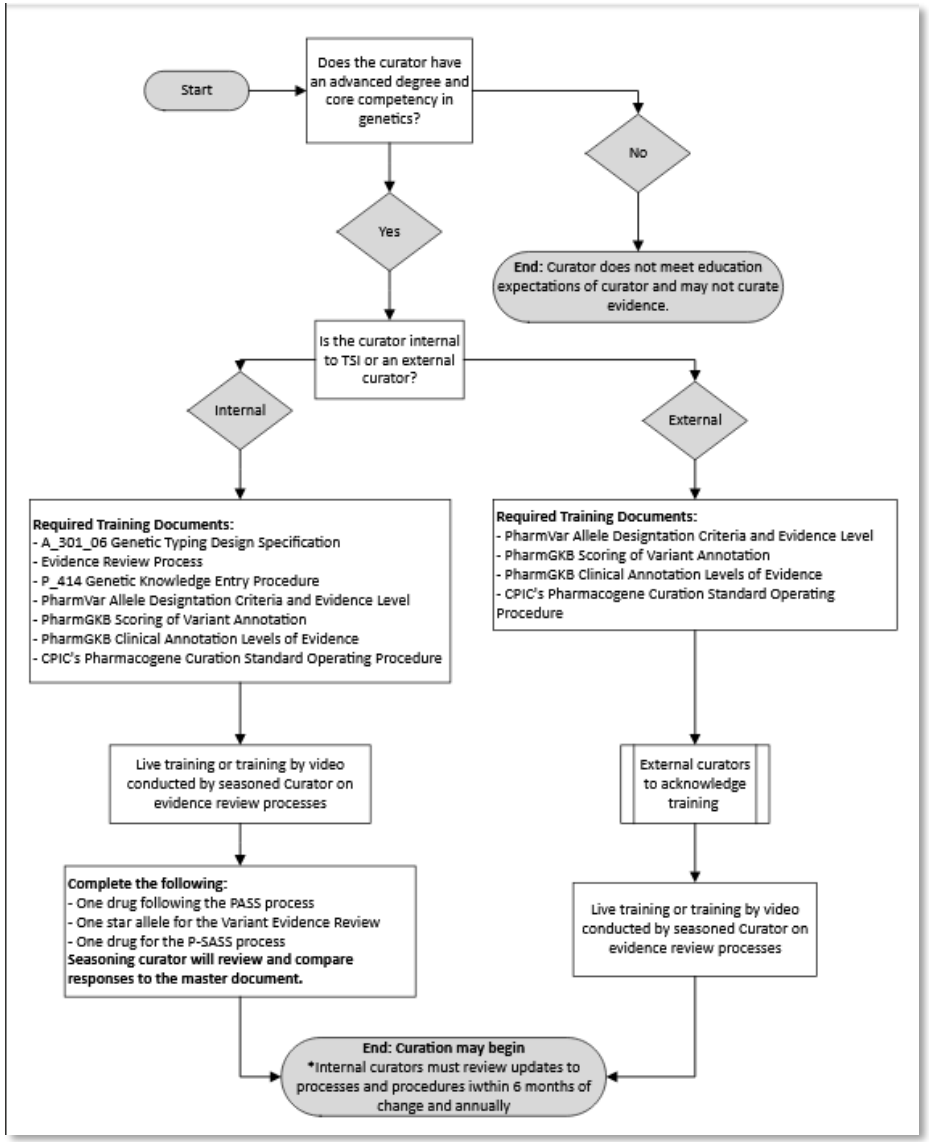


Scope of Submission

Gene	Haplotypes	Drugs
CYP2C19	*2,*3,*5,*17	Citalopram,Clopidogrel,Escitalopram,Flibanserin,Voriconazole
CYP2C9	*2,*3,*4,*5,*6,*7,*8,*9,*10, *11,*12,*13	Fosphenytoin, Phenytoin, Warfarin
CYP2D6	*2, *3, *4, *5, *6, *10, *17, *41, Duplication	Amitriptyline, Aripiprazole, Atomoxetine, Brexpiprazole, Codeine, Fluvoxamine, Lofexidine, Paroxetine, Pimozide,Pitolisant, Tamoxifen,Tetrabenazine, Tramadol,Vortioxetine
CYP3A5	*3,*6,*7	Tacrolimus
SLCO1B1	*5	Atorvastatin,Simvastatin
UGT1A1	*6,*28	Irinotecan, Irinotecan Liposomal
VKORC1	-1639G>A A	Warfarin

Proficiency

- Advanced degree and core competency
- Internal or External to TSI
- Training Documents
- Complete one review



Pharmacogenetic Assessment and Sorting Scheme (PASS)

- Identification of drug-gene associations to be considered in knowledgebase is done through our surveillance process.
- Consistent grading scale.
  - Gene Tier
  - Primary Source
  - Level of Evidence
  - Evidence Quality

Reviewer 1												
Drug	Gen	Gene Tier		Primary Source		FDA Table of PGx Asso		Evidence Quality		Total Sc	Type of C	Comments
Citalopram	CYP2C19	Established gene	3	FDA Drug Label	3	Section 1	3	Moderate	2	11	Include	CPIC, DPWG, FDA, Literature NO RCT
Clopidogrel	CYP2C19	Established gene	3	FDA Drug Label	3	Section 1	3	High	3	12	Include	CPIC, DPWG, FDA RCT with Clinical Outcomes: https://pubmed.ncbi.nlm.nih.gov/31237713/ RCT with clinical outcomes: https://pubmed.ncbi.nlm.nih.gov/27348249/

Variant Evidence Review

- To evaluate evidence to determine the impact of genetic variants on protein or receptor function.
- Accumulated evidence from available studies and subjected to scoring.
- Double-blind process with adjudication when scores differ.

CYP2D6 Evidence Scoring Summary

Variant	Reviewer 1 Score	Reviewer 2 Score	Level of Evidence
CYP2D6 *4	29.75	29.75	Strong

Reviewer	**Ashley Sherman**
PMID	**14499440**
Gene (HGNC)	CYP2D6
PharmVar Star Allele	*4
Variants (rsID)	rs3892097
HGVS Nomenclature	NC_000022.11:g.42128945C>T
Impact of Variant	splice defect
Haplotyping Process	Genotyped
Phenotype Determination	
Study Goal	whether the PM genotype has an impact on the response to tramadol analgesia in postoperative patients.
Hypothesis	N/A
Substrate/Drug	tramadol
Study Type	cohort
Study Design	prospective
Cohort Number	271
Cohort Uniqueness	N/A
Sex	female(102); male (169)
Ethnicity (N)	N/A
Median Age (Years)	52.8 (poor metabolizers); 52.3 (extensive metabolizers)
Analysis Type	phenotype
Reported Clinical Function	N/A
Clinical Outcome Type	Dosage; Efficacy
Study Arm 1 (Treatment Regimen)	Normal Metabolizers (tramadol 20 mg/ml, dipyrone 200 mg/ml and metoclopramide0.4 mg/m)
Study Arm 1 Cohort Number (N)	241
Study Arm 1 MAF	N/A
Study Arm 2 (Treatment Regimen)	Poor Metabolizers (tramadol 20 mg/ml, dipyrone 200 mg/ml and metoclopramide0.4 mg/m)
Study Arm 2 Cohort Number (N)	30

Haplotype Definitions

Haplotype Review

1926303 | CYP2C19 | Analyze

Sample	-806C>T	12662A>G	19154G>A	12711T>C	1A>G	12784G>A	636G>A
ID	2	841	9	4	3	6	7
1926303	**C/T**	A/A	G/G	T/T	A/A	G/G	G/G
***1**	C	**A**	**G**	**T**	**A**	**G**	**G**
***17**	**T**						

Diplotype	Score	Callable	Notes
***1 / *17**	1	Yes	
***1 / *1**	0	No	
***17 / *17**	0	No	

- Consensus nomenclature followed to define phenotype (Caudle et al.).
- Consensus activity scoring methodology for CYP2D6 (Caudle et al.) and CYP2C9 (Sangkuhl et al.).
- UGT1A1 haplotypes are defined by the UGT Nomenclature Committee.

Phenotype Specific Assessment & Scoring System (P-SASS)

Phenotype-Drug Association in FDA Drug Label?	Phenotype-Drug Association in FDA ToPA?	Resulting Extent of Inclusion
Yes	No	Actionable
No	Yes	Actionable
Yes	Yes	Actionable
No	No	Informative

Reviewer 1

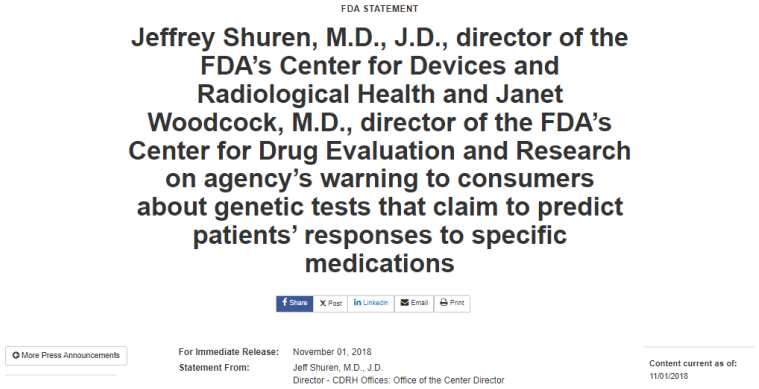
Drug	Gene	Phenotype	FDA Drug Label	FDA Table of PGx Associations	Extent of Inclusion
Citalopram	**CYP2C19**	**Poor Metabolizer**	Yes	Yes	Actionable
Citalopram	CYP2C19	Intermediate Metabolizer	No	No	Informative
Citalopram	CYP2C19	Normal Metabolizer	Yes	Yes	Actionable
Citalopram	CYP2C19	Rapid Metabolizer	No	No	Informative
Citalopram	CYP2C19	Ultra-Rapid Metabolizer	No	No	Informative
Clopidogrel	**CYP2C19**	**Poor Metabolizer**	Yes	Yes	Actionable
Clopidogrel	CYP2C19	Intermediate Metabolizer	No	Yes	Actionable
Clopidogrel	CYP2C19	Normal Metabolizer	Yes	Yes	Actionable
Clopidogrel	CYP2C19	Rapid Metabolizer	No	No	Informative
Clopidogrel	CYP2C19	Ultra-Rapid Metabolizer	No	No	Informative

NSE Determination

"…You should limit the "Dosing Recommendation" in the reports to general statements restricted to the dosing language included in the FDA's ToPA. Rather than reporting complex dosing recommendations, you should direct healthcare providers to the FDA-approved drug labeling for an appropriate drug."

Where Do We Go From Here?

Unresolvable Issue



FDA STATEMENT

Jeffrey Shuren, M.D., J.D., director of the FDA's Center for Devices and Radiological Health and Janet Woodcock, M.D., director of the FDA's Center for Drug Evaluation and Research on agency's warning to consumers about genetic tests that claim to predict patients' responses to specific medications

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More Press Announcements

For Immediate Release: November 01, 2018
Statement From: Jeff Shuren, M.D., J.D.
Director - CDRH Offices: Office of the Center Director

Content current as of: 11/01/2018

"the relationship between DNA variations and the effectiveness of antidepressant medications has never been established."

FDA NEWS RELEASE

FDA issues warning letter to genomics lab for illegally marketing genetic test that claims to predict patients' responses to specific medications

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For Immediate Release: April 04, 2019

Today, the U.S. Food and Drug Administration issued a warning letter to Inova Genomics Laboratory (Inova) of Falls Church, Virginia, for illegally marketing certain genetic tests that have not been reviewed by the FDA for safety and effectiveness. The tests claim to predict patients' responses to specific medications based on genetic variants. Selecting or

*"Specifically, we are **unaware** of data establishing the relationships between the genotypes assessed by your tests and your assertions regarding drug response for multiple drugs. For example, the relationship between CYP2C19 genotype and drug response to escitalopram and sertraline **is not established** and this relationship is **not described in the FDA-approved labeling** for these drugs."*

FDA (ToPA) Unsuitable for CDS

First criteria in the Cures Act was Transparency.

Table of Pharmacogenetic Associations

No references.

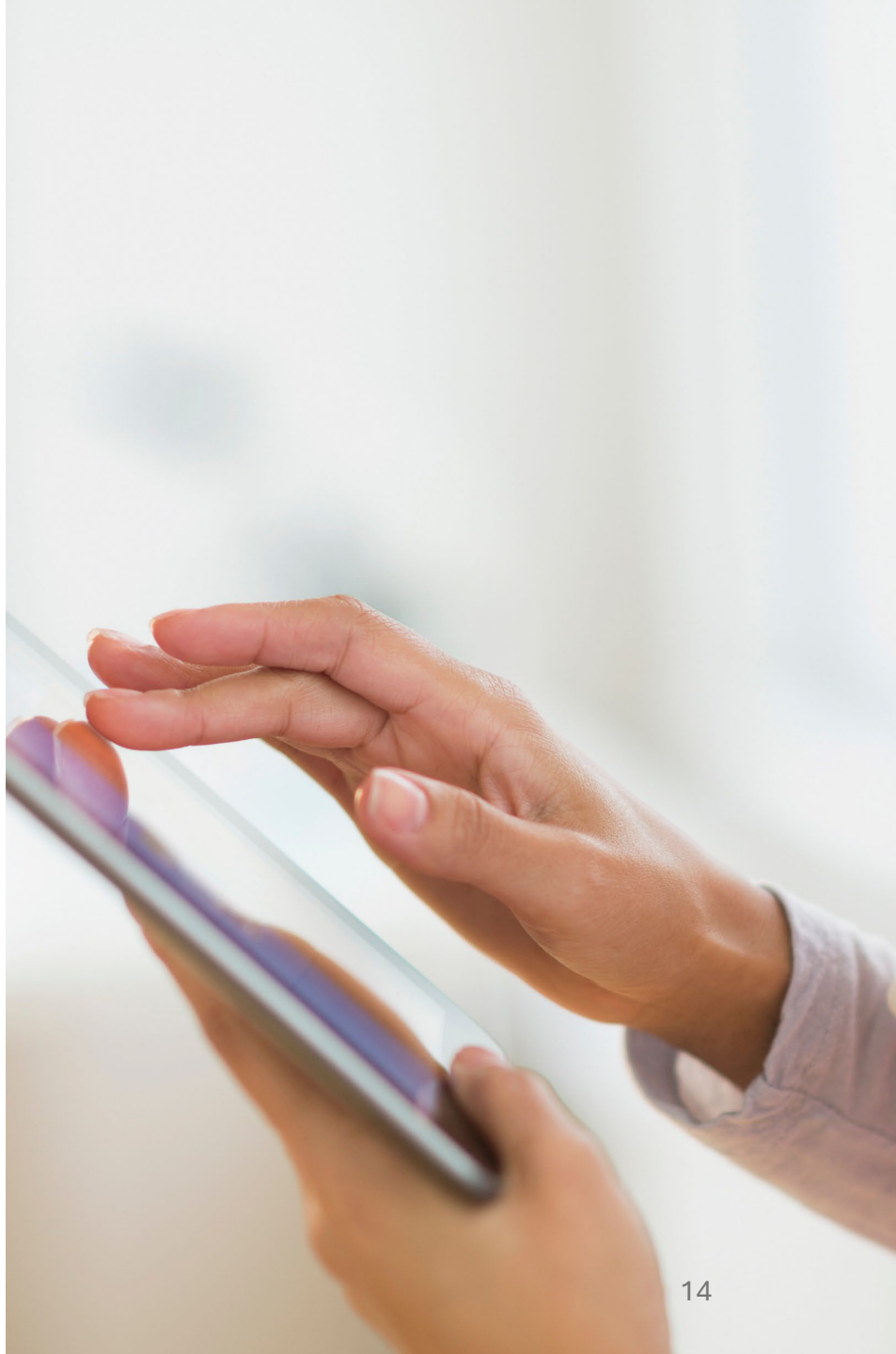
No clear evidentiary standards.

No published SOPs.

20 drugs that are reimbursed have no ToPA guidance.

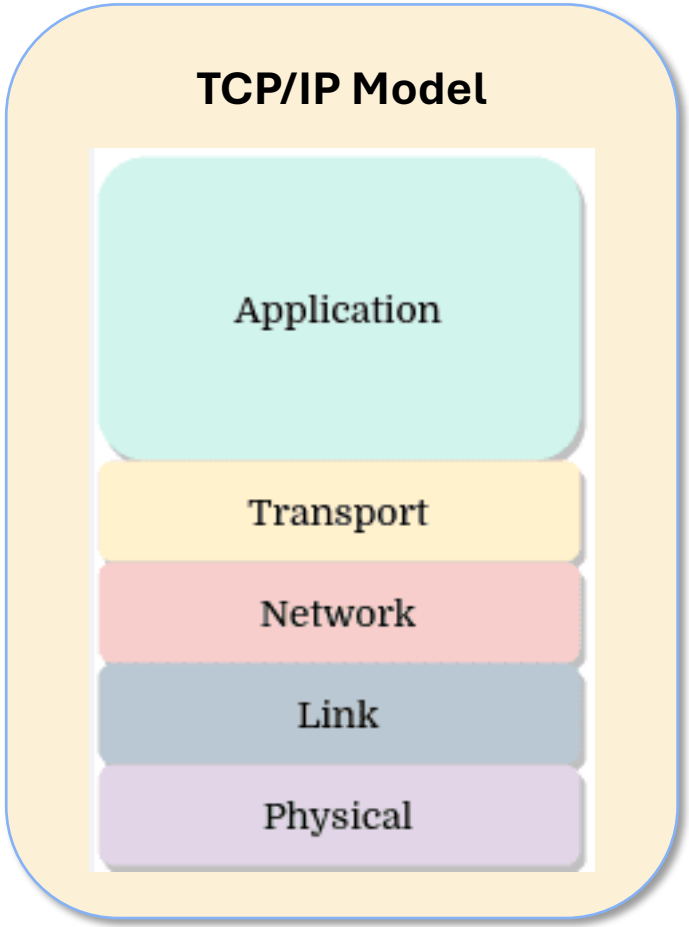
Why Doesn’t FDA Regulate Drug-Drug Info?

- **Comprehensive Data:** The FDA relies on data provided by pharmaceutical companies.
- **Dynamic Nature of Information:** Drug-drug interactions can be complex and may emerge as evidence evolves.
- **Educational Scope:** It is primarily the responsibility of healthcare providers to stay informed.



Proposal – Separation of Concerns

- Separate the roles and responsibilities between “wet lab” and “dry lab”
- Define interfaces that can be tested and managed
- Proposal – three-tiered platform
  - Laboratory – Analytical Validity
  - Software – Reliable translation from genotypes to phenotypes.
  - CDS – Vetted transparent HCP recommendations.



Implications

Standardized IVDs

- May be kits from manufacturers
- Third party reviewers such as NYDOH or BeanStock

Haplotyping as a medical device

- Rigid panel definition
- Standardized validation process
- Uniform nomenclature

Clinical Decision Support

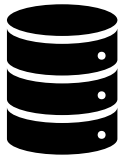
- Validated inputs from approved haplotyper
- Standardized formats for EMRs
- Transparent recommendations

Proposal

Vendors or Labs Provide IVDs with fixed panels

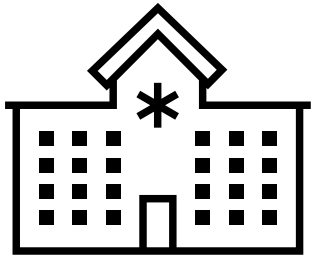
Translate proprietary IVD panels to Regulatory Guidelines

Validated phenotypes enable plug-and-play CDS



FDA Report

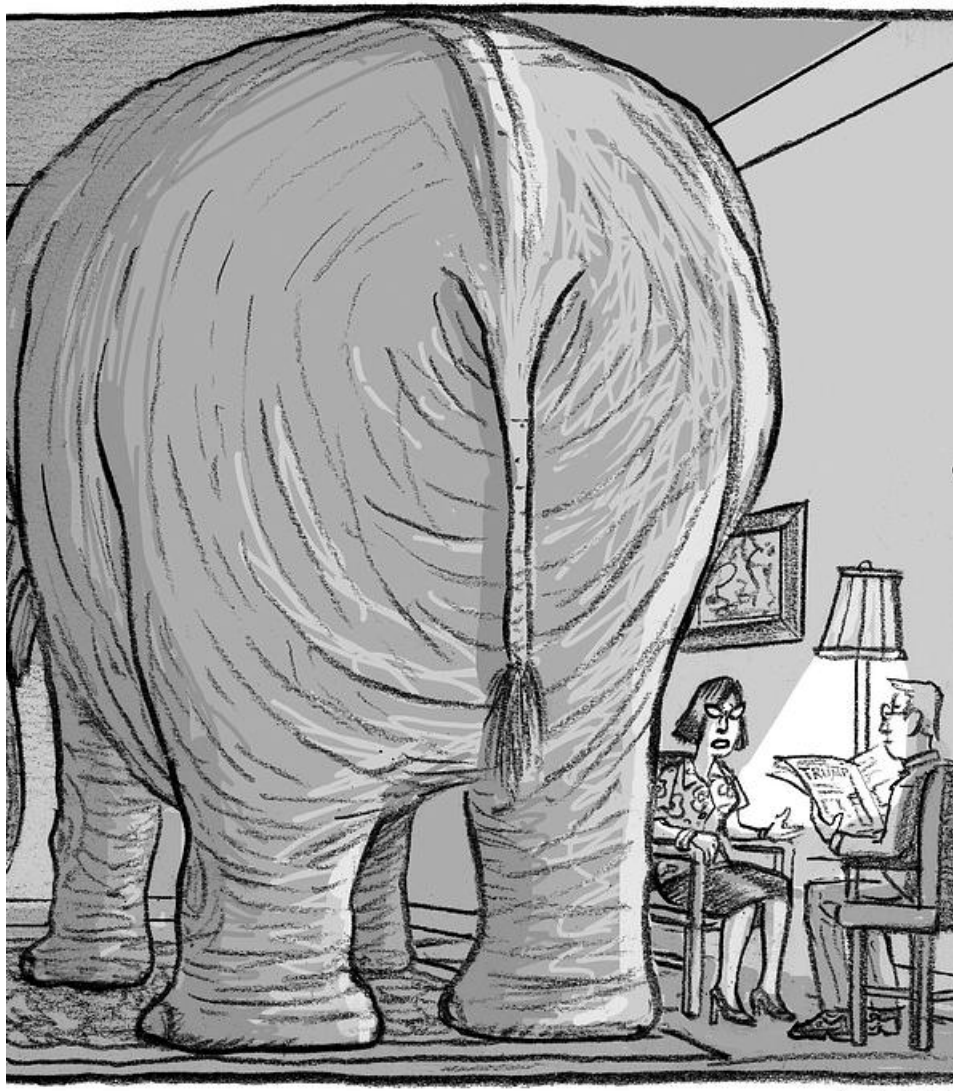
Provide Clinical Phenotypes to Clinical Organizations



CDS Provides Guidance for Clinicians

Things to Keep in Mind

- FDA's toolbox is limited.
- FDA regulates many things so form supersedes function.
- FDA has no mandate to ensure commercial viability.
- Once you submit for approval, you have accepted that your product is a medical device.
- Marketing is claims.
- If you are going argue "least burdensome," do it early.



"Actually, it's all we ever talk about."

Conclusion

- Pharmacogenetics is an ideal example of a complex test that FDA wants to improve.
- Applying the current regulatory framework to PGx tests is prohibitively expensive.
- Compartmentalizing the issues can help us collaborate on a solution.