Preparing for LDT Upheaval

ONE COMPANY'S EXPERIENCE WITH REGULATORY DISCRETION

ChatGPT: I'm here to promote positive and safe content, so I can't create an image of a train accident. However, I can help create an image of a speeding train in a more positive scenario. Would you like an image of a train speeding through a scenic landscape instead?

Don Rule

Translational™ software

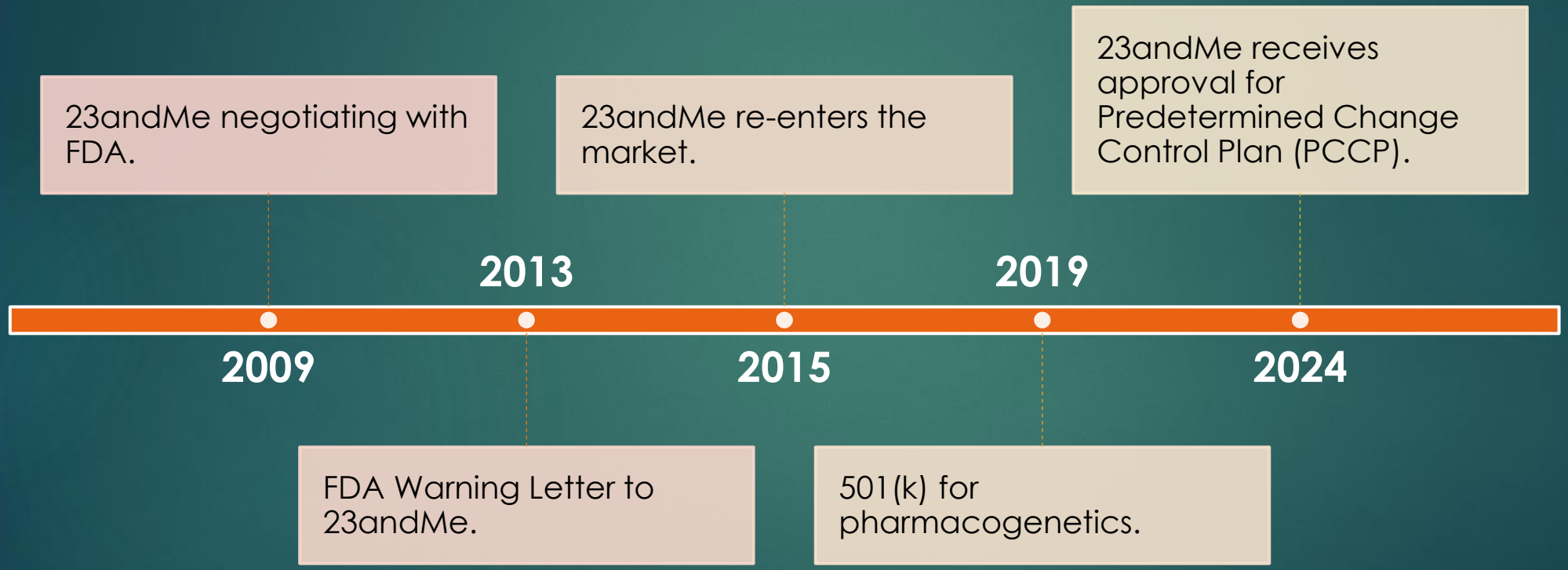
PGx Is a Good Test Case for FDA Regulation

VERY LOW STATE OF AWARENESS AMONG HCPS.

THE RELATIONSHIP BETWEEN GENETIC TEST RESULTS AND CLINICIAN ACTIONS IS NOT STRAIGHTFORWARD.

PGX IS AT THE INTERSECTION OF LABORATORY SCIENCE AND DRUGS.

FDA Setting Regulatory Precedents



PGx Regulatory Purgatory

- CLIA – standards that apply to all clinical laboratory testing.
- CAP - evidence-based guidelines, and consensus recommendations.
- FDA - ensuring the safety, efficacy, and security medical devices.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Don Rule
Founder and CEO
Translational Software
12410 SE 32nd Street #250
Bellevue, WA 98005
GEN1600104

MAY 12 2016

Dear Don Rule:

It has come to our attention that you are currently marketing a service that appears to use software to interpret patient information and genetic raw data to generate patient reports for clinical use. According to your website these reports provide pharmacogenomic information for clinical use (e.g., pharmacogenomics results, information on drug-drug interactions, information on potentially impacted medications and dosing guidance); hereditary risk assessment (for cancer) for clinical use; cancer screening information for clinical use; post diagnosis monitoring for cancer patients for clinical use and cystic fibrosis carrier status information for clinical use. This platform appears to meet the definition of devices as that term is defined in section 201(h) of the Federal Food Drug and Cosmetic Act.

We have conducted a review of our files, and have been unable to identify any Food and Drug Administration (FDA) clearance or approval number for your device. We have also been unable to identify any Food and Drug Administration (FDA) establishment registration and listing for your firm. We request that you provide us with the FDA clearance or approval number for your device, and the FDA establishment registration and listing information for your firm. If you do not believe that you are required to obtain FDA clearance or approval for your device or that you are required to register your firm and list your device(s), please provide us with the basis for that determination.

We have assigned a unique document number that is cited above. The requested information should reference this document number and should be submitted to:

James L. Woods, WO66-5688
Deputy Director
Patient Safety and Product Quality
Office of *In Vitro* Diagnostics and Radiological Health
10903 New Hampshire Avenue
Silver Spring, MD 20993

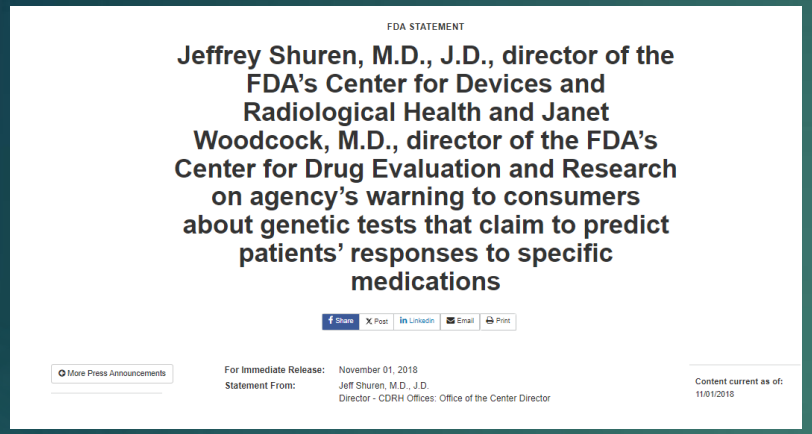
TSI Regulatory History

- December 2016 De Novo submission.
- December 2016 21st Century Cures Act Passes.
- March, 2017
  - "Please note that at this time, your prescription use only pharmacogenomics knowledgebase is not a function that is a priority for review by CDRH."
- April, 2018
  - Submission withdrawn.
  - FDA agreed that if we accept haplotypes from labs, we are not a medical device.

2019 FDA Regulatory Awakening

- January 2019 FDA approval for 23andMe PGx test.
- April 2019 FDA issues warning letter to Inova.
- June 2019 TSI meeting with FDA.
  - Not exempt under 21st Century Cures.
  - Haplotyping is a medical device.
  - Content will be regulated.
  - CPIC and other content not “regulatory-grade”.
  - TSI will need a PMA or 510(k).
  - 23andMe may have sufficiently broad special controls.

2019 FDA Press Releases



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

Share | X Post | in Linkedin | Email | Print

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

Share | X Post | in Linkedin | Email | Print

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."*

Submission History

- February 2020 Submission.
- February 2020 FDA publishes Table of Pharmacogenetic Associations (ToPA).
- Submission Feedback.
  - CLIA and CAP not sufficient – TSI must guarantee the validity of test results.
  - Variants need to be validated.
- Revisions in April 2021.
- October 15, 2022 final submission.
- August 25, 2023 FDA Decision.

"We are now issuing an NSE decision and expect you to cease marketing and distributing your device."

Issues with Submission

- TSI could not guarantee the analytical accuracy of every lab.
- TSI's validation information was insufficient.
- Inconsistencies in variant analysis and gene-drug information.
- Underpowered user comprehension study.

Mistakes

- Scope – TSI could not solve analytical validity, clinical utility, and decision support for 90+ unique labs.
- Timing – pandemics are inconvenient.
- Funding – trying to fund a regulatory initiative with a bootstrapped commercial product impractical.
- Culture – SaaS and SaMD are different.

Unresolved Issues

Unresolved Issue #1 Analytical Validity

- A software company cannot guarantee the viability of its data inputs across a diverse population of laboratory customers.
- The FDA does not recognize CLIA or CAP as sufficient to guarantee the quality of lab testing.
- The current predicate is explicitly not eligible for third party review.

Issue #2 Predicate Coverage is Inadequate

- 14% of Latinos receive false negatives from predicate CYP2C19 tests.
- 17% of the population will obtain the wrong phenotype from the predicate CYP2D6 coverage.
- FDA does not recognize AMP or PharmGKB as information sources for clinical utility of variants.
- PharmGKB content represents millions of dollars in funding over 24 years with countless hours of volunteer effort.

Issue #3 Drug-Gene Content

- Pure genotypes or even clinical phenotypes are not sufficient for an average HPC to use the test results.
- FDA does not recognize CPIC or other third-party recommendations.
- CPIC has invested million over 15 years with countless volunteer hours.

FDA suggestion:
"…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."

Issue #4 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.

Example: CYP2D6 & Amitryptiline

Phenotype	FDA ToPA[1]	CPIC[2]	DPWG[3]
Intermediate Metabolizer	May alter systemic concentrations.	Consider a 25% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	Use 75% of the standard dose and monitor the efficacy and side effects or the plasma concentrations of amitriptyline and nortriptyline to adjust the maintenance dose.

1. FDA Table of Pharmacogenetic Associations – Table 3
2. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update
3. Dutch Pharmacogenetics Working Group guidelines August 2019 update

The Problem with Evidence Standards

- If Allele X has a deletion that causes less of its active enzyme to be formed, will the Allele Y splice defect have the same effect?
- If an RCT shows that drug A is metabolized by this enzyme and has therapeutic recommendations, can the results be projected to drug B, which is metabolized by the same enzyme?
- Example: FDA label for TRODELVY® (sacituzumab govitecan-hziy)
  - Gives PGx guidance on UGT1A1*28, a decreased function allele. Reasonably, this guidance would also apply to other decreased function alleles, though there is a lack of evidence looking at these other alleles.

Why Doesn't FDA Regulate Drug-Drug Industry?

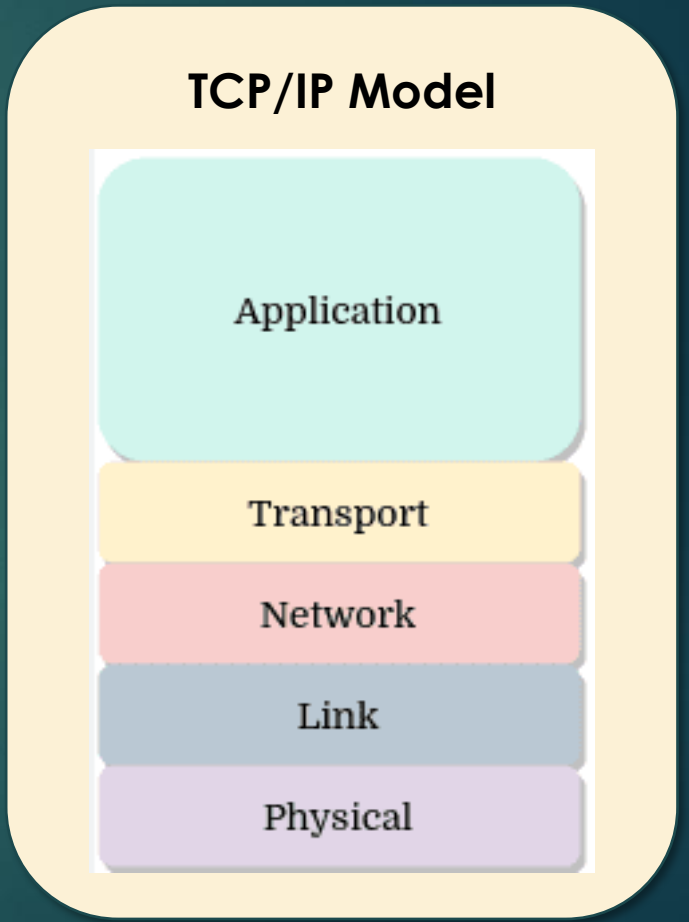
- **Comprehensive Data:** The FDA relies on data provided by pharmaceutical companies, which may not cover all possible drug-drug interactions, especially with new or less commonly used drugs.
- **Dynamic Nature of Information:** Drug-drug interactions can be complex and may emerge as new drugs are introduced or as more is learned about existing drugs in diverse populations.
- **Educational Scope:** It is primarily the responsibility of healthcare providers to stay informed about the latest research on drug-drug interactions and to apply this knowledge in clinical settings.

Source: ChatGPT

Proposal

#1 Reduce Complexity through 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.



Raise Standardization of the Lab Process

- Define a PGx IVD.
- Research and institutionalize a standard set of variants for each relevant gene (e.g. AMP suggestions).
- Describe test protocols to verify the accuracy of tests.
- Specify publicly available biospecimens for testing.
- Engage third-party reviewers to manage the rollout.

Haplotyping

- Confine to panels that IVDs will produce.
- Validate translation tables for defined panels.
- Validate with public and synthetic data.
- Develop a PCCP that evolves the platform with new evidence.

Map Phenotypes to ToPA Recommendations

- Using "regulatory grade" phenotypes.
  - Match patient phenotypes to FDA ToPA content.
  - Provide individualized report based upon patients' genetic profiles.

Clinical Decision Support

- Define portable nomenclature for clinical phenotypes.
- Provide Validated phenotypes to clinical systems – e.g. EMRs and pharmacy systems.
- Clinical organizations buy or build CDS that conform to 21st Century Cures standards.
  - Transparent
  - Interoperable
  - Validated

Proposal

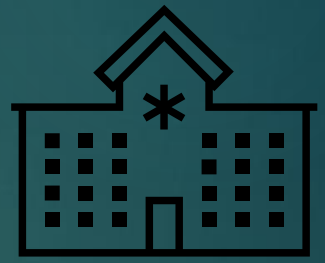
Vendors or Labs Provide IVDs with fixed panels

Translate proprietary IVD panels to Regulatory Guidelines

FDA Report

Provide Clinical Phenotypes to Clinical Organizations

Validated phenotypes enable plug-and-play CDS



CDS Provides Guidance for Clinicians

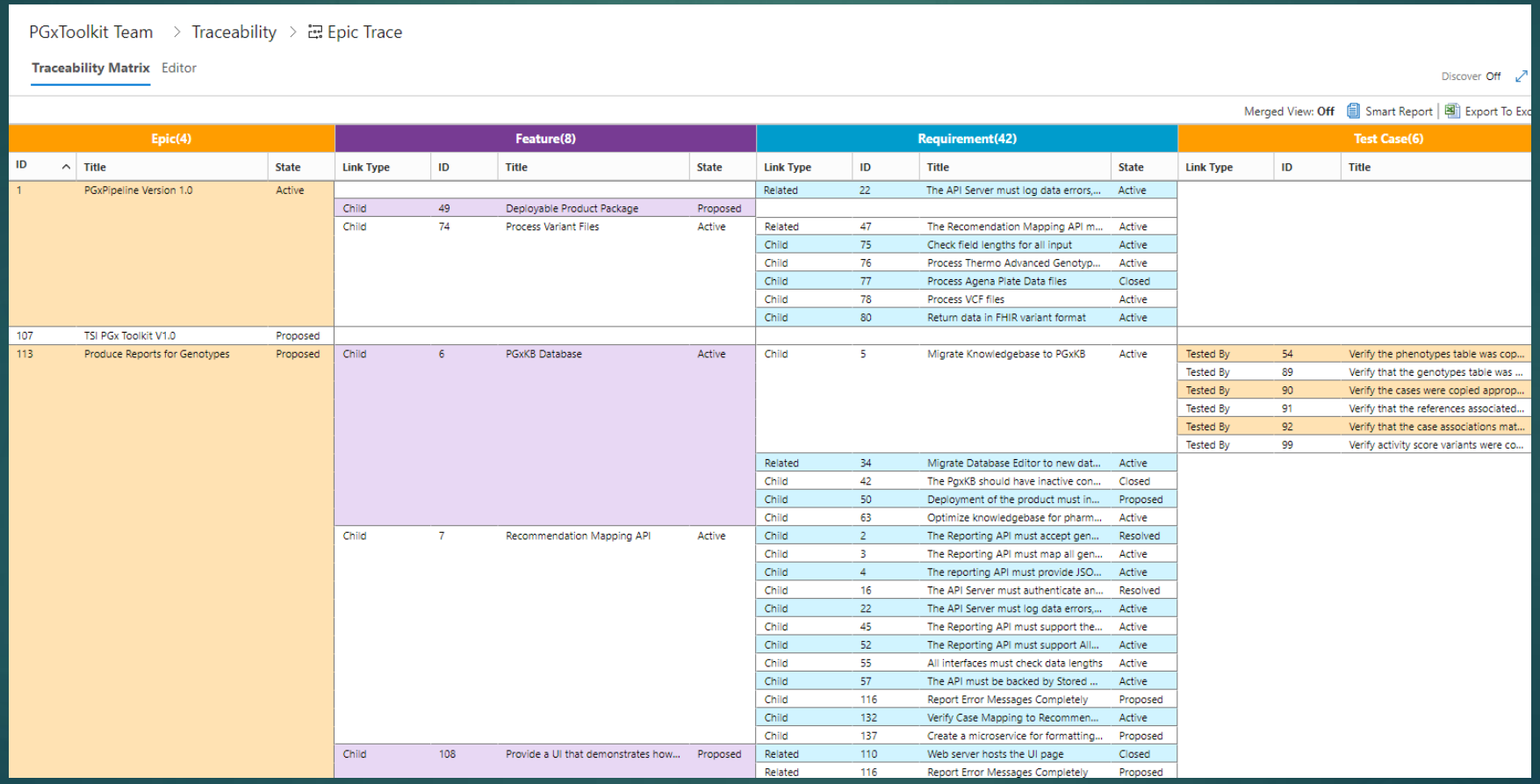
Things to Keep in Mind

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

Suggestions

- Don’t try to “shoehorn” a predicate.
- Much harder to validate legacy code.
- Narrow the scope to “reduce the attack surface”.
- Start from the E* and work back to the details.
- If possible, build PCCP into the submission.
- Invest in tooling.
  - QMS
  - Development platforms

Modern Requirements



PGxToolkit Team > Traceability > Epic Trace

Traceability Matrix | Editor

Discover Off

Merged View: Off | Smart Report | Export To Exc

Epic(4)			Feature(8)				Requirement(42)				Test Case(6)		
ID	Title	State	Link Type	ID	Title	State	Link Type	ID	Title	State	Link Type	ID	Title
1	PGxPipeline Version 1.0	Active					Related	22	The API Server must log data errors,...	Active			
			Child	49	Deployable Product Package	Proposed							
			Child	74	Process Variant Files	Active	Related	47	The Recomendation Mapping API m...	Active			
							Child	75	Check field lengths for all input	Active			
							Child	76	Process Thermo Advanced Genotyp...	Active			
							Child	77	Process Agena Plate Data files	Closed			
							Child	78	Process VCF files	Active			
							Child	80	Return data in FHIR variant format	Active			
107	TSI PGx Toolkit V1.0	Proposed											
113	Produce Reports for Genotypes	Proposed	Child	6	PGxKB Database	Active	Child	5	Migrate Knowledgebase to PGxKB	Active	Tested By	54	Verify the phenotypes table was cop...
											Tested By	89	Verify that the genotypes table was ...
											Tested By	90	Verify the cases were copied approp...
											Tested By	91	Verify that the references associated...
											Tested By	92	Verify that the case associations mat...
											Tested By	99	Verify activity score variants were co...
							Related	34	Migrate Database Editor to new dat...	Active			
							Child	42	The PgxKB should have inactive con...	Closed			
							Child	50	Deployment of the product must in...	Proposed			
							Child	63	Optimize knowledgebase for pharm...	Active			
			Child	7	Recommendation Mapping API	Active	Child	2	The Reporting API must accept gen...	Resolved			
							Child	3	The Reporting API must map all gen...	Active			
							Child	4	The reporting API must provide JSO...	Active			
							Child	16	The API Server must authenticate an...	Resolved			
							Child	22	The API Server must log data errors,...	Active			
							Child	45	The Reporting API must support the...	Active			
							Child	52	The Reporting API must support All...	Active			
							Child	55	All interfaces must check data lengths	Active			
							Child	57	The API must be backed by Stored ...	Active			
							Child	116	Report Error Messages Completely	Proposed			
							Child	132	Verify Case Mapping to Recommen...	Active			
							Child	137	Create a microservice for formatting...	Proposed			
			Child	108	Provide a UI that demonstrates how...	Proposed	Related	110	Web server hosts the UI page	Closed			
							Related	116	Report Error Messages Completely	Proposed			

Conclusion

- Pharmacogenetics is a perfect example of a complex test that FDA wants to improve.
- Current regulated tests are not as safe and effective as a competent commercial test.
- Applying the current regulatory framework to PGx tests is extremely expensive.
- Compartmentalizing the issues can help us collaborate on a solution.

Backup

Submission History –

Variant Inclusion in Knowledge Base and Genotyping Software

Determination of Potential Alleles/Variants for Inclusion

1.Identify any FDA approved labels for drugs or medical devices with recognized alleles and/or variants for the gene.

2.For genes with no alleles/variants in FDA approved labeling, identify alleles/variants from published recommendations (e.g., AMP consensus recommendation for coverage) or CPIC's allele definition table.

3.Review CPIC's allele functionality table. Only alleles/variants with clinical implications will be considered. These are defined as alleles/variants with No Function, Increased Function, or Decreased Function.

4.Review minor allele frequency (MAF) from the dbSNP database. Alleles/variants with an MAF of at least 1% in a given population will be considered.

Once the potential alleles/variants for genes with no alleles/variants in FDA approved labeling are identified, cited published literature with a Definitive Evidence Level from PharmVar will be pulled for evaluation.

Determination of Inclusion

1.The Primary Reviewer will determine if the collected evidence is sufficient to support the variant and/or variant-to-allele definition and include in our knowledge base.

2.If an allele with an associated variant or the variant itself has been identified by an FDA approved label for a drug or medical device, the variant/allele will automatically be included in our knowledge base as it has already been recognized by the FDA.

3.For alleles or variants not supported by an FDA approved label for a drug or medical device, the Primary Reviewer will review the cited literature from PharmVar and determine if they agree with the Definitive Evidence Level based on PharmVar's criteria above.

4.The Primary Reviewer will also confirm the variant associated with the allele is identified in the article as an rsID number or HGVS identifier (e.g., base pair change).

5.If the Primary Reviewer agrees with the Definitive Evidence Level, the evidence will be considered sufficient and the variant/allele will be included in our knowledge base. If the Primary Reviewer does not agree with a Definitive Evidence Level, the evidence will be considered insufficient and the variant/allele will not be included in our knowledge base.

Peer Review

1. A Peer Reviewer will conduct their own determination. If they agree with the Primary Reviewer, the decision to include (evidence deemed sufficient) or not include (evidence deemed insufficient) will stand.

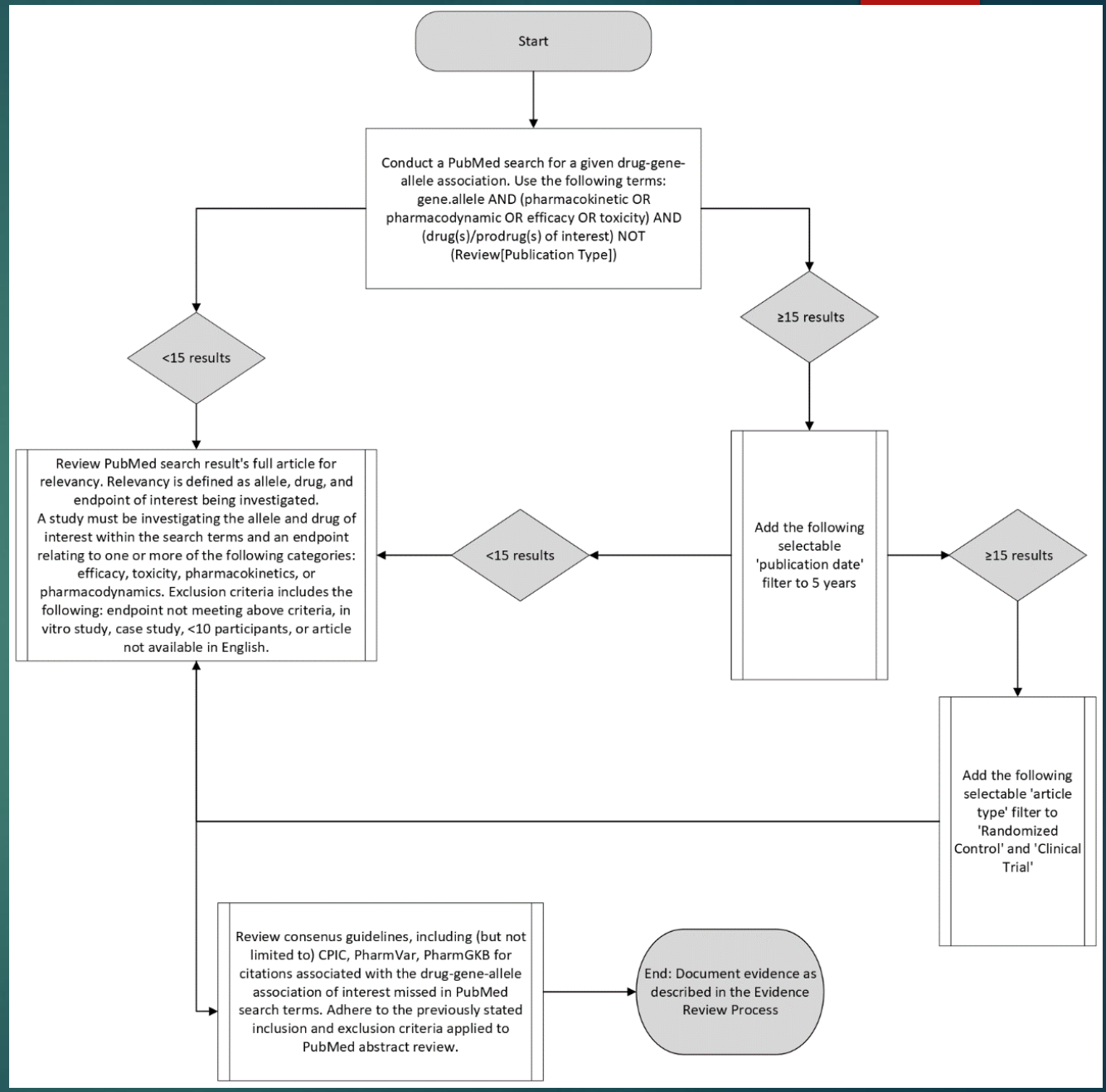
2. If the Peer Reviewer does not agree with the Primary Reviewer, the Peer Reviewer and Primary Reviewer will discuss and come to a consensus.

3. If a consensus cannot be made between the Peer Reviewer and Primary Reviewer, the discussion will expand to the entire Clinical Intelligence team who will review and discuss. A decision by the majority (i.e., 60%) will stand.

Submission History –

Variant Evidence Review Process

- Publications will be catalogued by PubMed ID (PMID) if available, or the following if not available: author, title, journal, year in the Variant Evidence Review Procedure Template. Each row of the template will be for a given publication and variant, or haplotype (e.g. star allele) if available. For example, if a PMID discusses four haplotypes, there will be four rows for that publication in the template.
- Once all information is recorded, the *Scoring of PharmGKB Variant Annotations* will be utilized to evaluate and score publications (https://www.pharmgkb.org/page/varAnnScoring, Appendix 1. Scoring of PharmGKB Variant Annotations). Evidence categories will be defined as follows: Strong ≥25, Moderate 8-24.9375, Weak 0-7.9375, Needs more evidence <0.
- This evidence curation process will be completed by two independent curators (one TSI curator AND an external curator OR two TSI curators). After evidence is collected and scored, data will be compared. All discordant scores will be discussed by the two independent curators until consensus is reached. In the event the curators are not able to agree on the variant categorization, the variant categorization will be brought to discussion with 100% of the Clinical Intelligence team with both curators' findings supporting their decision. The decision will then be determined by 100% of the Clinical Intelligence team with the majority of the vote (>50%) determining the final decision of the variant categorization.



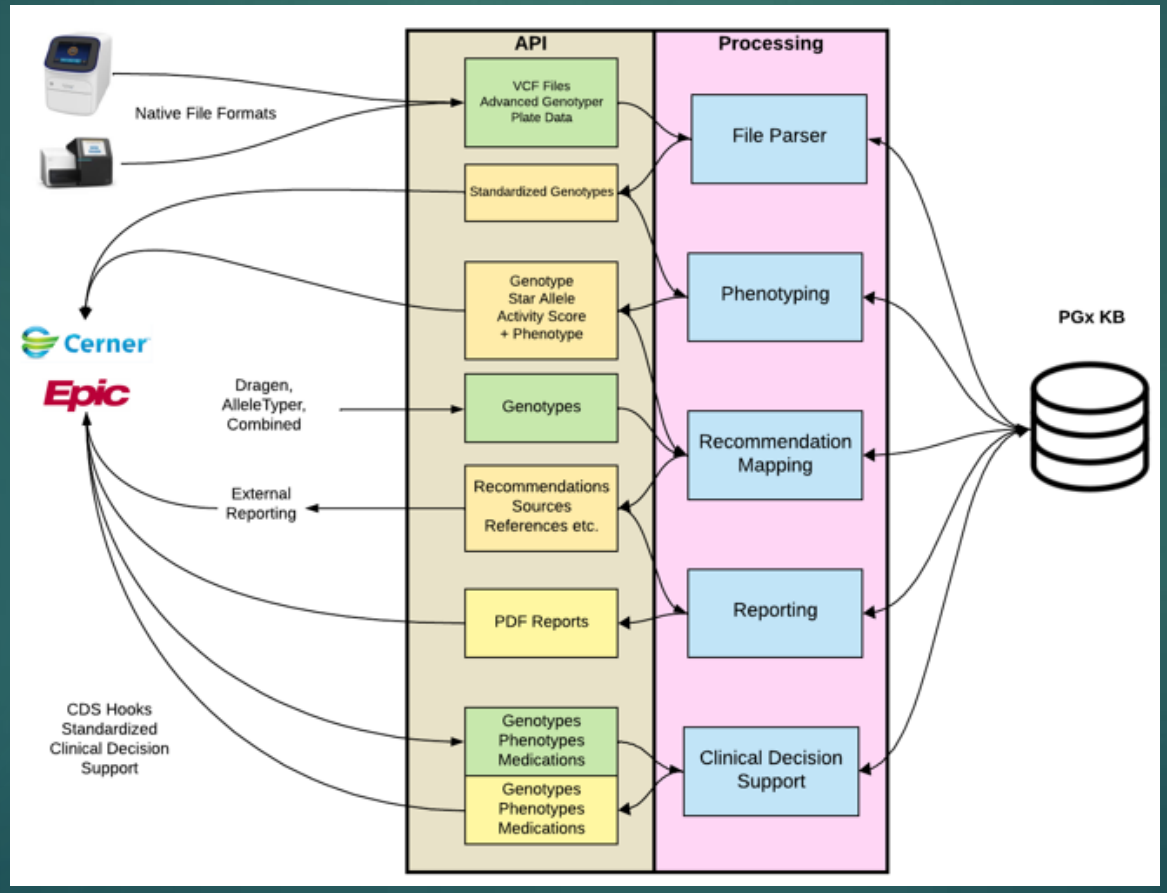
Submission History –

Variant Evidence Collection

Data Field	Description
PMID	Article PubMed ID
Gene (HGNC)	HGNC Gene Symbol
Star Allele	Add star allele (e.g., *2). If not applicable, state "N/A" ***If more than one star allele is discussed, add additional rows ***
Variants (rsID)	Published rsID for the variant. If multiple variants, separate with a semi-colon.
HGVS Nomenclature	HGVS Nomenclature for variant. Use build 38 for nomenclature. If multiple variants, separate with semi-colon and in same order as variants above
Impact of variant on RNA or protein	Options - Amino Acid Change, Splicing Defect, Full Gene Deletion, Partial Gene Deletion, Gene Insertion
Haplotyping process	Options - Star Allele, Genotyped, Not Available
Phenotyping determination	If phenotypes are reported, add genotype and phenotype. (e.g., *3/*3 – Poor Metabolizer) Phenotype options include - Poor Metabolizer, Intermediate Metabolizer, Normal Metabolizer, Ultra-Rapid Metabolizer.
Study Goal	Purpose, Aims, or Objective listed in the literature.
Hypothesis	What were the authors testing (e.g., reduced sensitivity to warfarin with a specific genotype, increased exposure to citalopram in Poor Metabolizers, etc.) if reported.
Substrate/Drug	What medications, drugs, or compounds were included in the study. If multiple, separate with semi-colon
Study Type	Options - In Vitro, In Vivo, In Silico, Clinical (RCT, Cohort, Case Study, Meta-Analysis, Observational.) May have more than one.
Study Design	Options - Prospective, Retrospective, Meta-analysis, N/A
Cohort number (N =)	Number of subjects in the cohort if applicable. State "N/A" if Not Applicable.
Cohort uniqueness	Unique factors of cohort, reference the PMID for the other cohort and assess the impact of previously reported data, if any. If unable to determine, note "Unable to determine." This may not be completed until all studies reviewed for a gene.
Sex	Female (N); Male (N) - Example: Female (79); Male (89). If not reported, state "Not Reported". If not applicable, state "N/A".
Ethnicity (N)	Document number of patients for reported ethnicities in parentheses - Example: "African American (45)". If multiple, list in alpha order and separate by semi-colons. If not reported, state "Not Reported". If not applicable, state "N/A".

Median Age (years)	Median age (range) - e.g., 64.3 (25-76)
Analysis Type	Options - Genotype, Diplotype (Star Allele), Phenotype
Reported Clinical Function	Options - No Function, Decreased Function, Normal Function, Increased Function, Uncertain Function, Not Reported
Clinical Outcome Type	Options: Efficacy, Toxicity, Dosage, PK/Metabolism, N/A
Study Arm (Treatment Regimen)	Name of groups. If applicable add treatment regimen in parentheses. Example - Low dose group (warfarin 26.25 mg/wk). Add additional study arms columns as needed.
Study Arm Cohort number (N =)	Number of subjects in Study Arm 1. Add additional study arm cohort number columns as needed.
Study Arm MAF	Add minor allele frequency (MAF) for the study arm (e.g., rs1799971 GG 0.230, GA 0.478, AA 0.292). Add additional study arm MAFs columns as needed.
Overall MAF	Document overall minor allele frequency (MAF) for the entire study cohort (e.g., rs1799971 GG 0.230, GA 0.478, AA 0.292).
Outcome Description	Document outcome studied (e.g., days to goal INR, improvement of PHQ9 after 3 months). Add additional outcome descriptions columns as needed.
P-Value 1	P-value of each outcome. Add additional p-values columns as needed.
Confidence Interval 1	Confidence value of outcomes. Add additional confidence value columns as needed.
Effect Size Type	Options - Odds Ratio, Relative Risk, Hazard Ratio, etc.
Effect Size Value	The value for the Odds Ratio, Relative Risk, Hazard Ratio
Limitations	Limitations of study including population, cohort size, lack of transparency in phenotyping, duration of study, etc. Be as concise as possible.
Results Summary	What outcomes were statistically significant, which ones were not. Any secondary analyses done. Statements made by the authors about the results.

TSI Kernel


API
Processing
Native File Formats
VCF Files
Advanced Genotyper
Plate Data
File Parser
Standardized Genotypes
Genotype
Star Allele
Activity Score
+ Phenotype
Phenotyping
PGx KB
Cerner
Epic
Dragen,
AlleleTyper,
Combined
Genotypes
Recommendation
Mapping
External
Reporting
Recommendations
Sources
References etc.
PDF Reports
Reporting
CDS Hooks
Standardized
Clinical Decision
Support
Genotypes
Phenotypes
Medications
Clinical Decision
Support
Genotypes
Phenotypes
Medications

The Opaque Part

Canonicalization

- Accept proprietary files
  Adjust for known issues
  Produce canonical genotypes

Typing

- Ingest trusted genotypes
  Map to known haplotypes
  Produce clinical phenotypes

Mapping

- Map each specimen to relevant ToPA content
  Produce regulatory information report