Unlocking the Potential of Pharmacogenomics

A Semantic Approach to Precision Medicine

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AGENDA

- Current Challenges In Building Healthcare Applications
- Pharmacogenomics (PGx) Use Case
- Datum’s Semantic Knowledge Platform
- Future Evolution of the Platform

PROBLEM

Developing Applications in Healthcare is complex

CHALLENGES IN BUILDING HEALTHCARE APPLICATIONS

1. Integration of domain-specific knowledge and evidences
2. Co-ordination across different faculties and disciplines
3. Strict compliance and data privacy requirements

SOURCES OF COMPLEXITY IN HEALTHCARE DATA

Diverse Data Sources

Healthcare knowledge bases and RWE come from various sources such as **Electronic health records (EHRs)**, **Genetic Tests**, **Clinical trials**, **other Patient-generated data**.

Integrating these diverse datasets is a complex task.

Data Standardization

Ensuring **consistency** and **standardization** across different data formats and structures is crucial for effective integration.

Lack of standardized data can hinder interoperability.

Semantic Interoperability

Healthcare knowledge bases and RWE may use **different ontologies** and **vocabularies**.

Achieving semantic interoperability to ensure that data from different sources can be accurately interpreted and combined is a significant challenge.

PHARMACOGENOMICS (PGX) USE CASE

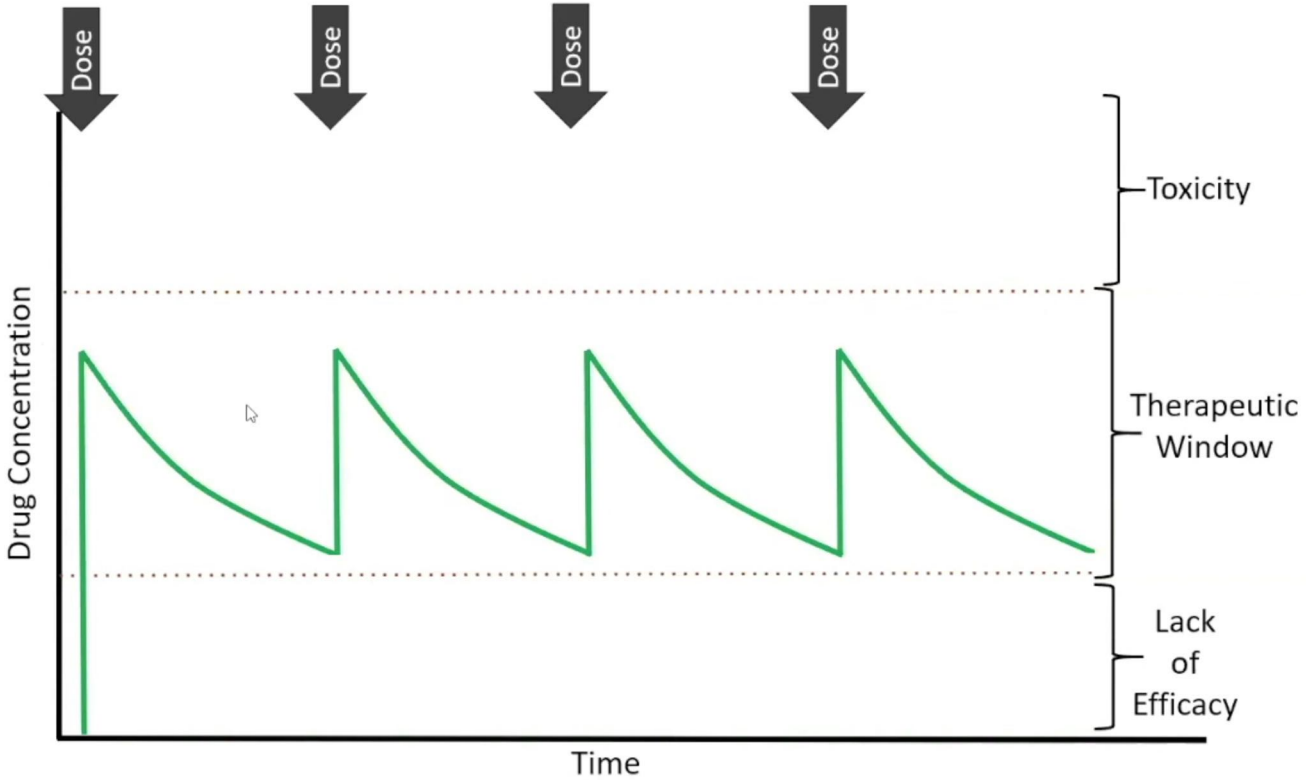
“HOW SOMEONE’S DNA AFFECTS THE WAY THEY RESPOND TO DRUGS”

US Centers for Disease Control and Prevention (CDC)

“THIS FIELD COMBINES PHARMACOLOGY (THE SCIENCE OF DRUGS) AND GENOMICS (THE STUDY OF GENES AND THEIR FUNCTIONS) TO DEVELOP EFFECTIVE, SAFE MEDICATIONS THAT CAN BE PRESCRIBED BASED ON A PERSON’S GENETIC MAKEUP”

MedlinePlus, US National Library of Medicine

INDIVIDUAL VARIATION WHEN TAKING SAME DOSE OF SAME DRUG



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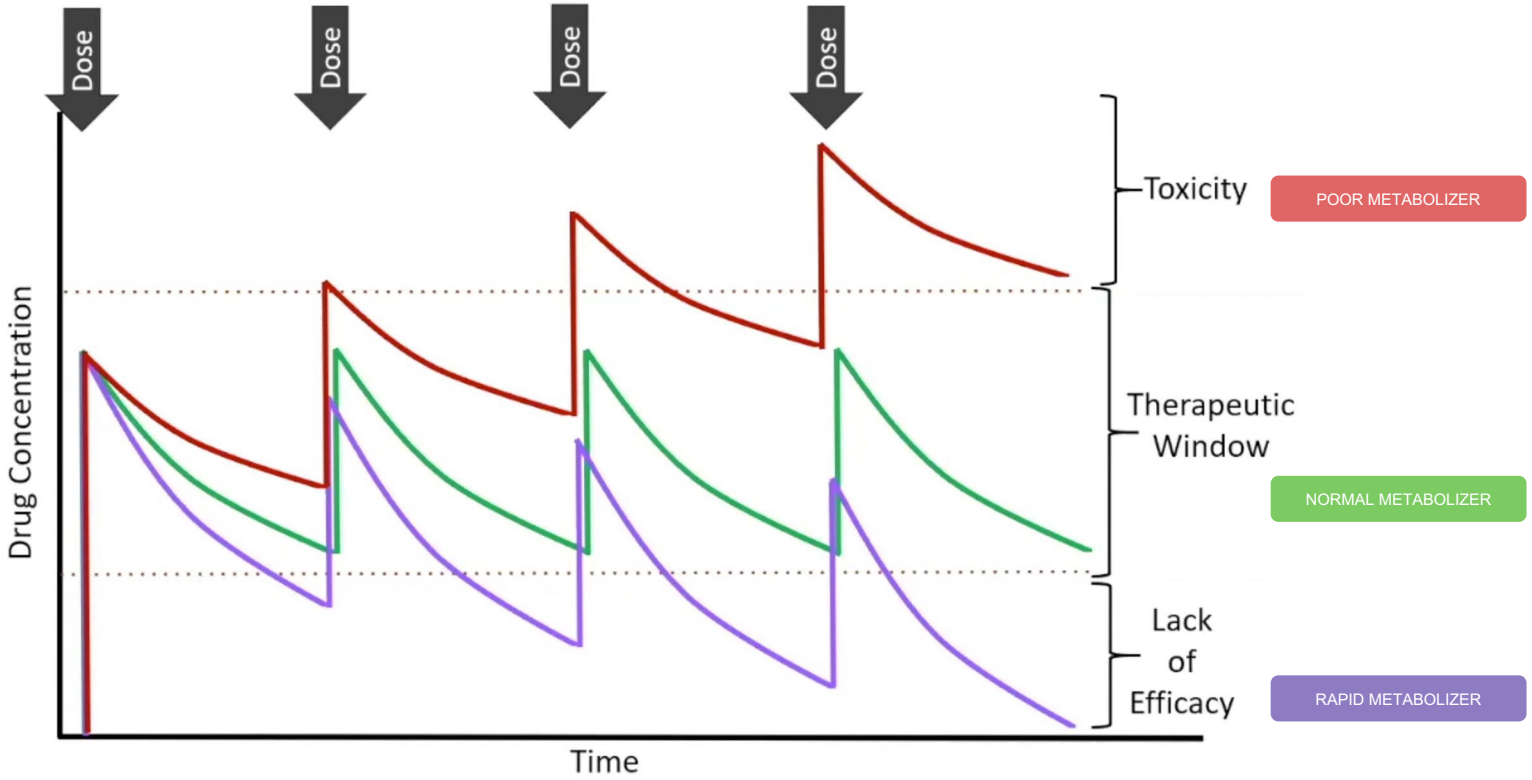

MULTIPLE STANDARD GUIDELINES FOR RECOMMENDATIONS

CPIC®
Clinical Pharmacogenetics Implementation Consortium

Search CPIC Website

Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2C19* Genotype and Clopidogrel Therapy: 2022 Update

Craig R. Lee[1], Jasmine A. Luzum[2], Katrin Sangkuhl[3], Roseann S. Gammal[4,5], Marc S. Sabatine[6], Charles Michael Stein[7], David F. Kisor[8], Nita A. Limdi[9], Yee Ming Lee[10], Stuart A. Scott[11,12], Jean-Sébastien Hulot[13], Dan M. Roden[14], Andrea Gaedigk[15], Kelly E. Caudle[5], Teri E. Klein[3], Julie A. Johnson[16] and Alan R. Shuldiner[17,*]

CYP2C19 catalyzes the bioactivation of the antiplatelet prodrug clopidogrel, and *CYP2C19* genotype impacts clopidogrel active metabolite formation. CYP2C19 intermediate and poor metabolizers who receive clopidogrel experience reduced platelet inhibition and increased risk for major adverse cardiovascular and cerebrovascular events. This guideline is an update to the 2013 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for the use of clopidogrel based on *CYP2C19* genotype and includes expanded indications for *CYP2C19* genotype-guided antiplatelet therapy, increased strength of recommendation for CYP2C19 intermediate metabolizers, updated *CYP2C19* genotype to phenotype translation, and evidence from an expanded literature review (updates at www.cpicpgx.org).

This document is an update to the 2013 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline on the clinical use of *CYP2C19* genotype test results for patients requiring antiplatelet therapy.[1] Since the previous update, results from prospective randomized clinical trials, multicenter pragmatic studies, and meta-analyses on *CYP2C19* genotype-guided antiplatelet therapy with clinical outcomes data have demonstrated the utility of this approach.[2–4] The purpose of this guideline is to provide clinicians with information that facilitates the interpretation of clinical *CYP2C19* genotype test results to guide clopidogrel prescribing. As in the previous guideline, recommendations for use of other laboratory tests, such as platelet function monitoring, as well as cost-effectiveness analyses, are beyond the scope of this document. The guideline does not focus on demographic and other clinical variables, such as adherence to therapy, age, diabetes mellitus, obesity, smoking, and concomitant use of other drugs that may influence clopidogrel efficacy and clinical decision making. CPIC guidelines are periodically updated at www.cpicpgx.org/guidelines/.

FOCUSED LITERATURE REVIEW

A systematic literature review focused on *CYP2C19* genotype and clopidogrel response was conducted (see **Supplementary Material** for more details). Evidence is summarized in **Tables S1–S4**.

GENE: *CYP2C19*

Background

The *CYP2C19* gene is highly polymorphic; the Pharmacogene Variation Consortium (PharmVar) has currently defined over 35 star (*) allele haplotypes,[7] including rare gene deletions (https://www.pharmvar.org/gene/CYP2C19; see *CYP2C19* Allele Definition Table online[8,9]). The frequencies of these star (*) alleles significantly differ across ancestrally diverse populations (see *CYP2C19* Allele Frequency Table online[8,9]). Alleles are categorized into functional groups as follows: normal function (e.g., *CYP2C19*1*), decreased function (e.g., *CYP2C19*9*), no function (e.g., *CYP2C19*2* and *3), and increased function (e.g., *CYP2C19*17*). Clinical allele function, as described in the

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Actueel ⌄ Dossiers Richtlijnen Beroepsontwikkeling ⌄ Bedrijfsvoering ⌄

← Vorige Dossiers › Farmacogenetica

Farmacogenetica

Altered metabolic capacity and clinical consequences

The cytochrome P450 enzymes, which include the iso-enzyme CYP2C19, are involved in the metabolism of many medicines. CYP2C19 metabolises approximately 8% of these medicines.
Variations in the gene that encodes for the CYP2C19 iso-enzyme can result in reduced, elevated or absent enzyme activity.
The population can be divided into four phenotypes, based on the metabolic capacity of CYP2C19 that is present:

- poor metaboliser (PM), severely reduced or absent metabolic capacity (two alleles with absent or reduced activity);
- intermediate metaboliser (IM), reduced metabolic capacity (one allele with absent or reduced activity and one allele with normal or elevated activity);
- extensive metaboliser (EM), “normal” metabolic capacity (two alleles with normal activity or one with normal activity and one with elevated activity);
- ultra-rapid metaboliser (UM), increased metabolic capacity (two alleles with elevated activity).

The degree of activity for the various alleles is presented in Table 1.
There is also a large variation in metabolic capacity within each phenotype group.

The difference in metabolic capacity can have therapeutic consequences if the plasma concentration is related to the effect or the occurrence of side effects. It may be necessary to change the standard dose or to opt for a different medicine.
As the genotype only determines a part of the metabolic capacity, the recommendations for dose adjustment based on the genotype are no more than a tool that can be used to achieve the desired plasma concentration. In order to optimise the dose, therapeutic drug monitoring (TDM) can be useful for substances that usually have a therapeutic guideline and where plasma concentration is related to effect or side effects.

IMPLEMENTING PRECISION MEDICINE IS HARD DUE TO

Data silos

Each precision medicine application development requires bespoke data effort (data models, data pipelines, database design, etc.)

Challenging to bring together multimodal, interoperable, datasets

Knowledge translation cost

Building precision medicine applications requires expensive back-and-forth between developers and scientists / clinicians

High chances of incorrect specifications (lost in translation) causing delays

Application layer gap

Current (traditional) approaches in translational medicine rely heavily on research & analytics, less on automation and agents

Bespoke applications developed end up in proof-of-concept wasteland due to lack of scalability

SOLUTION

The Datum Apollo Platform

APOLLO: PLATFORM TO BUILD AND DEPLOY SECURE BIOMEDICAL APPLICATIONS USING PRIVATE AND PUBLIC DATA

Data Centric Architecture

Semi-automated data ingestion, processing, management and analytics within a flexible and scalable infrastructure

Semantic knowledge graphs, scalable to 100's of open access and proprietary datasets

Infra for researchers & app builders

No code platform for scientists / clinicians, they build applications themselves.

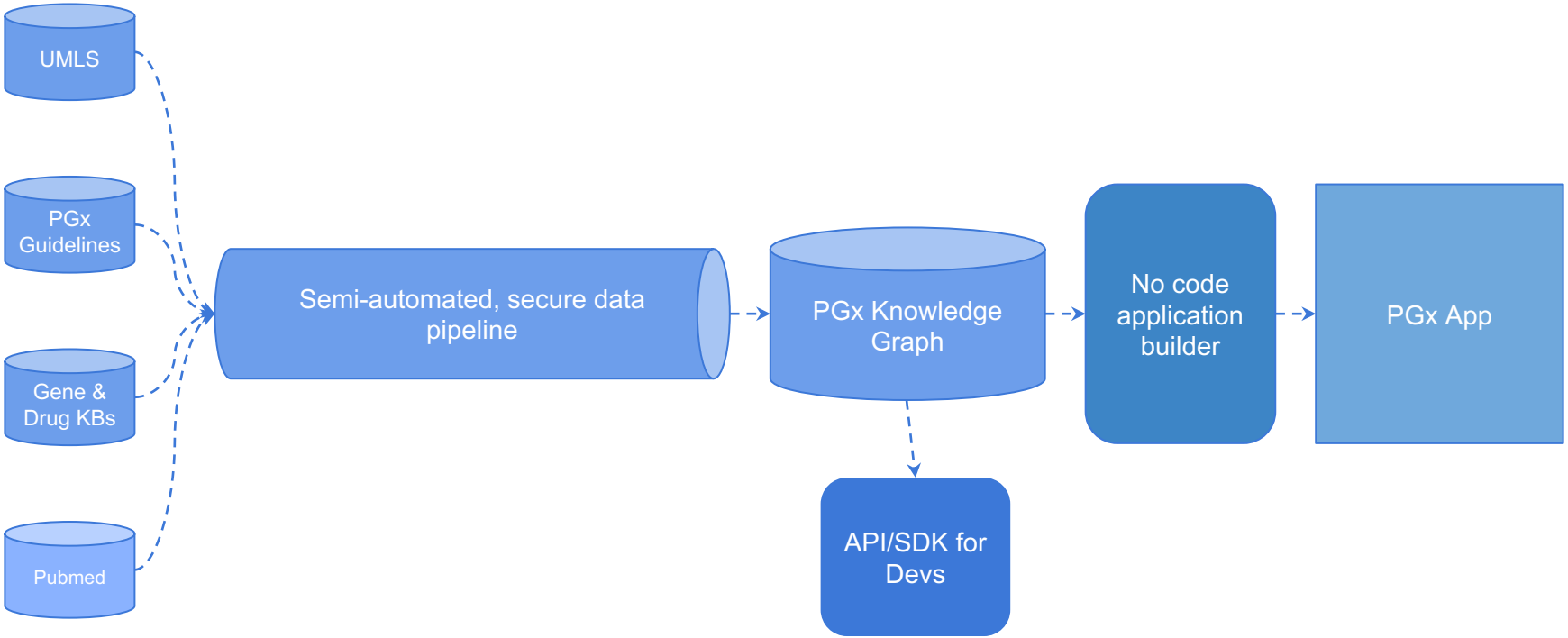
Out-of-the-box scalable applications development through powerful API/SDK

Ubiquitous smart agents

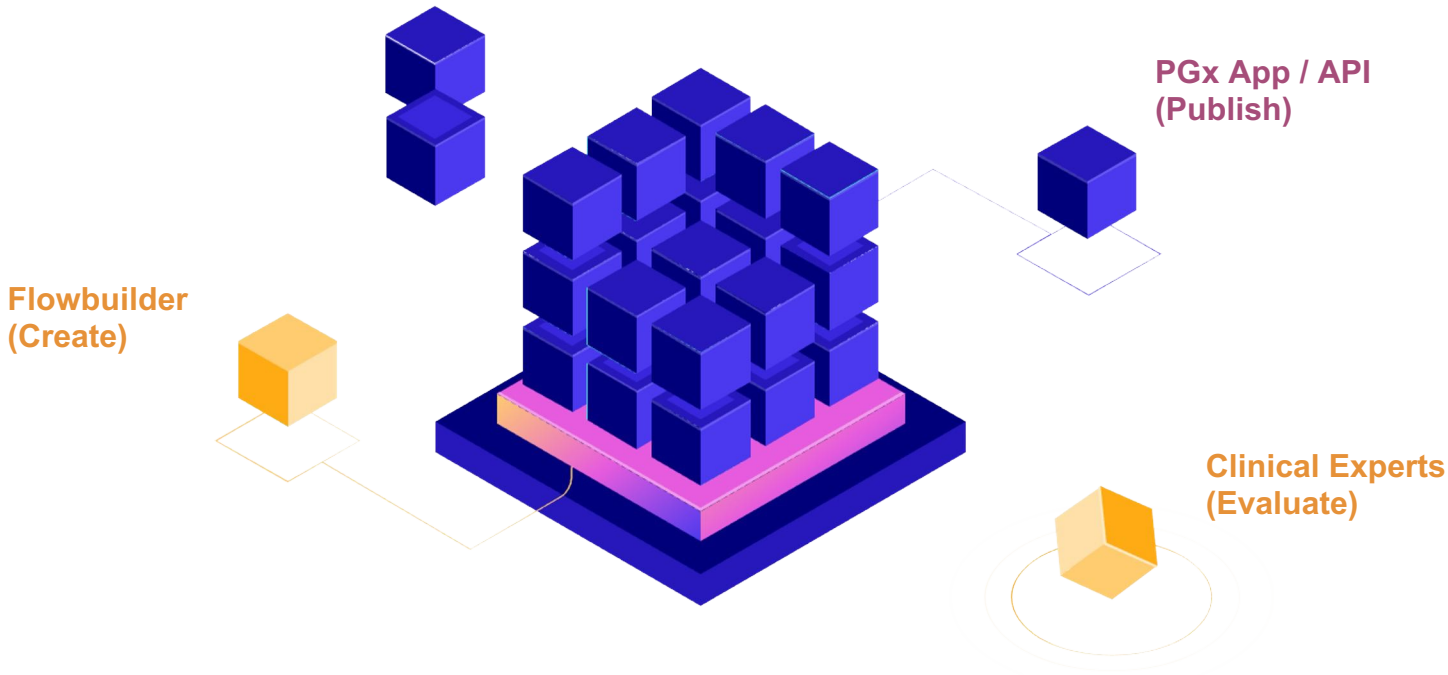
Operationalize knowledge through AI-ready apps grounded by our KG.

Integrate your proprietary data within a highly secure environment

APOLLO: HIGH LEVEL ARCHITECTURE



WORKFLOW ENABLED BY THIS APPROACH



CREATE: BUILDING THE KNOWLEDGE GRAPH (KG)

RDF Graph

Focus on standardization and interoperability

Highly flexible model to link different data sources

Baseline PGx KG

UMLS for standard biomedical vocabulary

Augmented with other datasets (PGx Guidelines, Drugs, Genes etc.)

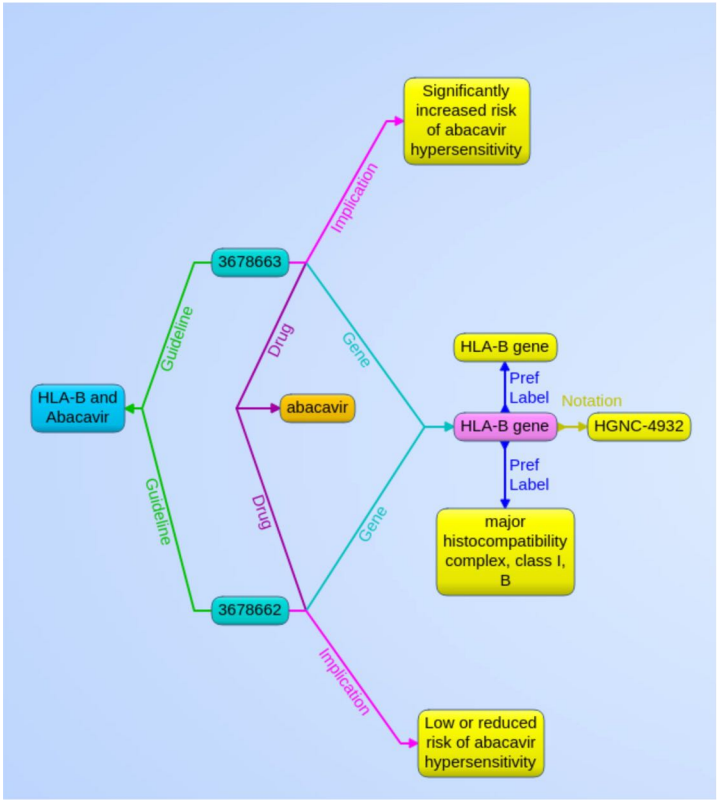
User Create Flows

Encode the complex decision-making logic for PGx as KG

Expert knowledge operationalized and linked to PGx KG

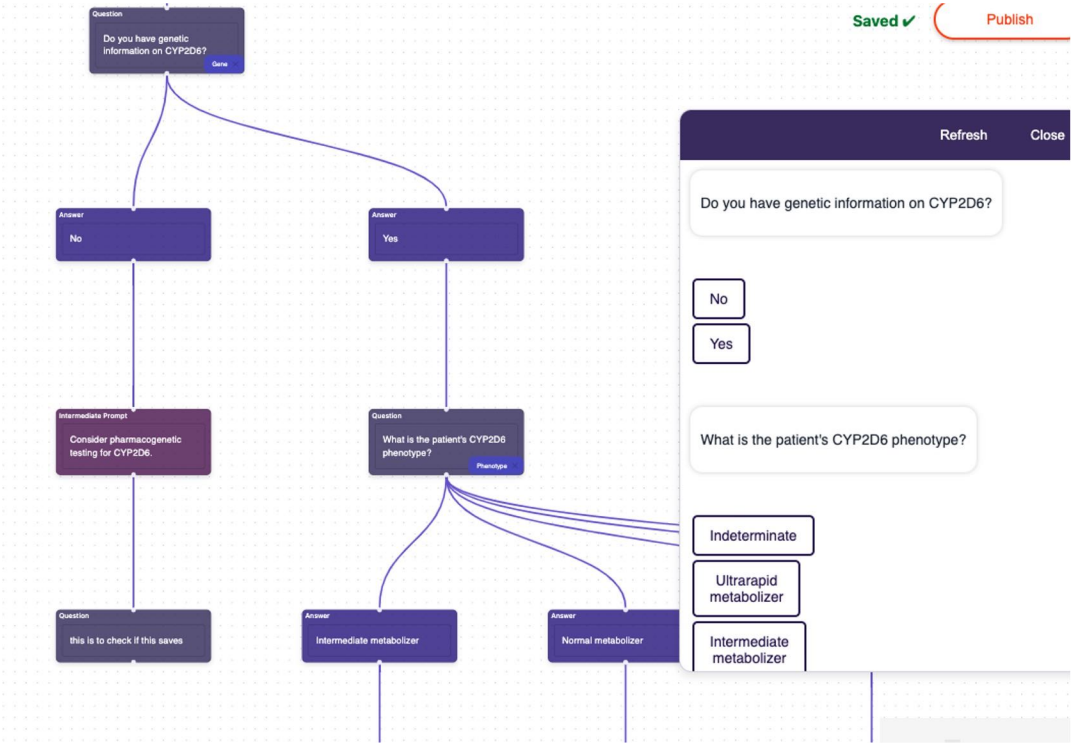
CREATE: PGx KNOWLEDGE GRAPH

- PGx Guidelines
  - Drug-Gene interaction
  - CPIC, DPWG
- Drug Knowledge Bases
  - Dailymed, RxNorm
- Gene & Gene Variant Knowledge Bases
  - PharmGKB
  - Clinvar
- Standard Vocabulary
  - HGNC, SNOMED, ICD, UMLS MTH



CREATE: NO-CODE FLOW BUILDER CONNECTED TO PGX KG

- Clinical experts create flows through a visual interface
- Nodes and edges linked with PGx KG
- Collaboration platform with custom publish workflow
- Enable powerful apps downstream



*will be largely automated by our AI copilot in the future

PUBLISH: DRUG-GENE INTERACTION TOOL

57yo black male with hypertension (HTN). Clinician considers adding clopidogrel 75mg/day to the patient's medical regimen. Genetic testing done for CYP2C19.

What is the patient's CYP2C19 phenotype?

Poor Metabolizer | Likely Poor Metabolizer | Ultra-Rapid Metabolizer | Rapid Metabolizer

Normal Metabolizer | Likely Intermediate Metabolizer | Intermediate Metabolizer

Avoid clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication.

SHOW EXPLANATION

You

what are the evidences for this recommendation?

PUBLISH: DEVELOPER API/SDK

- Give developers easy to use API to our PGx KG
- Well documented and easy to integrate
- APIs with different levels of abstractions
- Reinforces our commitment to FAIR (Findable, Accessible, Interoperable and Reusable) principles

```python
from datumbio import Apollo

# Use a valid UMLS key and Datum API Key for the username
client = Apollo(api_key=DATUM_API_KEY, umls_key=UMLS_API_KEY)

# Query umls
QUERY = 'chest pain'

result = client.search_umls(query=QUERY, limit=2)
print(result.to_json())
```

Related Concepts

```python
CUI = "C0008031"
```

```python
child_concepts = client.related_concepts(cui=CUI, rel='PAR', level=2)
child_concepts.to_pandas()
```

	code	label
0	C0155711	Complications and ill-defined descriptions of ...
1	C0184507	Sensory Component
2	C0184566	RNDx comfort alteration
3	C0333343	Body Cavity
4	C0460005	Structure of trunk, unspecified
5	C0678900	Cutaneous Sense
6	C0679031	Somesthetic Perception
7	C0851738	Cardiac signs and symptoms NEC

WHAT'S NEXT

- Collaborate with health systems, laboratories, and specialty pharmacies implementing PGx
- Grow and evolve the PGx Knowledge Graph
- Automatically generate flows using AI copilot
- Improved integration of KG and LLM to complement each other
- Make the API widely available to application builders
- Build out the evaluation workflow

THANK YOU

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