Providing Clinical Decision Support to Medical Providers Through Interpretation of Gene-Drug Interactions

John Flahive
PRIMES Conference
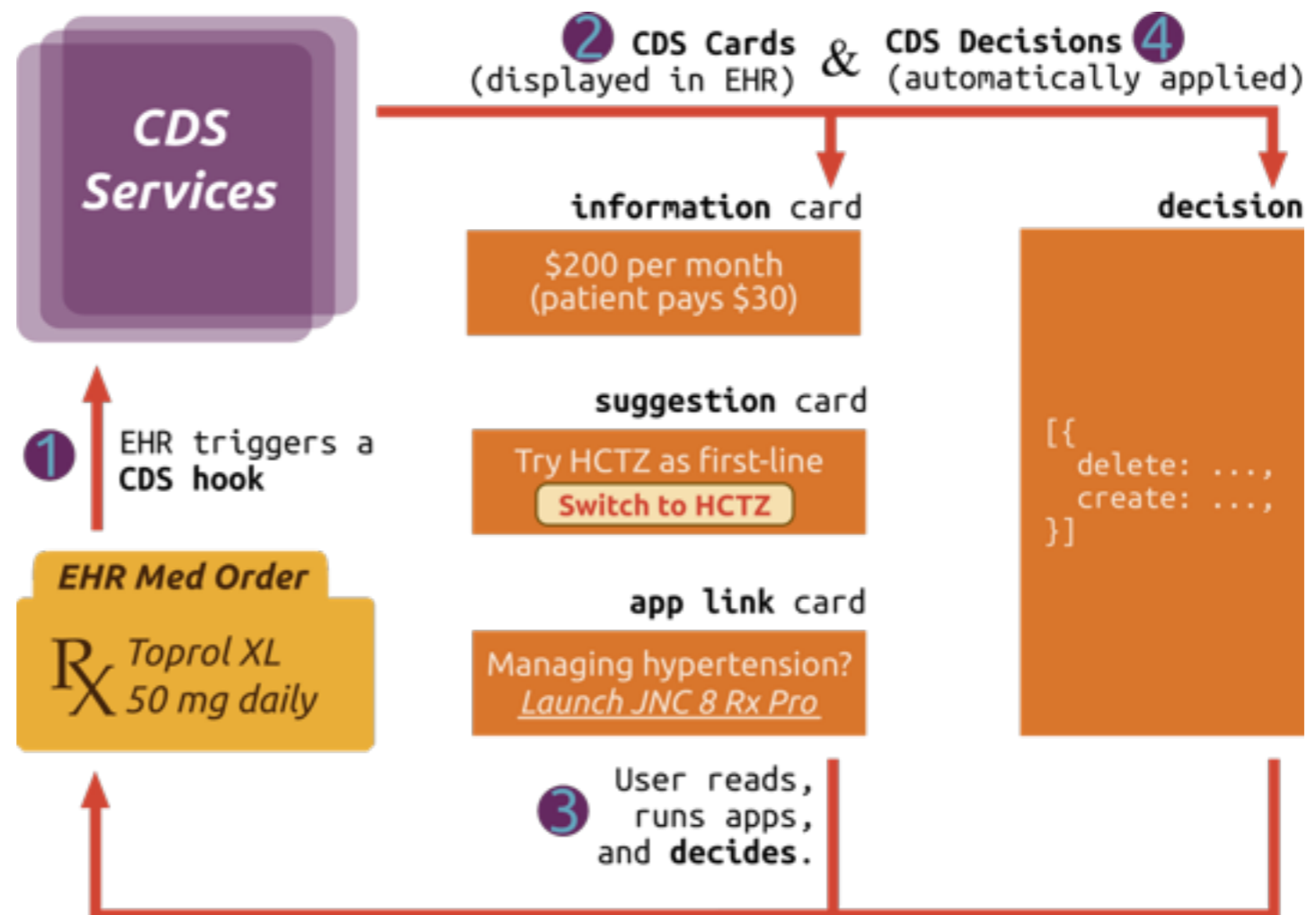Mentor: Gil Alterovitz
May 22nd, 2016

Background—Pharmacogenomics (PGX)

- TPMT and Thiopurine Drugs
  Gene
  Dangers: Myelosuppression and Myelotoxicity

- HLA-B * 57:01 and Abacavir
  Allele
  Dangers: Hypersensitivity

Background—
Clinical Decision Support (CDS)

- Support medical providers with extra information
  Improve quality and effectiveness of care
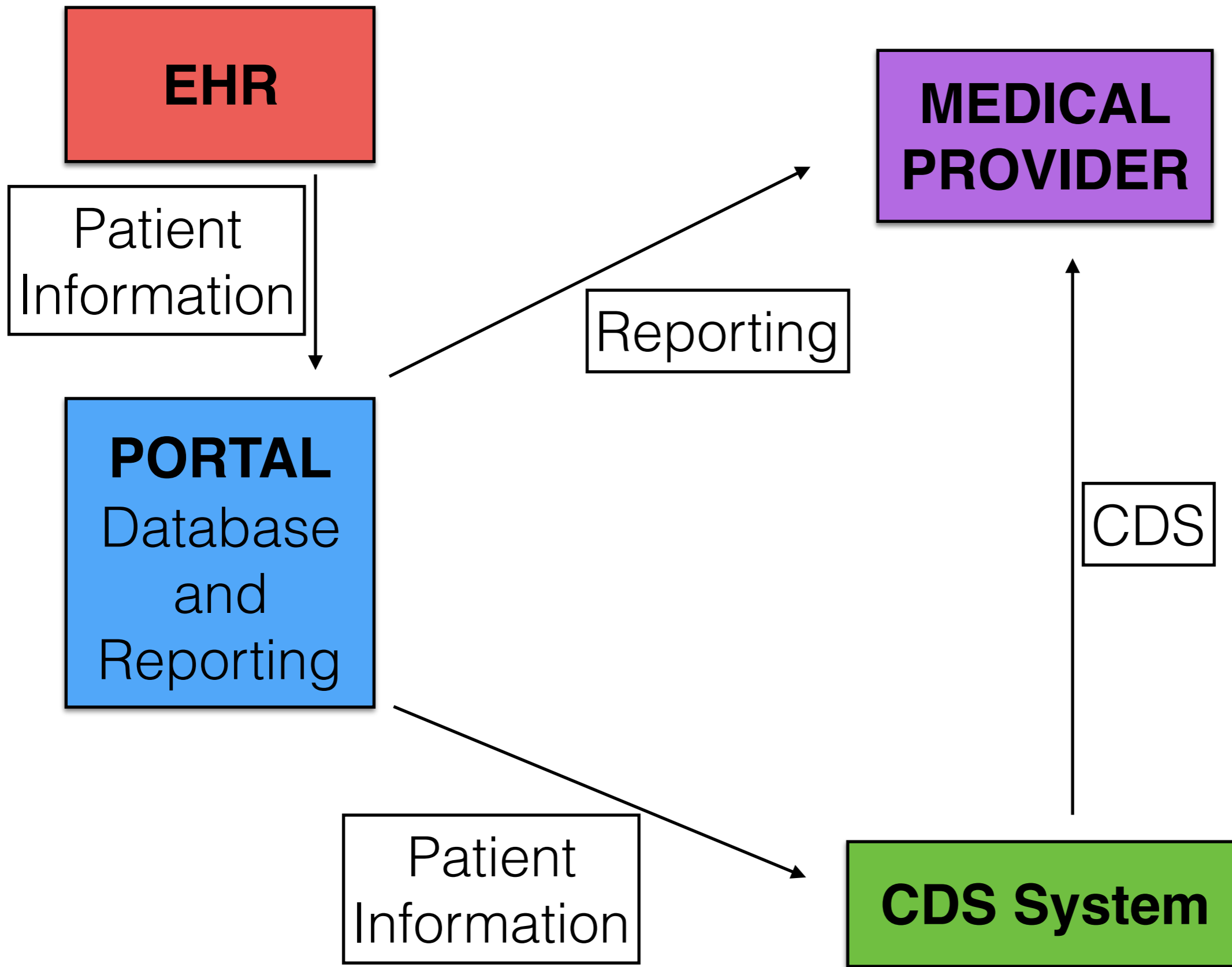
- **CDS Hooks**

Background—FHIR

- **F**ast **H**ealth **I**nteroperability **R**esource
  Exchange patient data uniformly and quickly

EHR	FHIR Format →	APPLICATION

Electronic Health Record

CDS Applications
Provider Applications

Application— PGxPortal

- **GOAL**– Provide interface between medical providers, a CDS system, and EHR

- **METHOD**– Medical providers see patient reporting taken from EHR

- **METHOD**– CDS system uses patient reporting to provide support to medical providers
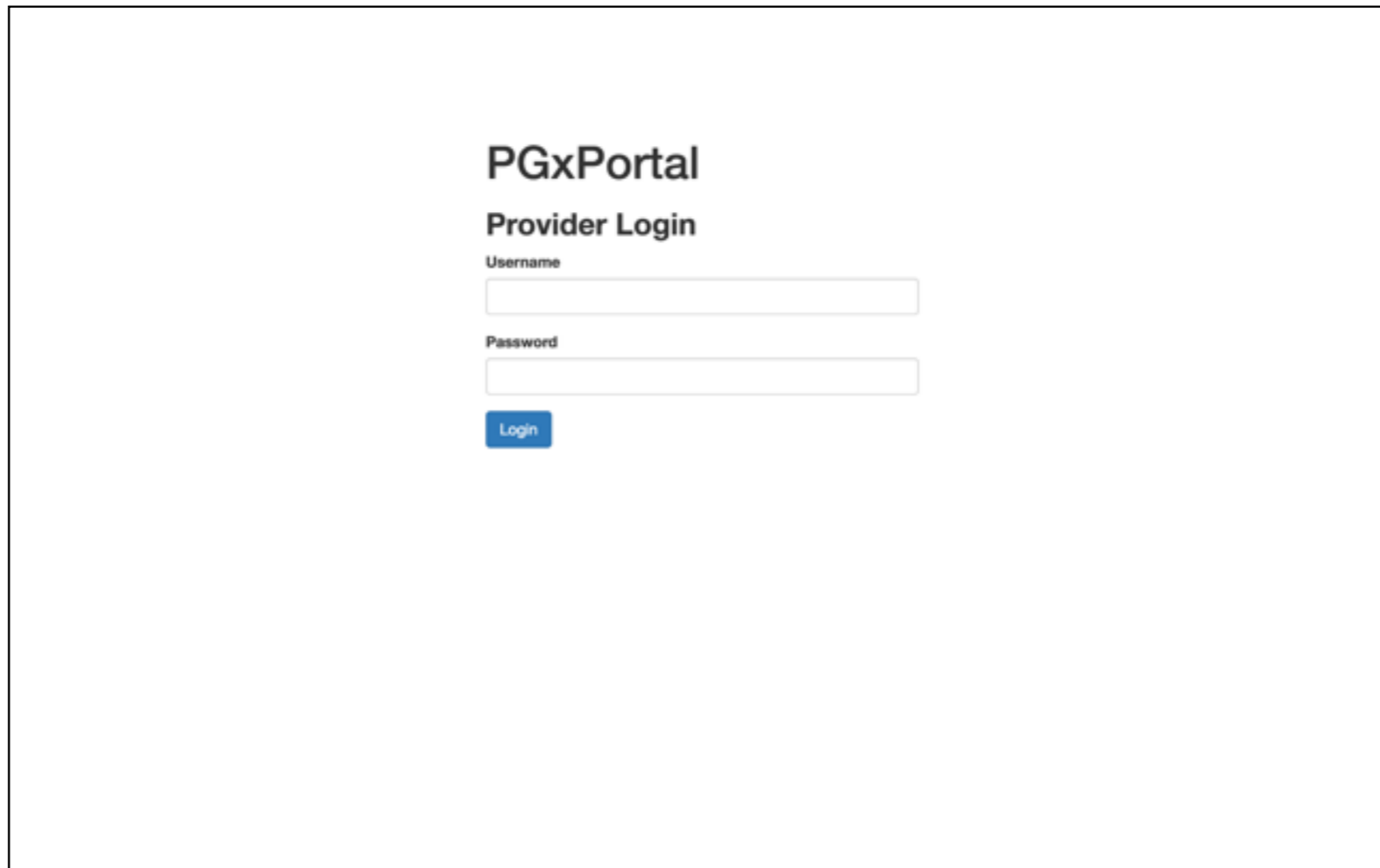
EHR

Patient Information

PORTAL
Database and Reporting

Reporting

MEDICAL PROVIDER

CDS

Patient Information

CDS System

Application— PGxPortal

Name	Gender	DOB	MRN	Reports		Genotypes
John Smith	Male	05-19-1999	1234567	DOWNLOAD	OPEN	SHOW
Jane Doe	Female	03-04-2001	7654321	DOWNLOAD	OPEN	SHOW
Test Patient	Male	12-12-2002	4567123	DOWNLOAD	OPEN	SHOW

Assigned Patient Report Permissions

Name	MRN	Providers With Approved Access	
John Smith	1234567	RandomProvider x	ADD NEW PROVIDER
Jane Doe	7654321	SecondProvider x	ADD NEW PROVIDER
Test Patient	4567123	RandomProvider x SecondProvider x	ADD NEW PROVIDER

Demonstration— PGxPortal

Genomics Advisor V2

Tests Currently Offered:

- Thiopurine methyltransferase (TPMT) Genotype
- Warfarin (CYP2C9/VKORC1) Genotype
- Cytochrome P450 2C19 (CYP2C19) Genotype

🔍 Search patients

Name	Gender	DOB	MRN	Reports		Genotypes	VCF
John Smith	Male	05-19-1999	1234567	DOWNLOAD	OPEN	SHOW	VIEW
Jane Doe	Female	03-04-2001	7654321	DOWNLOAD	OPEN	SHOW	VIEW
Test Patient	Male	12-12-2002	4567123	DOWNLOAD	OPEN	SHOW	VIEW
Daniel Adams	Male	11/05/1898	3217654	DOWNLOAD	OPEN	SHOW	VIEW

Q Search patients

Name	Gender	Genotypes	VCF
John Smith	Male	SHOW	VIEW
Jane Doe	Female	SHOW	VIEW
Test Patient	Male	SHOW	VIEW
Daniel Adams	Male	SHOW	VIEW

GENOTYPES: Daniel Adams, PATIENT

GENE	DIPLOTYPE	REPORT
TPMT	*1/*2	TPMT REPORT
CYP2C9	*1/*1	CYP2C9 REPORT
VKORC1	A/G	VKORC1 REPORT
CYP2C19	*1/*2	CYP2C19 REPORT

ALLELE	PRESENCE	REPORT
HLA-B*57:01	Missing	HLA-B*57:01 REPORT

Genome Browser

« **Human NCBI37/hg19** | 10:96,701,711..96,701,719 | 🔍 ●━━━━━━━━━ 🔍   + 🔍 🖨 ⚙ ? »
200bp   2kb   50kb   500kb

✖ Genome

A   T   C   T   T   G   G   A

✖ VCF

Powered by **Biodalliance** 0.13.7

substitution: T>C	✕
Location	10:96701715-96701715
Ref. allele	T
Alt. alleles	C
dbSNP membership	rs72558187

Genome Browser

« **Human NCBI37/hg19** 10:96,699,946..96,703,871   🔍 ○—————●————— 🔍   + 🄰 🖶 ⚙ ? »
    200bp   2kb   50kb   500kb

✕ Genome
96,700,000   96,700,500   96,701,000   96,701,500   96,702,000   96,702,500   96,703,000   96,703,500

✕ VCF

Powered by **Biodalliance** 0.13.7

substitution: C>T	✕
Location	10:96702047-96702047
Ref. allele	C
Alt. alleles	T
dbSNP membership	rs1799853

Assigned Patient Report Permissions

Name	MRN	Providers With Approved Access	
John Smith	1234567	RandomProvider [X]	ADD NEW PROVIDER
Jane Doe	7654321	SecondProvider [X]	ADD NEW PROVIDER
Test Patient	4567123	RandomProvider [X] SecondProvider [X]	ADD NEW PROVIDER
Daniel Adams	3217654	RandomProvider [X] SecondProvider [X]	ADD NEW PROVIDER

Administrative Tools

Add Patient

Main Provider

Full Name

Gender

DOB

MRN

FHIR ID

[Add Patient]   [Cancel]

Administrative Tools

Add Provider

Provider Name

Username

Password

Admin ☐

Register Cancel

Update Patient Report Files

Select Affymetrix File:

Choose Files   No file chosen

Upload Affymetrix File   Add Data To Reporting

Update Patient Report Files

Select Affymetrix File:

[Choose Files] TEST_DMET..._TPMT.txt

[Upload Affymetrix File] [Add Data To Reporting]

FILE CONTENT:

```
#SJAccession=1326601520A
#PatientName=TEST PATIENT
#DMETfile=DNL_CLIA_1641_1326601520A.dmet_GT.txt
#DNL ID=DNL_1641
#PatientID=1111111
#SampleType=Blood
#TranslationFile=DMET_Plus.v1.20120731.translation
#AnnotationFile=DMET_Plus.v1.20120731.dc_annot.mod230.csv
#ReporterBuild=0.22.2
#VerifiedList=VerifiedbyAffy_Mar11 marker list.txt
#GeneSymbol=TPMT
#PharmGKBLink=http://www.pharmgkb.org/do/serve?objId=PA356&objCls=Gene
Q-PCR Determined Copy Number    Not Determined
Q-PCR Probe ID  N/A
Called Interpretation Code      UNIQ
Called Diplotypes Possible      Missing
Called Novel Diplotypes Possible        -
Number Non-reference Probe Sets 1
Probe Set ID    Affy Verified   Genome Position dbSNP RS ID     Genotype        Call    Contributes To Alleles  Description
AM_13979        Y       Ch6:18139214    rs2842934       C/T     Ref/Var -       TPMT_c.474C>T(I158I)
Number Reference only Probe Sets        7
Probe Set ID    Affy Verified   Genome Position dbSNP RS ID     Genotype        Call    Contributes To Alleles  Description
AM_13986        Y       Ch6:18143955    rs1800462       G/G     Ref/Ref *2      TPMT*2_c.238G>C(A80P)
AM_13985        Y       Ch6:18143901    rs72552739      G/G     Ref/Ref *3D     TPMT_c.292G>T(E98X)
AM_13980        Y       Ch6:18139228    rs1800460       G/G     Ref/Ref *3A,*3B,*3D     TPMT*3B_c.460G>A(A154T)
AM_13978        Y       Ch6:18134078    rs6921269       G/G     Ref/Ref *24     TPMT*24_c.537G>T(Q179H)
AM_13977        N       Ch6:18131012    rs1800584       G/G     Ref/Ref *4      TPMT*4_c.626-1G>A(SpliceDefect)
AM_13976        Y       Ch6:18130993    rs56161402      G/G     Ref/Ref *8      TPMT*8_c.644G>A(R215H)
AM_13973        Y       Ch6:18130918    rs1142345       A/A     Ref/Ref *3A,*3C,*3D     TPMT*3C_c.719A>G(Y240C)
```

Record Access Logs

[Download Log]

AdminProvider loaded reports page.	04/16/2016 at 1:17:22 PM
AdminProvider loaded the provider tools page.	04/16/2016 at 1:17:21 PM
AdminProvider loaded reports page.	04/16/2016 at 1:17:15 PM
AdminProvider logged in.	04/16/2016 at 1:17:15 PM
AdminProvider logged in.	04/16/2016 at 1:16:44 PM
AdminProvider loaded the provider tools page.	04/16/2016 at 1:16:36 PM
AdminProvider loaded the provider tools page.	04/16/2016 at 1:16:34 PM
AdminProvider logged in.	04/16/2016 at 1:16:17 PM
AdminProvider loaded the logs page.	04/16/2016 at 1:15:49 PM
AdminProvider loaded report update page.	04/16/2016 at 1:15:48 PM
AdminProvider logged in.	04/16/2016 at 1:15:46 PM
AdminProvider loaded the provider tools page.	04/16/2016 at 1:15:44 PM
AdminProvider logged in.	04/16/2016 at 1:15:44 PM
AdminProvider loaded the provider tools page.	04/16/2016 at 1:08:04 PM
AdminProvider loaded the provider tools page.	04/16/2016 at 1:08:01 PM
AdminProvider loaded the provider tools page.	04/16/2016 at 1:07:58 PM
AdminProvider loaded the provider tools page.	04/16/2016 at 1:07:57 PM
AdminProvider logged in.	04/16/2016 at 1:07:56 PM

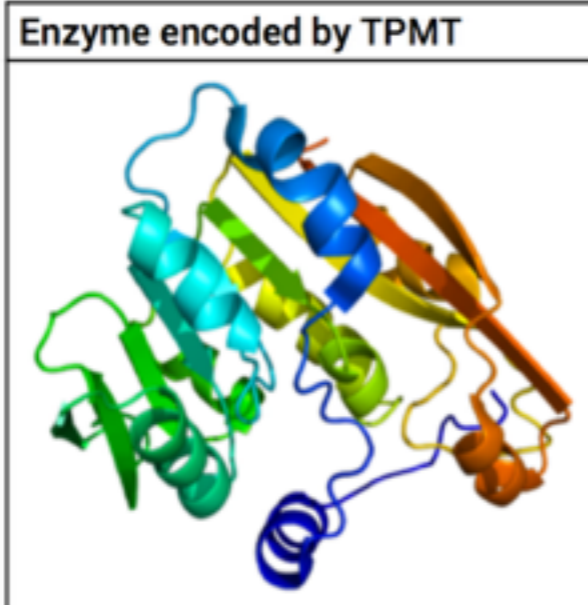# General report for John Smith.

This report outlines clinical decision support (CDS) guidelines for patient John Smith. This report uses the guidelines outlined in the DIGITizE pilot to provide CDS for the TPMT gene and HLA-B*57:01 allele.
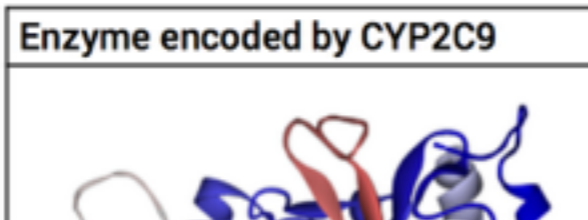
TPMT report.

This report specifies the patient's diplotype for TPMT, and includes clinical decision support data for the specified diplotype.
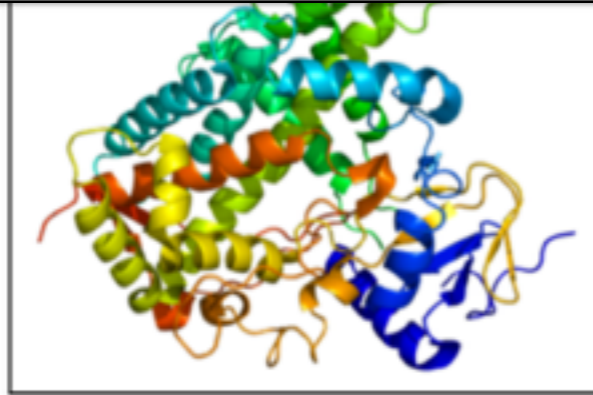
Enzyme encoded by TPMT

TPMT Diplotype
*1/*1
This patient has NO risk for myelotoxicity with standard dosing of thiopurine therapy.

CYP2C9 report.

This report specifies the patient's diplotype for CYP2C9, and includes clinical decision support data for the specified diplotype.
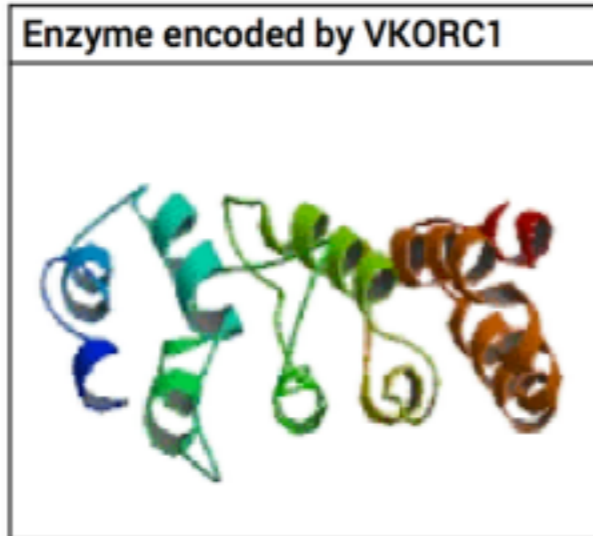
Enzyme encoded by CYP2C9

CYP2C9 Diplotype
*1/*1
Clinical decision support data for CYP2C9 not currently supported.

not currently supported.

VKORC1 report.

This report specifies the patient's diplotype for VKORC1, and includes clinical decision support data for the specified diplotype.

Enzyme encoded by VKORC1

VKORC1 Diplotype
A/G
Clinical decision support data for VKORC1 not currently supported.

HLA-B*57:01 report.

This report specifies the presence of the HLA-B*57:01 allele, and includes clinical decision support data for the specified diplotype.

HLA-B*57:01 Presence
Positive
The HLA-B*57:01 allele is present in this patient. This allele is associated with high risk of severe hypersensitivity to abacavir. HLA-B*57:01 positive patients should NOT be prescribed abacavir. Please choose an alternate antiretroviral.

Application—
PGxPortal

- Patient data input currently through **DMET** files
  Product provided by Affymetrix
  Provides star allele nomenclature for diplotype
  of specific gene

- Example for TPMT
  Could provide *1/*1
  In addition, provides certain specific variations
  found in TPMT

Application—
CDS System

Demonstration—CDS System

Rx View

Treating:

Choose a problem ⬍

Medication:

Search for a drug...

abacavir 300 MG Oral Tablet

Take [1]   **pill by mouth** [daily ⬍]

Start date ☑   **End date** ☑

2016-05-20   2016-06-20

["HLA-B*57:01 genotype test not available! A HLA-B*57:01 genotype test is recommended before prescribing abacavir per the FDA's black box warning regarding the risk of serious hypersensitivity reactions in patients that carry this allele. A HLA-B*57:01 genotype test does not appear to have been ordered for this patient. Please order an HLA-B*57:01 genotype test."]

```
{
  "resourceType": "MedicationOrder",
  "dateWritten": "2016-05-20",
  "dateEnded": "2016-06-20",
  "status": "draft",
  "patient": {
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  },
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        "system": "http://unitsofmeasure.org",
        "code": "{pill}"
      },
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        "repeat": {
          "frequency": 1,
          "period": 1,
          "periodUnits": "d"
        }
      }
    }
  ],
  "medicationCodeableConcept": {
    "text": "abacavir 300 MG Oral Tablet",
    "coding": [
      {
        "display": "abacavir 300 MG Oral Tablet",
        "system": "http://www.nlm.nih.gov/research/umls/rxnorm",
        "code": "242679"
      }
    ]
  }
}
```

Rx View

Treating:

Choose a problem

Medication:

Search for a drug...

Azathioprine 25 MG Oral Tablet

Take 1   pill by mouth   daily

Start date ☑   **End date** ☑

2016-05-20   2016-06-20

["Testing has been performed and indicates that this patient is at INCREASED risk for myelotoxicity with standard dosing of thiopurine therapy. Based on a test result, this patient is predicted to be an intermediate TPMT metabolizer. The patient is at risk for myelosuppression with normal doses of azathioprine. A normal starting dose of azathioprine (e.g. 2-3 mg/kg/day) should be reduced to 0.6 – 2 mg/kg/day."]

```
{
  "resourceType": "MedicationOrder",
  "dateWritten": "2016-05-20",
  "dateEnded": "2016-06-20",
  "status": "draft",
  "patient": {
    "reference": "Patient/1288992"
  },
  "dosageInstruction": [
    {
      "doseQuantity": {
        "value": 1,
        "system": "http://unitsofmeasure.org",
        "code": "{pill}"
      },
      "timing": {
        "repeat": {
          "frequency": 1,
          "period": 1,
          "periodUnits": "d"
        }
      }
    }
  ],
  "medicationCodeableConcept": {
    "text": "Azathioprine 25 MG Oral Tablet",
    "coding": [
      {
        "display": "Azathioprine 25 MG Oral Tablet",
        "system": "http://www.nlm.nih.gov/research/umls/rxnorm",
        "code": "199310"
      }
    ]
  }
}
```

GENOTYPES: Daniel Adams, PATIENT

GENE	DIPLOTYPE	REPORT
TPMT	*1/*2	TPMT REPORT

["Testing has been performed and indicates that this patient is at INCREASED risk for myelotoxicity with standard dosing of thiopurine therapy. Based on a test result, this patient is predicted to be an intermediate TPMT metabolizer. The patient is at risk for myelosuppression with normal doses of azathioprine. A normal starting dose of azathioprine (e.g. 2-3 mg/kg/day) should be reduced to 0.6 – 2 mg/kg/day."]

Development— PGxPortal

- Developed as a web application using the **MEAN** stack

- **M**ongoDB, **E**xpress, **A**ngularJS, **N**ode
  MongoDB: Backend, **REST**ful API
  Express: Routing
  AngularJS: Web Design
  Node: Hosting (Locally), Development

- **Re**presentational **S**tate **T**ransfer
  HTTP GET, POST, PUT, DELETE

Development— PGxPortal

- CDS System connects to Portal's RESTful API
  Communication in FHIR format
  1. Is support for current drug supported?
  2. Does patient genetic information affect
     current drug's metabolism?

- Gene-drug interaction information provided through
  published medical studies and papers
      DIGITizE Pilot CDS paper for HLA-B allele and
      TPMT gene

Future Work

- Receive and store more patient genetic information Encoded genetic variants in VCF files, view in genome browser on portal web application

- Predict possibly dangerous gene-drug interaction through combination of known gene-drug rules with more genetic information

Acknowledgements

- MIT PRIMES

- Program Director Slava Gerovitch

- Dr. Gil Alterovitz and his PRIMES Group
  Gaston Fiore, Michael Mintz, Brett Johnson

- Parents