"INdiana GENomics Implementation Opportunity for the UnderServed"

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Genomic Medicine X
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Requirements for genetic testing implementation

1. Have clinical value in the practice setting

   AND

2. Be economically viable in such settings

   i. Genetic testing should only be widely implemented if it can be shown to be high value medicine.

   ii. Genetic testing will only be widely implemented if providers are properly incentivized to adopt it

Economic analysis alongside clinical studies will generate the information needed to support widespread adoption

Pharmaco-genetic-economic research requires an interdisciplinary approach

Informaticians
(Regenstrief, CCBB)

Economists
(IUSPH)

Geneticists
(IIPM, IUSM, IUSON)

Indiana Genomics Implementation Opportunity for the Under Served

Acronym: InGenIOUS funded by NHGRI-IGNITE

Testing the effect of prospective, reactive pharmacogenetics genotyping on health care costs and adverse events.

Endpoints:

- Total health care costs
- Adverse events

Eskenazi & IU Health patients randomized to

- 2,000 genotype guided therapy
- 4,000 standard of care (not contacted)

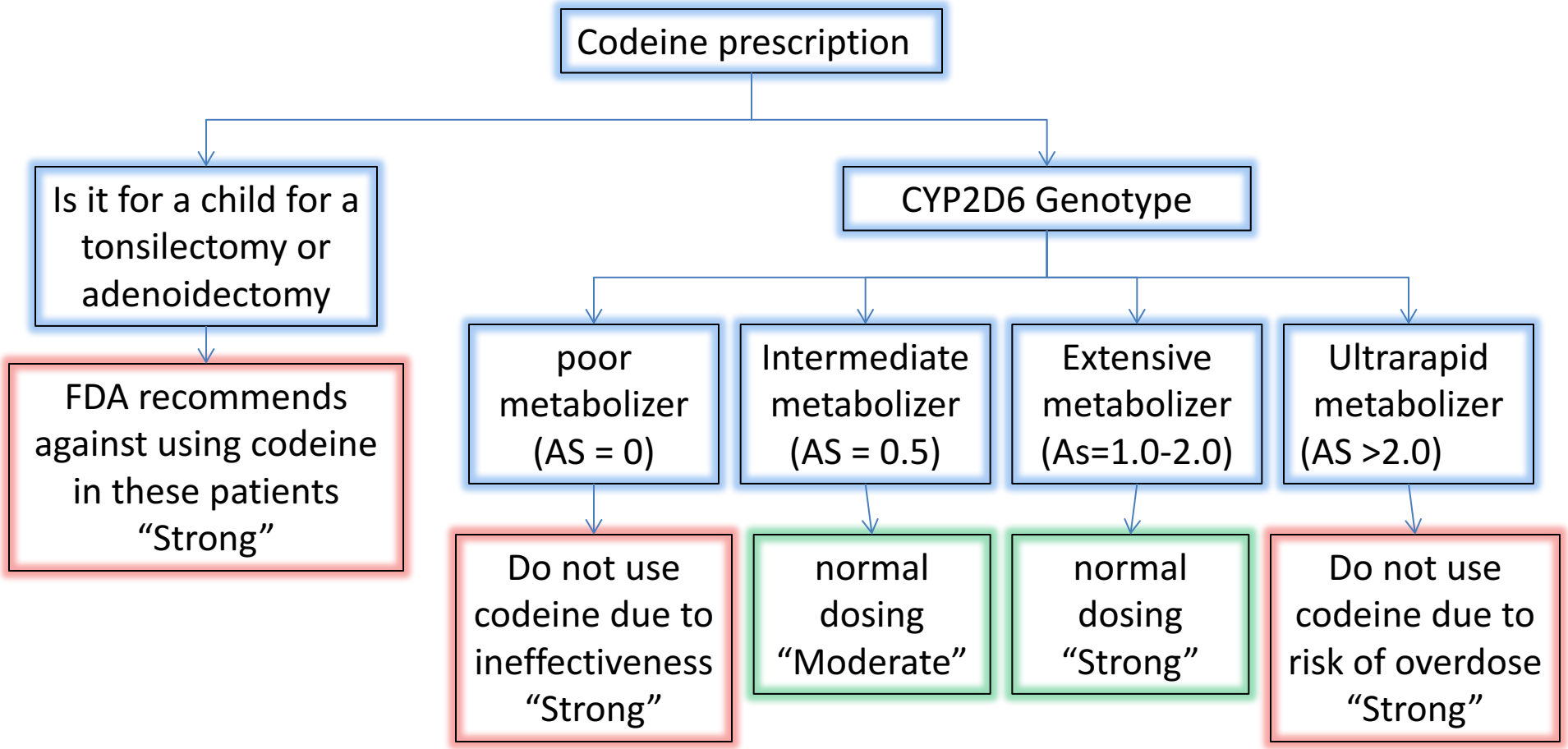
INGENIOUS drug list

- Amitryptyline
- Aripiprazole
- Atazanavir
- Atomoxetine
- Azathioprine
- Capcitabine
- Citalopram
- Clopidogrel
- Codeine
- Doxepin
- Efavirenz
- Escitalopram
- Esomeprazole
- 5-Fluorouracil
- Lansoprazole
- Mercaptopurine
- Nortriptyline
- Omeprazole
- Pantoprazole
- Phenytoin
- Rasburicase
- Simvastatin
- Tacrolimus
- Thioguanine
- Tramadol
- Venlafaxine
- Voriconazole
- Warfarin

INGENIOUS Gene List

CYP2D6
CYP2C19
CYP2C9
CYP3A5
CYP2B6
CYP4F2

VKORC1
TPMT
ITPA
SLCO1B1
HLA-B
DPYD
G6PD



AS = Activity Score:

0 = two nonfunctional alleles

0.5 = one nonfunctional and one partial function alleles

1.0 = two partial function or one full function and one nonfunctional alleles

1.5 = one functional and one partial functional alleles

2.0 = two full functional alleles

>2.0 more than two alleles

Classification of recommendation: based on the strength of the literature base:
Strong, moderate, or weak.

InGenIOUS Genotyping

51 SNPs in 16 genes

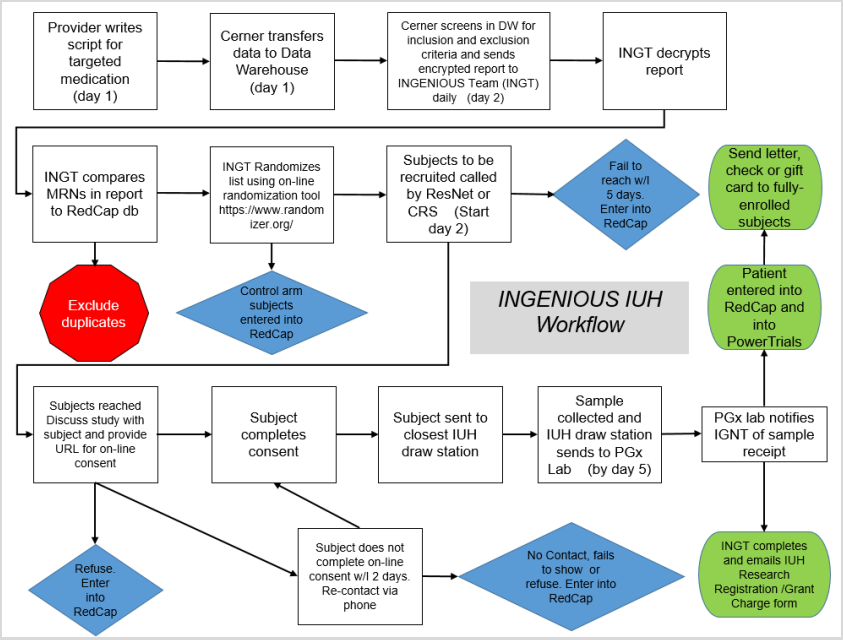
Genotyping assays:

- Instrument: QuantStudio (Life Technologies, Inc)
- Genotyping using OpenArrays™ (TaqMan assays)
- Copy number variations (CYP2D6) (TaqMan assays) using 96-well plates
- Accurate, flexible (sample number, changing assays, data output), good throughput, simple workflow

CLIA approved, CAP certified

General Project Summary – Current Status

Two Different Workflows Required for Recruitment

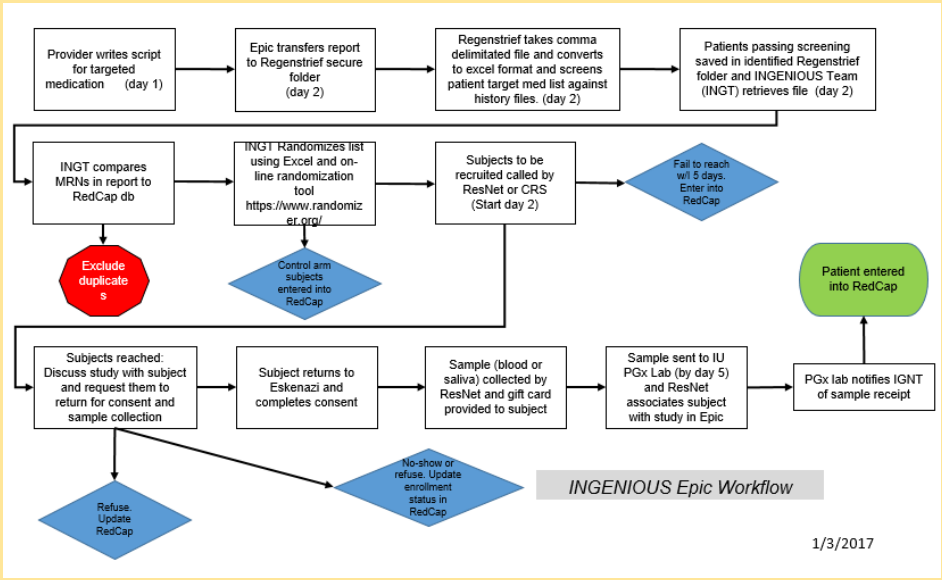


Indiana University Health System

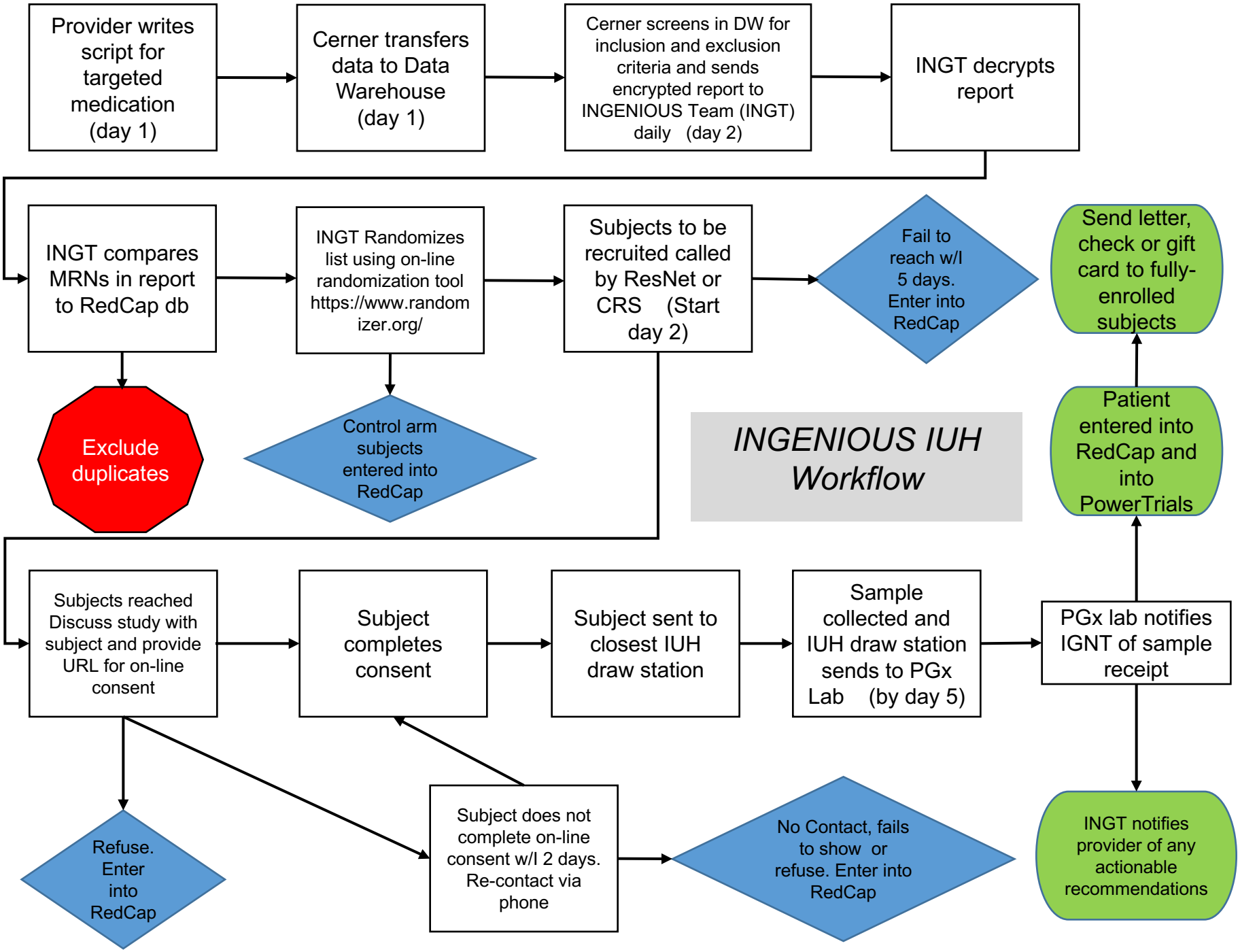
- 18 Hospital locations
- 122 outpatient clinics
- On-line recruitment
- Manual screening

Eskenazi Health System

- 1 Hospital location
- 70+ outpatient clinics
- On-line recruitment
- Manual screening



IGNITE
Implementing GeNomics In practicE


Provider writes script for targeted medication (day 1)
Cerner transfers data to Data Warehouse (day 1)
Cerner screens in DW for inclusion and exclusion criteria and sends encrypted report to INGENIOUS Team (INGT) daily (day 2)
INGT decrypts report
INGT compares MRNs in report to RedCap db
INGT Randomizes list using on-line randomization tool https://www.randomizer.org/
Subjects to be recruited called by ResNet or CRS (Start day 2)
Fail to reach w/I 5 days. Enter into RedCap
Send letter, check or gift card to fully-enrolled subjects
Exclude duplicates
Control arm subjects entered into RedCap
INGENIOUS IUH Workflow
Patient entered into RedCap and into PowerTrials
Subjects reached Discuss study with subject and provide URL for on-line consent
Subject completes consent
Subject sent to closest IUH draw station
Sample collected and IUH draw station sends to PGx Lab (by day 5)
PGx lab notifies IGNT of sample receipt
Refuse. Enter into RedCap
Subject does not complete on-line consent w/I 2 days. Re-contact via phone
No Contact, fails to show or refuse. Enter into RedCap
INGT notifies provider of any actionable recommendations

INGENIOUS enrollment status

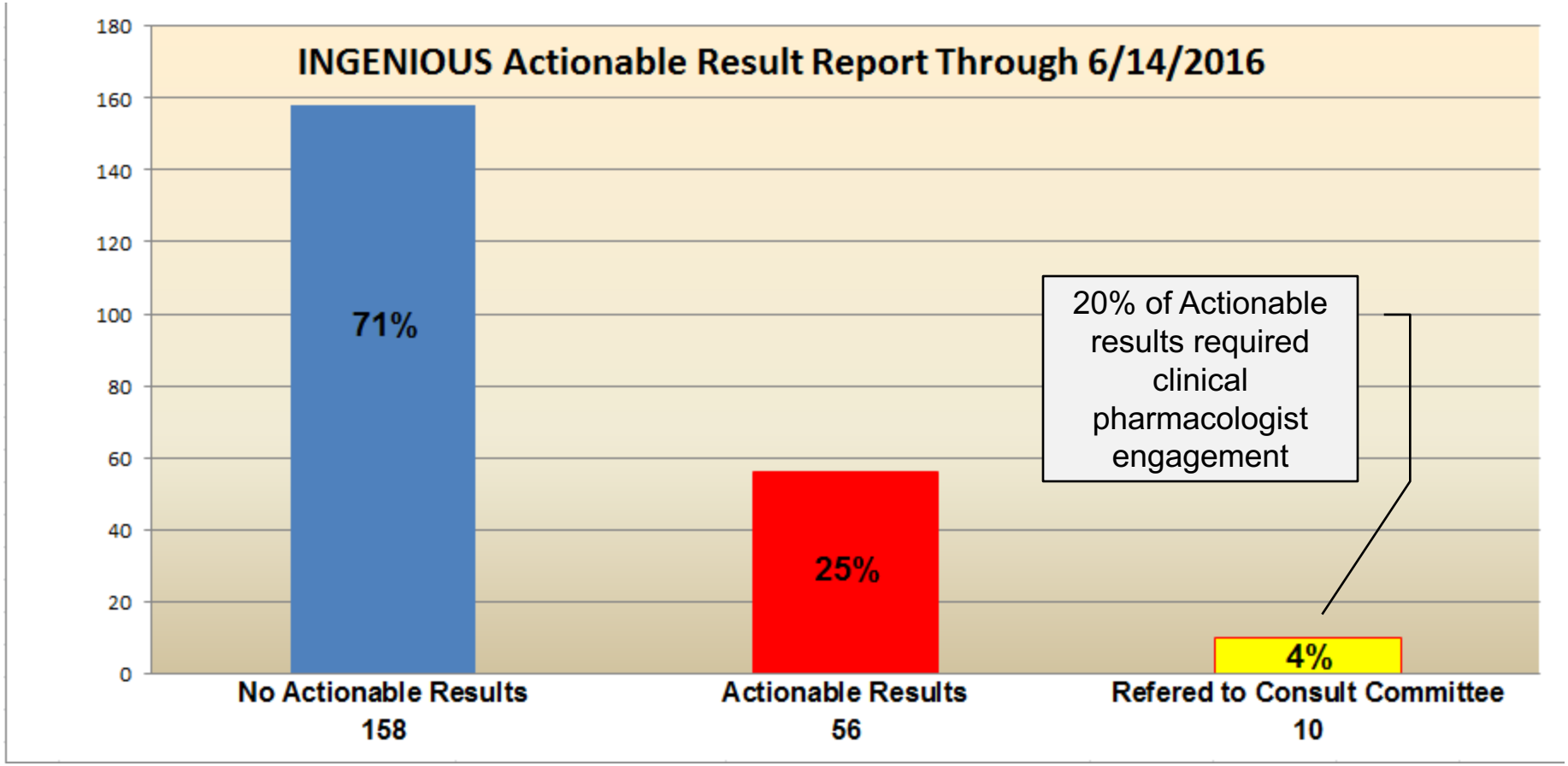
- Current enrollment:
  - Genotyped arm: ~500 subjects
  - Contol arm: ~1,300 subjects
- Current enrollment rate:
  - Genotyped arm 20-30 per week.
  - Control arm 50-60 per week.
- Includes subjects from Eskenazi and 6 of the 18 IU Health hospitals and associated clinics with additional hospitals continuing to be added.

Numbers of each trigger medication enrolled in the INGENIOUS trial

tramadol	289	Phenytoin	30
PPI's	258	Azathioprine	26
Codeine	184	Doxepin	25
Clopidogrel	177	Tacrolimus	16
Escitalopram	165	Capcitabine	15
Amitriptyline	170	Efavirenz	11
Warfarin	145	Simvastatin	21
Citalopram	142	Atomoxetine	8
Aripiprazole	86	Voriconazole	4
Venlafaxine	58	Mercaptopurine	2
Nortriptyline	60	5-Fluorouracil	3

INGENIOUS Actionable Results

A significant number of actionable results (recommended change in selection or dose of drug) are being reported to Eskenazi providers

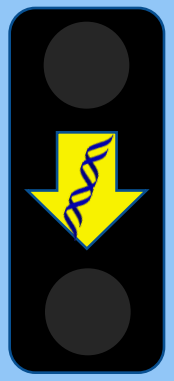
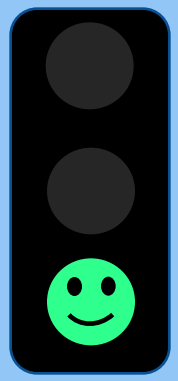
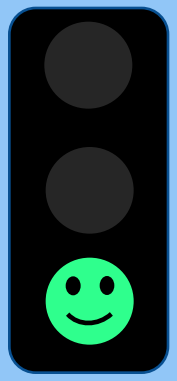
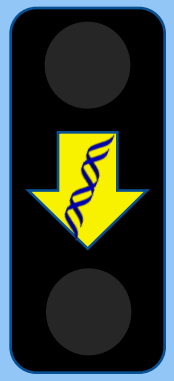
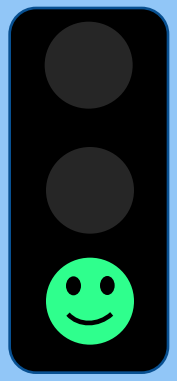
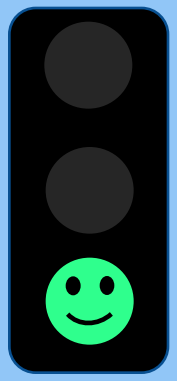
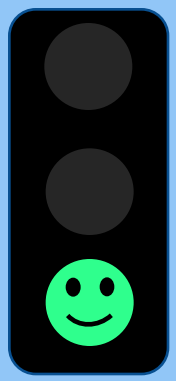
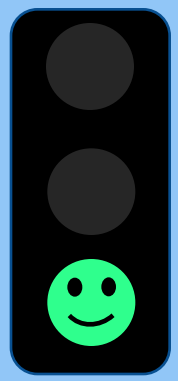
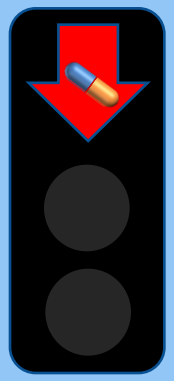
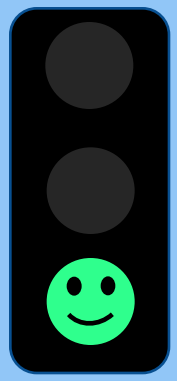
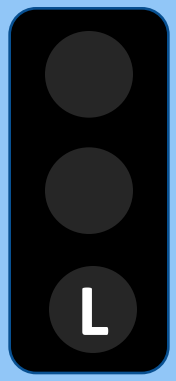
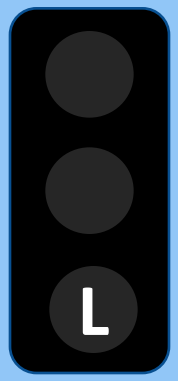


* Data from INGENIOUS Redcap Database of 214 Complete Results

Indiana University Precision Genomics Oncology Clinic

- Patients with refractory cancers or tumors of unknown origin
- Somatic tumor genomics done by Nantomics, Foundation Medicine, or Paradigm.
- Germline pharmacogenetics done by Indiana University Pharmacogenomics Laboratory.
- Working to extract PGx results from whole genome sequencing.

John Doe March 2 2017

CYP3A	CYP2D6	CYP2C19	CYP2B6	CYP2C9	TPMT	DPYD
						
Liver Function	**Renal Function**	**Stomach pH**	**QTc**	**Cardio-toxicity**	**Peripheral Neuropathy**	**HTN**
						

Acknowledgments

On behalf of the Indiana University site of the NIH-IGNITE network

IU Health Precision Genomics Clinic

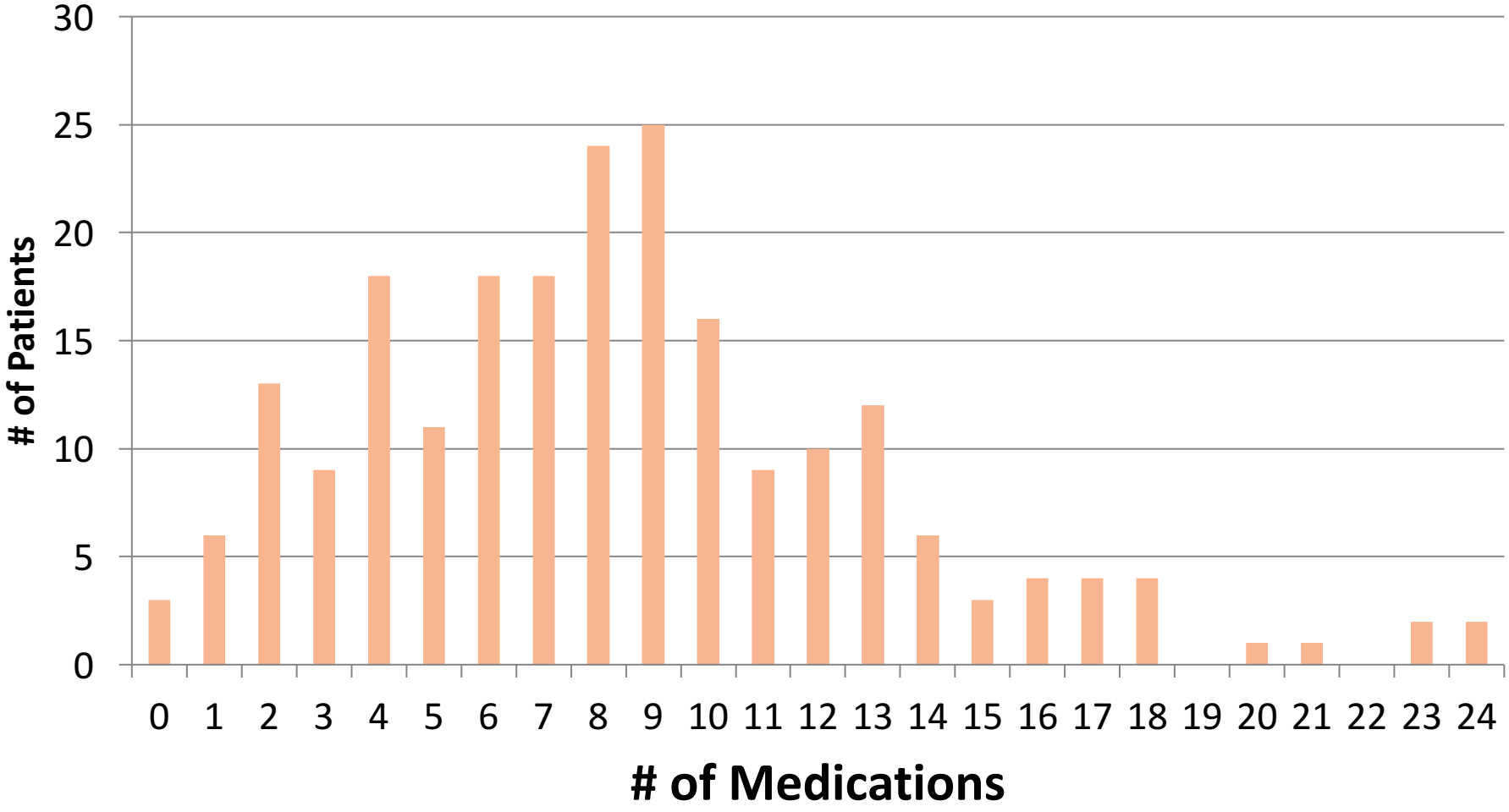
Funding:
NIH-NHGRI IGNITE network
IU School of Medicine Strategic Research Initiative
IU Precision Medicine Initiative-Grand Challenge
Indiana Institute for Personalized Medicine

Extra slides

Example genotype report

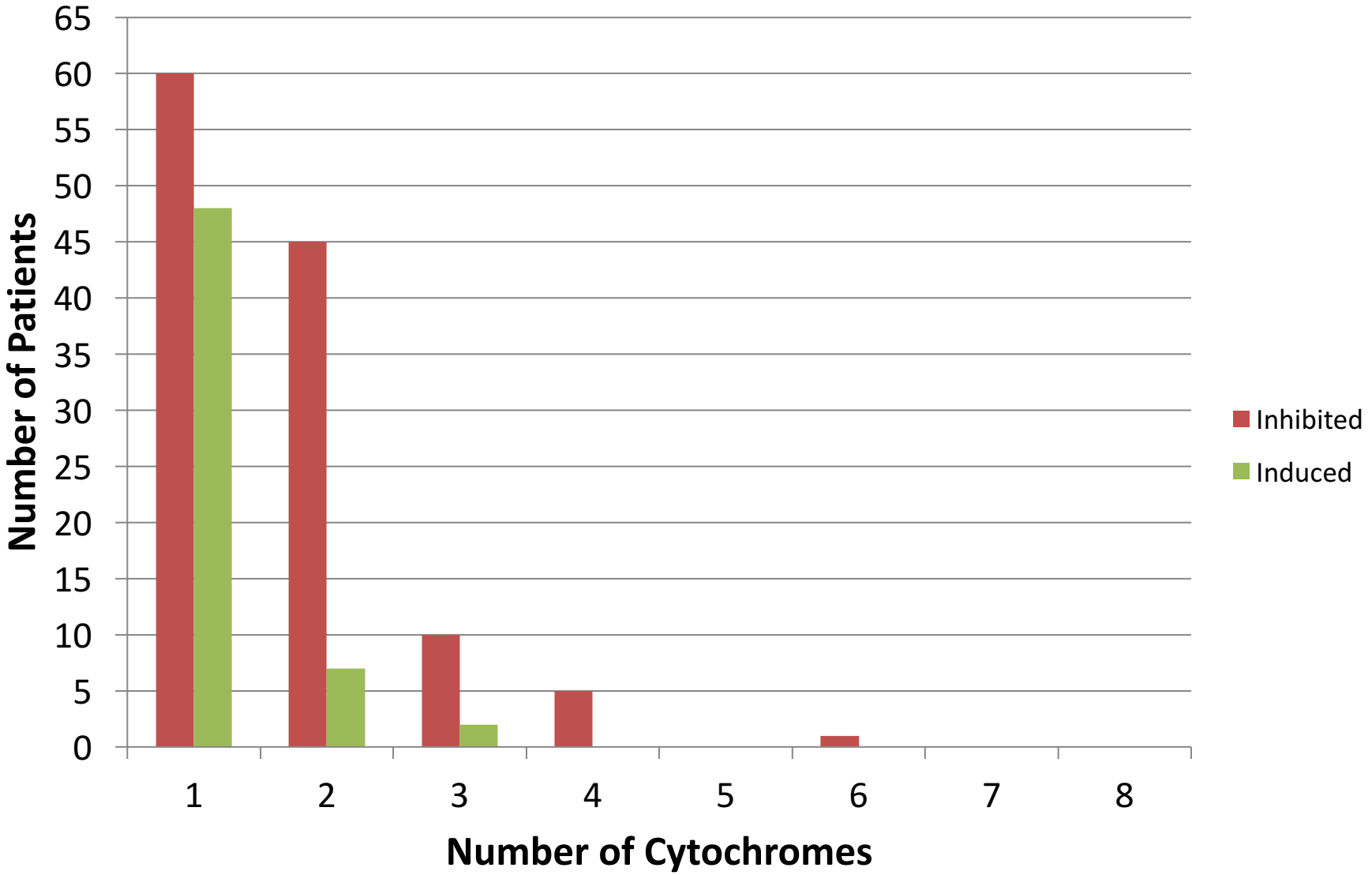
Gene	Result	Predicted Metabolizer Status*
TPMT	*1/*1	Normal Metabolizer
CYP2C19	*1/*1	Normal Metabolizer
SLCO1B1	*1/*1	Normal Metabolizer
CYP2C9	*1/*3	Reduced/Intermediate Metabolizer
VKORC1	G/G	Normal Metabolizer
CYP2D6	*1/*1	Normal Metabolizer
CYP3A5	*1/*1	Normal Metabolizer
CYP3A4	*1/*1	Normal Metabolizer
CYP2B6	*6/*6	**Poor Metabolizer**
ITPA	C/C	Normal Metabolizer
DPYD	*1/*1	Normal Metabolizer
CYP4F2	*1/*1	Normal Metabolizer
G6PD	No variant detected	Normal Metabolizer
IFNL3 (IL28B)	C/T	Reduced/Intermediate Metabolizer
SV2C	G/A	Increased Risk
RARG	C/C	Normal Risk
FCAMR	C/T	Increased Risk
rs3125923	A/G	Increased Risk
rs28714259	G/G	Normal Risk

Frequency of concurrent medication use in patients in the Precision Genomics Clinic is high



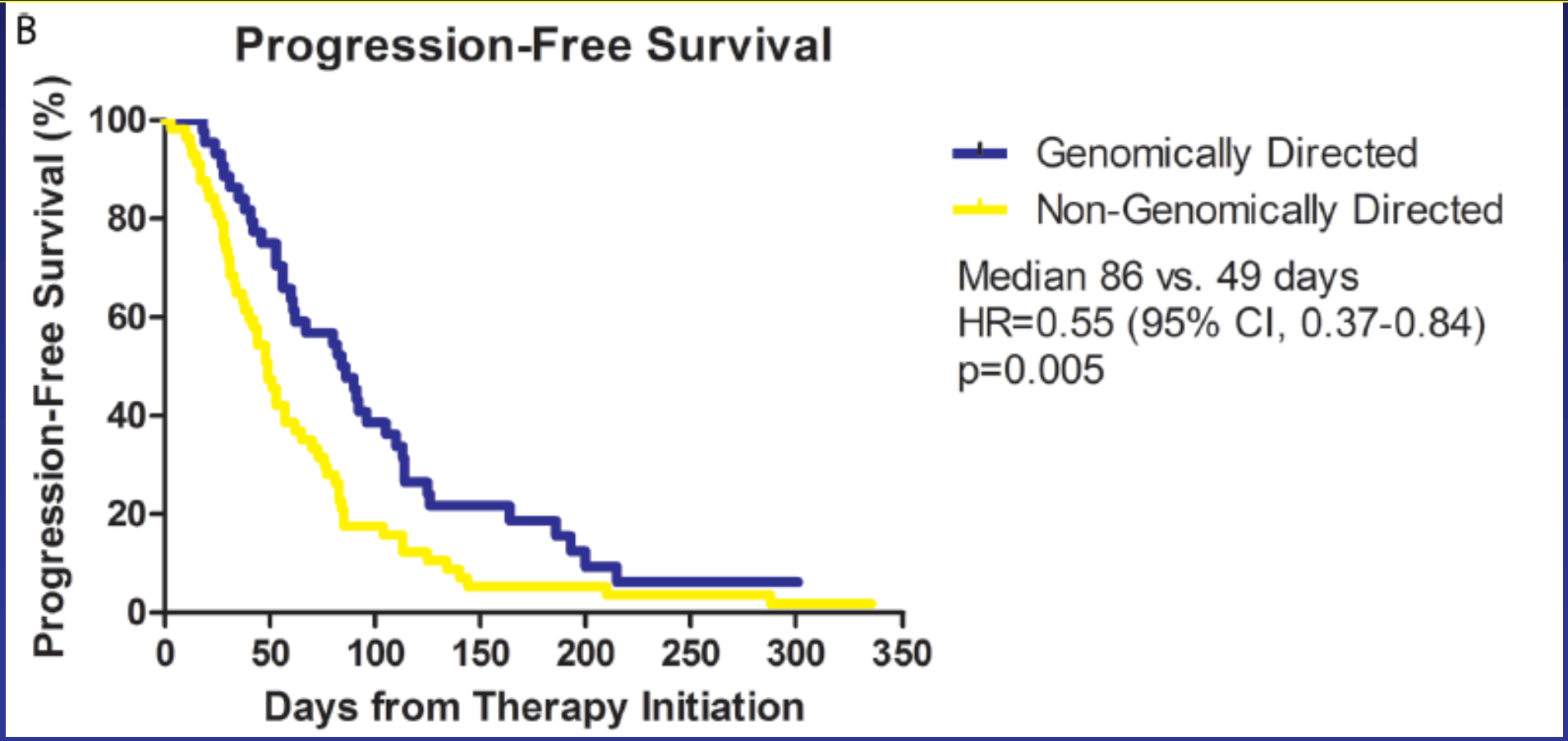
Hyder, 2015, unpublished

Many patients have at least one Cytochrome P450 Enzymes Inhibited or Induced



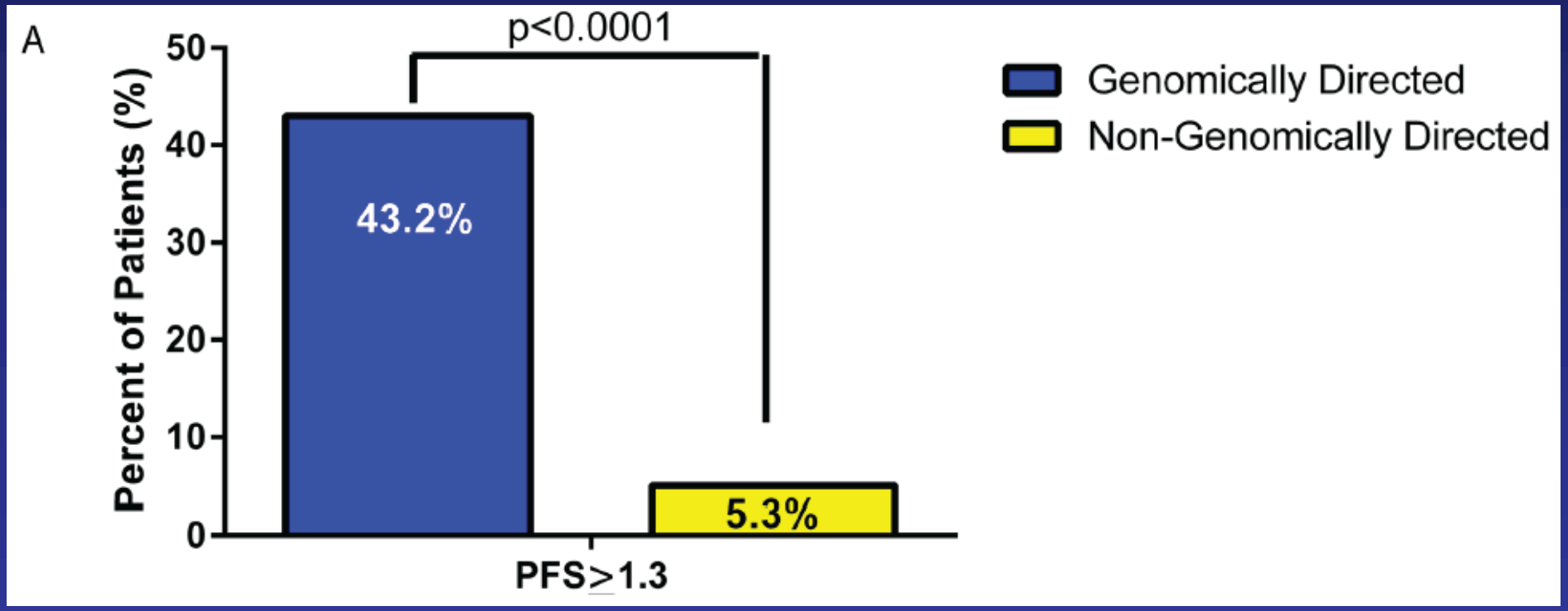
Hyder, 2015, unpublished

Genomic guided therapy improves outcomes



Radovich et al., Oncotargets 2016

Genomic guided therapy improves outcomes



Radovich et al., Oncotargets 2016

Acknowledgments

Publications

Other items to discuss