Implementation of pharmacogenetics at Indiana University School of Medicine

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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:

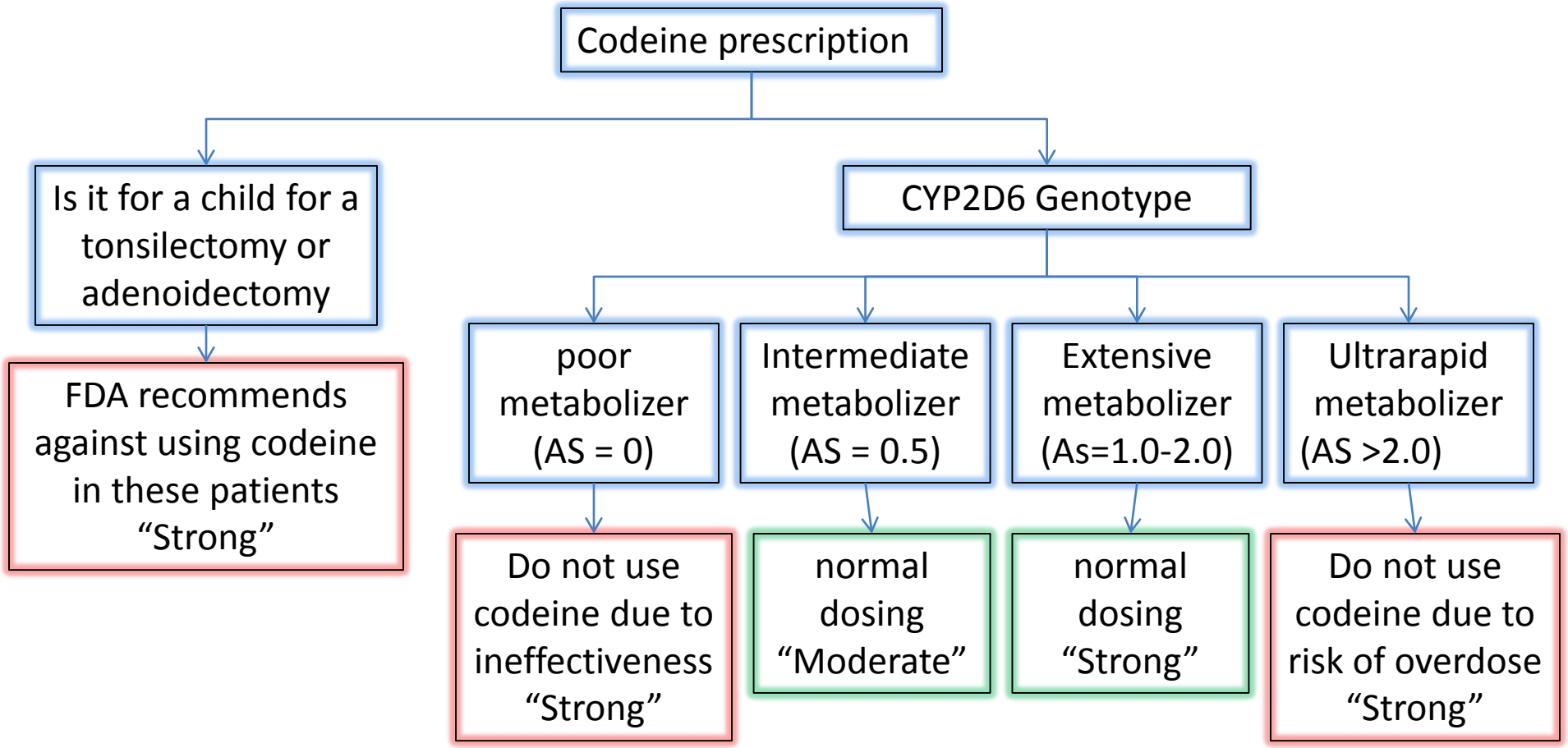
- Total health care costs
- Adverse events

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



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 Gene List

CYP2D6
CYP2C19
CYP2C9
CYP3A5
CYP2B6
CYP4F2

DPYD
G6PD
INFL3
ITPA
SLCO1B1
TPMT
VKORC1

InGenIOUS Genotyping

51 SNPs in 16 genes

Genotyping assays:

- Instrument: QuantStudio (FisherScientific)
- 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

Validation: GeT-RM DNAs

https://wwwn.cdc.gov/clia/Resources/GetRM/

Genetic Testing Reference Materials Coordination Program

2 papers by Pratt *et. al.*

Consensus characterization of ~200 Coriell DNA samples for PGx genotypes

Currently working on 3rd project for CYP2D6

Clinical laboratories need verified reference materials for all genotypes for validation and quality assurance!

Reporting PGx Results

- Created Patient report generator – StaralleleInterpretor – that takes curated results from instrument

Cerner Epic

- Requires different formatting for each system

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

New CPT Codes for 2018

CPT Code	New Code Descriptor	Prelim. Determinations
81230	CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism), gene analysis, common variant(s) (eg, *2, *22)	81227 (NLA - $176.03)
81231	CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3,*4, *5 *6, *7)	81227 (NLA - $176.03)
81232	DPYD (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, common variant(s) (eg, *2A, *4, *5, *6)	81227 (NLA - $176.03)
81247	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice) gene analysis; common variant(s) (eg, A, A-)	81227 (NLA - $176.03)
81248	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice) gene analysis; known familial variant(s)	81322 ($58.72)
81249	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice) gene analysis; full gene sequence (13 exons)	81295 ($152.54)
81283	IFNL3 (interferon, lambda 3) (eg, drug response), gene analysis, rs12979860 variant	81322 ($58.72)
81328	SLCO1B1 (solute carrier organic anion transporter family, member 1B1) (eg, adverse drug reaction), gene analysis, common variant(s) (eg, *5)	81227 ($176.03)
81335	TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3)	81227 ($176.03)
81346	TYMS (thymidylate synthetase) (eg, 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s) (eg, tandem repeat variant)	81227 ($176.03)

INGENIOUS enrollment status

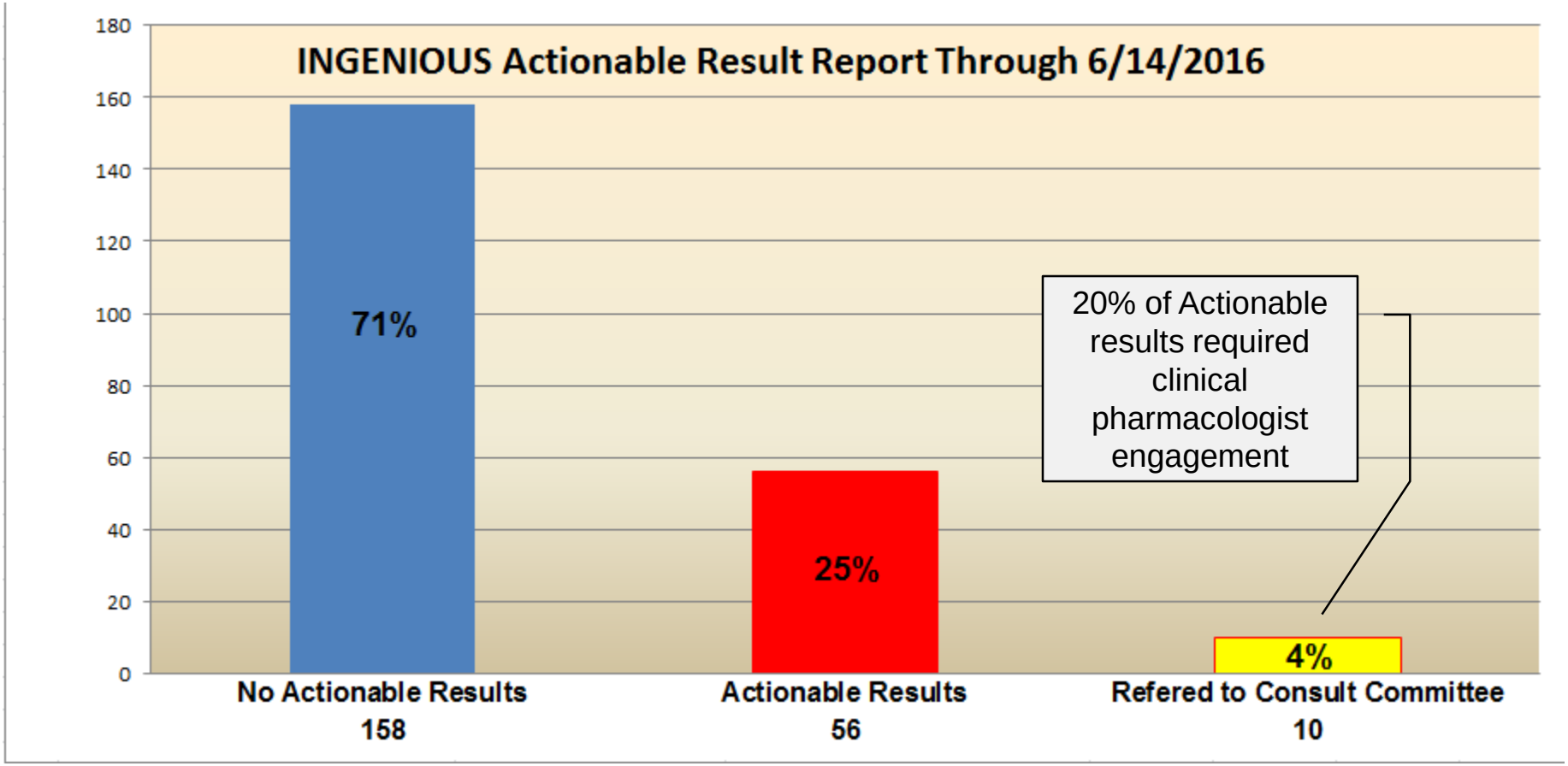
- Current enrollment:
  - Genotyped arm: 839 subjects
  - Contol arm: 2421 subjects
- Current enrollment rate:
  - Genotyped arm 20-30 per week.
  - Control arm 50-60 per week.
- Includes subjects from Eskenazi and 9 of the 18 IU Health hospitals and associated clinics with additional hospitals continuing 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

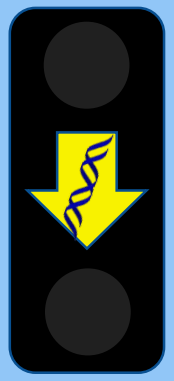
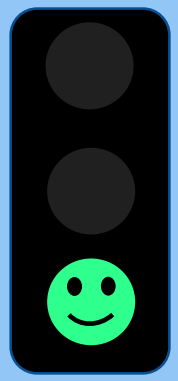
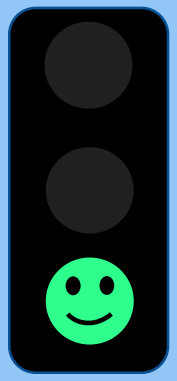
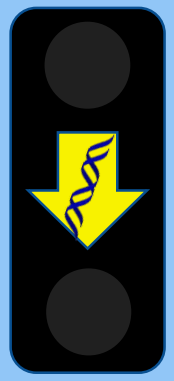
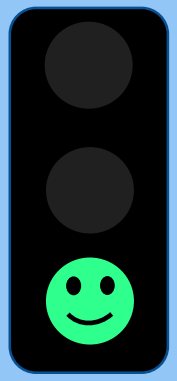
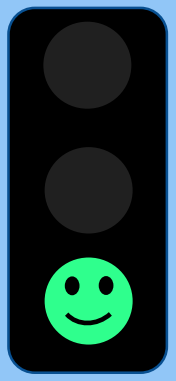
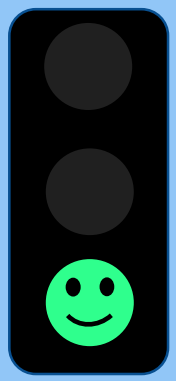
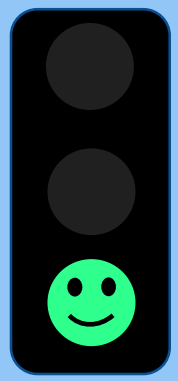
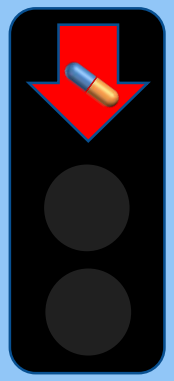
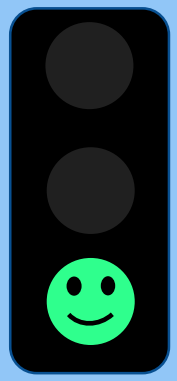
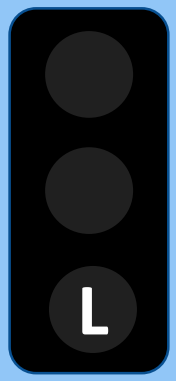
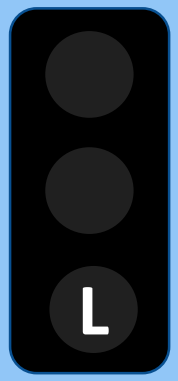


* Data from INGENIOUS Redcap Database of 214 Complete Results

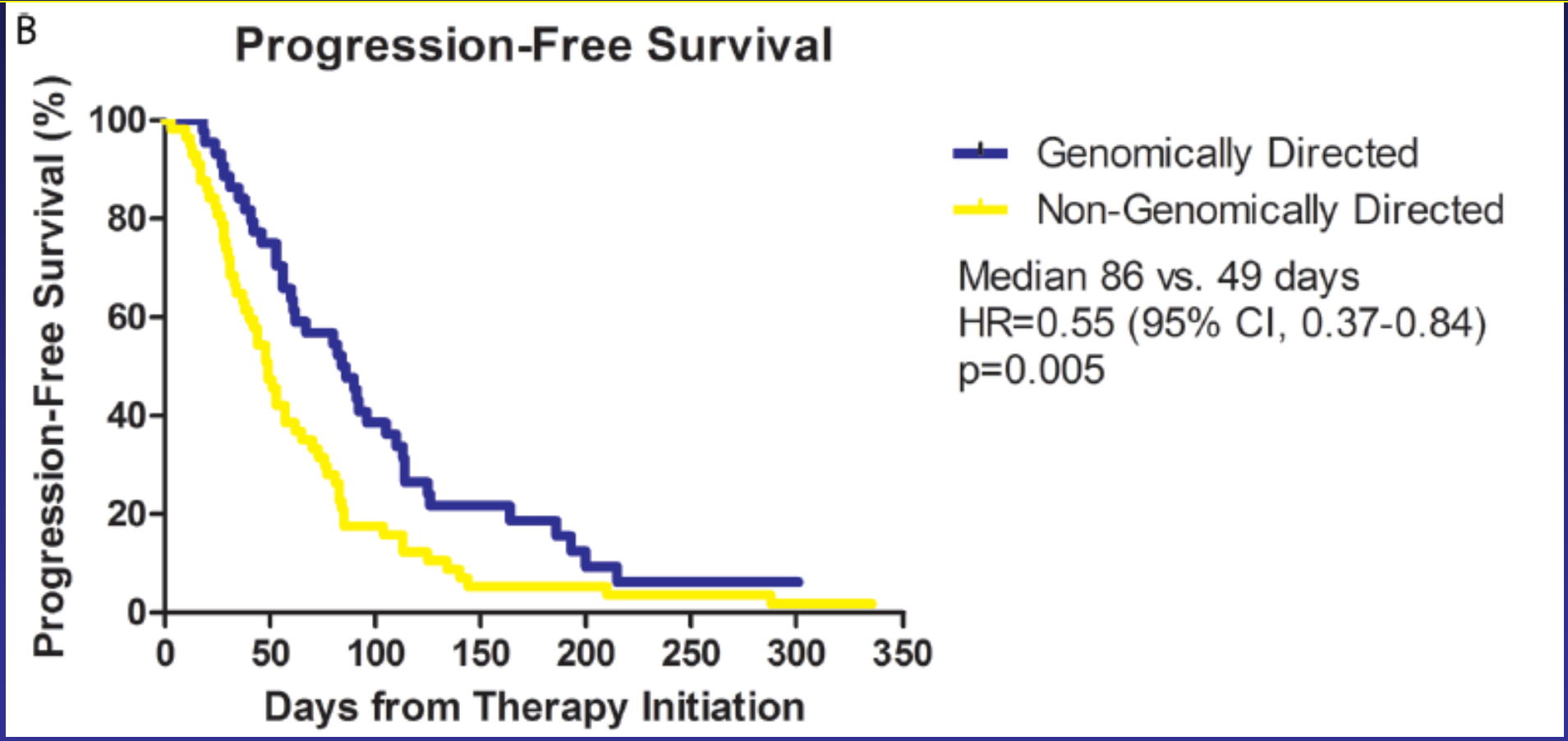
Indiana University Precision Genomics Oncology Clinic

- 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**
						

Genomic guided therapy improves outcomes



Radovich et al., Oncotargets 2016

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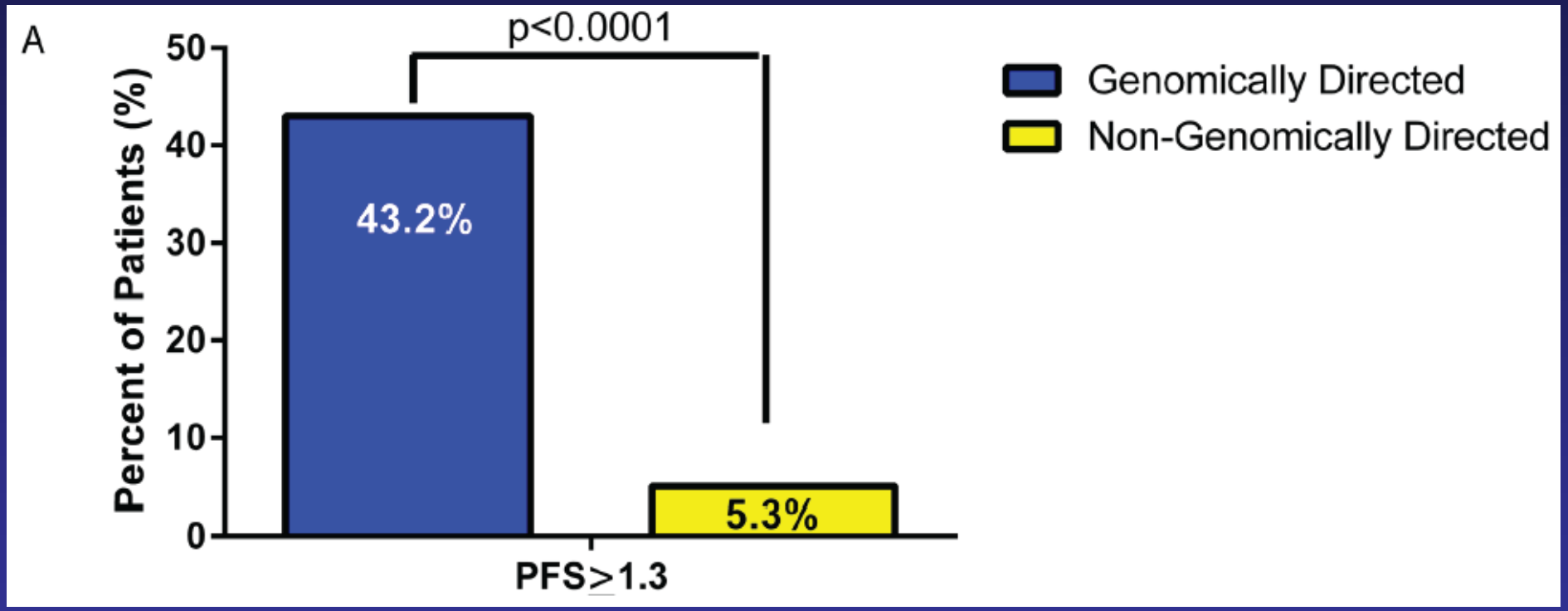

Radovich et al., Oncotargets 2016

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IU Health Precision Genomics Clinic

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