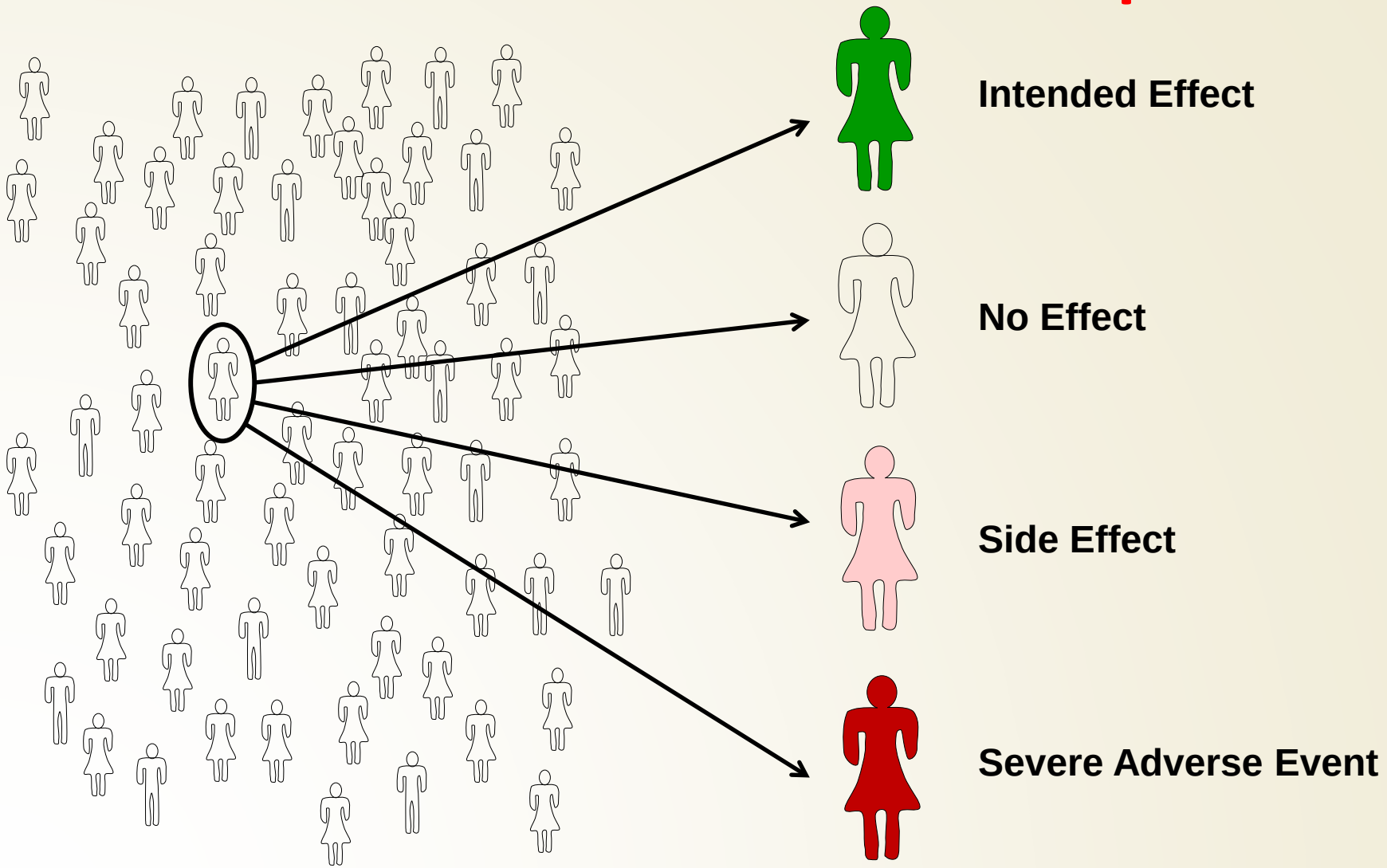
Bridging the Gap Between the Laboratory and Clinic in Precision Medicine

Sara Van Driest, MD, PhD
Assistant Professor of Pediatrics and Medicine
March 16, 2017

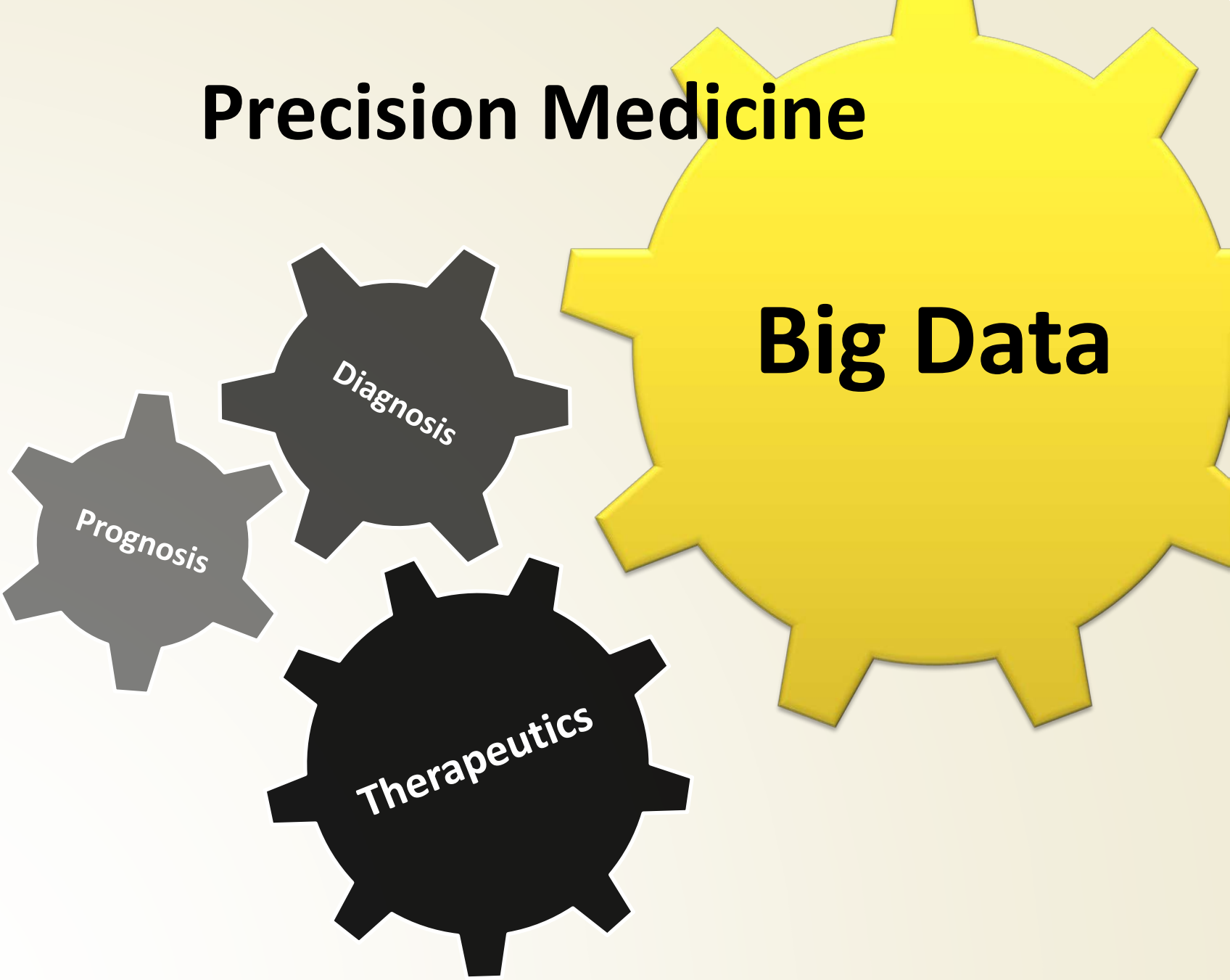
VANDERBILT School of Medicine

Monroe Carell Jr. Children's Hospital at Vanderbilt

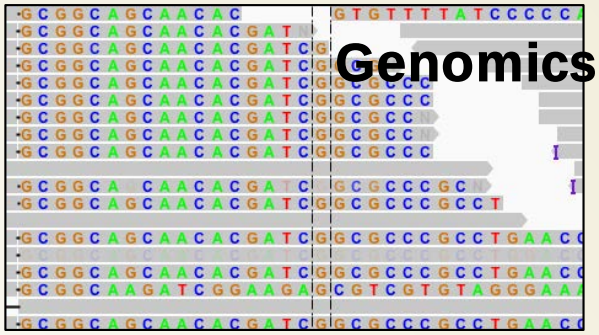
Which treatment is best for this ~~problem~~? patient?

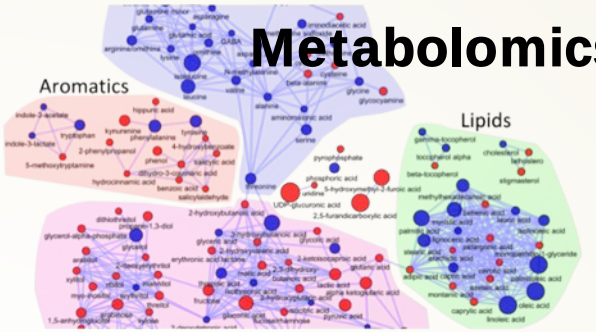


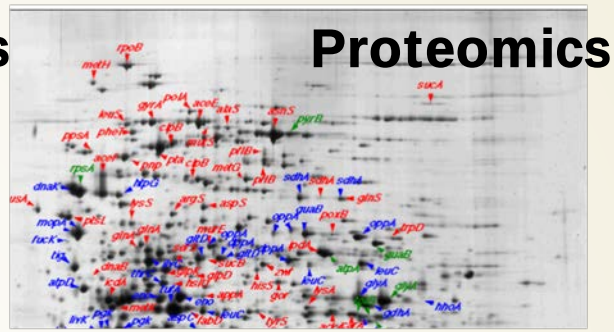
Precision Medicine

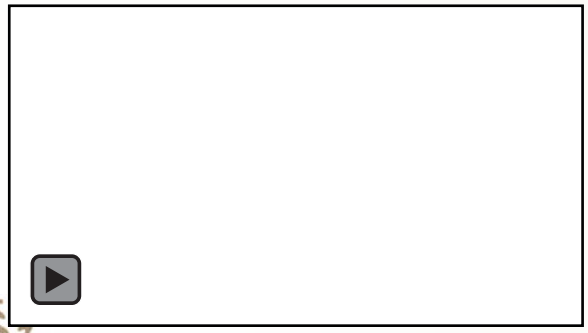


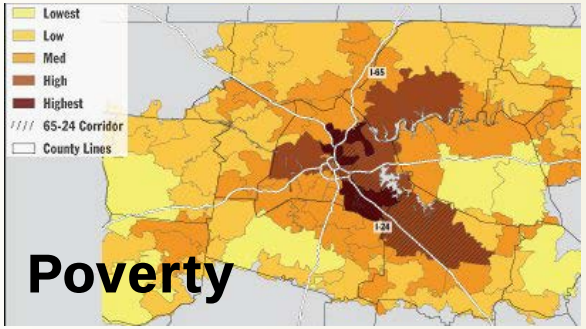
Many Sources of Big Data

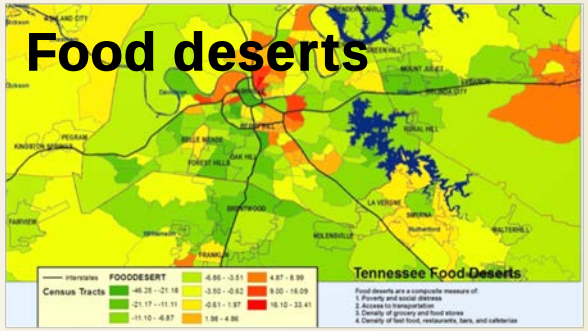


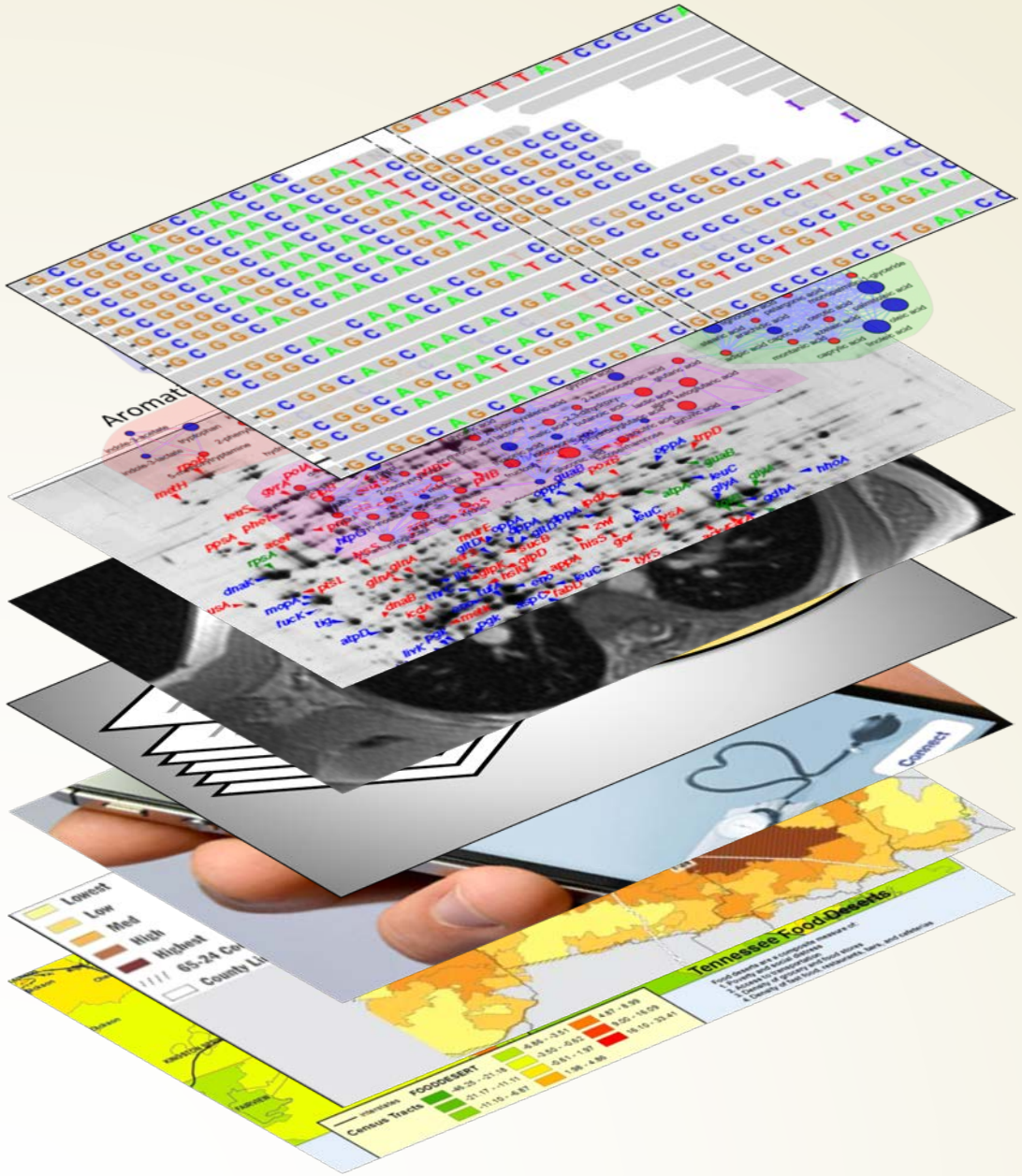






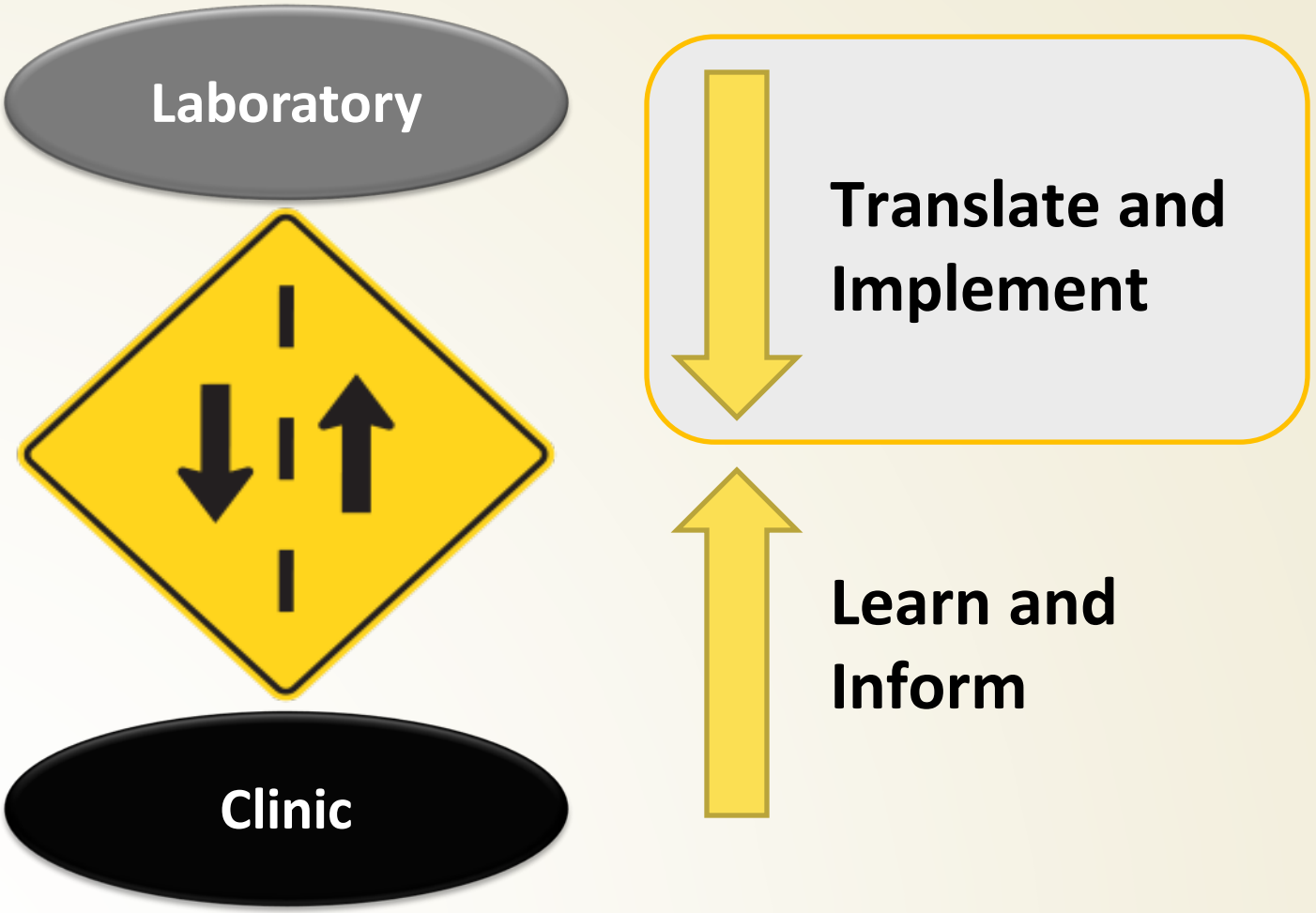




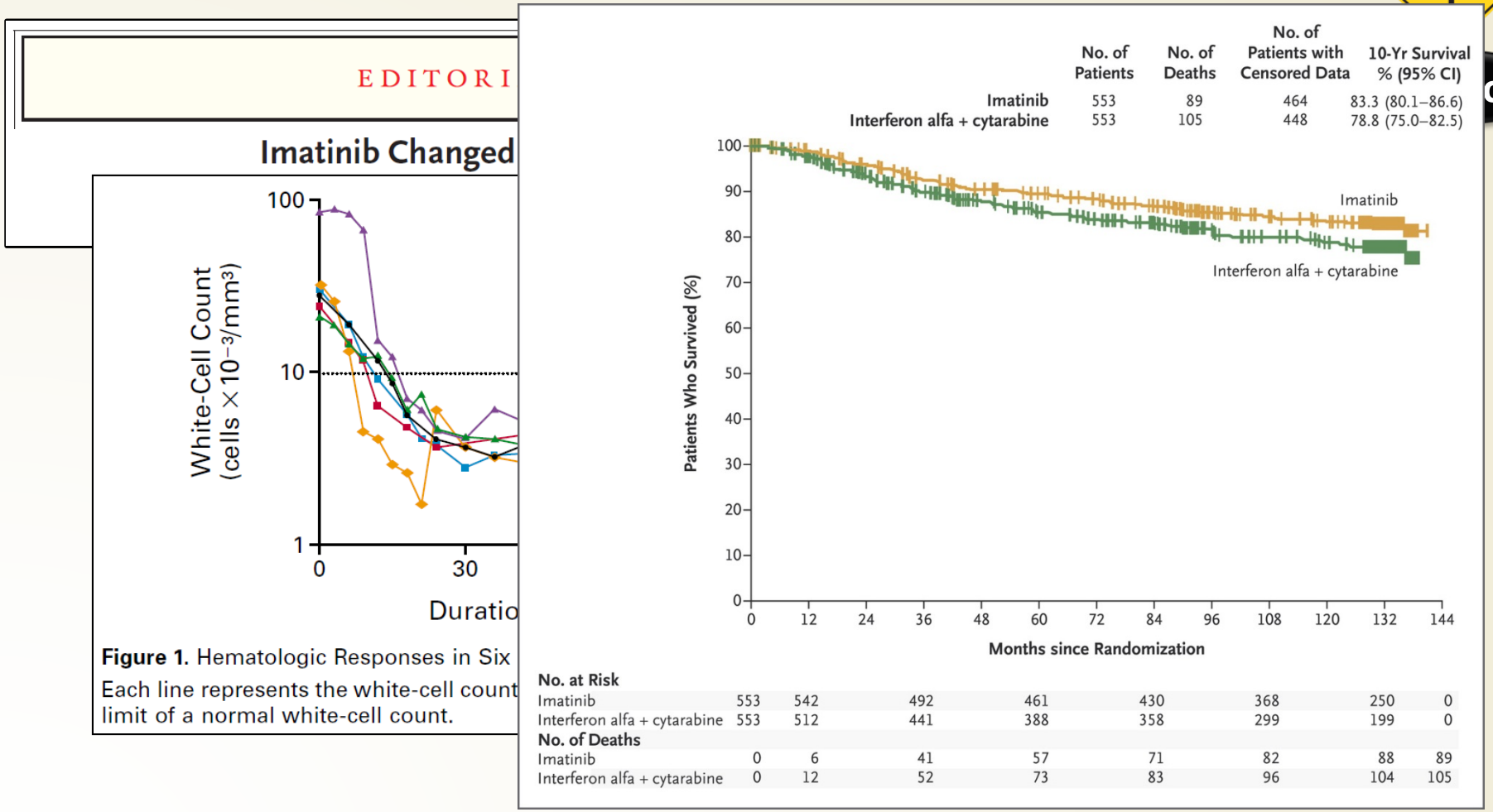


The challenge and opportunity: integrating multiple datasets for discovery and implementation

Road Map


Laboratory
Translate and Implement
Learn and Inform
Clinic

Precision Medicine in the Clinic: Cancer



Longo. *NEJM.* 2017.
Druker et al. *NEJM*. 2001.
Hochhaus. *NEJM*. 2017.

Precision Medicine in the Clinic: Cancer

- Acute Lymphoblastic Leukemia
- Acute Myeloid Leukemia
- Anaplastic Large Cell Lymphoma
- Basal Cell Carcinoma
- Bladder Cancer
- Breast Cancer
- Chronic Lymphocytic Leukemia
- Chronic Myeloid Leukemia
- Colorectal Cancer
- GIST
- Gastric Cancer
- Glioma
- Inflammatory Myofibroblastic Tumor
- Lung Cancer
- Medulloblastoma
- Melanoma
- Myelodysplastic Syndromes
- Neuroblastoma
- Ovarian Cancer
- Prostate Cancer
- Rhabdomyosarcoma
- Thymic Carcinoma
- Thyroid Cancer

Overview of Targeted Therapies for Cancer

The FDA has approved multiple targeted drug cancer therapies, and many more are being studied in clinical trials either alone or in combination with other treatments. A partial list of currently approved targeted therapies for solid malignancies and their molecular targets is provided below.

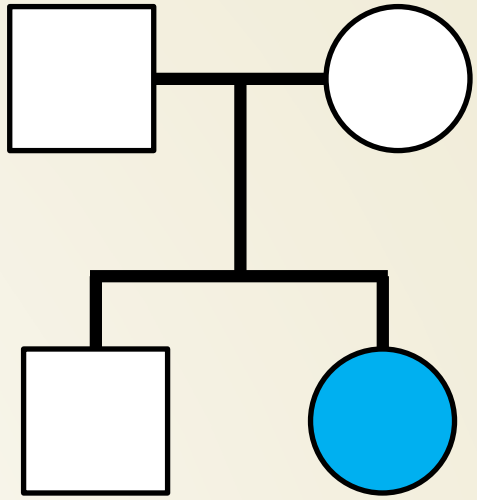
Agent	Target(s)	FDA-approved indication(s)
Ado-trastuzumab emtansine (Kadcyla)	HER2 (ERBB2/neu)	• Breast cancer (HER2+)
Afatinib (Gilotrif)	EGFR (HER1/ERBB1), HER2 (ERBB2/neu)	• Non-small cell lung cancer (with EGFR exon 19 deletions or exon 21 substitution (L858R) mutations)
Aldesleukin (Proleukin)		• Renal cell carcinoma • Melanoma
Alectinib (Alecensa)	ALK	• Non-small cell lung cancer (with ALK fusion)
Alemtuzumab (Campath)	CD52	• B-cell chronic lymphocytic leukemia
Atezolizumab (Tecentriq)	PD-L1	• Urothelial carcinoma • Non-small cell lung cancer
Axitinib (Inlyta)	KIT, PDGFRβ, VEGFR1/2/3	• Renal cell carcinoma
Belimumab (Benlysta)	BAFF	• Lupus erythematosus
Belinostat (Beleodaq)	HDAC	• Peripheral T-cell lymphoma
Bevacizumab (Avastin)	VEGF ligand	• Cervical cancer • Colorectal cancer • Fallopian tube cancer • Glioblastoma • Non-small cell lung cance • Ovarian cancer

MY CANCER GENOME®
GENETICALLY INFORMED CANCER MEDICINE

Precision Medicine in the Clinic: Rare Disease

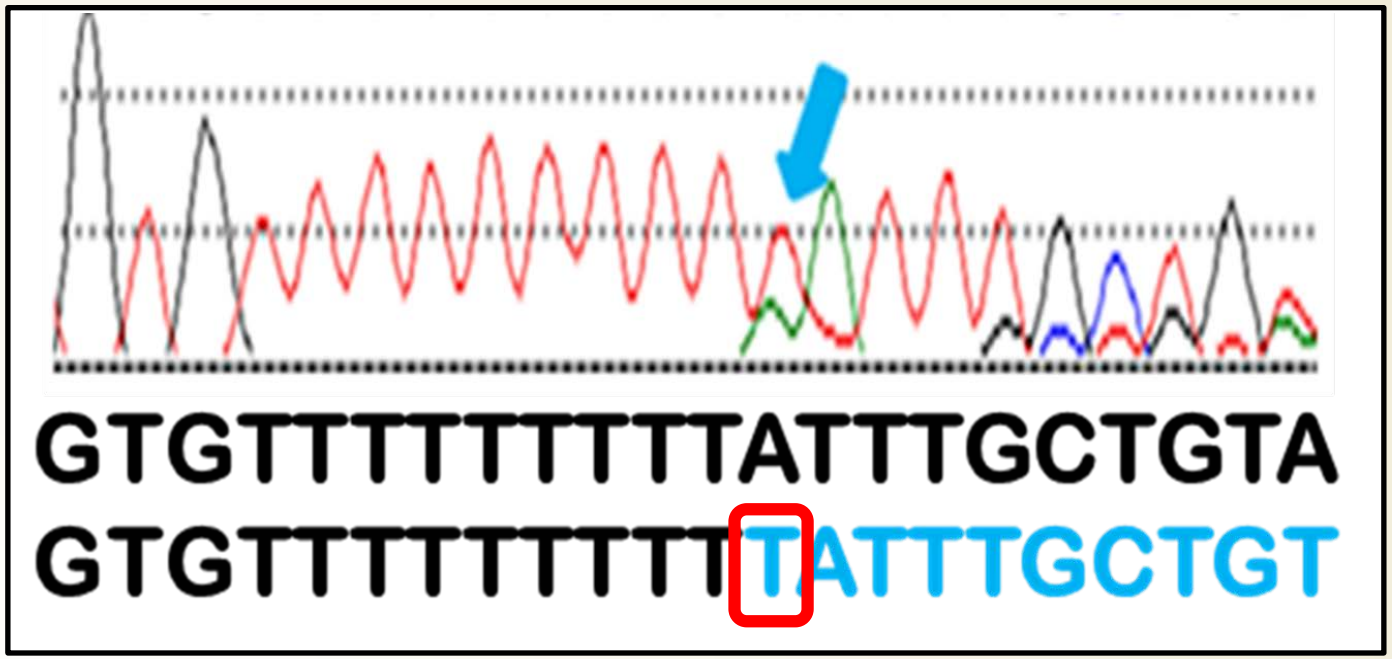
4 year old girl

- Short stature
- Thin, translucent skin
- Large head (macrocephaly)
- Small hands & fixed finger flexion (camptodactyly)



Case courtesy of John A. Phillips III
Undiagnosed Diseases Network

Precision Medicine in the Clinic: Rare Disease



Mosaic for *ZMPSTE24*

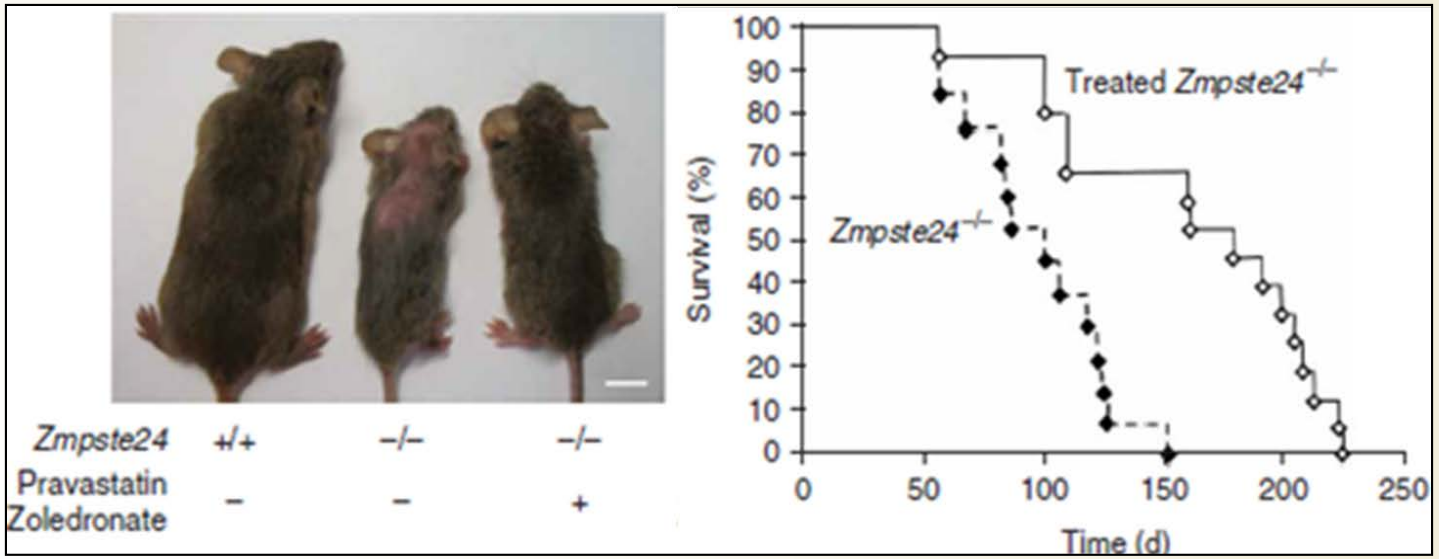
c.1077dupT(p.L362fs18X)

Case courtesy of John A. Phillips III
Undiagnosed Diseases Network

Precision Medicine in the Clinic: Rare Disease

ZMPSTE24

- Zinc metalloproteinase associated with Progeria



Patient started on a statin/bisphosphonate trial

Varela et al. *Nat Med.* 2008.
Case courtesy of John A. Phillips III

Precision Medicine in the Clinic: Common Drugs

CYP2C19 Reduced-Function Alleles,
No. of Events/

If not otherwise contraindicated:

Increased Risk
arriers

CLARITY
EXCELS
TRITON-
AFIJI
FAST-MI
RECLOS
ISAR
CLEAR-P
Intermou
Overall

Percent Treated with Alternative Drug

Percent of Patients

Adjusted Hazard Ratio
LOF-Clopidogrel vs LOF-Alternative: 2.21 (1.13-4.33) p=0.021
LOF-Alternative vs non-LOF: 0.81 (0.48-1.35) p=0.41

Cumulative MACE Rate (%)

LOF_CLOP
NON-LOF
LOF_ALT

Log-rank p=0.016
Log-rank p=0.15

Time (months)

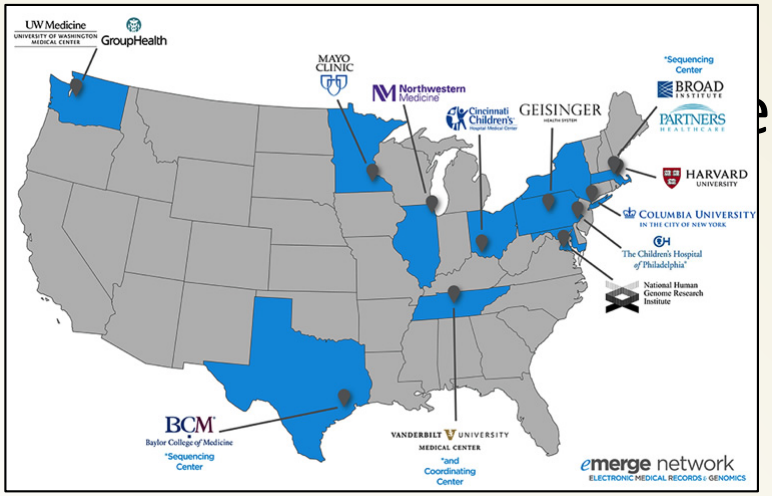
NO. at risk							
LOF_CLOP	226	112	89	76	63	39	3
NON-LOF	1243	759	636	577	451	293	28
LOF_ALT	346	245	221	195	161	112	9

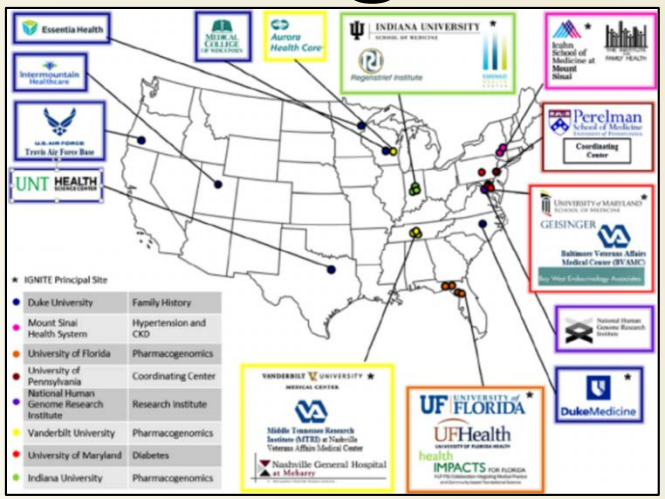
LOF = Loss of function

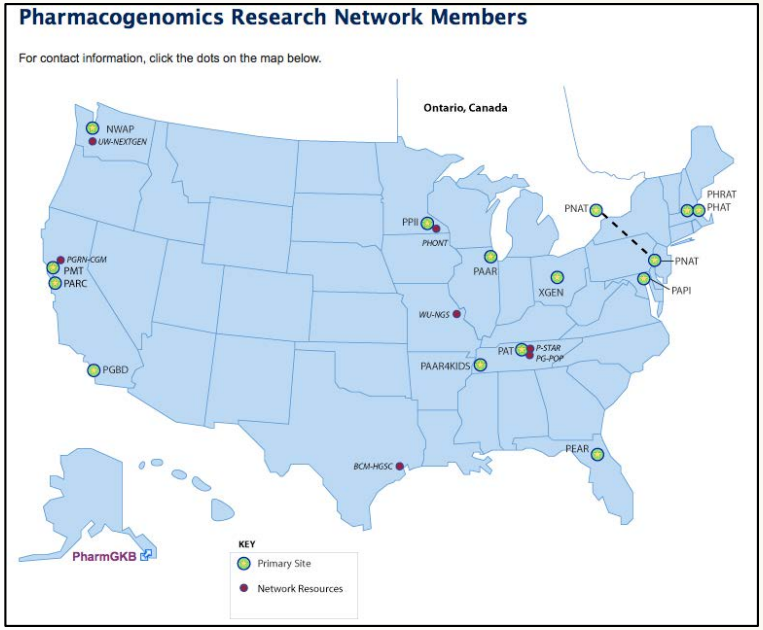
IGNITE
Implementing GeNomics In practicE

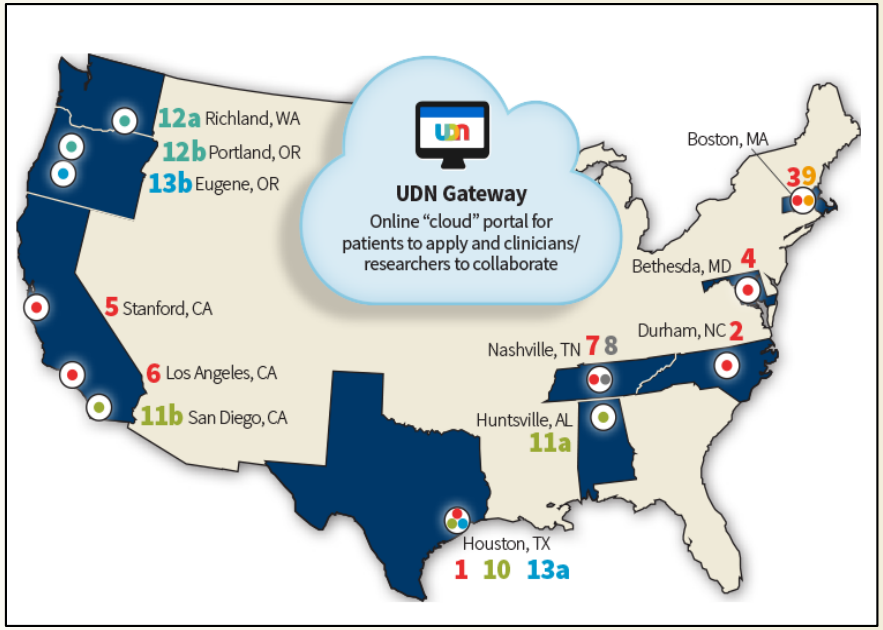
Mega et al. *JAMA*. 2010.
Peterson et al. *Clin Pharmacol Ther*. 2016.
Cavallari 2016, AHA

Precision Medicine in the Clinic: Challenges







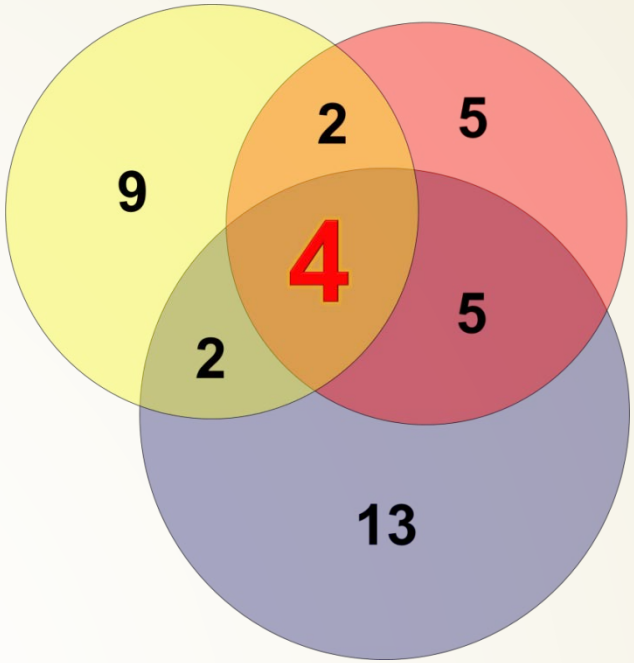


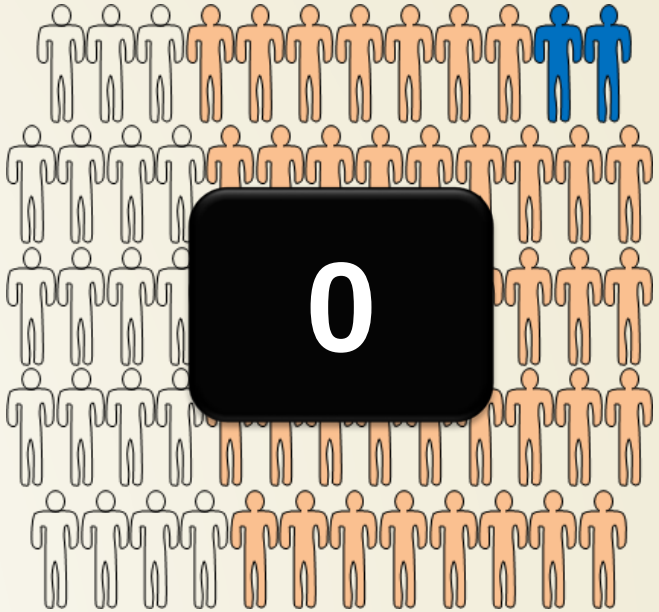
Precision Medicine in the Clinic: Challenges

1. Widespread Implementation
2. Genomic Interpretation

2022 People
2 LQT Genes

122 Variants



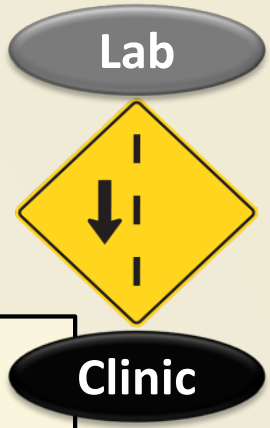


Van Driest et al. *JAMA.* 2016.

Precision Medicine in the Clinic: Challenges

1. Widespread Implementation
2. Genomic Interpretation
3. Special Populations

Precision Medicine in the Clinic: Challenges



If not otherwise contraindicated:

- ☐ Prescribe prasugrel (Effient) 10 mg daily

  Prasugrel should not be given to patients:
  - history of stroke or transient ischemic attack
  - >= 75 years of age
  - with body weight < 60 kg

- ☐ Prescribe ticagrelor (Brilinta) 90 mg twice daily

  Ticagrelor should not be given to patients:
  - history of severe hepatic impairment
  - intracranial bleed

- ☑ Continue with clopidogrel (Plavix) prescription

  Primary override reason:
  - ☐ Contraindicated for prasugrel or ticagrelor
  - ☐ Potential side effects
  - ☐ Provider/Patient opts for clopidogrel
  - ☐ Cost

Precision Medicine in the Clinic: Challenges

Current Drug-Gene Interactions

Clopidogrel – *CYP2C19*

Warfarin – *CYP2C9* and *VKORC1*

Simvastatin – *SLCO1B1*

Thiopurine Drugs – *TPMT*

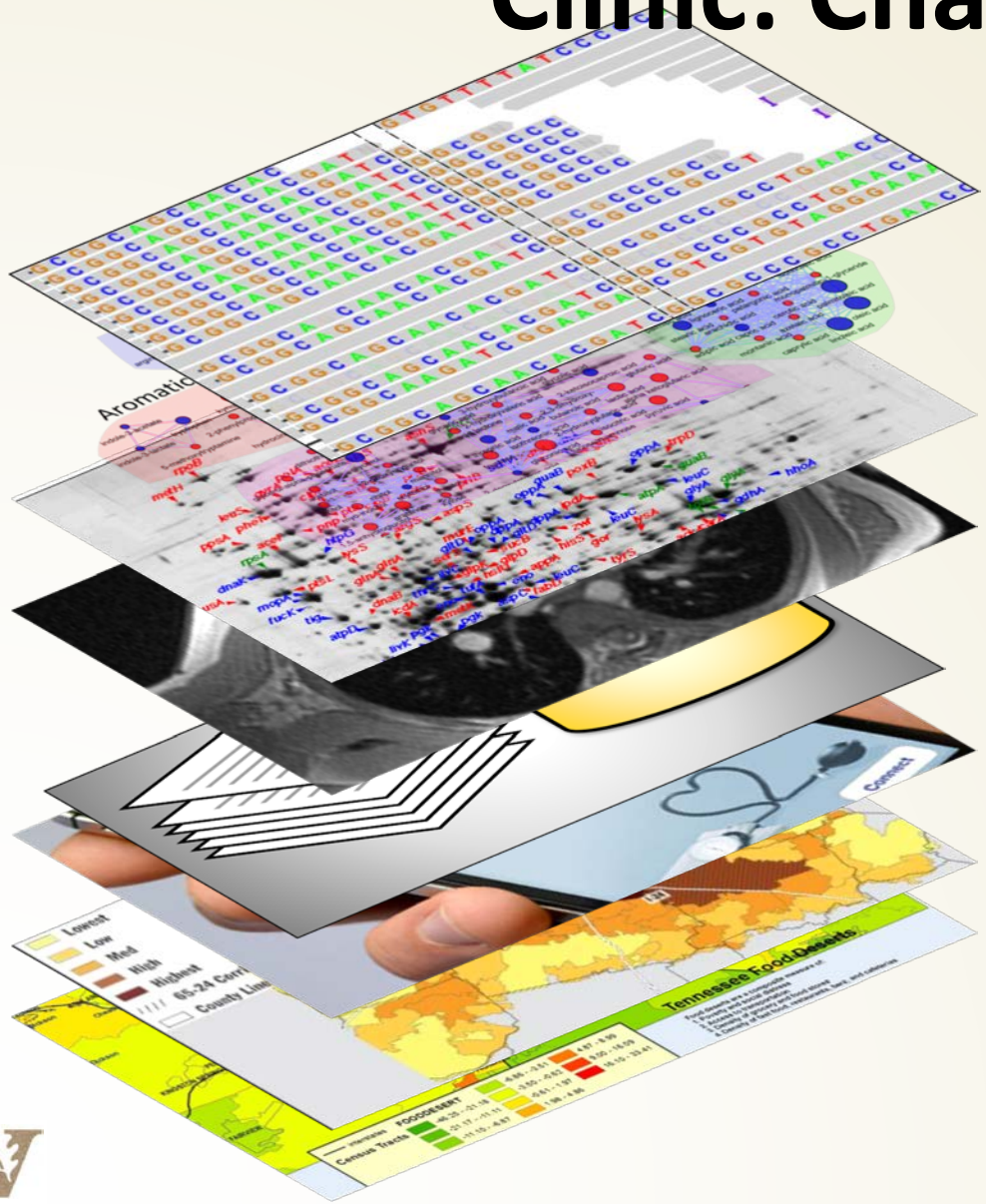
Tacrolimus – *CYP3A5*

Pharmacogenetics for Safe Codeine Use in Sickle Cell Disease

Roseann S. Gammal, PharmD,[a] Kristine R. Crews, PharmD,[a] Cyrine E. Haidar, PharmD,[a] James M. Hoffman, PharmD, MS,[a] Donald K. Baker, PharmD, MBA,[a] Patricia J. Barker, PharmD,[a] Jeremie H. Estepp, MD,[b] Deqing Pei, MS,[c] Ulrich Broeckel, MD,[d] Winfred Wang, MD,[b] Mitchell J. Weiss, MD, PhD,[b] Mary V. Relling, PharmD,[a] Jane Hankins, MD, MS[b]

Gammal et al. *Pediatrics*. 2016.

Precision Medicine in the Clinic: Challenges



Genomics

Metabolomics

Proteomics

Images

EHRs

mHealth

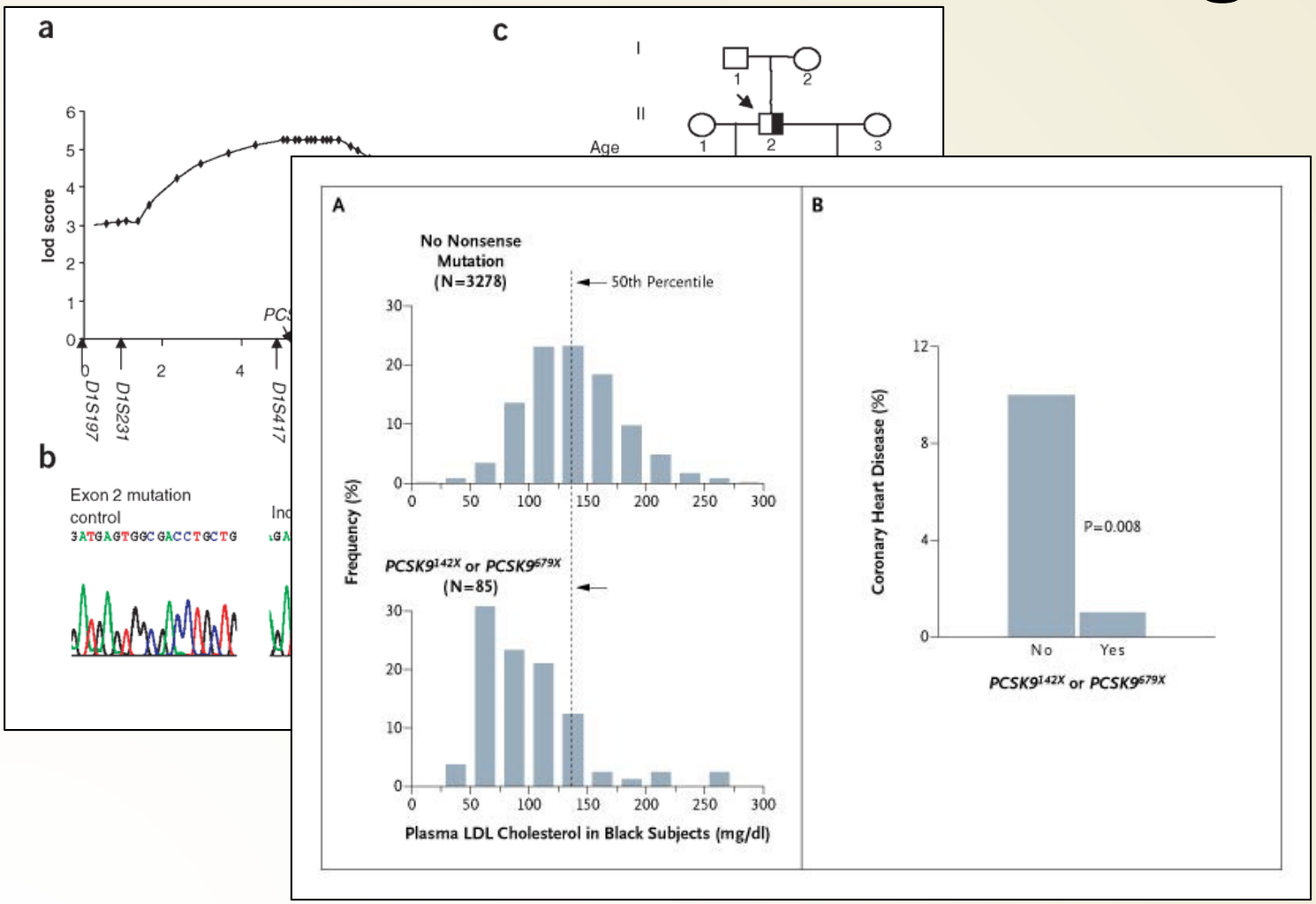
Sociocultural determinants of health

Road Map

Translate and Implement

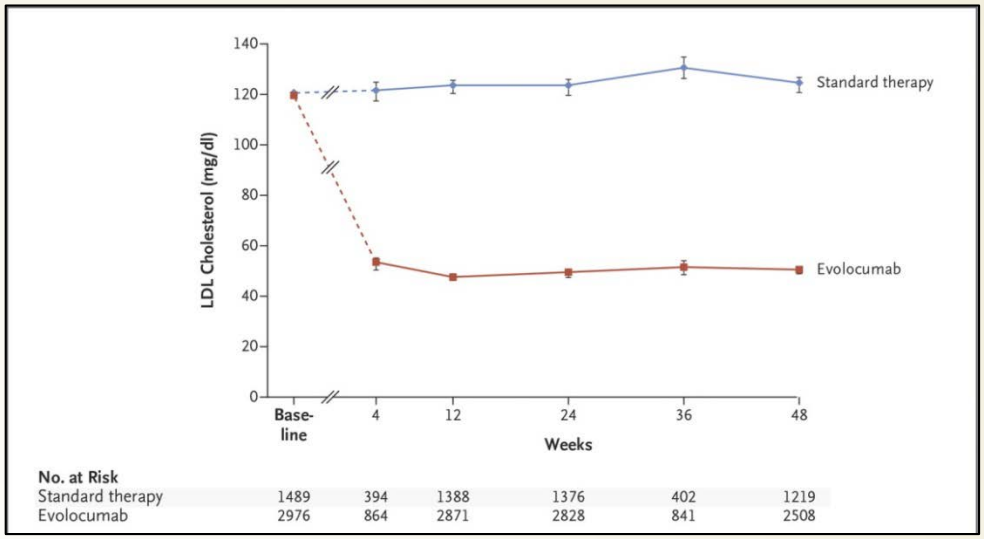
Learn and Inform

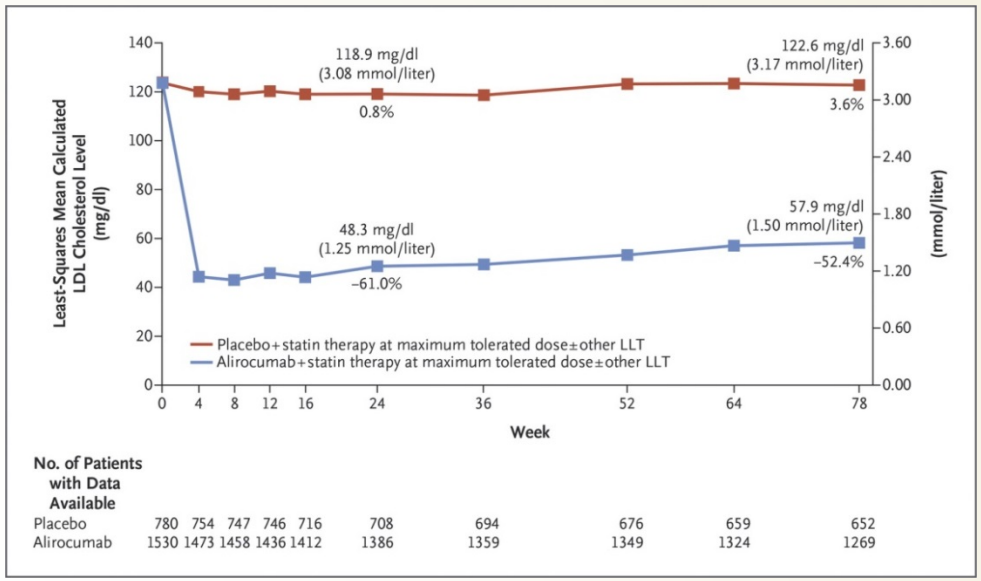
The Clinic in Precision Medicine: New Drugs



Abifadel et al, *Nat Genetics.* 2003.
Cohen et al, *NEJM.* 2006.

The Clinic in Precision Medicine: New Drugs

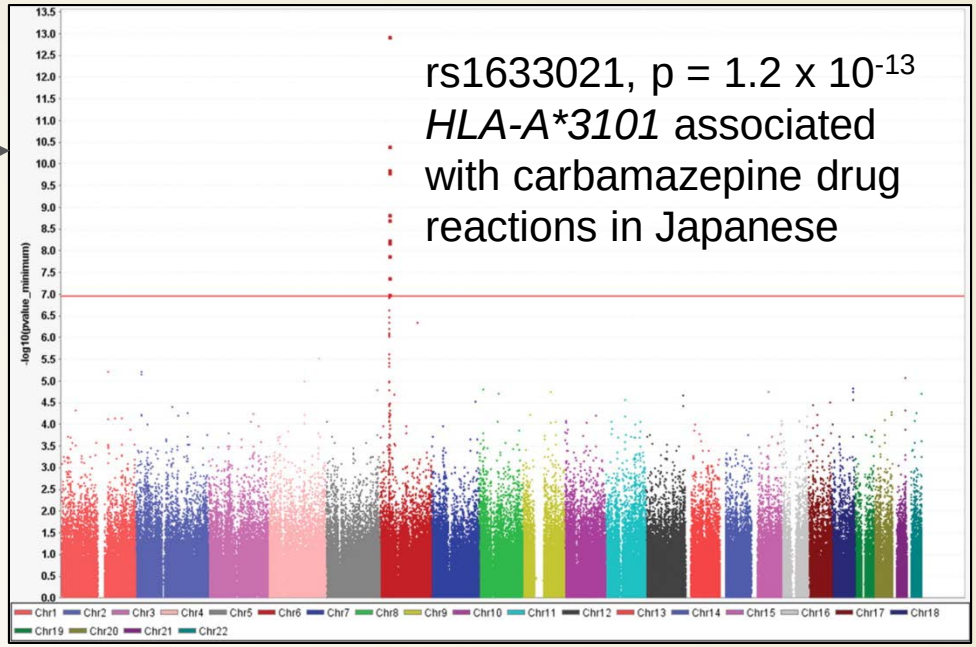




Sabatine et al, *NEJM.* 2015.
Robinson et al, *NEJM.* 2015.

The Clinic in Precision Medicine: "Old" Techniques

Phenotype → Dense genomic information →



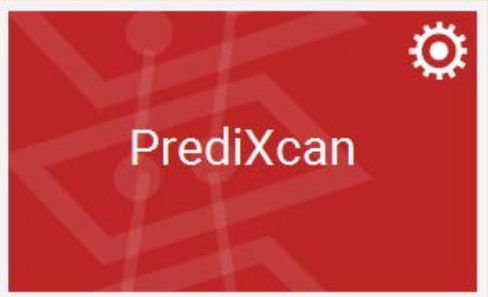
Ozeki et al, *Hum Mol Gen.* 2011.

The Clinic in Precision Medicine: New Techniques

Use: Genome-wide genotype and transcriptome datasets to train additive models of gene expression levels

'Impute': Gene expression levels based on genome-wide genotyping in the test cohort

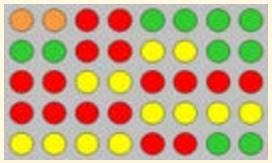
Ask: Which genes have expression levels associated with the phenotype?



Gamazon et al, *Nat Gen.* 2015.

The Clinic in Precision Medicine: New Techniques

Phenotype

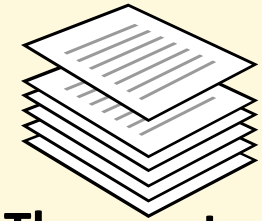


Dense genomic information

Associated genotypes

PheWAS

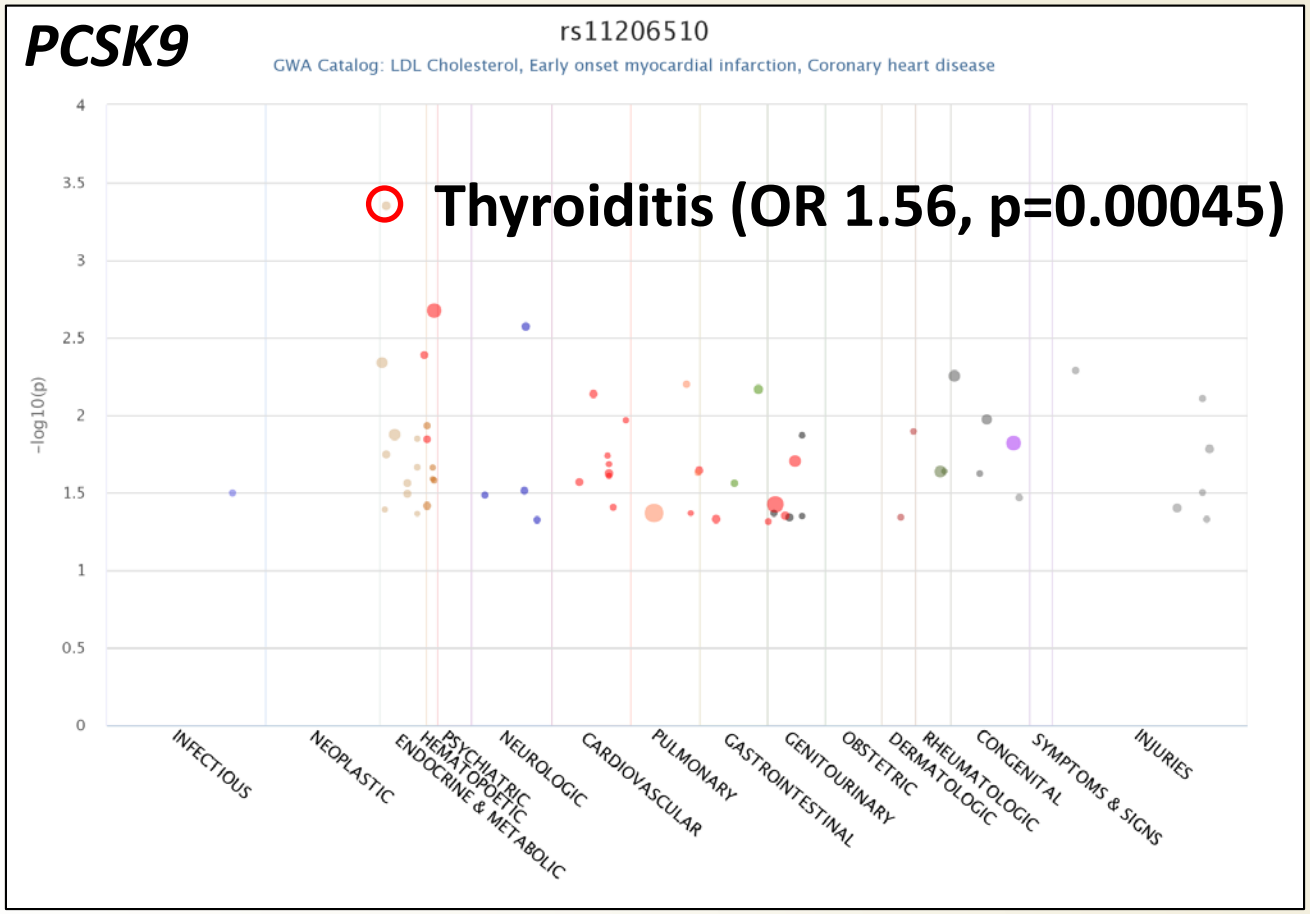
Genetic variant



The curated EHR-based phenome

Associated phenotypes

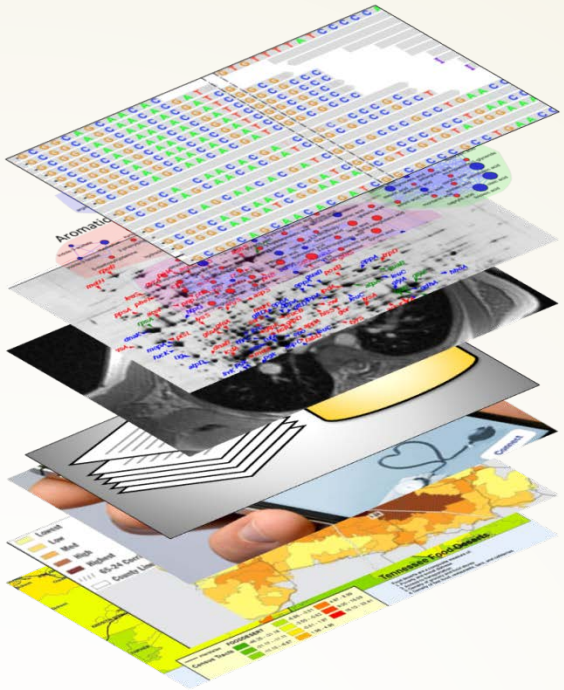
The Clinic in Precision Medicine: New Targets



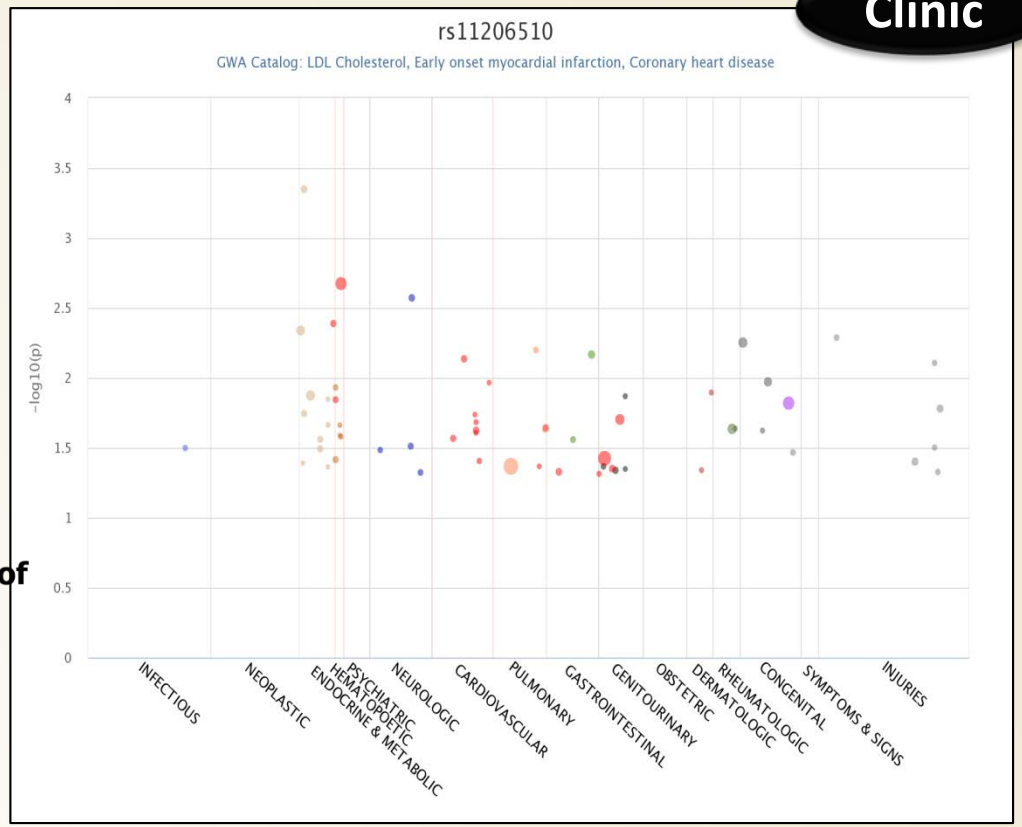
Denny et al, *Nat Biotechnol.* 2013.
https://phewascatalog.org/

The Clinic in Precision Medicine: Drug Effects

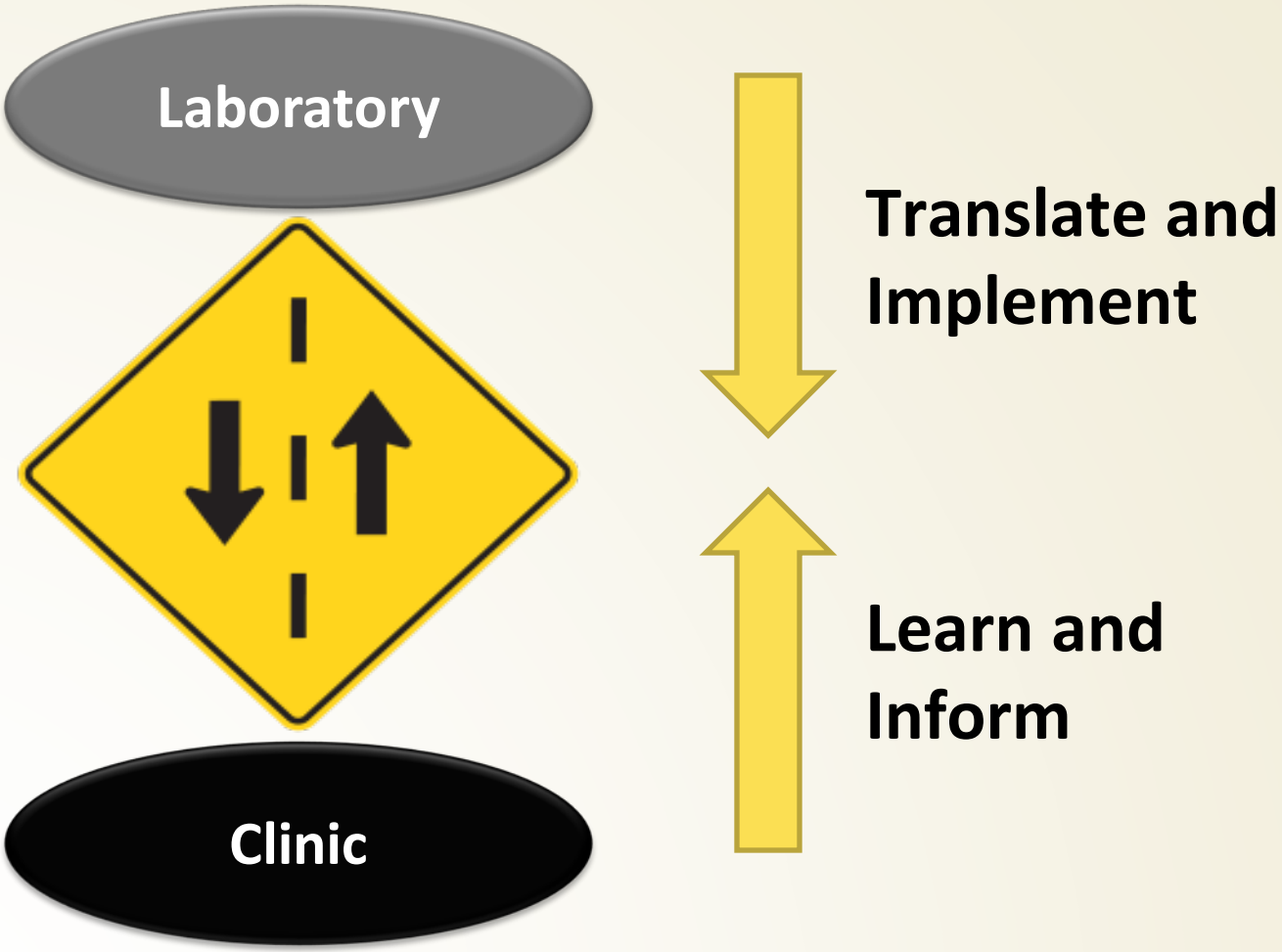
Exposure Variables



- Genomics
- Metabolomics
- Proteomics
- Images
- EHRs
- mHealth
- Sociocultural determinants of health



Road Map


Laboratory
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General Conclusions

- Genomic-guided therapy is here.
- EHRs are pivotal in their enabling role for targeting therapy based on “big data.”
- EHRs and other clinical observations will also help define potential new therapeutic avenues.
- New techniques continue to emerge.

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  - Dan Roden
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