Implementing Population Preemptive Genetic Screening into Clinical Practice

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Disclosure Statement

Presenter has no relevant financial or non-financial interests to disclose.

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Objectives

- Discuss the clinical value of testing for pharmacogenetics and medically actionable predispositions
- Describe essential steps in implementing a pre-emptive genetic screening program
- Describe the educational programs and resources for providers and patients
- Discuss the tools imbedded in the electronic health record to allow ongoing use of genetic data

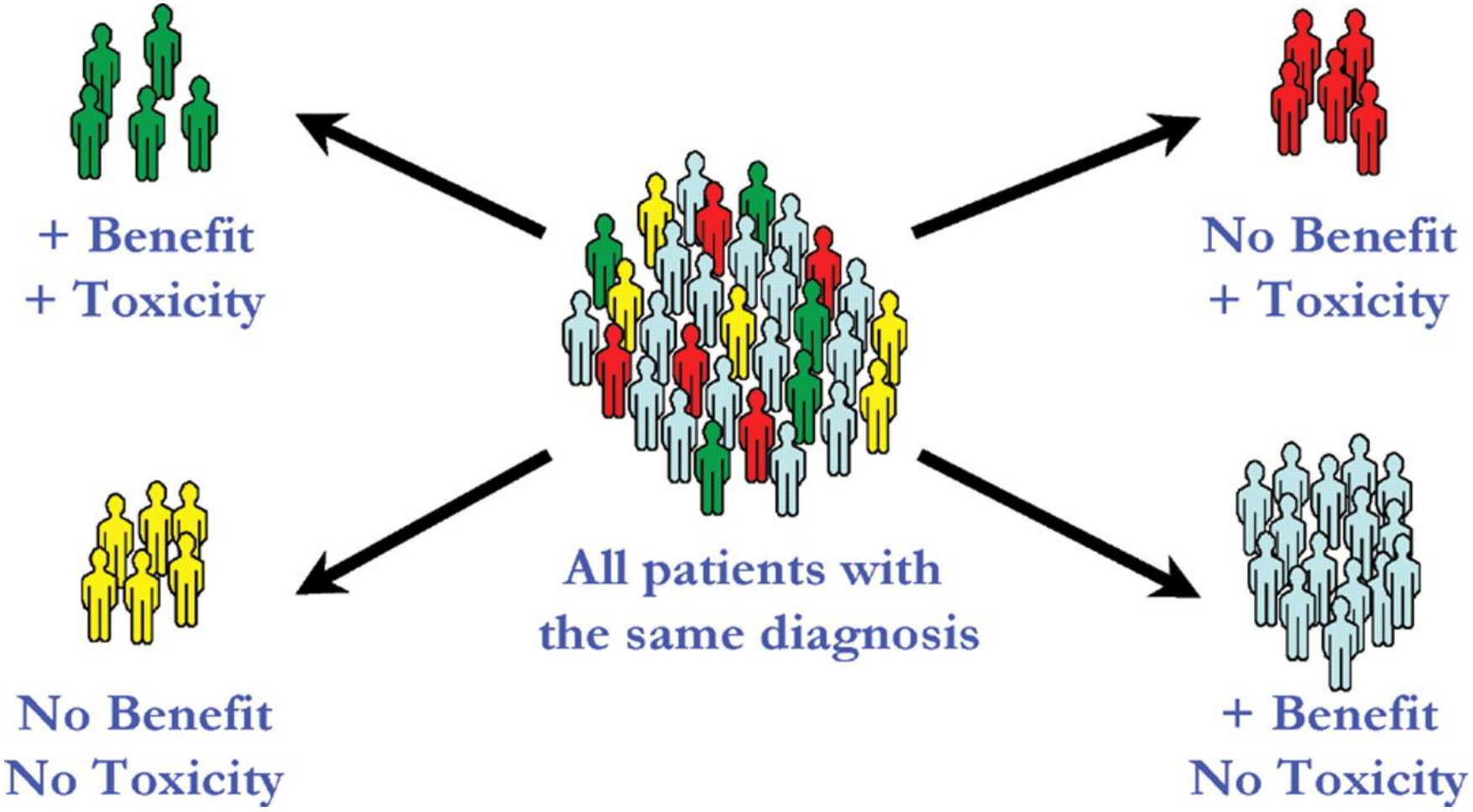
Categories of Genomic Medicine

- Pharmacogenetic variation
  - Genetic variants of drug metabolism
- Mendelian conditions
  - Single Mendelian variants of large effect
- Multi-genic complex conditions
  - Multiple risk variants each with small effect
- Cancer genomics
  - Sequence variation between tumor and normal cells

PHARMACOGENETICS

=

How genes affect a person's response to drugs



From Marsh and McLeod. Hum. Molec. Genet. 15:R89-93, 2006

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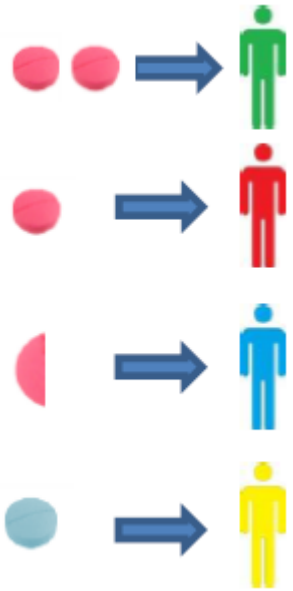
Types of Metabolizers



	For some antidepressants...	
Ultra rapid metabolizer (UM)	→	Lack of response
Extensive normal metabolizer (EM)	→	Expected response
Intermediate metabolizer (IM)	→	Exaggerated response
Poor metabolizer (PM)	→	Adverse effects

Genotyping to identify an individual's metabolism can help to minimize adverse events and increase drug efficacy

Clinical Pharmacogenetics Implementation Consortium (CPIC)

- Address barriers to implementation of pharmacogenetic tests into clinical practice
- Developed peer-reviewed guidelines are
  - Published in a leading journal
  - Enable the translation of genetic laboratory test results into actionable prescribing decisions for specific drugs
  - Center on genes or around drugs

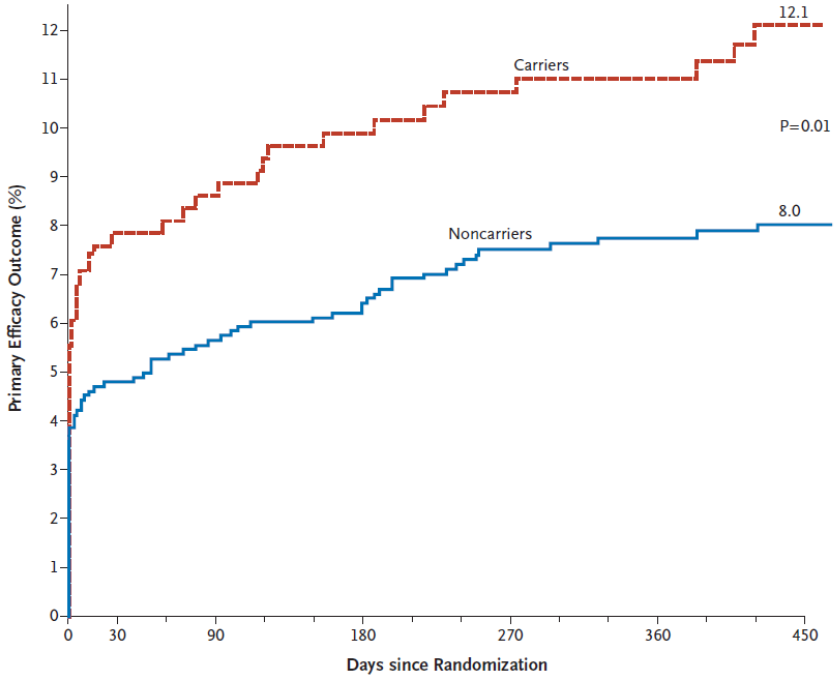
The Plavix Story...

- Bioactivated by cytochrome P450 2C19
- CYP2C19 is the gene encoding this cytochrome
- Variation in this gene can affect how well the enzyme works
- 1 abnormal copy = reduced enzyme activity
- 2 abnormal copies = no enzyme activity
- ~20% have at least one abnormal copy = "Plavix non-responder"

ORIGINAL ARTICLE

Cytochrome P-450 Polymorphisms and Response to Clopidogrel

N ENGL J MED 360;4 NEJM.ORG JANUARY 22, 2009



Primary efficacy outcome = death from cardiovascular causes, MI or stroke

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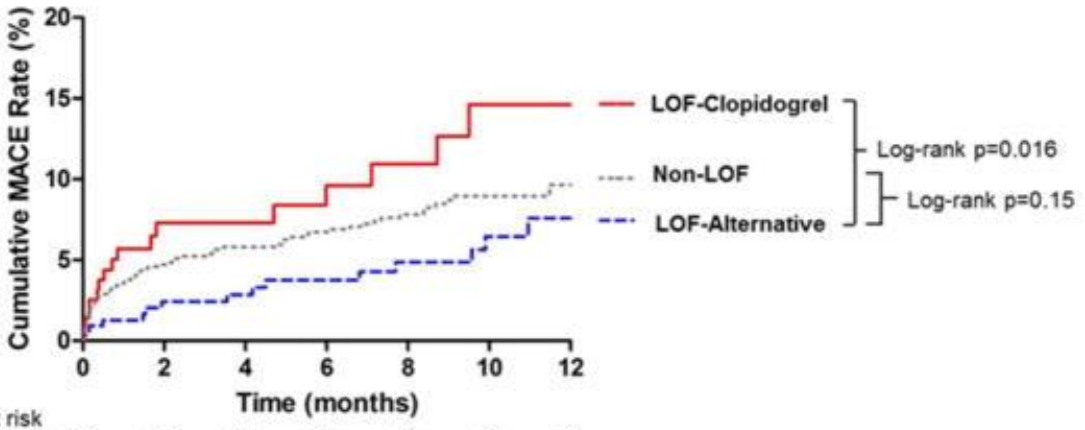
Multisite Investigation of Outcomes With Implementation of *CYP2C19* Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention

Clinical Implementation of *CYP2C19* Genotype-Guided Antiplatelet Therapy after PCI at 7 U.S. Institutions

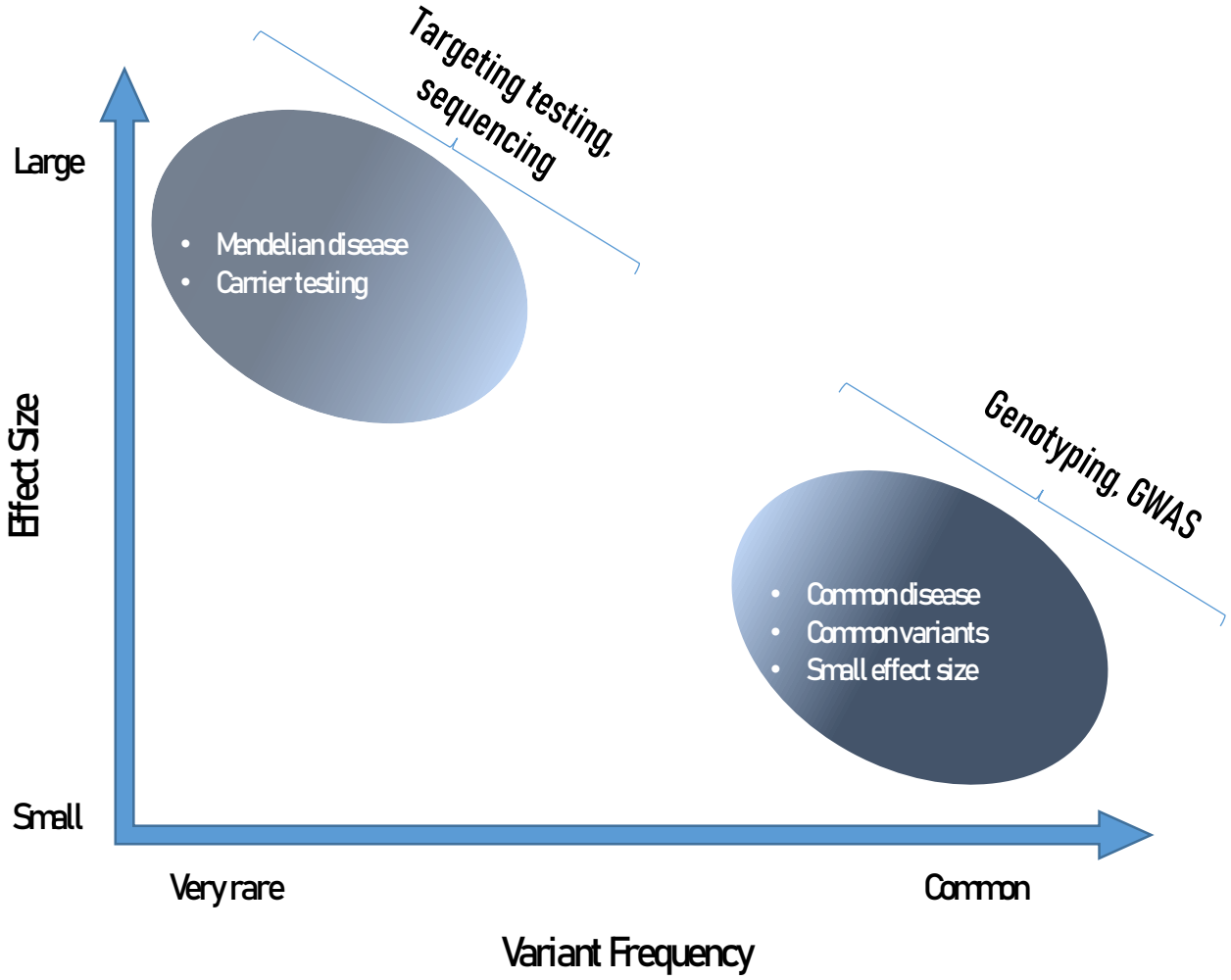
↓

Kaplan-Meier Survival Estimates of MACE in Relation to *CYP2C19* Genotype and Antiplatelet Therapy



No. at risk							
LOF-Clopidogrel	226	112	89	76	63	39	3
Non-LOF	1243	759	636	577	451	293	28
LOF-Alternative	346	245	221	195	161	112	9

Spectrum of Genetic Disease



Modified from: Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. Nature 2009;461:747-753

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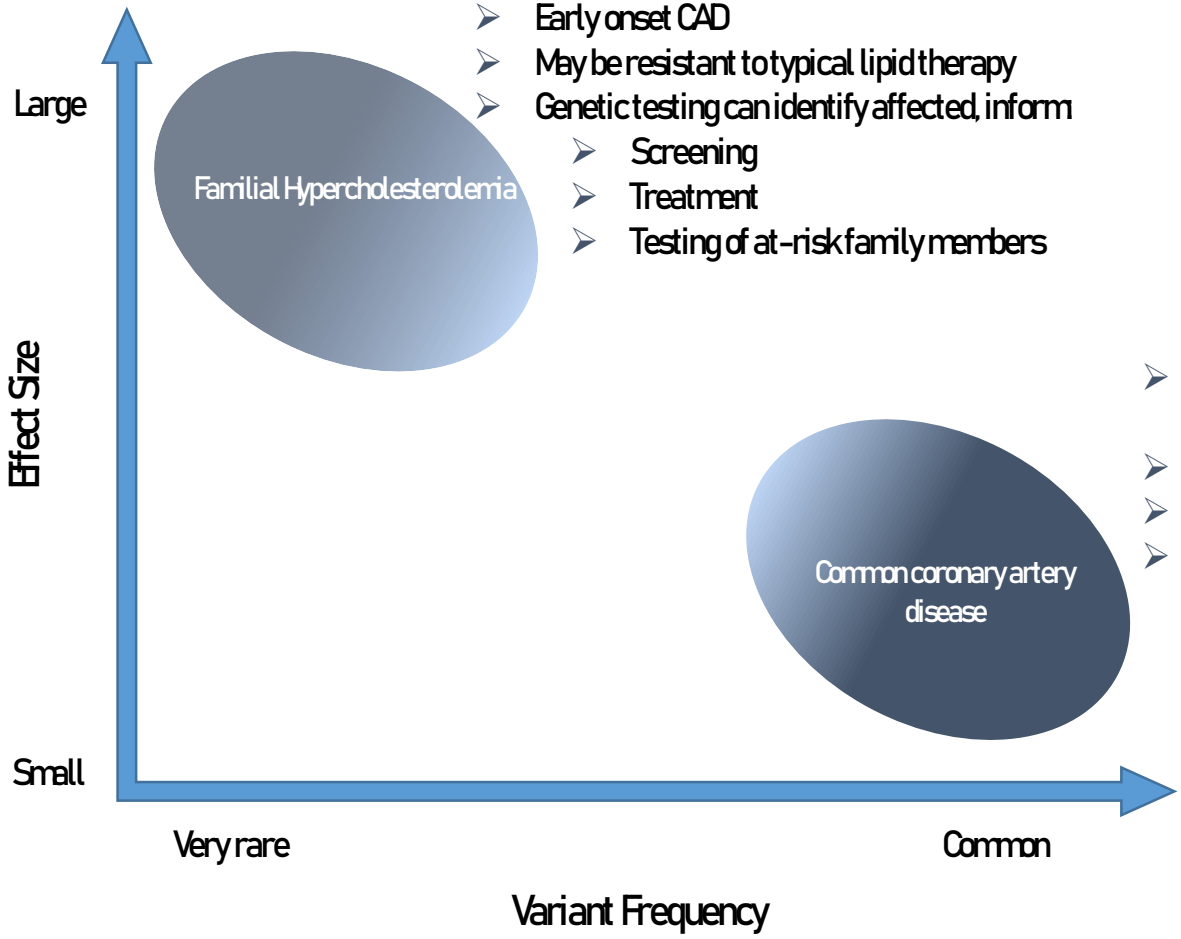
Coronary Artery Disease



- Three known genes PCSK9, APOB, LDLR
- Early onset CAD
- May be resistant to typical lipid therapy
- Genetic testing can identify affected, inform
  - Screening
  - Treatment
  - Testing of at-risk family members

- ~200 genetic risk variants known
  - PCSK9 included
- Later onset CAD
- Lifestyle significant contributor
- Genomic risk may inform
  - Screening
  - Treatment

Modified from: Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. Nature 2009;461:747-753

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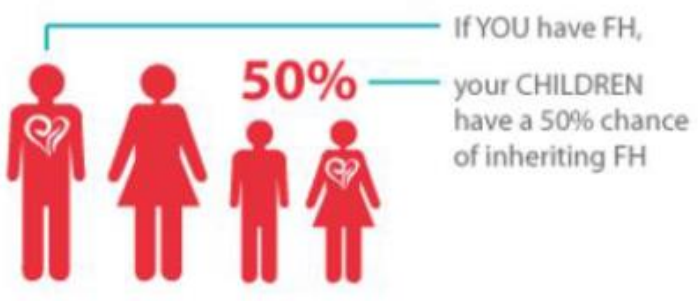
FAMILIAL HYPERCHOLESTEROLEMIA



- Inherited disorder characterized by markedly elevated LDL cholesterol leading to premature cardiovascular disease
- Multiple genes with both homozygous and heterozygous disease states

- Largely under recognized in the United States
- Presentation can vary depending on whether an individual is homozygous or heterozygous for a mutation in *LDLR, APOB, or PCSK9*

Untreated FH leads to
20X increase
In heart disease risk

- LDL levels can vary widely in people with same mutation
- Cascade screening may reveal carriers of mutation who don't meet clinical criteria
  - Treatment still appropriate due to lifetime exposure to LDL

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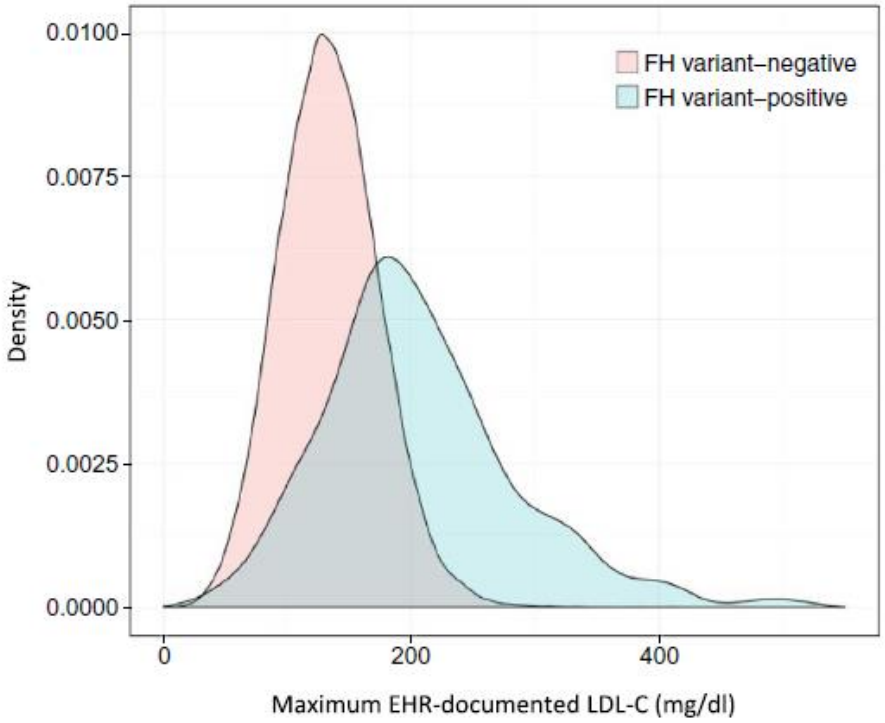
FH A Case for Preemptive Genetic Screening

- Estimated that 90% of those affected are not diagnosed
- ~50K whole exome patients from the Geisinger MyCode project
- 229 heterozygous carriers of 1 of 25 pathogenic variants in *LDLR*, *PCSK9*, and *APOB*
- FH variant carriers had higher LDL than non-carriers, however there was significant overlap in the levels as displayed in the figure
- This can make diagnosis of FH difficult without knowing if a variant is present



Abul-Husn et al. Genetic identification of familial hypercholesterolemia within a single U.S. health care system. *Science Magazine*. 354 (2016). PMID: 28008010

Modified from Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. Nature 2009;461:747-753

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How do we find these patients?

- Personal or family history early onset conditions or multisystemic condition
- Multiple generations affected with similar condition

OR

Use preemptive genetic screening

Geisinger

NorthShore
University HealthSystem

SANFORD
imagenetics

Healthy
NV
Project℠

VA | U.S. Department of Veterans Affairs

Genetic and genomic medicine at Sanford Health

HEALTH SERVICES DIVISION

1. Bemidji

- Total Population 150,308
- 5 Year Population Growth Projection 0.2%
- Median Household Income $50,245
- Unemployment Rate 5.3%
- Population over 65 Years 20.8%

2. Bismarck

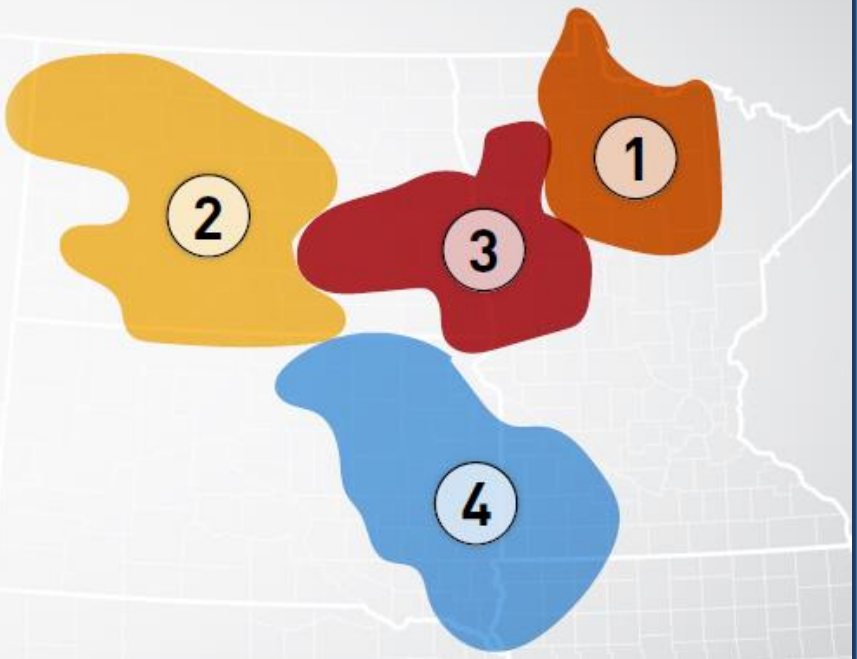
- Total Population 324,620
- 5 Year Population Growth Projection 17.8%
- Median Household Income $74,368
- Unemployment Rate 2.4%
- Population over 65 Years 14.4%

3. Fargo

- Total Population 436,590
- 5 Year Population Growth Projection 6.8%
- Median Household Income $58,988
- Unemployment Rate 2.4%
- Population over 65 Years 16.3%

4. Sioux Falls

- Total Population 581,991
- 5 Year Population Growth Projection 3.7%
- Median Household Income $60,730
- Unemployment Rate 2.3%
- Population over 65 Years 15.5%



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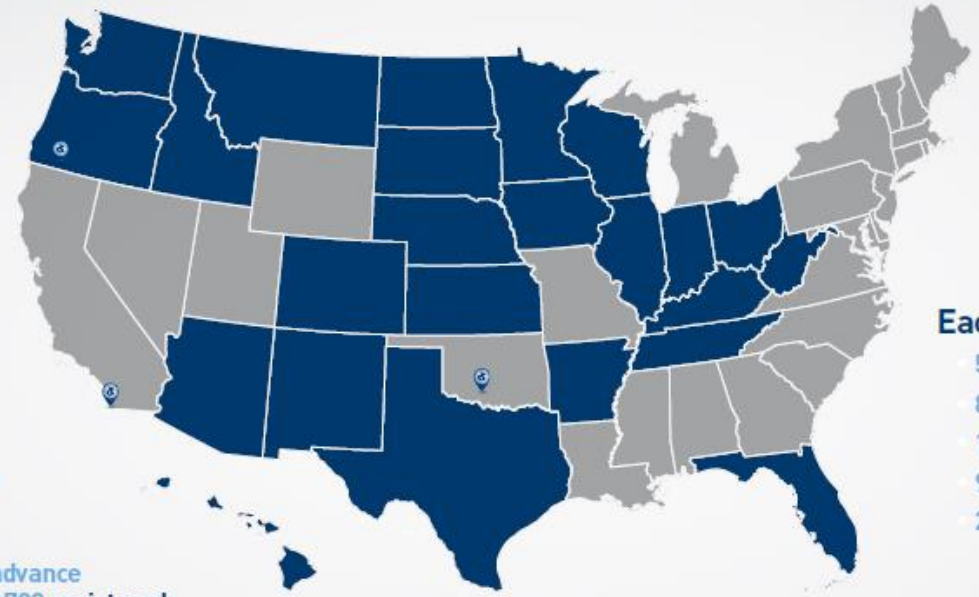
SANFORD HEALTH TODAY

- 44 medical centers
- $6.1 billion in annual revenue
- 482 clinics
- 242 senior living facilities
- 188,574 Sanford Health Plan Members
- 1,453 physicians, 1,001 advance practice providers and 9,703 registered nurses delivering care in more than 80 specialty areas
- 48,622 employees



Health Service Delivery Area

World Clinics

Each year, Sanford provides:

- 5.3 million outpatient and clinic visits
- 84,466 admissions
- 136,436 surgeries and procedures
- 9,537 births
- 210,129 emergency department visits

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2014

PHILANTHROPY NEWS DIGEST
PND – a service of Foundation Center

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HOME > NEWS > T. DENNY SANFORD GIVES $125 MILLION TO ESTABLISH GENOMIC...

T. Denny Sanford Gives $125 Million to Establish Genomic Initiative for Internal Medicine

JANUARY 8, 2014

Sanford Health in Sioux Falls, South Dakota, has announced a gift of $125 million from T. Denny Sanford to establish Sanford Imagenetics, a first-of-its-kind program that aims to integrate genomic medicine into primary care for adults.

Starting later this year, the program will offer Sanford H opportunity to undergo genetic testing and counseling t internists with unprecedented patient-specific informati with patients' genetic information will improve their abil effective treatment or medication for a range of conditic

1/7/2014

Sanford Health Announces $125M Gift to Fund Genomic Initiative for Internal Medicine

Denny Sanford's gift launches Sanford Imagenetics

SANFORD imagenetics

(Sioux Falls, SD) Sanford Health announced today Denny Sanford, the preeminent health care philanthropist in the United States, will gift the organization $125 million to establish Sanford Imagenetics, a first-of-its-kind program in the country that integrates genomic medicine into primary care for adults.

"Mr. Sanford's generosity to this organization is humbling," said Kelby Krabbenhoft, president and CEO of Sanford Health. "Including this $125 million gift, Denny has given Sanford Health nearly a billion dollars. It's an incredible honor as well as a tremendous responsibility."

CLINICAL LANDSCAPE

- Genetic testing as an application of precision medicine continues to grow in utility and accessibility
- Providers need access to this information in a usable format, but also need resources to support its management
- Our challenge was two-fold
  - to develop a program to address the growing clinical applicability of genetics in medicine and
  - to design the clinical model that provides support and leverages the electronic health record to display results in a meaningful way and provide decision-support as appropriate

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KEY GOALS FOR CLINICAL MODEL

- Increase baseline knowledge and understanding of the role of genetics in medicine
- Provide support resources for genetics evaluation and testing resources
- Develop a clinical screening testing that can be applied in the primary care setting

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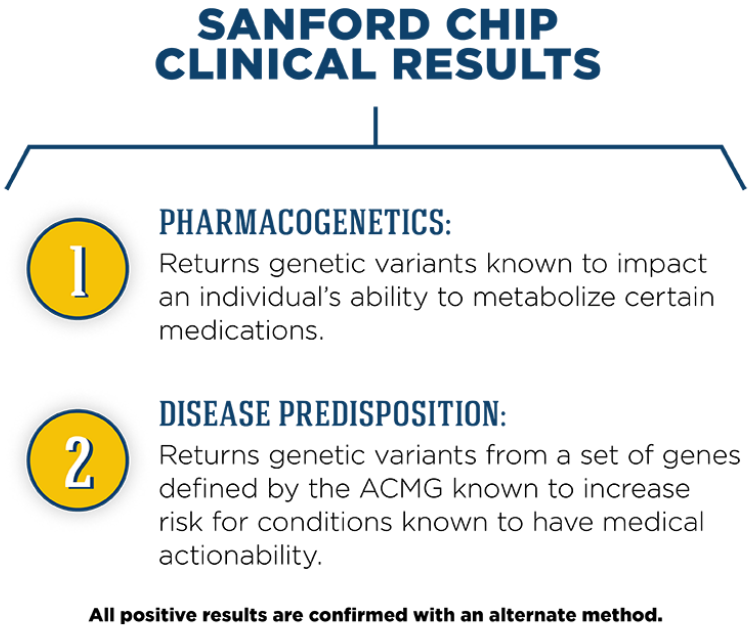
Launch education program

- **Identify initial target population for education**
  - internal medicine
  - 20-hour lecture series developed including various genetic principals
  - required for internal medicine physicians system-wide
- **Develop a system-wide education program**
  - 8 20-minute modules including content derived from initial lecture series
  - required for all providers
  - content developed internally delivered via digital modules
- **Provide in-person education**
  - routine clinic education sessions with a genetic counselors and pharmacists
  - content focused on pharmacogenetics and our preemptive genetic screen

Increase awareness of role of genetics in medicine

- Embedded genetic counselors in all internal medicine clinics
  - now embedding in all primary care including family medicine
  - currently have 25 genetic counselors for the health care system
- Partnered with a local university to establish a master's in genetic counseling program
  - 16 total graduates, > 25 % have been hired into Sanford Health
- Hired dedicated laboratory genetics counselors to help our physicians with results interpretation and return of results
- Increased telehealth presence for genetic counseling

Offer preemptive genetic screening program



- Minimize adverse drug reactions
- Reduce time to therapeutic dosing

- Advise on management: Surveillance, Treatment
- Facilitate cascade testing for at-risk family members

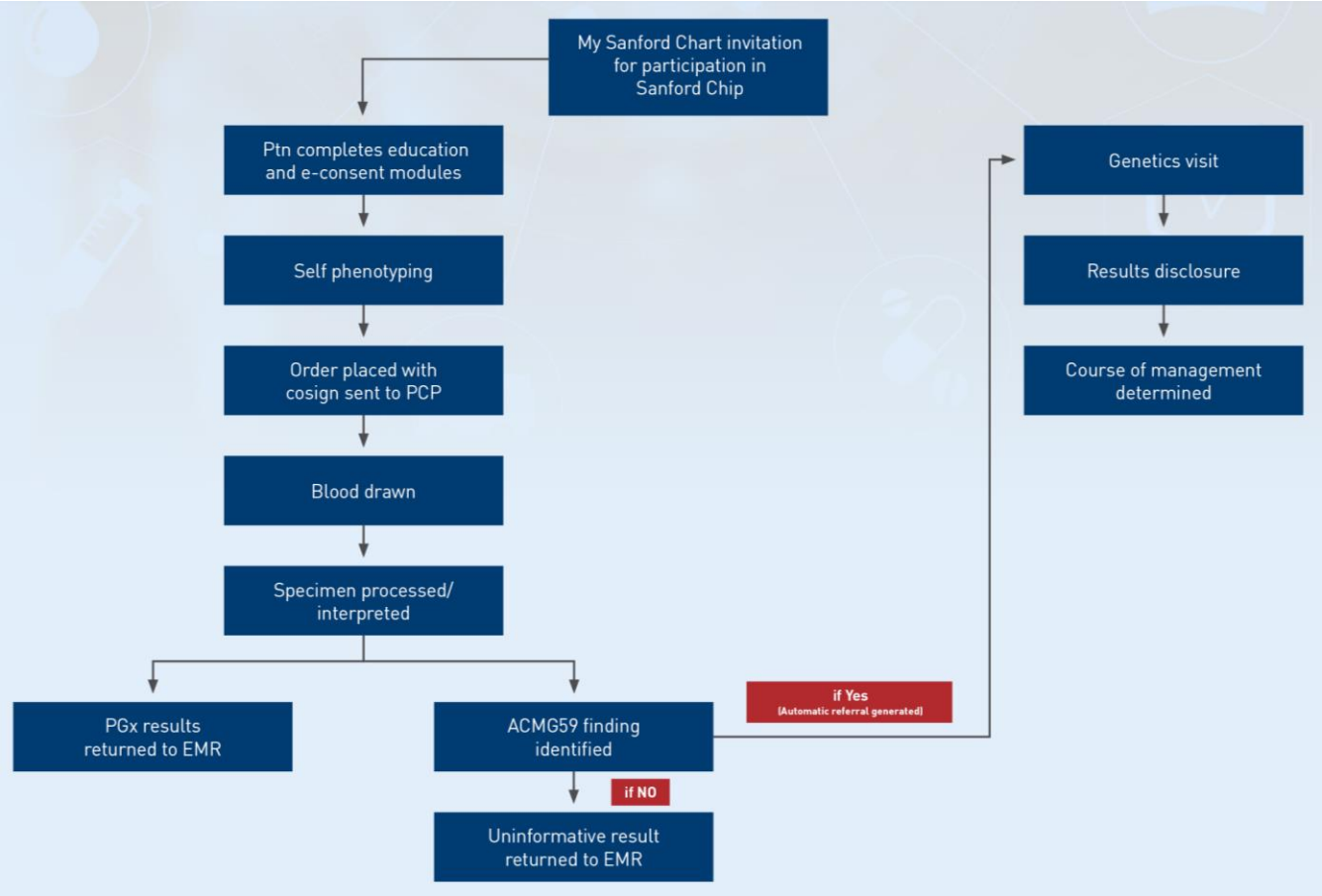
The Sanford Chip is a laboratory developed test which is clinically validated by the Sanford Medical Genetics Laboratory.

Test offered clinically for $49.

More than just a lab test...

- Clinical genetic counselors
- Laboratory genetic counselors
- Education team
- Pharmacists
- Imagenetics Specialists
- Clinical decision support
- Administrative team dedicated to the operations
- Bioinformaticians, medical informaticians, system engineers, and IT support
- CLIA- and CAP-Certified Medical Genetics Laboratory

Sanford Chip Enrollment and Return of Results



Qualifying criteria:

- 18 years old
- Sanford patients with existing provider relationship
- MySanfordChart account

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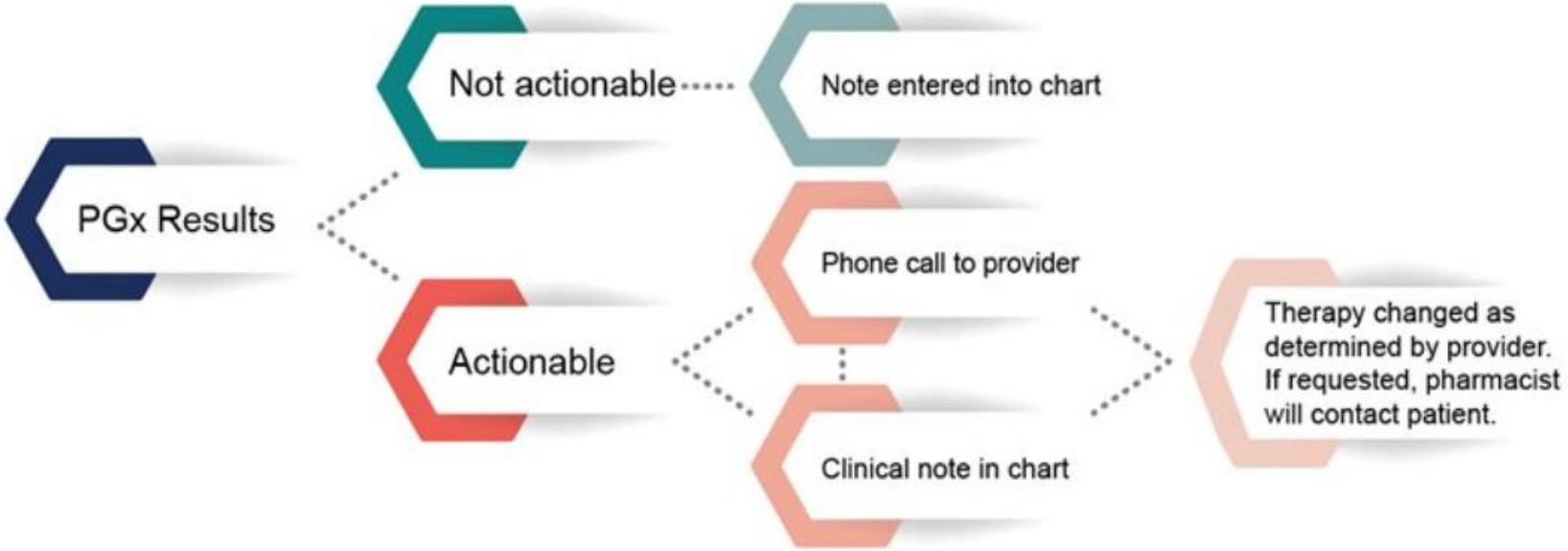
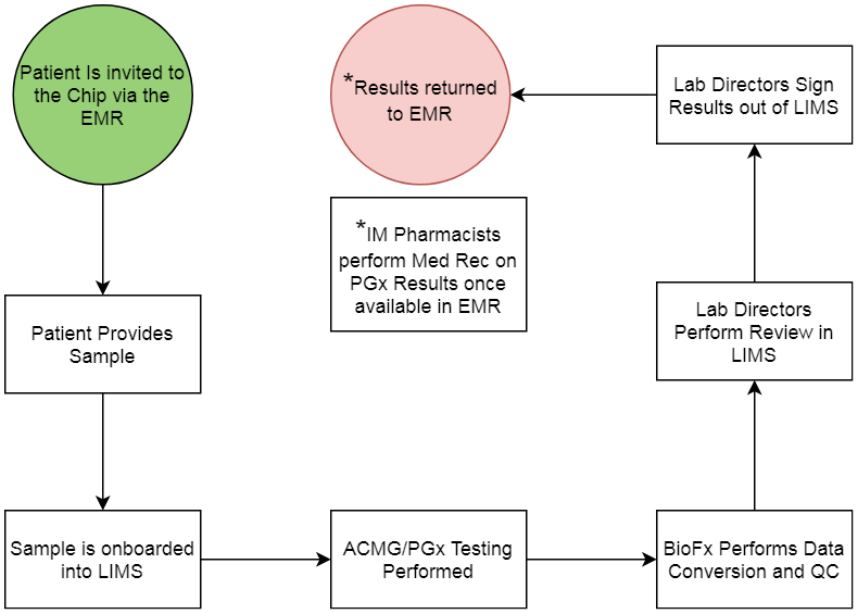
PGx Results Workflow

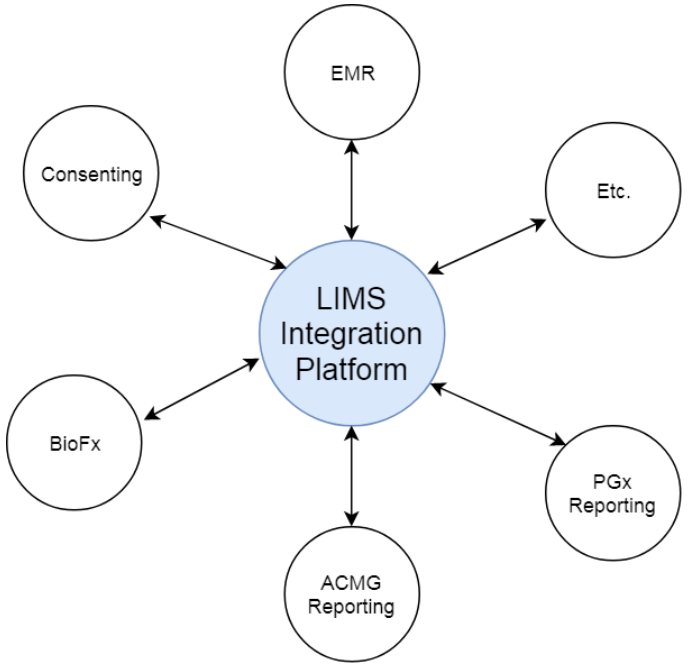


Workflow/Data Movement



Connectivity and Data processing

Integration Architecture



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Discrete results returned to the EMR

- Results
  - LABORATORY RESULTS
    - BLOOD
    - ENDOCRINE TESTING
    - GENETICS
    - INFECTIOUS DISEASE
    - MICROBIOLOGY
    - URINE
    - VIRAL TESTING
  - OTHERS

	1 8/28/2018 1414
GENETICS	
BASIC PHARMGX PANE...	
CYP2C19 Phenotype	Intermediate M... *
CYP2C19 Genotype	*1/*2 *
CYP2D6 Phenotype	Normal Metabol... *
CYP2D6 Genotype	*1/*1 *
CYP2C9 Phenotype	Normal Metabol... *
CYP2C9 Genotype	*1/*1 *
CYP2C9/VKORC1 Phen...	Low Warfarin S... *
VKORC1 Phenotype	Intermediate W... *
VKORC1 Genotype	-1639G>A G/A *
CYP3A5 Phenotype	Poor Metabolizer *
CYP3A5 Genotype	*3/*3 *
DPYD Phenotype	Normal Metabol... *
DPYD Genotype	*1/*1 *
SLCO1B1 Phenotype	Normal Function *
SLCO1B1 Genotype	*1/*1 *
TPMT Phenotype	Normal Metabol... *
TPMT Genotype	*1/*1 *

Res	Component	Value	Units
1	TPMT GENOTYPE	*1/*1	
1	CYP2C9 GENOTYPE	*1/*1	
1	CYP2C19 GENOTYPE	*1/*2	
1	CYP2D6 GENOTYPE	*1/*1	
1	CYP3A5 GENOTYPE	*3/*3	
1	VKORC1 GENOTYPE	-1639G>A G/A	
1	DPYD GENOTYPE	*1/*1	
1	SLCO1B1 GENOTYPE	*1/*1	
1	TPMT PHENOTYPE	Normal Metabolizer	
1	CYP2C9 PHENOTYPE	Normal Metabolizer	
1	CYP2C19 PHENOTYPE	Intermediate Metabolizer	
1	CYP2D6 PHENOTYPE	Normal Metabolizer	
1	CYP3A5 PHENOTYPE	Poor Metabolizer	
1	VKORC1 PHENOTYPE	Intermediate Warfarin Sensitivity	
1	DPYD PHENOTYPE	Normal Metabolizer	
1	SLCO1B1 PHENOTYPE	Normal Function	
1	CYP2C9/VKORC1 PHENOTYPE	Low Warfarin Sensitivity	

Result comments:
Complete interpretive report under separate document

Method: MOLECULAR GENETICS MG

Last received: 8/29/2018 0835

Order-Level Documents - 08/28/2018:

Scan on 9/1/2018 9:40 AM by Scanned, Document : PHARMACOGENETIC RESULTS

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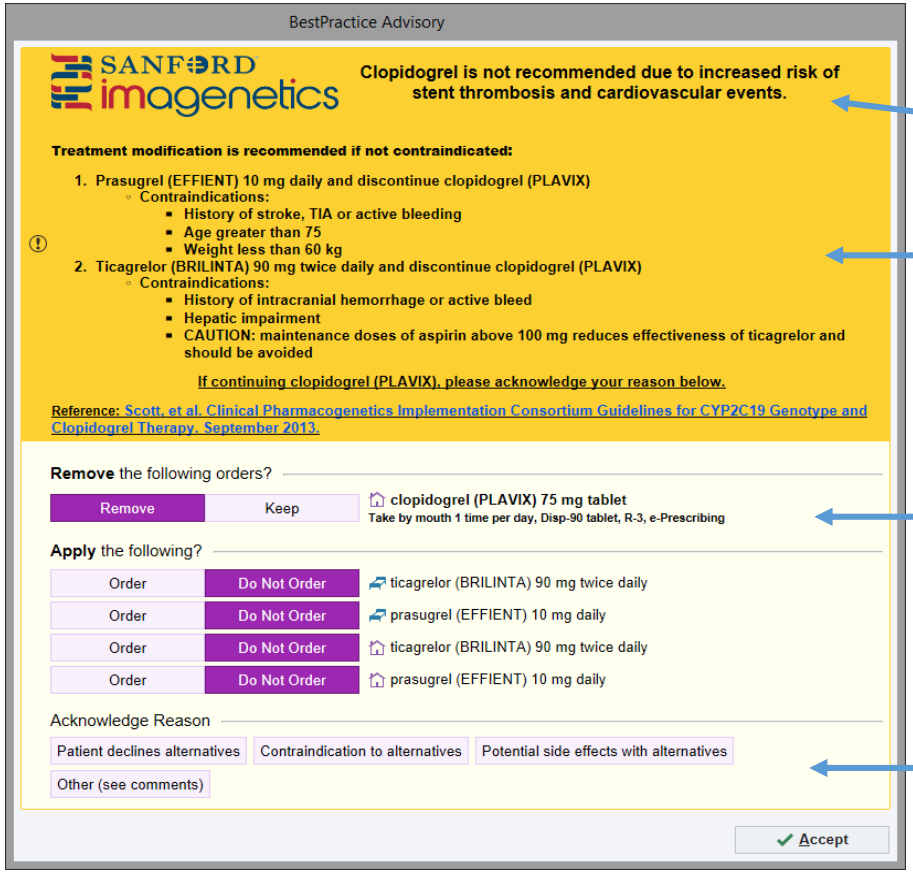
Embed results-driven decision support

Example clinical decision support for pharmagenetics results:



Summary statement of clinical scenario

Details of recommendations

Suggested alternate orders

Mandated override reason

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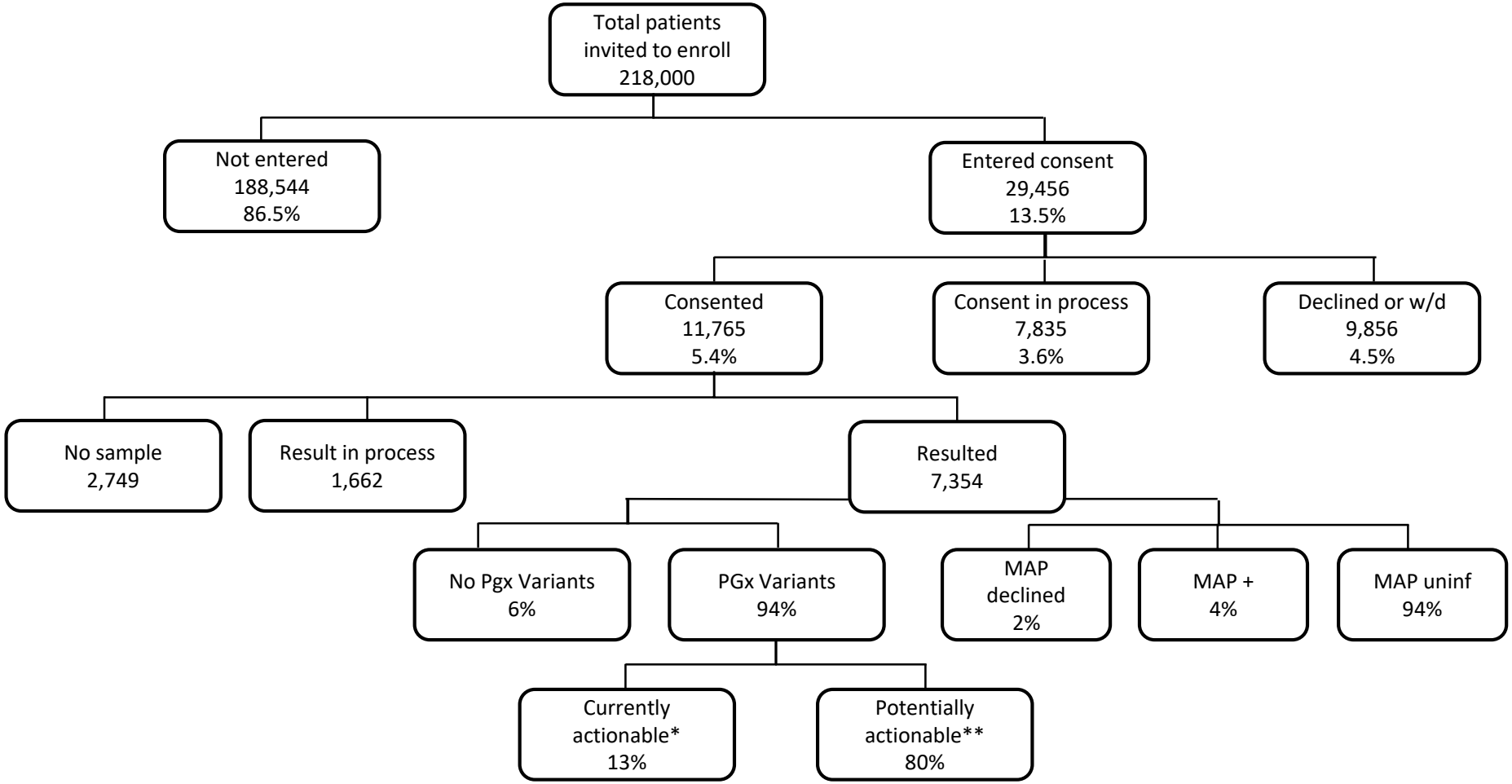
Disease-specific health maintenance reminders

Monoallelic variant in *TP53*

01/10/2020	Ultrasound of Abdomen and Pelvis
07/10/2020	Brain MRI
07/10/2020	Rapid Whole Body MRI
10/03/2021	Colonoscopy
10/03/2021	Upper Endoscopy
07/15/2024	Pap Smear

Sanford Chip Stats



*Patient is currently on medication impacted by pgx results
**Patient has pgx variants that could impact response if prescribed
w/d: withdrawn

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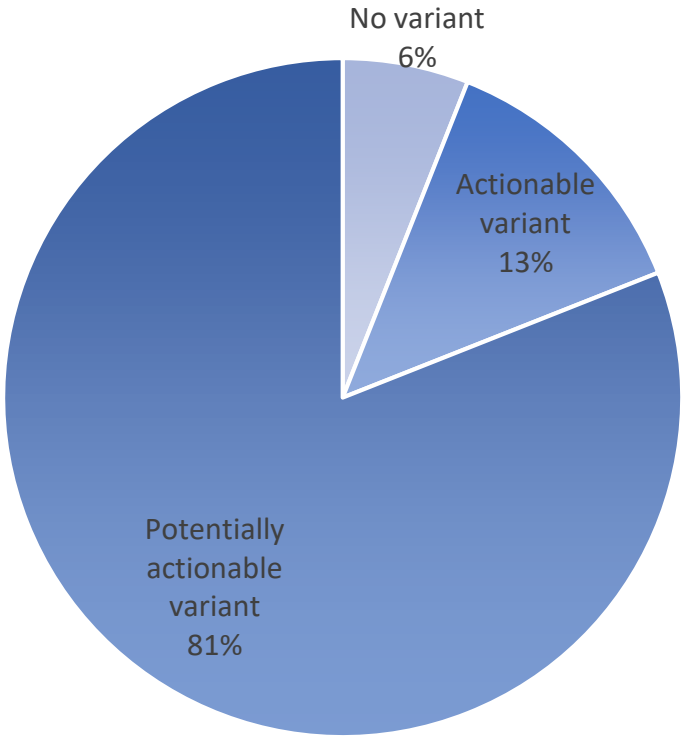
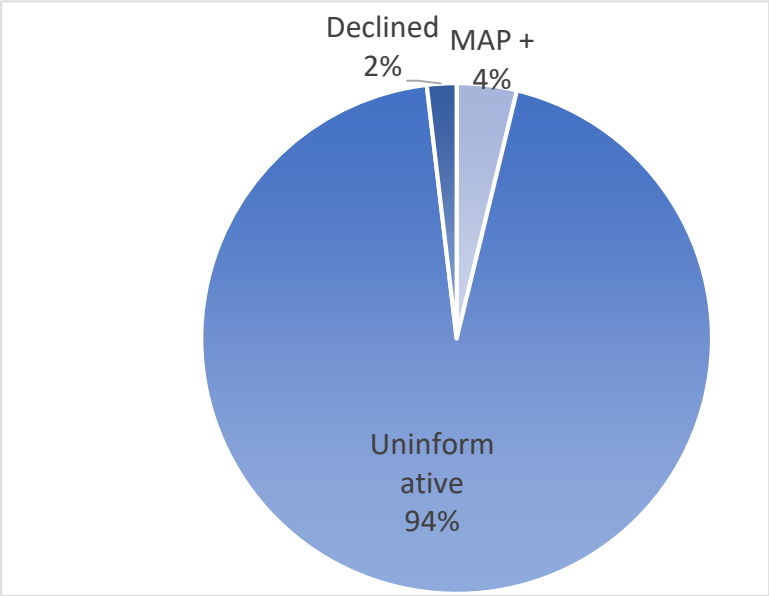
Pharmacogenetic results

>90% of patients carry a genetic variant that will impact their ability to metabolize certain medications.

- ~30% of Sanford patients have a reduced ability to metabolize clopidogrel which leads to decreased efficacy of the med
- ~30% of Sanford patients have a reduced ability to metabolize some commonly prescribed SSRI's (citalopram and excitalopram) which can lead to reduced efficacy and treatment failure
- ~29% of Sanford patients may have an increased incidence of myopathy/myalgia with simvastatin (and possibly atorvastatin)
- ~13% of Sanford patients will have a reduced ability to metabolize codeine and tramadol causing a decrease in therapeutic effect



Medically actionable predisposition results

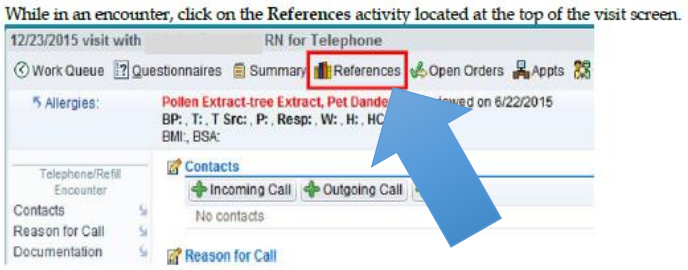


Condition	Total Identified
Cardiomyopathy/ARVC	32
Familial Hypercholesterolemia	16
Hereditary breast and other cancers	24
Hereditary colon cancer (includes MUTYH carriers)	120
Hereditary Paraganglioma	1
Long QT syndrome	8
Malignant Hyperthermia	10
Wilson Disease Carrier	51
	262

- 86% have received or are scheduled to received counseling
- 6% have not scheduled
- 8% have cancelled or declined counseling

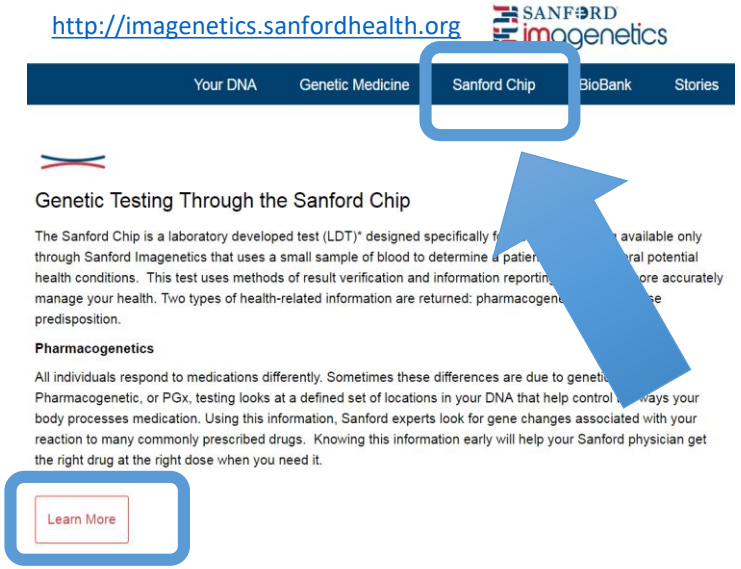
Example educational resources

OneChart Search "Imagenetics:"



Sanford Imagenetics Sharepoint
https://internal.sanfordhealth.org/departments/imagenetics/Pages/default.aspx

http://imagenetics.sanfordhealth.org



Preemptive Genetic Screening: Benefits, Risks, Limitations

Benefits:

- Improved long-term health outcomes
  - Identification of predisposition prior to onset of disease expected to improve outcomes with use of appropriate screening/intervention
- Decreased cost
  - Reduced disease onset = reduced overall health care costs
- Increased patient engagement and compliance

Risk and Barriers:

- Returning results
- Cost
- Ethics
  - Unknown penetrance
  - Lack of long-term outcome data
  - Insurance implications

Clinical and infrastructure impacts

- **Identify affected individuals previously undiagnosed**
  - Advise on management: surveillance, treatment
  - Facilitate cascade testing for at-risk family members
- **Deliver low-cost preemptive pharmacogenetic testing**
  - Minimize adverse drug reactions
  - Reduce time to therapeutic dosing
- **Develop systems required to incorporate genomic data into the medical record**
  - EMR functionality
  - Self-characterization
  - E-consent
  - Clinical decision support
  - Data warehousing
  - Education

Key Lessons

- Provide ongoing genomics education for all clinical staff: providers, nursing, clerical
- Establish clinical resources for follow-up
- Create tools in the EMR to support clinical application of genomic information

QUESTIONS

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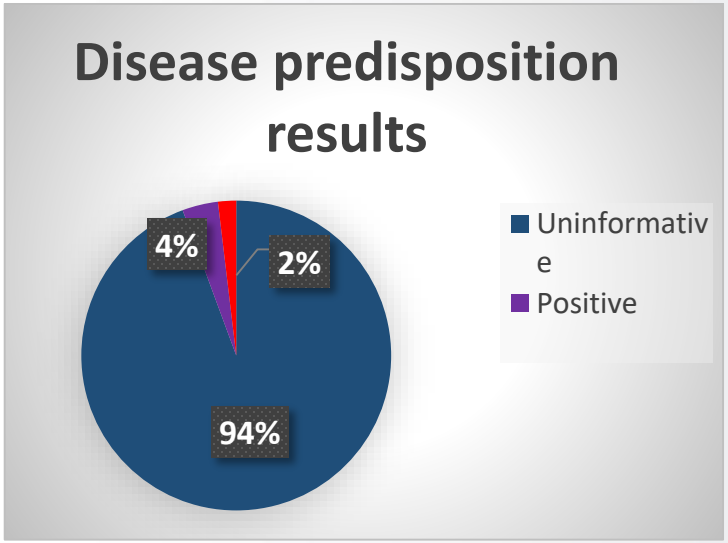
SANFORD CHIP – DISEASE PREDISPOSITION RESULTS



RESULTS REPORTED

(AS OF OCTOBER 24, 2019)

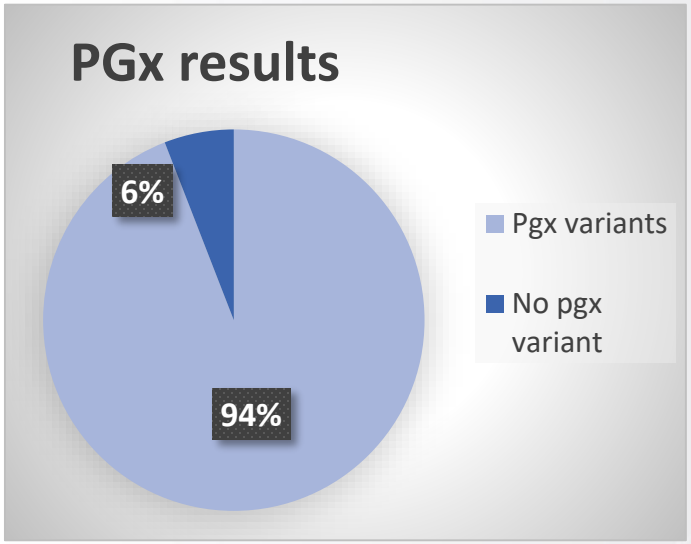
6789 resulted, 262 Positive

PCP offices return uninformative results, genetics returns positive results

Condition	Total Patients	Gene	Patients per gene
Hereditary breast and other cancers	24	BRCA1	11
		BRCA2	11
		TP53	2
Hereditary colon cancer	120	APC I1307K	4
		MUTYH	109
		MSH6	2
		PMS2	5
Hereditary Paraganglioma	1	SDHC	1
Malignant Hyperthermia	10	RYR1	10
Cardiomyopathy/ARVC	32	PKP2(2), DSC2(1),DSP(1)	4
		TNNI3	2
		LMNA (CMT car)	1
		MYBPC3	12
		TNNT2	8
		MYH7	3
		MYL2	1
		GLA Monoallelic	1
Long QT syndrome	8	SCN5A (2),KCNH2 (2)	4
		KCNQ1	4
Wilson Disease Carrier	51	ATP7B	51
Familial hypercholesterolemia	16	APOB	11
		LDLR	5

SANFORD imagenetics

SANFORD CHIP – PHARMACOGENETIC (PGX) RESULTS



Actionable drug gene interactions:

Drug class	Patients per risk condition	Gene	Patients per gene
SSRI antidepressants	441	CYP2D6	73
		CYP2C19	386
Tricyclic antidepressants	75	CYP2D6	19
		CYP2C19	64
Codeine/Tramadol	47	CYP2D6	47
Statins	357	SLCO1B1	357
Plavix*	22	CYP2C19	22

7050 RESULTS REPORTED

PHARMACY PROVIDES A CONSULT NOTE ON EACH PATIENT

*THIS ONLY INCLUDES CHIP RESULTS, NOT TESTS DONE FOR THE CATH LAB

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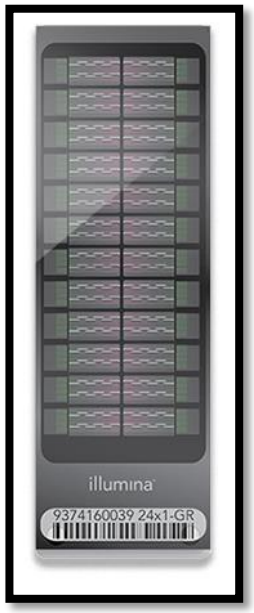
Sanford Chip

Disease Predisposition

Illumina GSA1.0

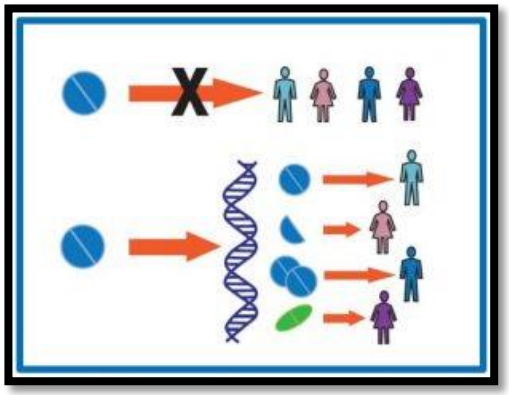
- Pre-designed Genome-wide 650,000 markers
- ~50,000 custom markers



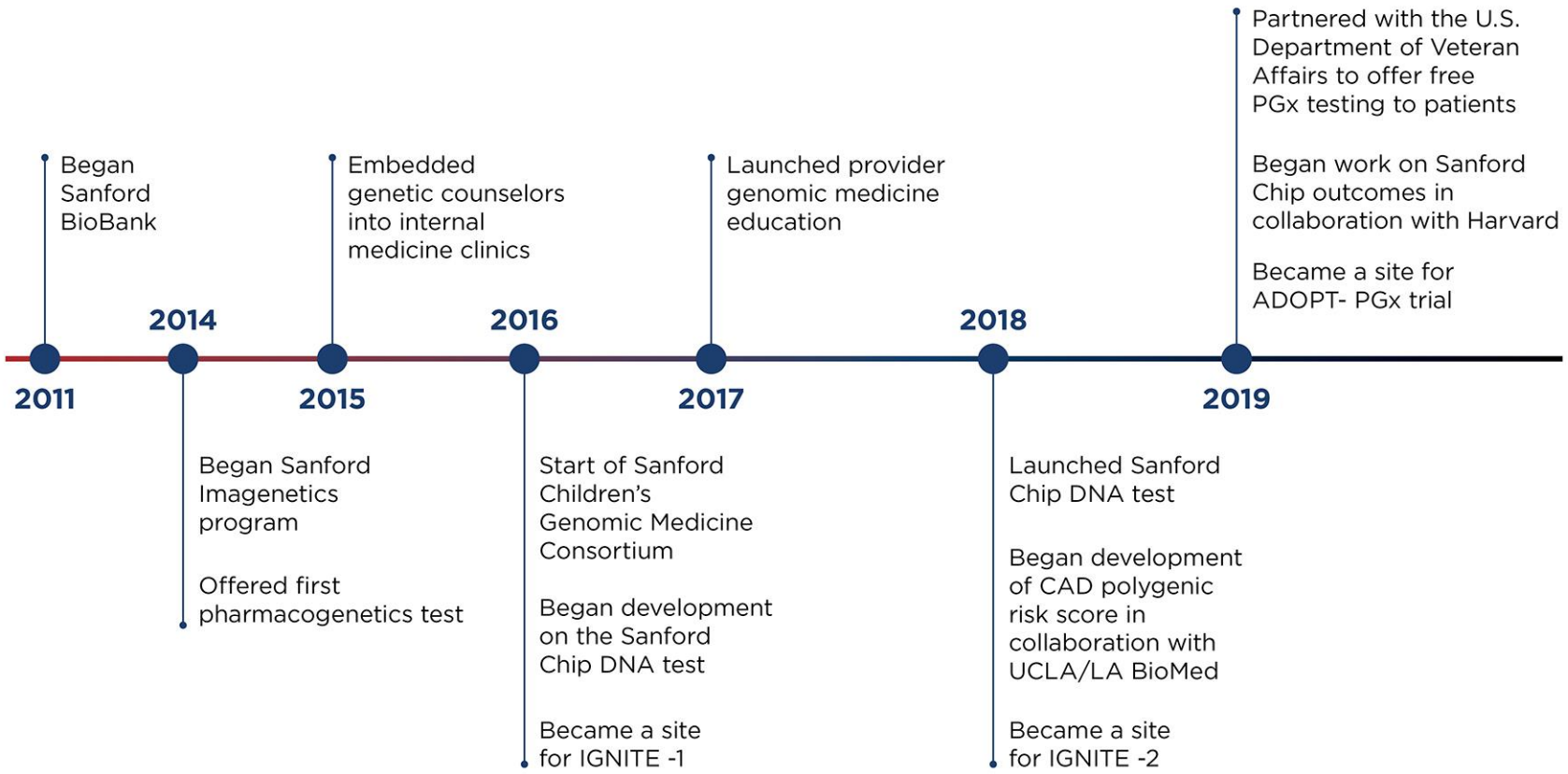
Pharmacogenetics

Currently 8 gene panel

- QuantStudio 12K Flex
- Fluidigm Biomark HD platform



SANFORD IMAGENETICS MILESTONES



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