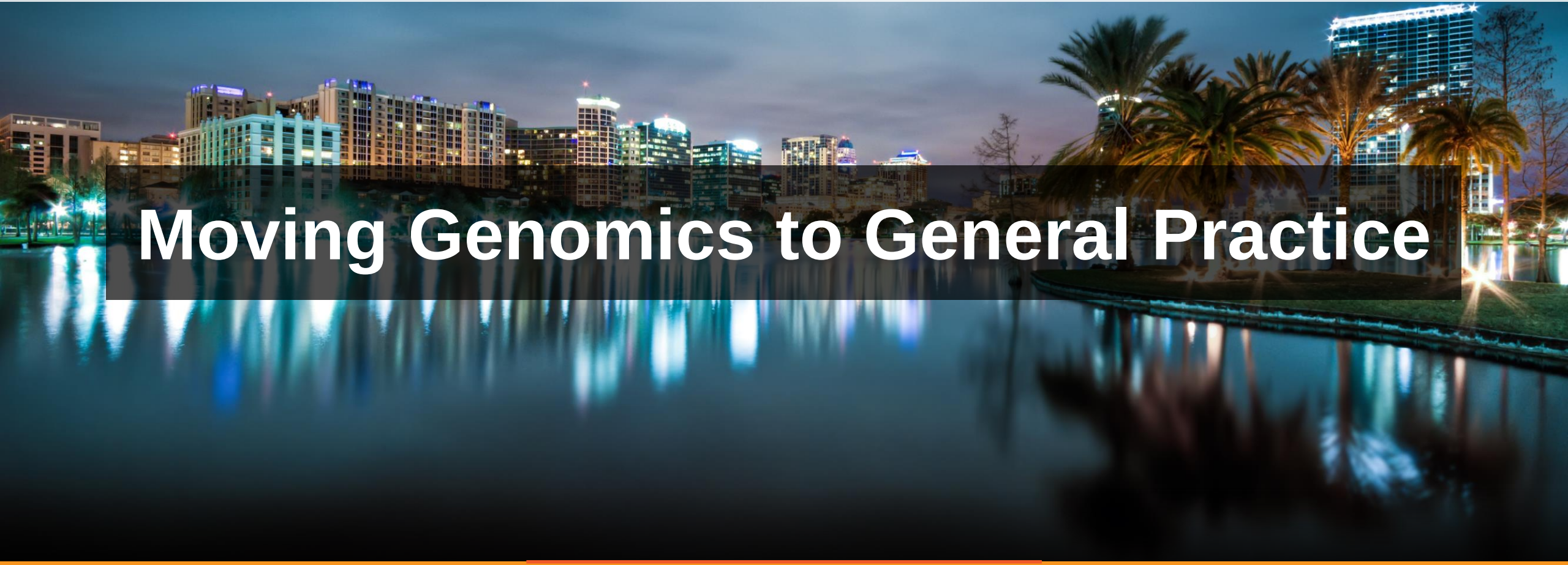
PRECISION MEDICINE SUMMIT

A HIMSS EVENT

FEBRUARY 11, 2019

ORLANDO, FL



Moving Genomics to General Practice

www.HIMSSConference.org | **#PrecisionHIT**

Moving Genomics to General Practice

Nephi Walton MD MS FACMG
Genomic Medicine Institute

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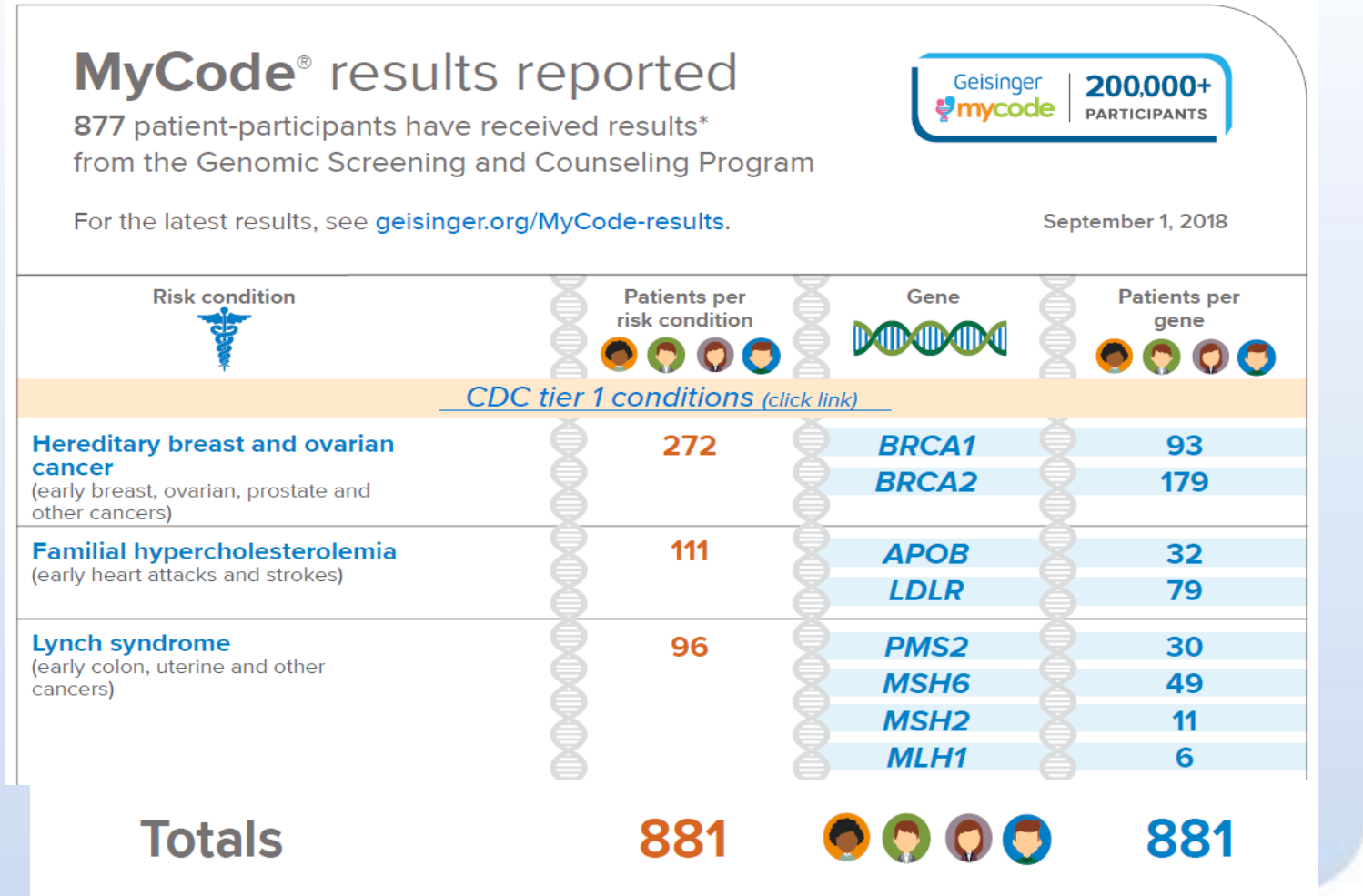
MyCode Return of Results Program

- 200,000+ consented
- 140,000 sequenced
- 1000+ results returned
- Return results for all ACMG reportable conditions



MyCode® results reported

877 patient-participants have received results*
from the Genomic Screening and Counseling Program

Geisinger mycode | 200,000+ PARTICIPANTS

For the latest results, see geisinger.org/MyCode-results.

September 1, 2018

Risk condition	Patients per risk condition	Gene	Patients per gene
CDC tier 1 conditions (click link)			
Hereditary breast and ovarian cancer (early breast, ovarian, prostate and other cancers)	272	*BRCA1*	93
		BRCA2	179
Familial hypercholesterolemia (early heart attacks and strokes)	111	*APOB*	32
		LDLR	79
Lynch syndrome (early colon, uterine and other cancers)	96	*PMS2*	30
		MSH6	49
		MSH2	11
		MLH1	6
Totals	**881**		**881**

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Precision Health Pilot

- Preventative measure
- 1000 patients sequenced as a routine part of clinical care
- Offered through patient's primary care provider
- Return results for all ACMG reportable conditions

Genetics by the Numbers

- 46 Chromosomes
- ~20,0000-23,000 genes
- ~3 billion base pairs in the human genome
- BRCA2 is 83,736 base pairs
- Every time you have child they will incur 100 to 200 new mutations
- Mutation rate increases with the age of the father

Genetic mutations do not usually give you super powers

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What your genes can tell physicians

- What diseases you are likely to develop
- How you will react to medication
- How you will respond to infectious diseases
- How you will behave
- How you will sleep
- What you eat

What is Medical Genetics/Genomic Medicine

- Started in the late 1940s
- Did not require an MD – PhDs were often practitioners
- Dysmorphologists – Syndrome identification
- Familial risk identifiers

We did not even know how many chromosomes we had until 1956

First disease gene mapped in 1983

Pop Quiz! -

In what decade was the following statement printed?

"Of all the applications of medical genetics, the one potentially most valuable is in the field of preventative medicine."

Pop Quiz!

In what decade was the following statement printed?

"Of all the applications of medical genetics, the one potentially most valuable is in the field of preventative medicine."

Answer: 1946

The Role of a Clinical Geneticist

- Diagnosis
- Management
- Prevention
- Risk Assessment
- Counseling

Challenges in Clinical Genetics

- More than 6000 known genetic disorders
- Nationwide shortage of clinical geneticists
- Getting more referrals from specialists
- Shortage of genetic counselors

Challenges in Clinical Genetics

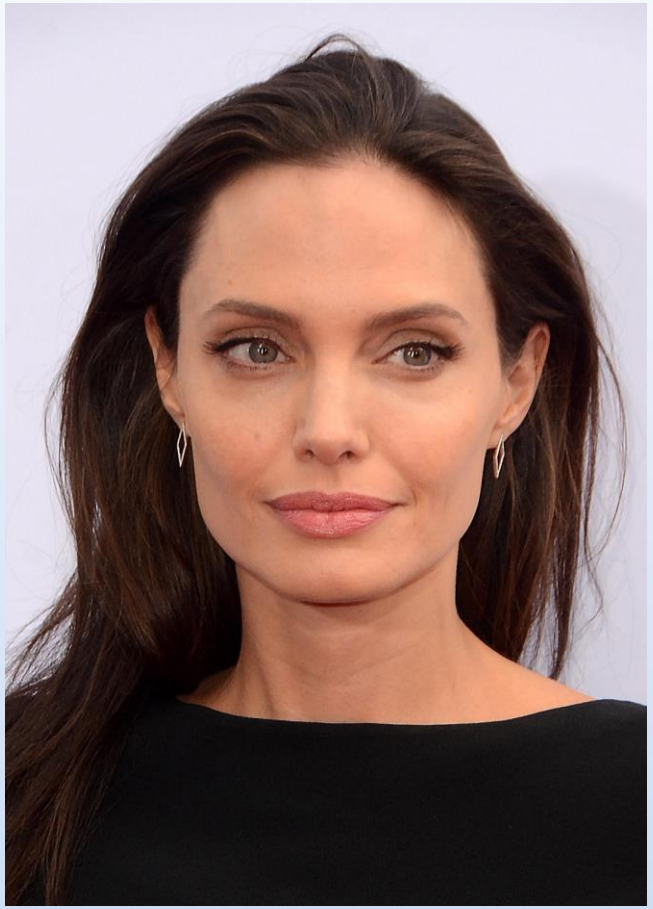
- Healthy people getting direct to consumer tests
  - – MTHFR challenge
- Poor reimbursement for testing and services
- Uncertainty in classification of variants and diagnosis
- Poor access to data that is crucial in our field
- Up to one year wait times to see a geneticist

Physicians outside of clinical genetics are not prepared to understand, deliver or manage genetic test results

Systems that allow physicians access to quick and accurate knowledge about genetic conditions are the only way to solve this information overload

No one can acquire and maintain the knowledge to diagnose and manage over 10,000 diseases.

Genomic medicine will move from a specialty which did not even require an MD degree to become an integral part of practice that is required of everyone with an MD degree



Found to have a pathogenic variant in BRCA1

Elected to have a bilateral mastectomy

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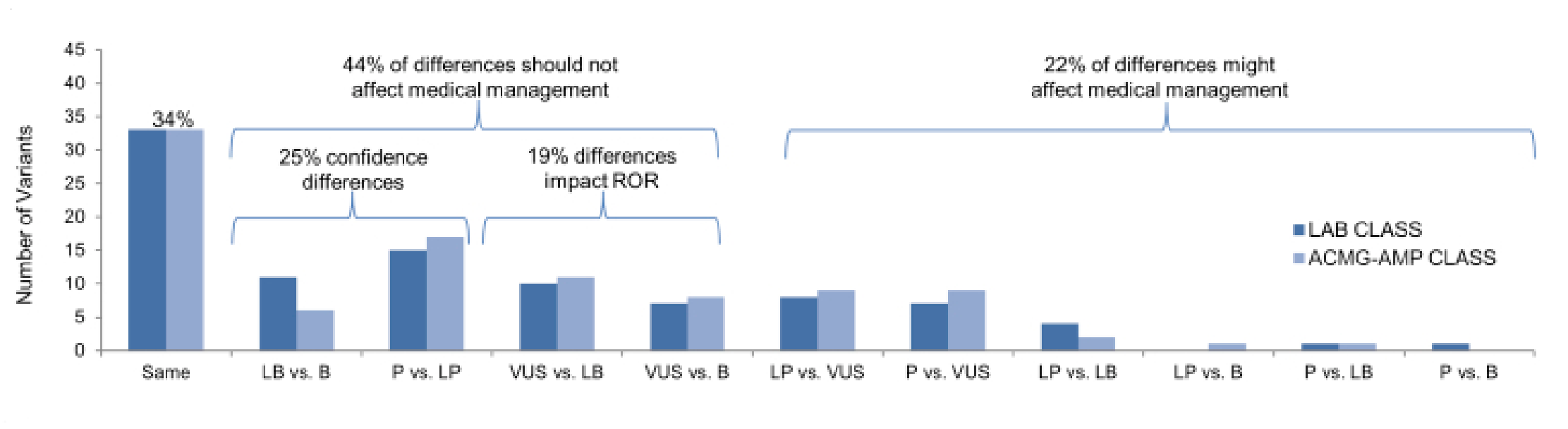
Discrepancies in Variant Classification Between 9 Laboratories



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Amendola, Laura M. et al. “Performance of ACMG-AMP Variant-Interpretation Guidelines among Nine Laboratories in the Clinical Sequencing Exploratory Research Consortium.” *American Journal of Human Genetics* 98.6 (2016): 1067–1076. *PMC*. Web. 8 June 2017.

Concordance of Variant Classification for BRCA1 and BRCA2

Table 1. Concordance between variant classifications from the reference laboratory and all database entries, as well as database entries from contributing commercial laboratories

Concordance	ClinVar	GeneDx	Invitae	Ambry
Concordant—identical classification	73.2%	81.5%	85.4%	80.7%
Partially concordant—multiple classifications with ≥1 concordant	12.3%	—	—	—
Discordant—opposite classification	0.1%	0.1%	0%	0.1%
Discordant—RL uncertain classification	0.3%	0.7%	0.7%	1.2%
Discordant—DB uncertain classification	14.0%	17.7%	13.8%	18.1%
Proportion of VUSs with a definitive RL classification	—	42.5% (322/757)	63.2% (151/239)	56.9% (58/102)

Abbreviations: —, not applicable; DB, database; RL, reference laboratory; VUS, variant of uncertain significance.

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Gradishar William.et al. “Clinical Variant Classification: A Comparison of Public Databases and a Commercial Testing Laboratory.” *Oncologist. 2017 Apr 13. pii: theoncologist.2016-0431.* .

BRCA1 and BRCA2 are two of the most well studied genes in the Human Genome…

AND WERE EVEN SCREWING THOSE UP!

Also Keep in mind the people classifying these variants are the "experts" not general practice physicians

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Elisha Cooke-Moore vs Curry County Health

Elisha Cooke-Moore vs
Curry County Health

Bilateral mastectomy and hysterectomy based on Incorrect interpretation of a genetic testing report by clinician

1.8 Million dollar lawsuit

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FGFR3 Mutation - Achondroplasia

The discordance in variant classification we have now is primarily based on testing done on people with disease

When you start testing healthy people it's a completely different ball game!

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Exome Sequencing

Now a common clinical test

Reports on the expressed portion of the human genome

Generates data on all your expressed genes

Resulting data is 6-8 Gigabytes of crucial health information

What does the physician get?

PDF

Genomic Data Life Cycle

Sequencing is performed on one individual

Exome generates 6 to 8 GB of data

Whole genome generates 100 to 200 GB of data

Data is processed to produce a list of candidate genes changes

Further refined to a list of reportable variants put into a PDF

So what happens to the other 6GB to 200GB of data?

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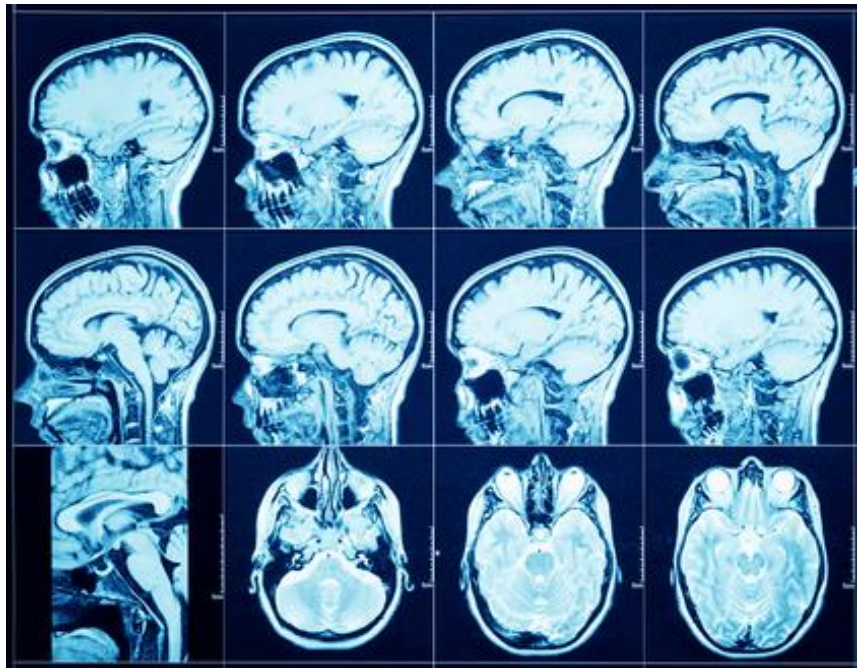
MRI Analogy



VS

PACS System for Genomics

Data is too large for EHR data structures

Different kind of data requires a specialized viewer

Frequently changes – new data added

Requires specialist interpretation

May be useful for any physician to view especially at point of care

Integration of genomic data into the EMR for patient management and decision support is crucial to enabling general practice physicians to practice genomic medicine

Summary of Challenges

- No way to store genetic data
- Clinical Genetics workforce will not scale to handle sequencing everyone
- No way to utilize genetic data in a clinical workflow
- Clinicians outside genomics not equipped to manage genetic testing results

Genetic Data – What to Store

1. Discrete Variants with Known Health Related Effects
    1. Point Mutations, Indels
    2. Copy Number Variants
2. Filtered Data
    1. VCF
3. Raw Data
    1. BAM, FastQ

Genetic Data – Where to Store

1. In EHR
2. In External Database linked to EHR

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Discrete Variants

Currently reported as in a PDF

Workarounds include creating lab values that store variants

Only in past year has ability to store discrete variants been available

Getting Genetic Variants into the EHR

Epic has recently implemented “Genomic Indicators”
Will allow for clinical decision support around genomic variants
Gives genomics a home in the EHR – finally a place to put the data

Consortium for Agile Genomics – Getting Data From The Lab

HOLD UP!!!!

PDF from the lab ok to put into the system automatically

Discrete variant information as a genomic indicator – NOT OK

Why?

Bad Things Can and DO Happen

Case

- Patient in her 20s evaluated for connective tissue disease
- Clinically evaluated as hypermobile EDS
- Aortopathy panel sent
- VUS in gene for Loeys Dietz
- Cardiac MRI normal

Case – continued

- Patient seen by Ob/Gyn provider
  - Provider sees genetic test
  - Assigns diagnosis of Loeys Dietz in Epic
  - Patient instructed that she MUST have a C-section
  - Schedules monthly echocardiogram
- Patient calls genetics department

Providing too much information or too little…

Providing information that could be used the wrong way potentially exposes the patient to unnecessary and potentially harmful action.

Hiding potentially useful information prevents patient from receiving the appropriate action.

Where is the balance?

If malpractice is any indication…

Only a handful of cases regarding taking action because of wrong interpretation.

Versus….

57% of all genomic medical malpractice cases could have been avoided if genetic testing had been performed

Pharmacogenomics

New clinical exome laboratory offers PGx variants as option to patient.

General response - Yay!

My response – Uh Oh!

Multiple patients with pharmacogenomic results

- Who counsels the patient
- Is there a liability associated with not acting on results
- How do physicians find the report?

The rest of the DATA!

Which data is used?

- Raw Data
- Filtered Data
- Annotated Data
- Copy number call from exome/genome

Storing – “The rest of the data”

No place to store VCF files

No place to store discrete phenotypic information

A Genotype- Phenotype Archiving and Communication System (GPACS)

NIH SBIR grant in partnership with PhenoSolve (SimulConsult)

Grant Number NIH 1R43HG010322-01, PI: Segal, MM

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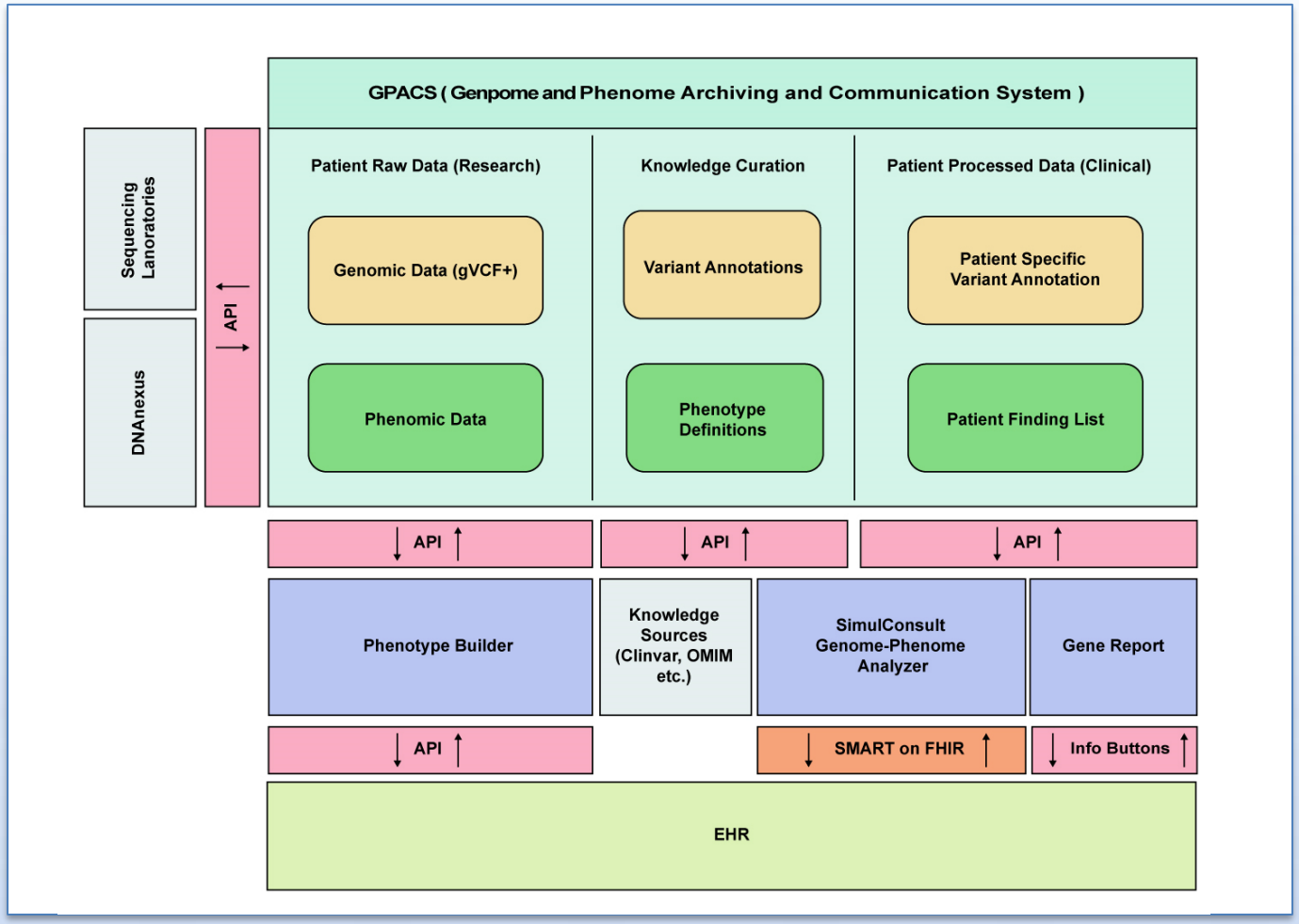
GPACS



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Phenotype Builder

Extracts phenotypic elements from free text and ICD10 codes

Builds phenotypic profile of HPO terms

Stores HPO terms in GPACS

We Have Genetic Data in the EHR – Now What?

Make sure genetic data is used accurately/effectively

- Diagnosis
- Clinical Decision Support
- Information Delivery to Providers
- Information Delivery to Patients
- Take Actions

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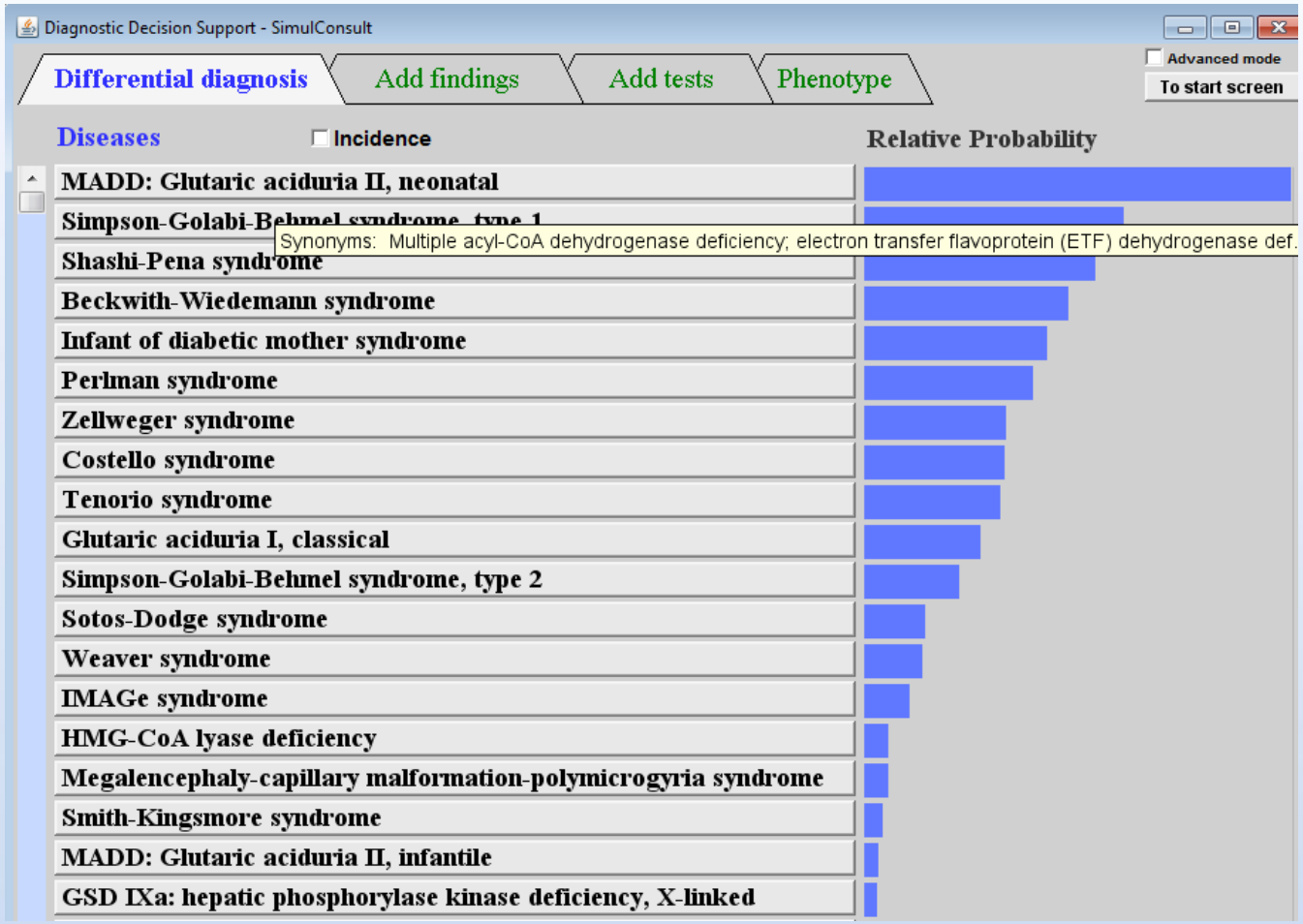
Use of Genomic Information in Clinic - Simulconsult



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eMERGE PGx

Clinical Decision Support built for

- CYP2C19 and Clopidogrel
- SLCO1B1 and Simvastatin

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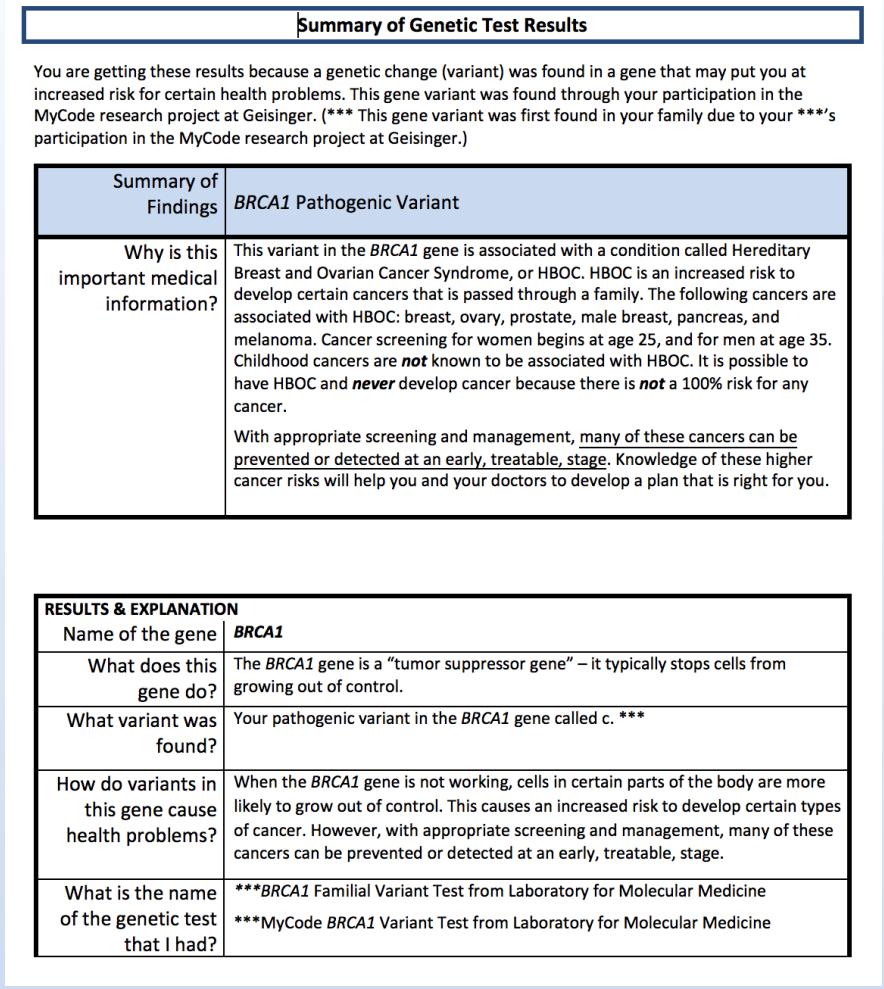
Delivering Information to Patients and Providers

- Working with Epic to implement this with genomic indicators
- Infobutton will reside next to the genomic indicator
- Provides information related to gene or variant

Compass/Gene Report

- HL7 compliant web service
- Activated through InfoButtons or direct web-link
- Delivers different information based on user - patient vs provider
- Delivers information specific to variant, sex, and age



Summary of Genetic Test Results

You are getting these results because a genetic change (variant) was found in a gene that may put you at increased risk for certain health problems. This gene variant was found through your participation in the MyCode research project at Geisinger. (*** This gene variant was first found in your family due to your ***'s participation in the MyCode research project at Geisinger.)

Summary of Findings	*BRCA1* Pathogenic Variant
Why is this important medical information?	This variant in the *BRCA1* gene is associated with a condition called Hereditary Breast and Ovarian Cancer Syndrome, or HBOC. HBOC is an increased risk to develop certain cancers that is passed through a family. The following cancers are associated with HBOC: breast, ovary, prostate, male breast, pancreas, and melanoma. Cancer screening for women begins at age 25, and for men at age 35. Childhood cancers are ***not*** known to be associated with HBOC. It is possible to have HBOC and ***never*** develop cancer because there is ***not*** a 100% risk for any cancer. With appropriate screening and management, many of these cancers can be prevented or detected at an early, treatable, stage. Knowledge of these higher cancer risks will help you and your doctors to develop a plan that is right for you.

RESULTS & EXPLANATION	
Name of the gene	***BRCA1***
What does this gene do?	The *BRCA1* gene is a "tumor suppressor gene" – it typically stops cells from growing out of control.
What variant was found?	Your pathogenic variant in the *BRCA1* gene called c. ***
How do variants in this gene cause health problems?	When the *BRCA1* gene is not working, cells in certain parts of the body are more likely to grow out of control. This causes an increased risk to develop certain types of cancer. However, with appropriate screening and management, many of these cancers can be prevented or detected at an early, treatable, stage.
What is the name of the genetic test that I had?	****BRCA1* Familial Variant Test from Laboratory for Molecular Medicine ***MyCode *BRCA1* Variant Test from Laboratory for Molecular Medicine

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Implementation of Chatbots

Partnership with Clear Genetics

Use Chatbots for:

- Consenting patients
- Following up on test results
- Patient questions
- Cascade testing

Clear Genetics

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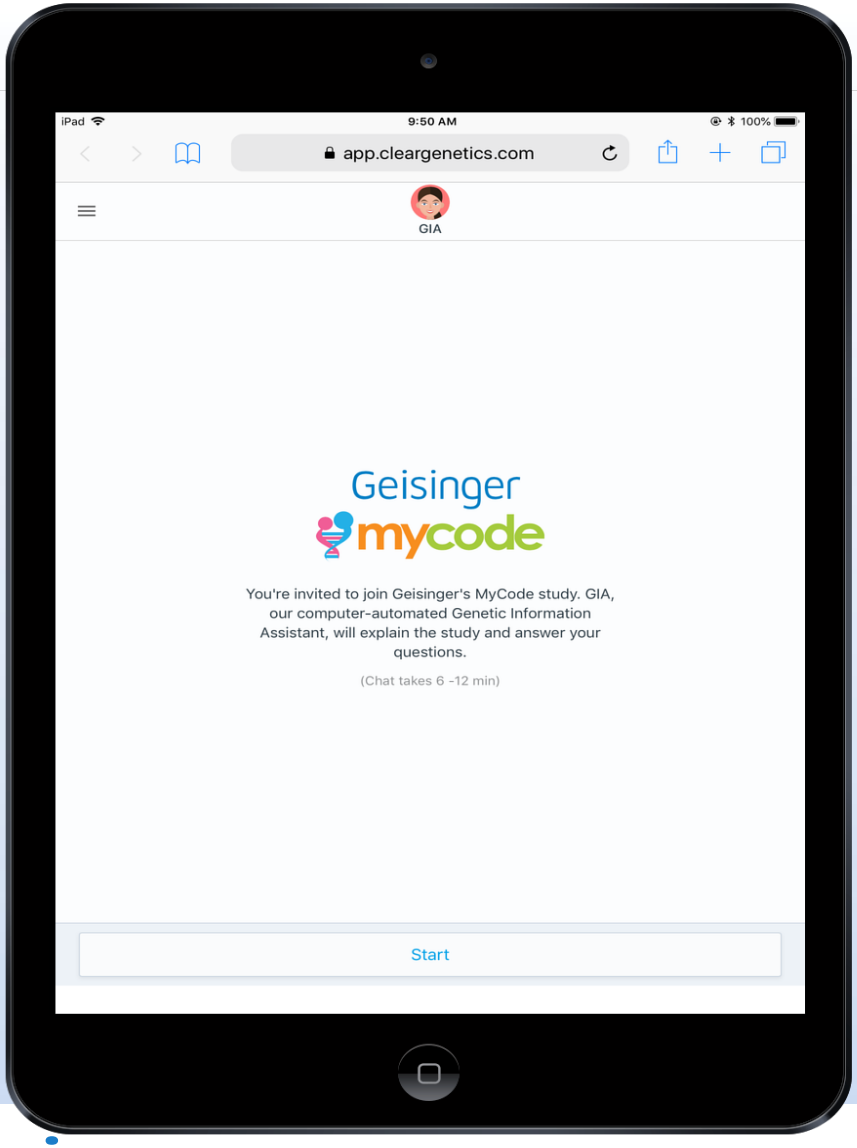
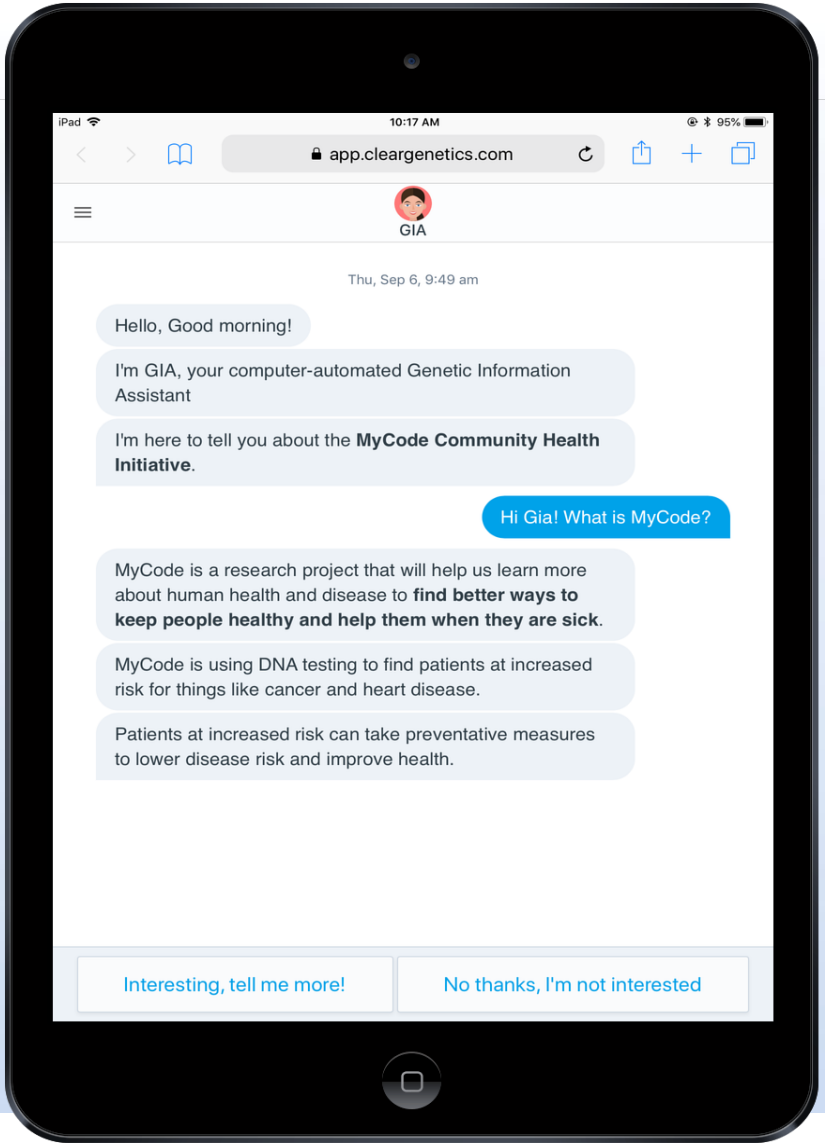
•Chatbot work by Amy Sturm and Tara Schmidlen

Consent Chatbot





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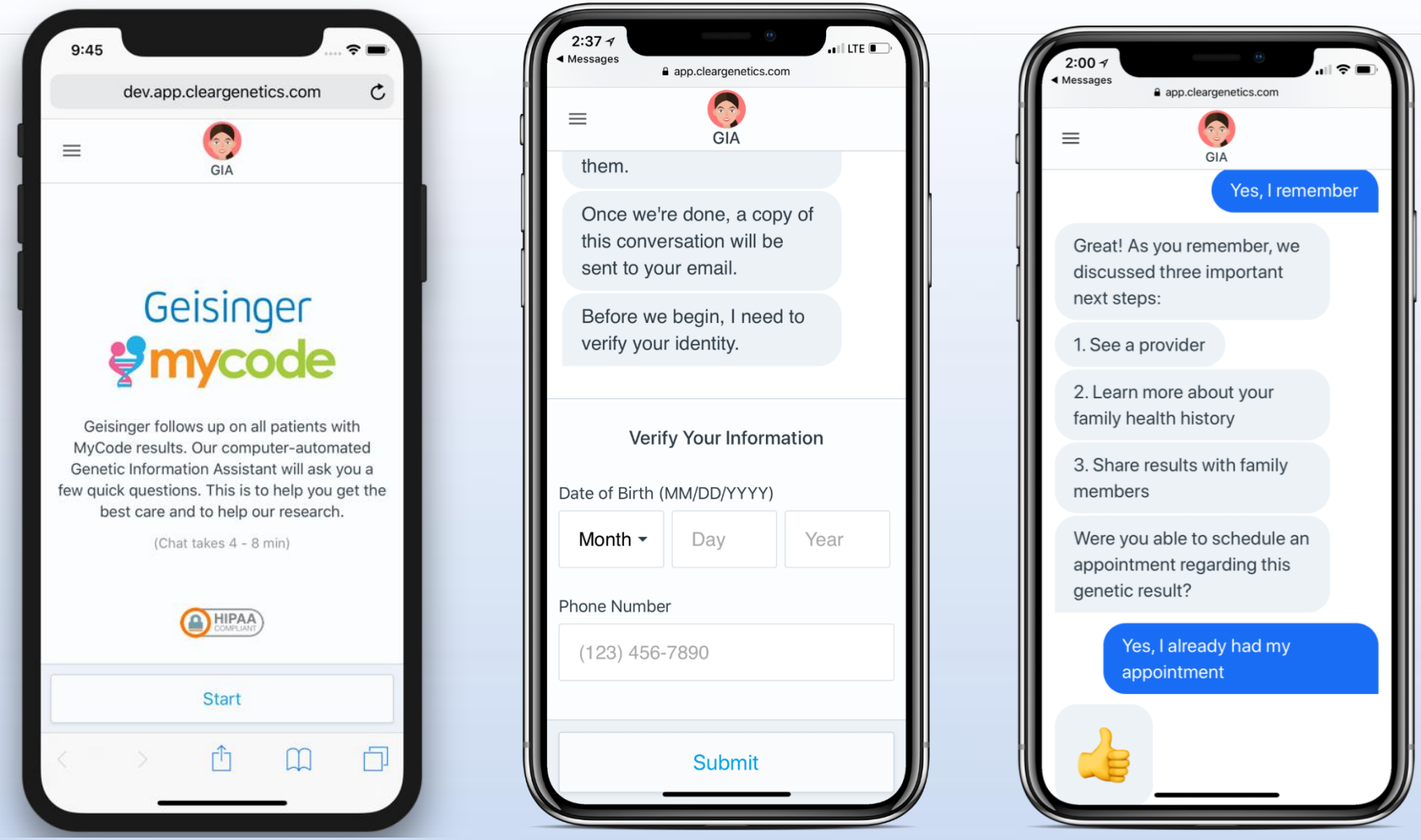
Patient Follow-Up Chatbot



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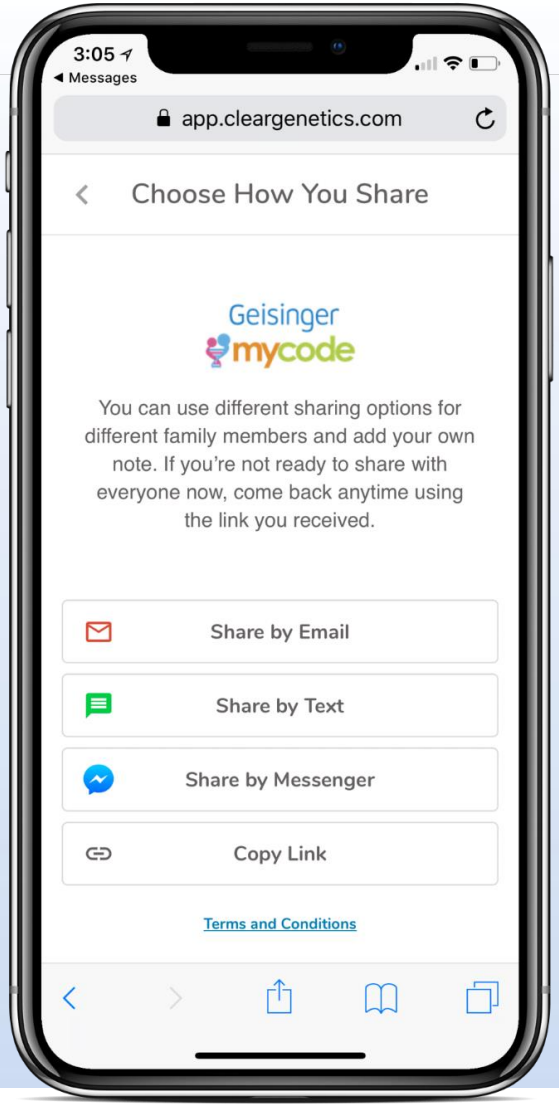
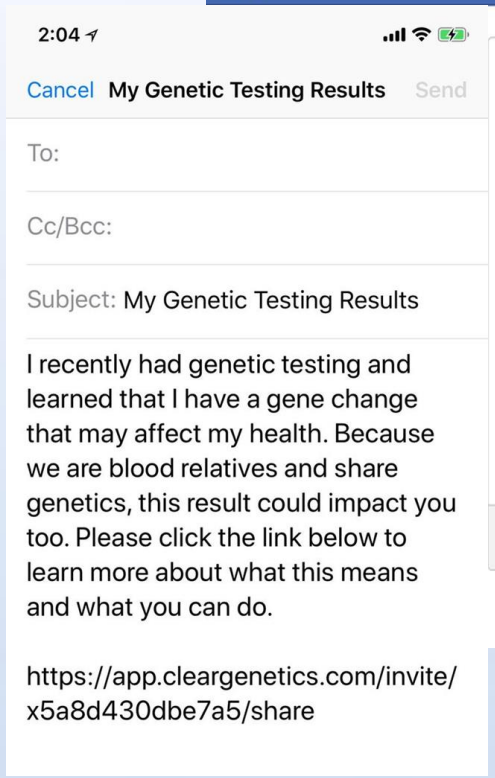
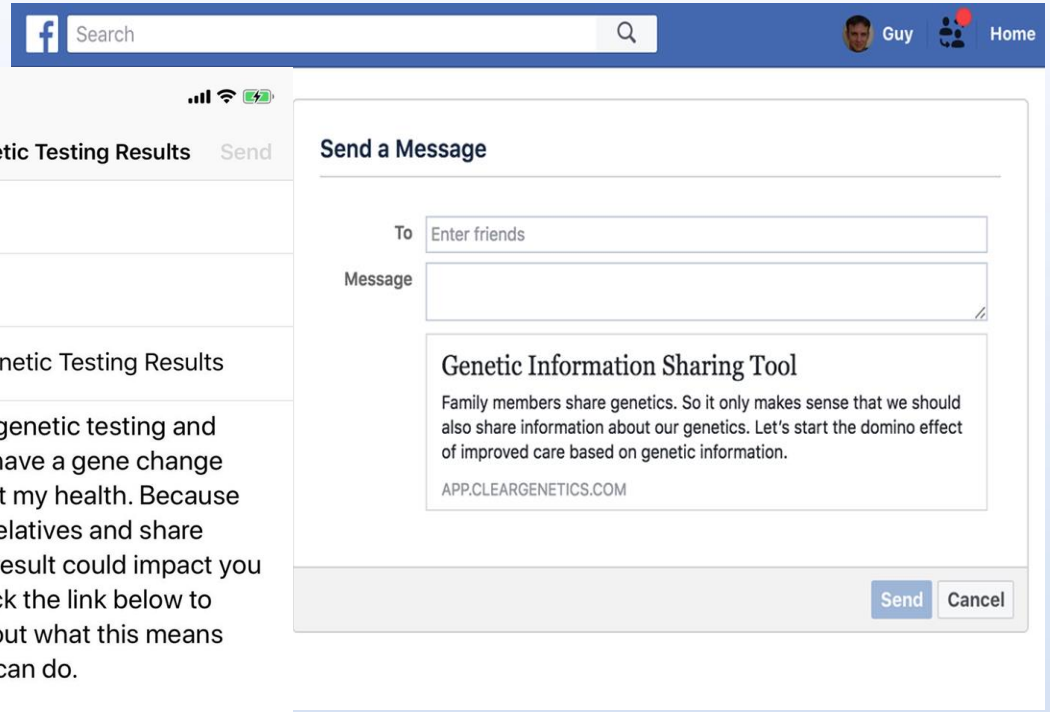
Family Sharing Tool







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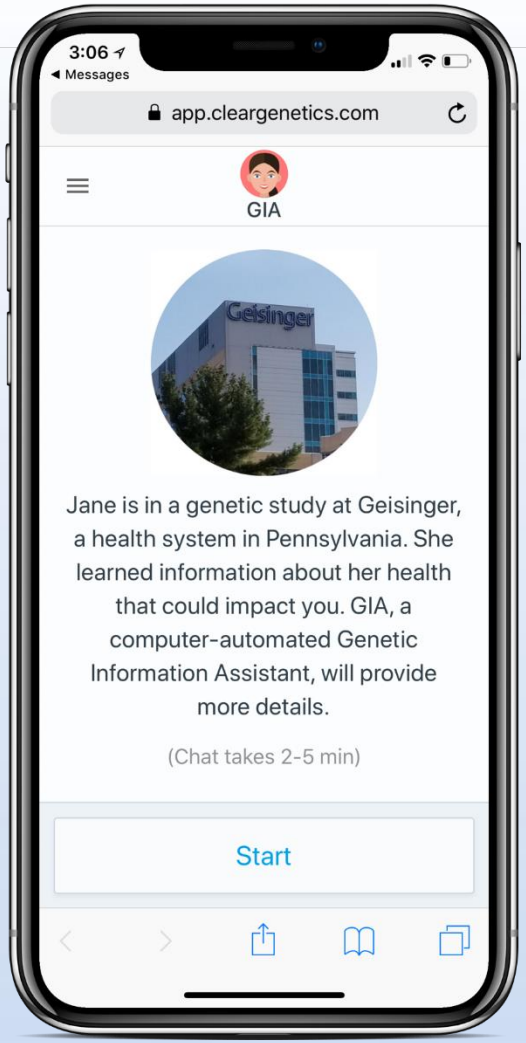
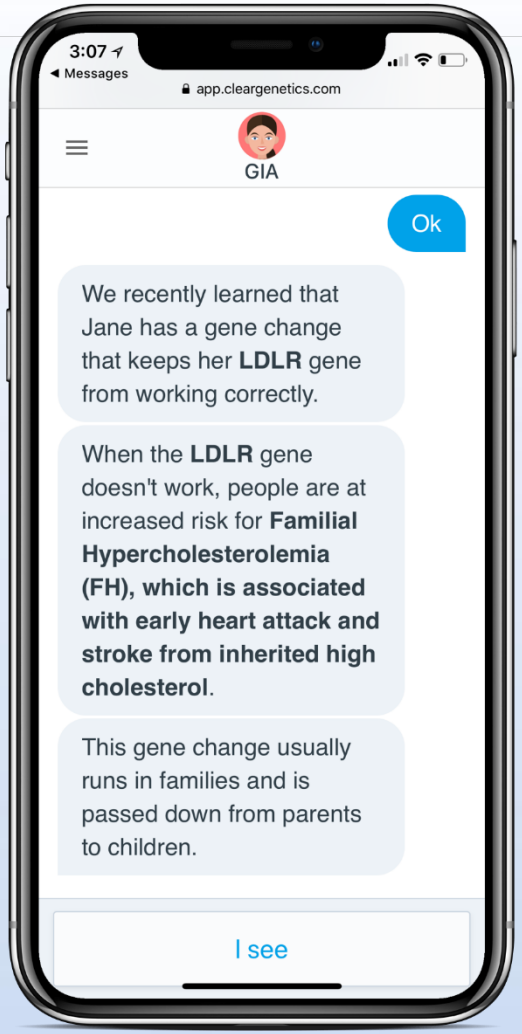
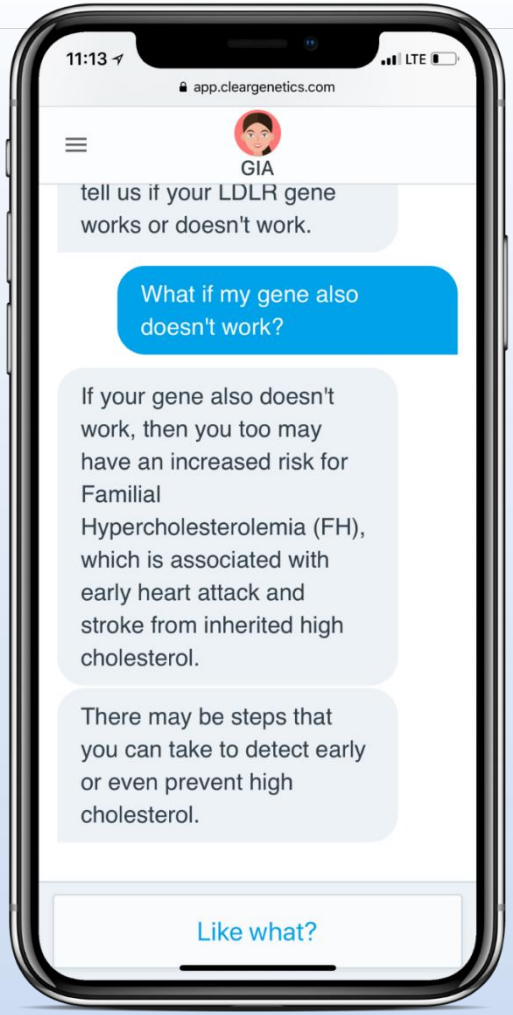
Cascade Chatbot







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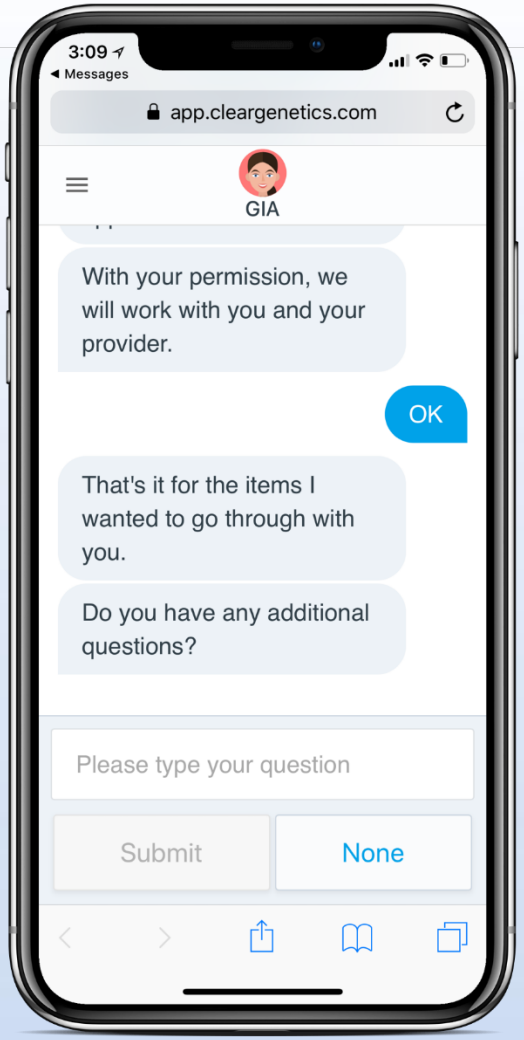
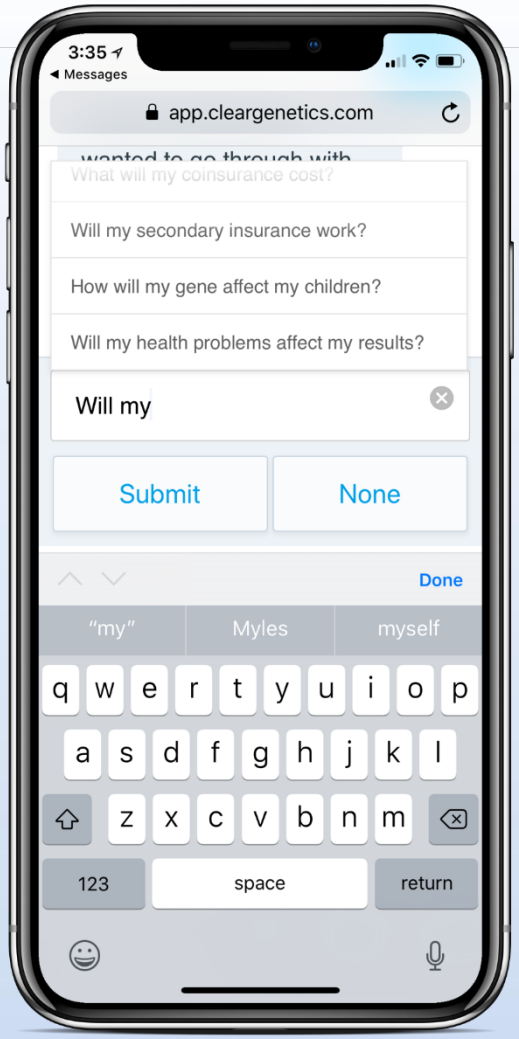
Smart FAQ





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What's Next?

- How do we integrate all genomic information into the workflow?
- Which variants do we include and who decides?
- When working outside an "expert" whose consensus guidelines are used?
- How can we effectively use information in real-time to impact patient care?

Acknowledgements

Geisinger
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- Grant Wood

QUESTIONS?