National Human Genome Research Institute

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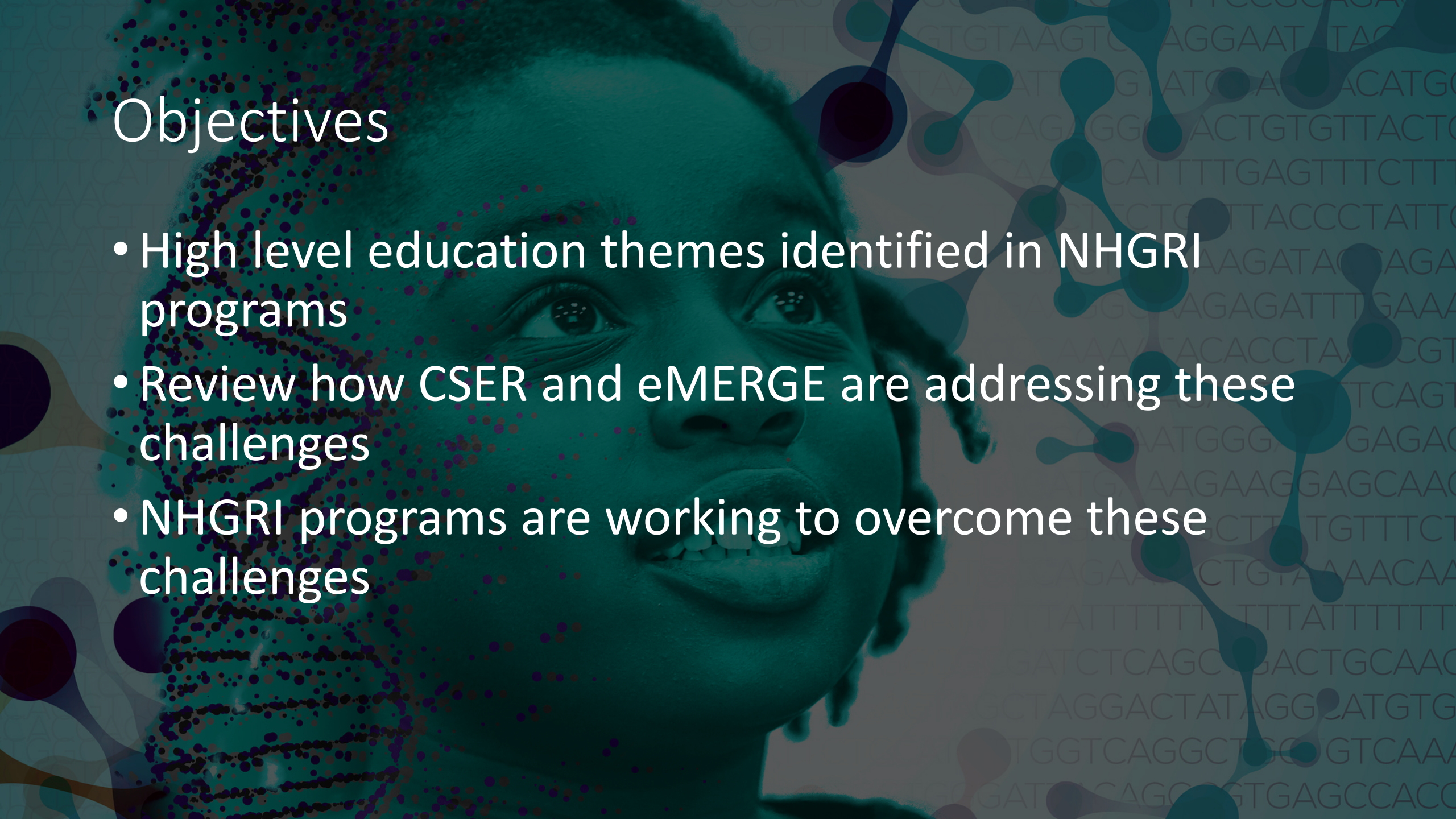
Clinical Sequencing Evidence-Generating Research

emerge network
ELECTRONIC MEDICAL RECORDS AND GENOMICS

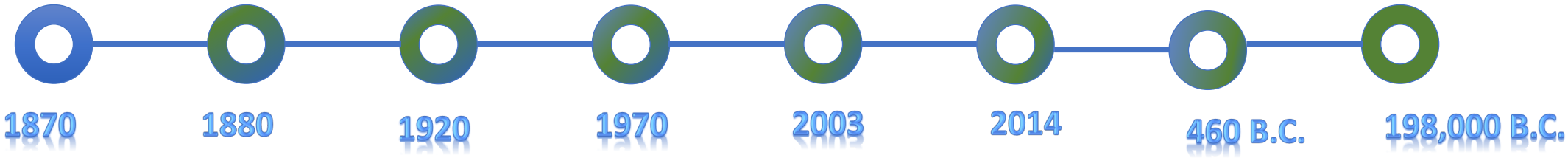
ISCC In-Person Meeting: CSER/eMERGE

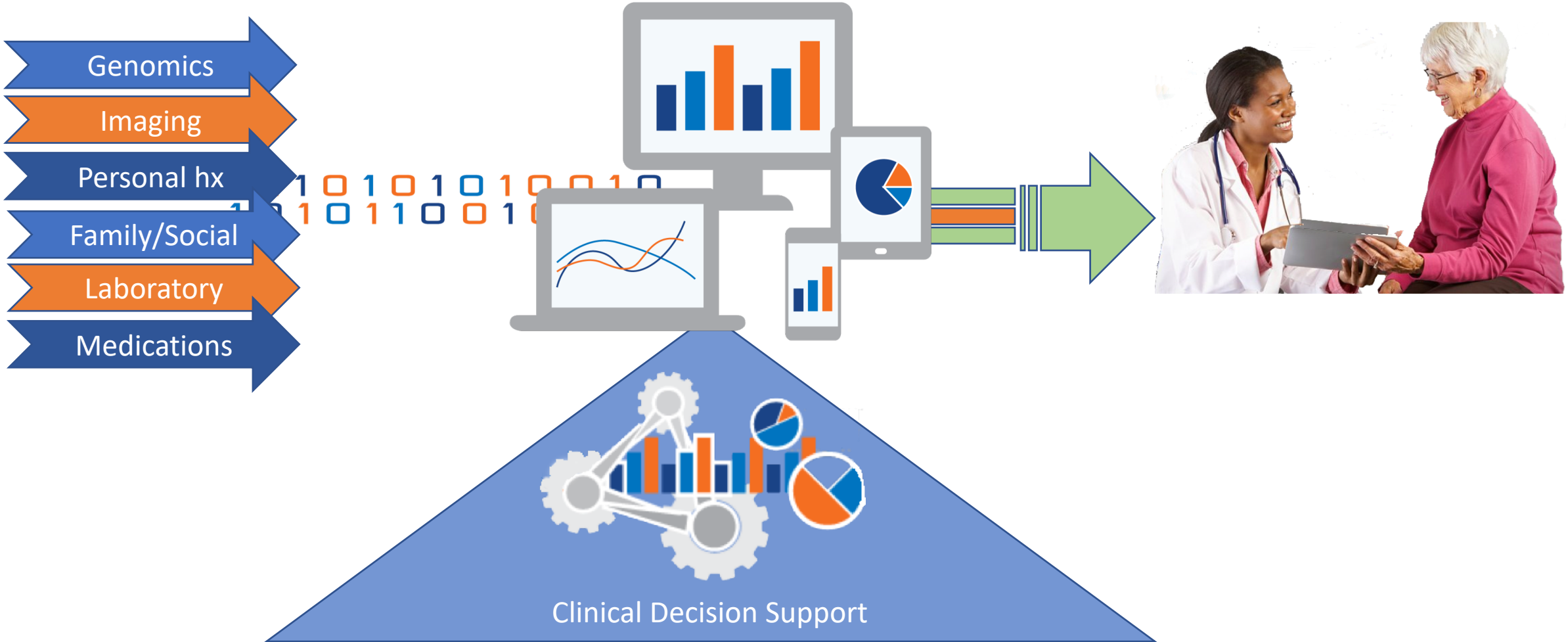
Overcoming the Challenges of Volume and Rate of Change

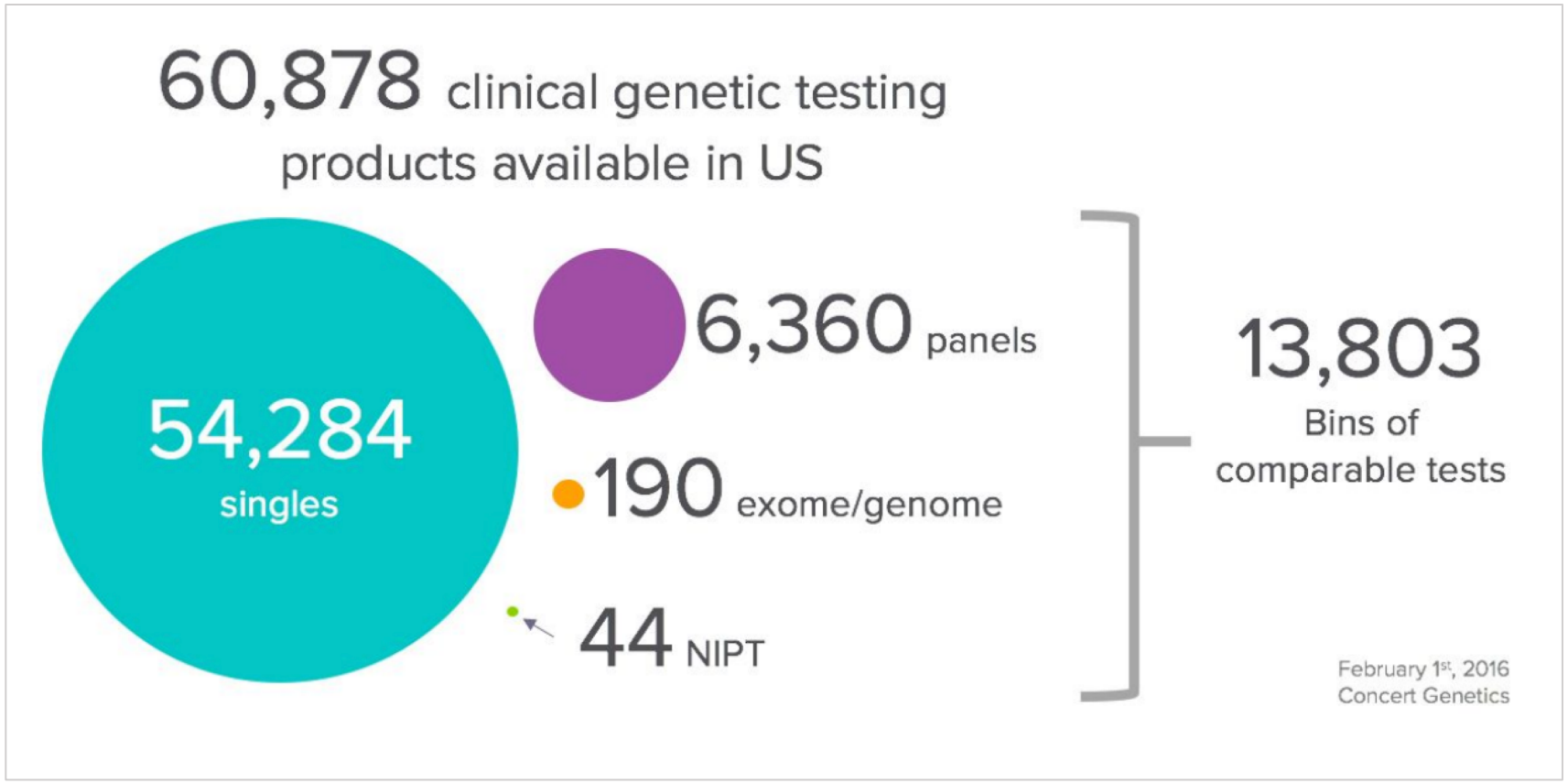


Objectives

- High level education themes identified in NHGRI programs
- Review how CSER and eMERGE are addressing these challenges
- NHGRI programs are working to overcome these challenges


1870
1880
1920
1970
2003
2014
460 B.C.
198,000 B.C.


Genomics
Imaging
Personal hx
Family/Social
Laboratory
Medications
Clinical Decision Support



On average, 10 new products enter the market each day

Source: Concert Genetics (2016). The Current Landscape of Genetic Testing. Downloaded from https://www.concertgenetics.com/resources/current-landscape-of-genetic-testing/

Source: Kelly M. East, MS, CGC Certified Genetic Counselor Clinical Applications Lead HudsonAlpha Institute for Biotechnology, Huntsville, AL

Genomics Changing the Paradigm?

- Is there a difference between genetics and other medical test?
  - Volume and complexity exist in all fields i.e. pacemaker reports, ACMG 59 has 23,000 pathogenic variants
- Unique Genomic medicine challenges
  - Understanding impacts beyond the patient
  - Genomics is fragmenting diagnosis
  - Results of test will change with time. This is not new, but updates now affect the entire family. Unique changes include variant reclassification, somatic variation...
  - Complexity, in volume and intricacy, of genomic risk
  - New issues
    - Psychology impact of results (survivors guilt)– Did I cause this? Pre-vivors? Is this heightened in genetics?

Educational Spectrum

- Physicians – what specialty
- Genetic counselors
- PA/Nurse practitioners
- Nurses
- Medical Assistance
- Administrative assistants
- Pharmacist
- Radiologist

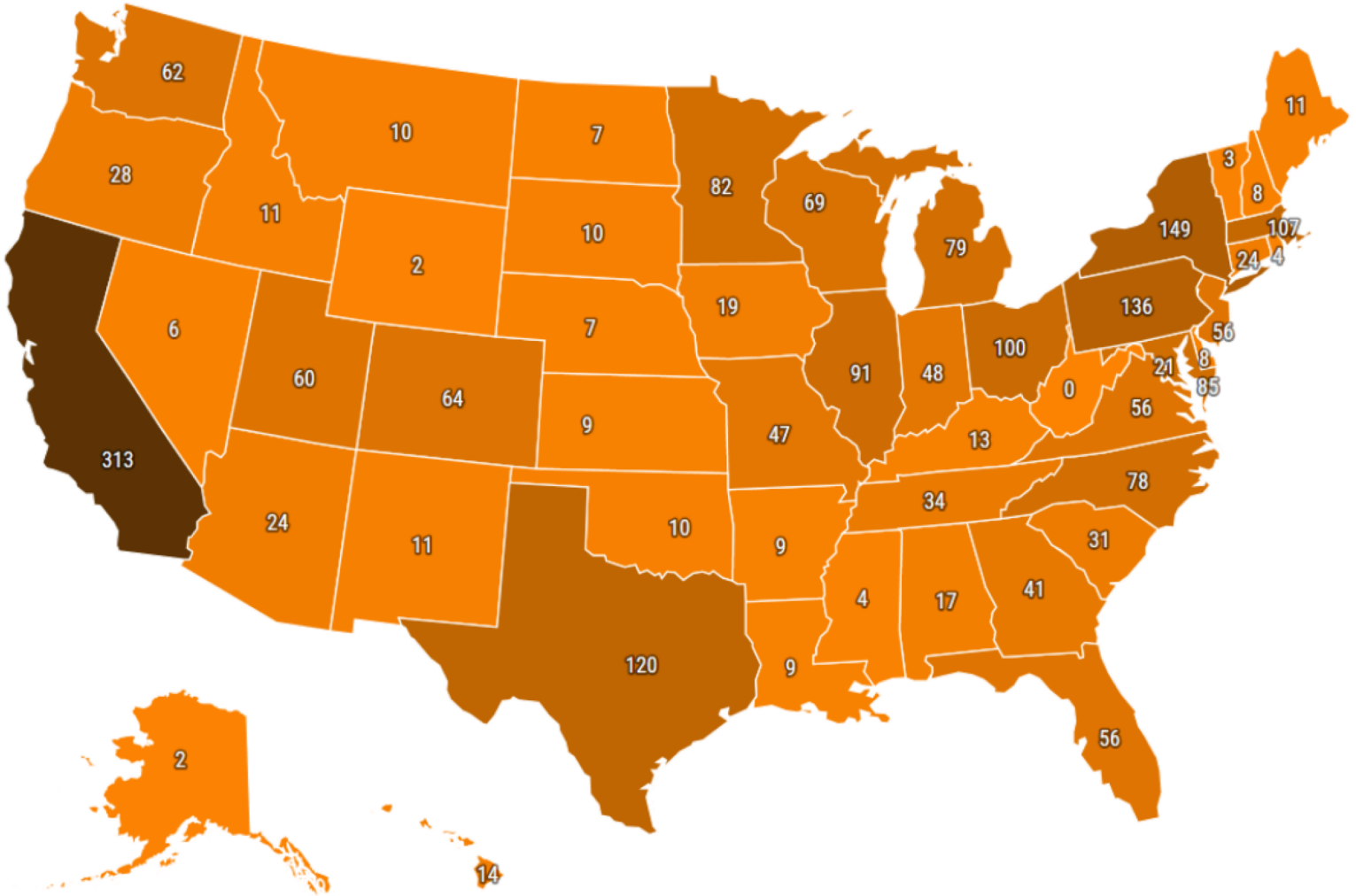
- Pathologist
- Social workers
- Case managers
- Paramedics
- New groups
  - Genetic resource specialist – discussed at CSER
  - Health care interpretation services

Genomic Medicine Affects All Aspects of Medicine

Over half of responding US genetic counselors (52%) work in ten states

60% work in metro areas

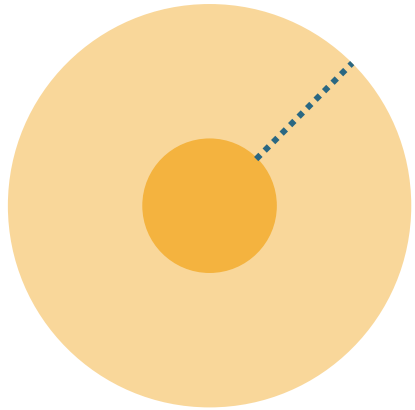
Figure 2. PSS Respondents: United States



Source: NSGC Professional Status Survey 2018: Demographics & Methodology
Source: Kelly M. East, MS, CGC Certified Genetic Counselor Clinical Applications Lead HudsonAlpha Institute for Biotechnology, Huntsville, AL

1. Make more genetics providers…

Patients who need genetics services



Medical Geneticists and Genetic Counselors

Source: Kelly M. East, MS, CGC Certified Genetic Counselor Clinical Applications Lead
HudsonAlpha Institute for Biotechnology, Huntsville, AL

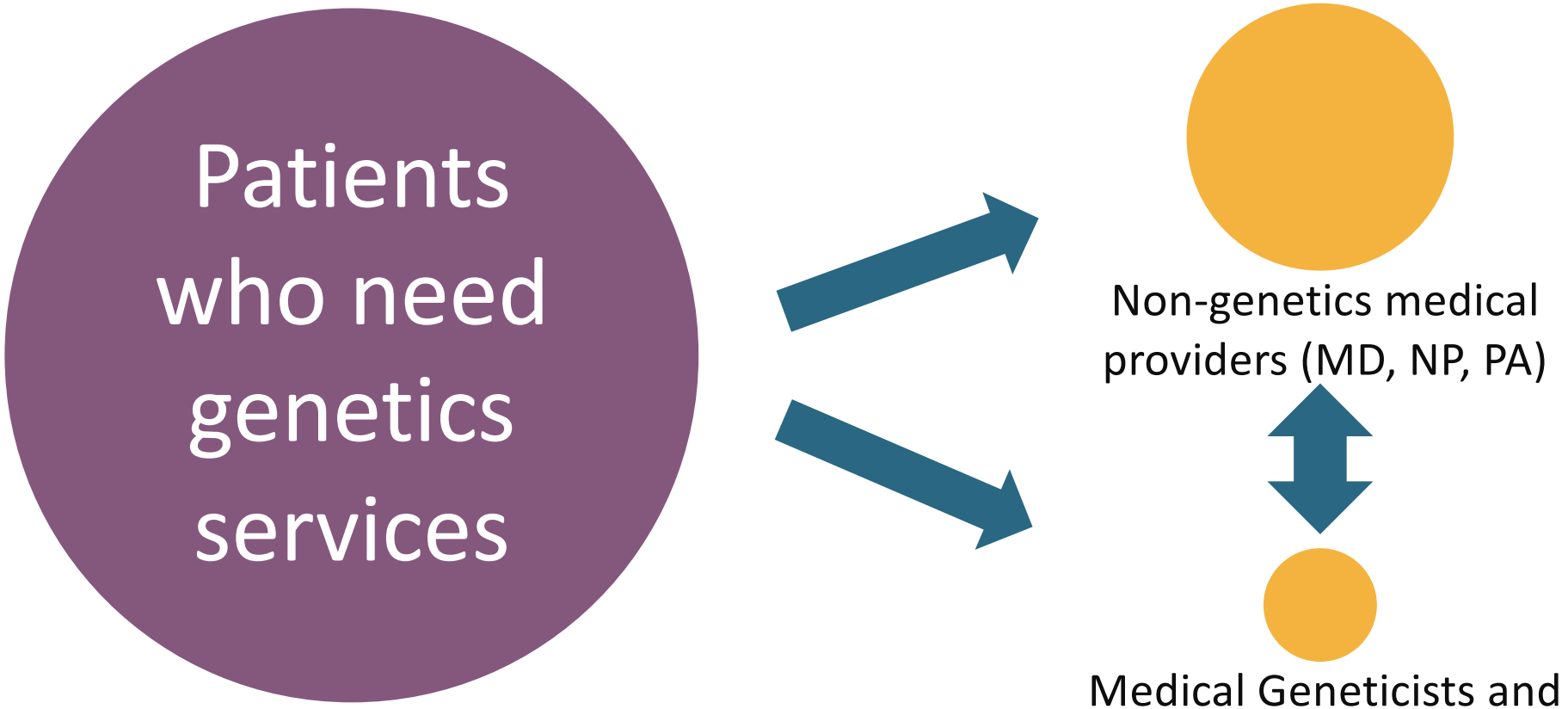
2. Increase capacity of existing genetics providers…

Patients who need genetics services

Medical Geneticists and Genetic Counselors

Source: Kelly M. East, MS, CGC Certified Genetic Counselor Clinical Applications Lead HudsonAlpha Institute for Biotechnology, Huntsville, AL

3. Train other healthcare providers to do genetics…



Source: Kelly M. East, MS, CGC Certified Genetic Counselor Clinical Applications Lead HudsonAlpha Institute for Biotechnology, Huntsville, AL

Defining necessary knowledge and skills

- ISCC Framework for development of genomics practice competencies
- Specific competencies vary depending on practice setting
- Five “entrustable professional activities” that together constitute the mass of elements that define a profession.

Source: Korf, BR, et al. 2014. Framework for development of physician competencies in genomic medicine: report of the Competencies Working Group of the Inter-Society Coordinating Committee for Physician Education in Genomics. *Genetics in Medicine,* doi:10.1038/gim.2014.35.

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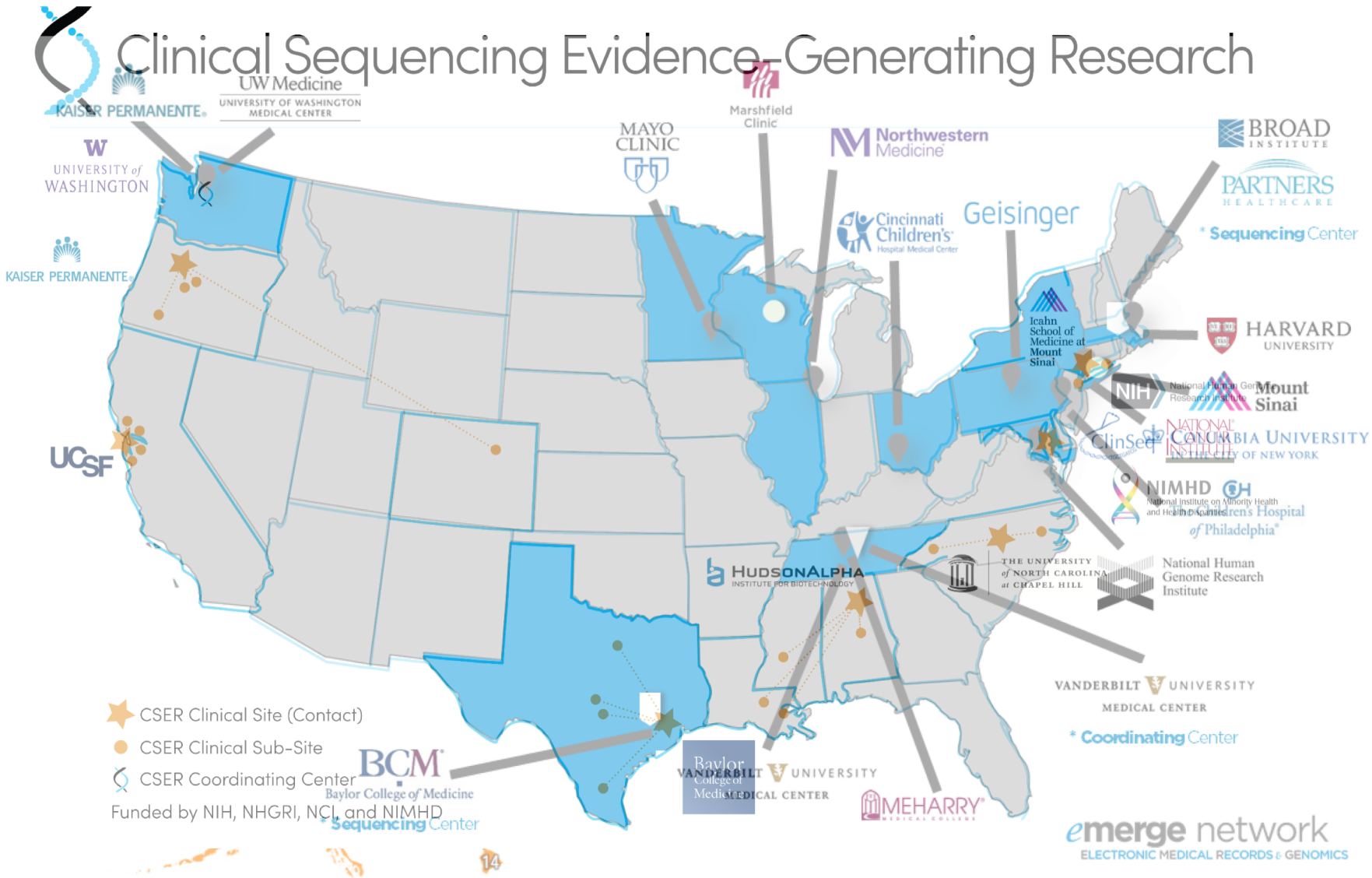
ELECTRONIC MEDICAL RECORDS AND GENOMICS

How to overcome.

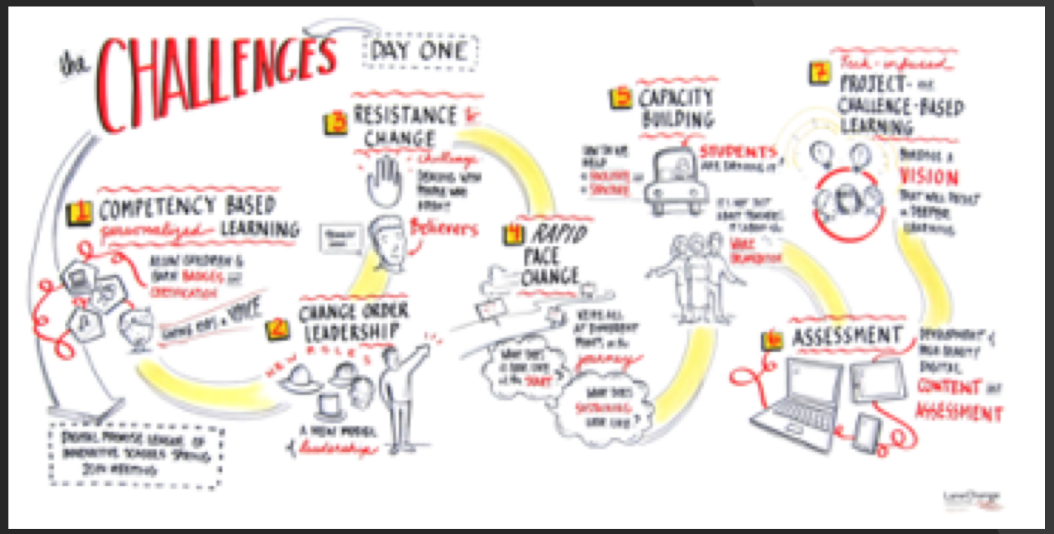
- CSER
  - Study the effectiveness of integrating genome sequencing into the clinical care of diverse and underserved individuals
- eMERGE
  - eMERGE is a national network organized and funded by the National Human Genome Research Institute (NHGRI) that combines DNA biorepositories with electronic medical record (EMR) systems for large scale, high-throughput genetic research in support of implementing genomic medicine.

Clinical Sequencing Evidence-Generating Research



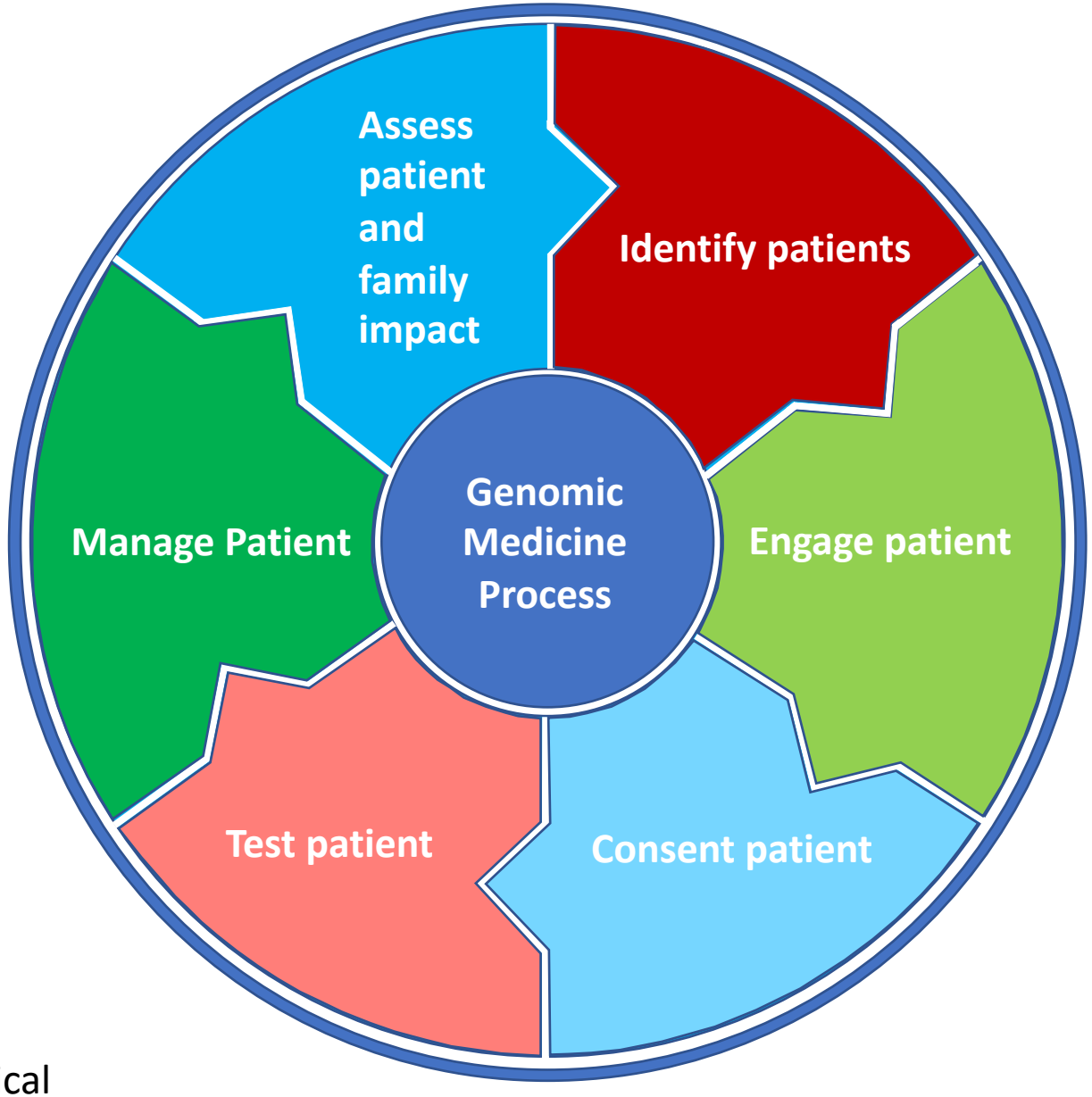
Educational Challenges

- Consistently and frequently updated
- Reputable material
- Broad geographic distribution
- Change indoctrinated practices
  - Aspirin in CAD primary prevention
  - MTHFR, KIF6
- Capture the impact of the decision
- Must improve efficiency of education



- Immersive and experiential learning
- Interdisciplinary/interprofessional education
- Electronic and web based approaches

Source: Rubanovich, CK, et al. 2018. Physician preparedness for big genomic data: a review of genomic medicine education initiatives in the United States. *Human Molecular Genetics,* 27(2), 250-258.



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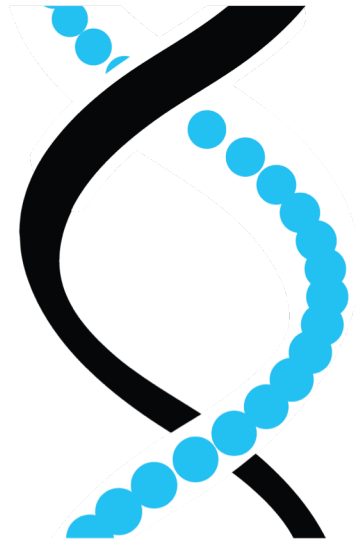

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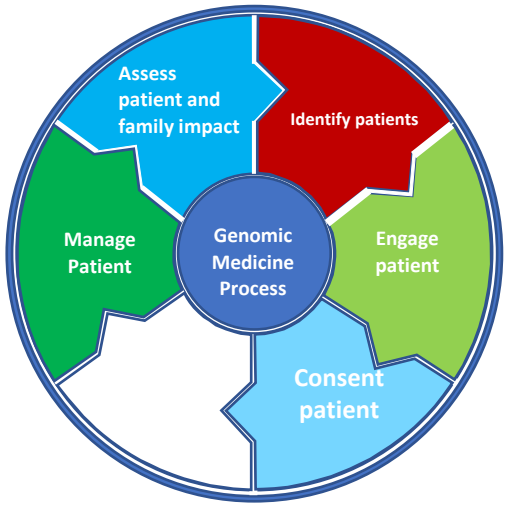
Evidence-Generating
Research



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Clinical Sequencing Exploratory Research

Guide to Interpreting Genomic Reports: A Genomics Toolkit

A guide to genomic test results for non-genetics providers

Created by the Practitioner Education Working Group of the Clinical Sequencing Exploratory Research (CSER) Consortium

Diagnostic Results Related to Patient Symptoms or Primary Results: Pathogenic and Likely Pathogenic Variants

Key Points

- Pathogenic variants in disease genes related to phenotype (or symptoms) means that a cause of the patient's symptoms has been identified.
- Clinically, both pathogenic and likely pathogenic variants are treated the same—as if they are likely disease causing.
- Identifying a specific genetic diagnosis may provide information on the likelihood of other associated medical problems and more specific disease management.

Genomic variants are typically classified on a five-point scale to indicate the likelihood that the particular variant is associated with disease.

Introduction and Overview to Genomic Test Reports

Key Points

- The use of genomic tests (gene panels, exome sequencing, genome sequencing) is increasing in the clinical and research setting.
- An individual's genetic code contains millions of differences when compared to the human reference sequence. These differences, referred to here as variants are also sometimes called mutations.
- Genetic variants may be benign and have no impact or may be pathogenic and causative of disease. When it is unclear whether a variant has an impact it is referred to as a variant of uncertain significance.
- Genomic tests are often performed to make a diagnosis and explain symptoms. Results related to symptoms are called diagnostic or primary results while results that are unrelated to symptoms are called incidental or secondary results.
- Results of genomic testing may have medical and personal value to both the individual who underwent testing as well as his relatives.

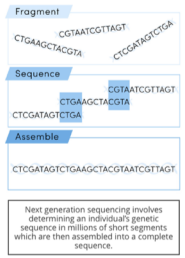
This guide is intended for healthcare providers faced with understanding and interpreting their patients' genomic test reports. This guide is not intended to help select a test, but rather to help providers navigate test results.

Genetic Tests vs. Genomic Tests

Genetic testing allows for the identification of changes in chromosomes, genes, or proteins (a gene's encoded product). The results can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disorder.

While genetic testing has been performed for decades, over the past few years there has been a tremendous increase in the number and scope of genetic tests ordered due to improvements in technology and decreases in cost. Genomic tests that explore multiple genes (panels), most genes, and even tests that explore a person's entire genome, have become a reality. Yet, many healthcare providers have not been trained in how to understand the output of these increasingly common tests.

Next Generation Sequencing (NGS), used in diagnostic testing, generally involves determining the patient's genetic sequence in millions of short segments, called "reads" (each approximately 100 basepairs in length), assembling the reads into a complete sequence, then determining what **genetic variants** are present and interpreting what they mean.



Next generation sequencing involves determining an individual's genetic sequence in millions of short segments which are then assembled into a complete sequence.

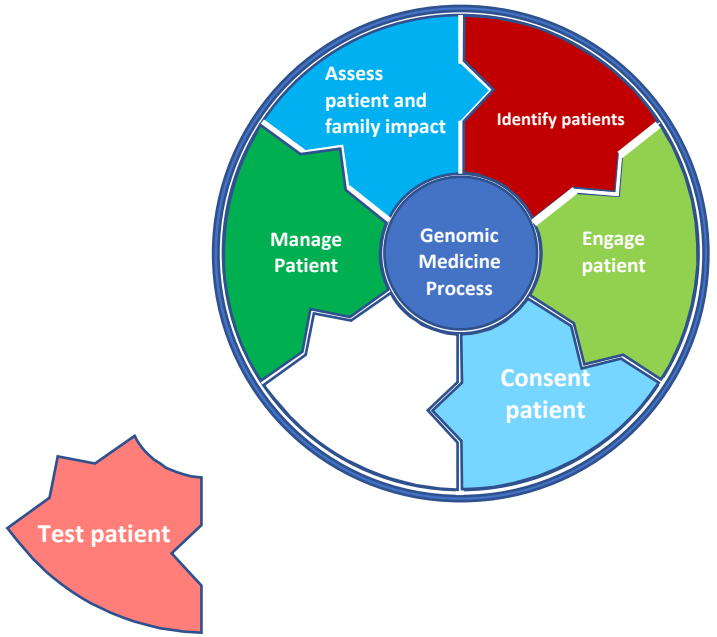
NGS is extremely flexible and has been implemented for sequencing only a few genes (e.g., hereditary breast cancer panels) a whole **exome** (all of the coding regions of DNA) or a whole **genome** (entire DNA sequence including both coding and noncoding regions).

NGS is now routinely performed in clinical diagnostic laboratories that perform genetic testing and are regulated by CAP and CLIA certifications. However, much is still unknown about when to use which kind of test (gene panels, exome testing, and genome testing), and for what clinical purpose. There are CPT codes for these new NGS tests, but insurance coverage is variable.

For exome or genome sequencing, potentially millions of variants are identified that differ between the patient and the "**reference sequence**" used for comparison. Most genetic variants have little or no known impact on human health, so the variants must be filtered to identify the few that are medically meaningful. Genomic data from an individual's parents provides information that can help filter out benign genetic variants and identify **de novo variants** (variants that are not inherited). Generation of the sequence data, **variant calling**, and variant interpretation are all critical steps for providing accurate test results.

Genomic testing is often done for an individual patient (**singleton**) or for a **trio** (includes patient, mother, and father); however other formats are possible depending on the disease of interest and family structure. Not all laboratories handle the testing and interpretation of parental samples in the same way. In some labs all three individuals are sequenced and interpreted comprehensively at the same time. In other labs the parental samples are only tested after the patient's sample.

https://www.ashg.org/education/csertoolkit/index.html



In development

Improving engagement between providers

"GenomeDiver" at Icahn School of Medicine at Mt. Sinai

- "Trouble ticket" concept for variant interpretation
- Does it improve efficiency and change outcomes with having improved access?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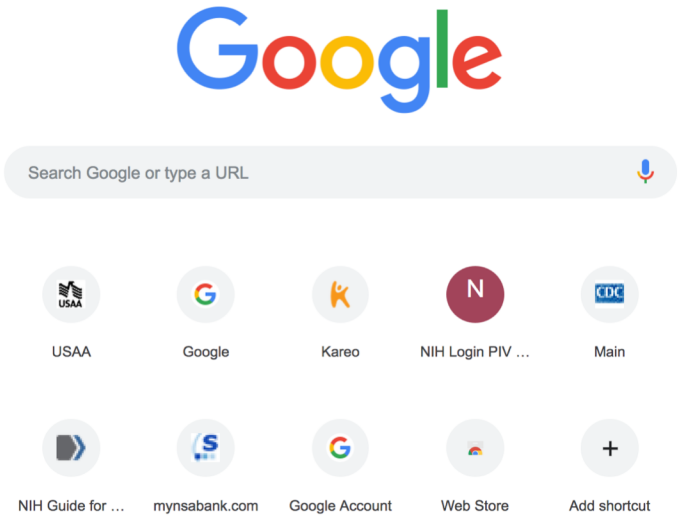
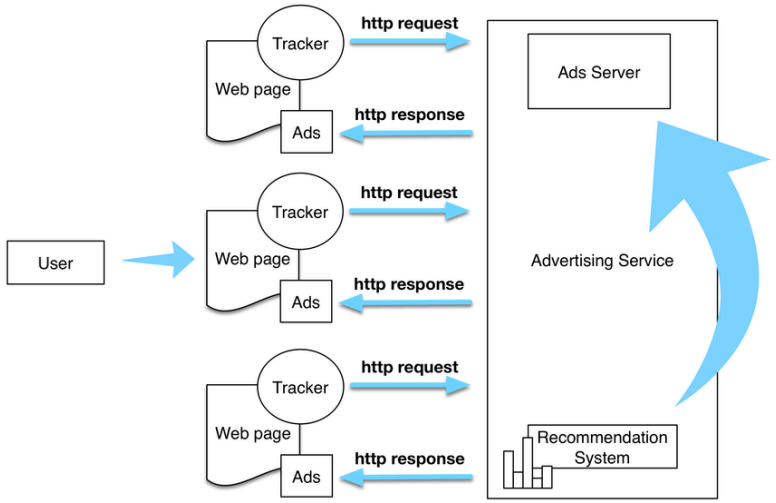
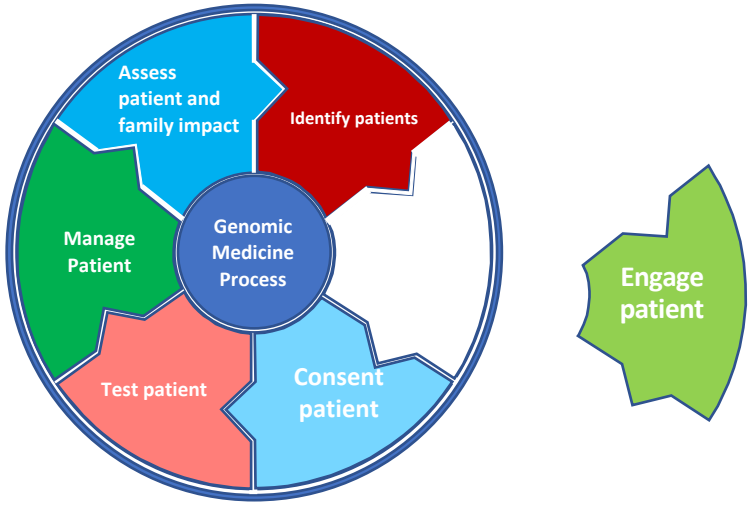




What can we do to meet challenge?

- Improving efficiency of education
- Automating process



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IMAGene

Individualized Medicine through Application of GENomics

Educational tools

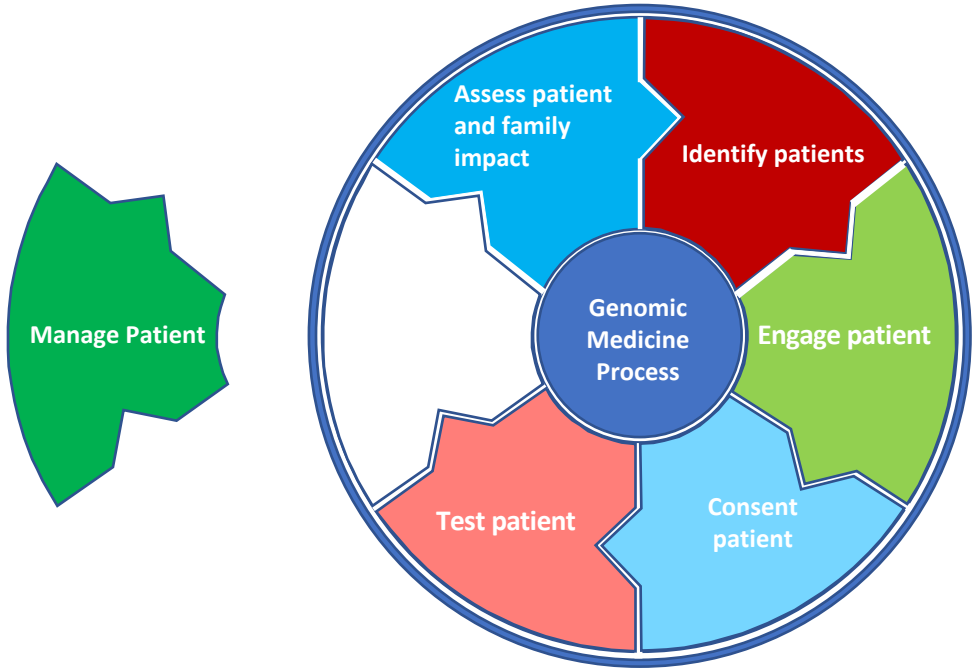
IMAGene | Helps you learn about genomic screening to determine which genetic tests are best

Learning Genetics | Presents introductory videos about components of genetics

MyResults.org | Provides information about genetic test results and disease risks

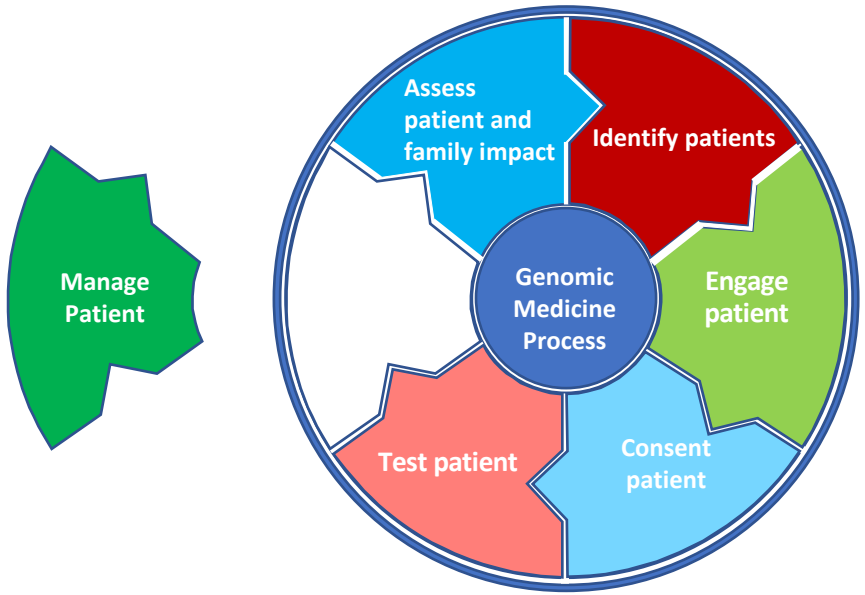
Lectures & Videos | Seminars covering precision medicine, large genomics data, and up and coming tools

https://emerge.mc.vanderbilt.edu/resourcelibrary/



Working on Standards

- Creating SMART on FHIR standard to transmit results of genetic sequencing from lab to EMR
  - **open specifications** to integrate apps with Electronic Health Records, portals, Health Information Exchanges, and other Health IT systems.
- Once this moves from a document/pdf structure, it allows the site to utilize components of the report
- Opens ability for interactive Clinical Decision Support for components of the data

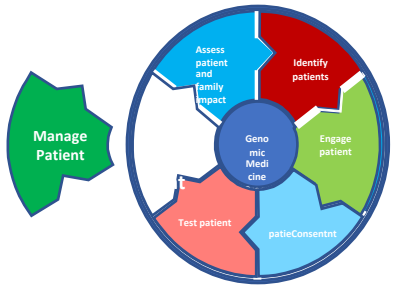


Provider Acceptance CDS

- eMail survey of 1161 physicians including 208 cardiologist
- 18.1% response rate
- 97.6% of clinicians favor a CDS tool to that assists in managing patient with Familial Hyperlipidemia (1:200)

CDS_KB
CLINICAL DECISION SUPPORT KNOWLEDGEBASE

Mayo Clin Proc Innov Qual Outcomes v.2(2); 2018 Jun
PMC6124345



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GeneInsight Clinic
for better care

FAQ | Lab Resources | User Guide | Support | Change Password | Password Recovery Fehrs-Battey, Amber Log Out

Patient Search | Patient Reports | Users

Enter one or more fields t
Patient Name (last,first)
Patient ID#
Patient Date of Birth
Report Identifier
Referring Provider
Variant(s)[1]
Specimen(s)

14 patients found for the sea

		Name
		Blue, Bobby
		Duck, Plucky
		Mendel, Greg
		Pan, Peter
		Patient, Demo
		Pig, Hamton
		Prime, Optimu
		Bunny, Buster
		Coyote, Calam
		D, Dizzy

Commu

Samuel J. Aronso
Samantha Baxter,

Variant classification ch

Benign
Likely benign
Unknown significance
Likely pathogenic
Pathogenic

High al
32
56
26

Demo

Arranged By: Date | Newest on top

PHS GeneInsight Support 7/18/2011
GIC Alert Summary
PHS GeneInsight Support 7/13/2011
GIC Variant Alert
PHS GeneInsight Support 7/13/2011
GIC Report Alert
PHS GeneInsight Support 7/11/2011
GIC Alert Summary
PHS GeneInsight Support 7/4/2011
GIC Alert Summary

Older

PHS GeneInsight Support 6/27/2011
GIC Alert Summary
PHS GeneInsight Support 6/20/2011
GIC Alert Summary
PHS GeneInsight Support 6/13/2011
GIC Alert Summary
PHS GeneInsight Support 6/6/2011
GIC Alert Summary
PHS GeneInsight Support 5/30/2011
GIC Alert Summary
PHS GeneInsight Support 5/27/2011
GIC Report Alert
PHS GeneInsight Support 5/23/2011
GIC Alert Summary
PHS GeneInsight Support 5/19/2011
GIC Alert Summary
PHS GeneInsight Support 5/19/2011
GIC Variant Alert
PHS GeneInsight Support 5/19/2011
GIC Variant Alert

GIC Variant Alert

PHS GeneInsight Support

You forwarded this message on 8/8/2011 10:14 AM.
Extra line breaks in this message were removed.

To: Varugheese, Matthew

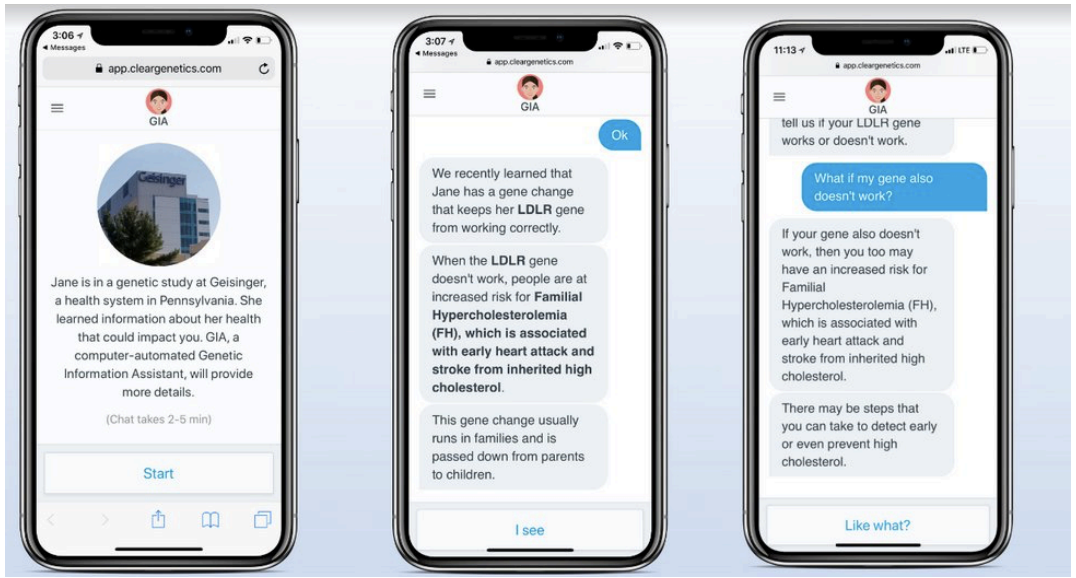
New Alerts for Variant ACTC c.301G>A (p.Glu101Lys)
1) High - The category for the ACTC c.301G>A (p.Glu101Lys) association to HCM changed from Unknown Significance to Pathogenic.
Affects 1 report(s).
DEMO-00006 Ref Provider(s): Provider One M.D.
http://gis-demo2.hpcgg.partners.org/gic/a/1094

The diagnostic test information transmitted by this email and the GENEINSIGHT CLINIC (sm) generally is intended to be used as an adjunct to the diagnosis and management of clinical conditions associated with specific genetic sequence findings. All transmittals received through GENEINSIGHT CLINIC (sm) must be reviewed and validated by appropriately qualified, trained and licensed clinical personnel before being used for any purpose. Variants alerts associated with a particular patient may not be complete or relevant to such patient. Lack of identified variants alerts does not imply or express that no relevant knowledge relating to applicable variants is available from other sources. Any action taken by clinician in response to this email or transmittals received from the GENEINSIGHT CLINIC (sm) is solely at clinician's discretion and clinician assumes full responsibility for such action.

-- Message Origin Information ----------
Created: 07/13/2011 14:48:00
Sent: 07/13/2011 14:50:00
Recipient: mvarugheese@partners.org
Clinic: DEMO
Server: gis-demo2.hpcgg.partners.org

Genet Med 2012;14(8):713-719

Automating process



- Chatbots being used to:
  - Consent patients
  - Answer basic questions about genetics
- Creating videos for returning negative results

NHGRI programs

- Realize that genomics touches every aspect of medical care
- How do we meet the rapid change in our understanding?
- How do we leverage information technology to meet these requirements?
- How do we deal with this new complexity?
- How do ensure that the knowledge is distributed?
- Measuring impact of implementation

Acknowledgements

Kelly East

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Heidi Rehm

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BCM Baylor College of Medicine

Boston Children's Hospital — Until every child is well

BROAD INSTITUTE

Cincinnati Children's Hospital Medical Center

The Children's Hospital of Philadelphia

Columbia University in the City of New York

Geisinger

Harvard University

Kaiser Permanente

Marshfield Clinic Health System

Mayo Clinic

Meharry Medical College

Mount Sinai

Northwestern Medicine

Partners Healthcare

Vanderbilt University Medical Center

UW Medicine — University of Washington Medical Center

National Human Genome Research Institute

Rongling Li
Program Director

Ken Wiley
Program Director

Jyoti Dayal
Program Director

Sheethal Jose
Program Analyst

Robb Rowley
Program Director

Teri Manolio,
Director, Division of Genomic Medicine


The Forefront
of Genomics®