Caring

Geisinger

Patient-Centered Precision Health In A Learning Health Care System: Geisinger's Genomic Medicine Experience

Marc S. Williams, MD, FAAP, FACMG, FACMI

Professor and Director Emeritus, Genomic Medicine Institute

@Marc_GeneDoc

Overview

- Define terms in common use and provide background for GenomeFIRST
- Describe the opportunity for synthesis between genomics/precision health and the learning healthcare system
- Present the Geisinger experience with implementation of a genomic medicine program in the context of an integrated system

A face of our project

- 53 year old woman enrolled in MyCode Community Health Initiative
- History of a basal cell carcinoma removed at age 33
- Currently treated for Crohn's disease
- Receives regular medical care, but has declined mammography for the last 5 years
- Primary caregiver for her grandchildren

Assertion

Healthcare delivery is increasingly influenced by two emerging concepts: Precision medicine (health) and the learning healthcare system.


PRECISION HEALTH
meaning, definition, explanation...

Genomic Medicine

- Includes
  - Traditional single gene disorders (genetics)
  - Analysis of the whole genome (genomics)
  - Analysis of subsets of the whole genome
    - Exome sequencing
    - Pharmacogenomics
  - Family History

Genomic Medicine ≠ Personalized Medicine

"Personalized medicine is the practice of clinical decision-making such that the decisions made maximize the outcomes that the patient most cares about and minimizes those that the patient fears the most, on the basis of as much knowledge about the individual's state as is available."

Pauker and Kassirer N Engl J Med 316:250-258, **1987***

Precision Medicine

- Currently--Intuitive medicine
  - Care for conditions that can be diagnosed only by their symptoms and only treated with therapies whose efficacy is uncertain and watching for empiric response.
  - Empiric ‘trial and error’
- Future—Precision medicine
  - The provision of care for diseases that can be precisely diagnosed, whose causes are understood, and which consequently can be treated with rules-based therapies that are predictably effective.
  - Expect genomics to play a key role in this

Adapted from The Innovator’s Prescription A Disruptive Solution for Healthcare. Christensen , Grossman and Hwang, 2009

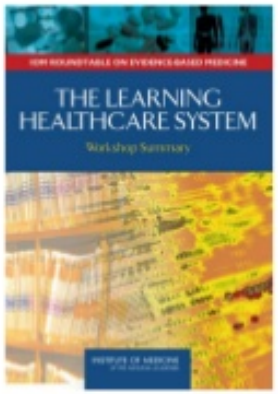
Precision Health

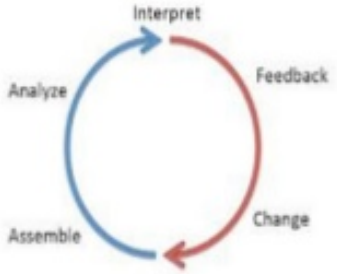
- Emphasizes prevention while encompassing the interventions inherent in precision medicine
- We view our project as a population precision health effort, and have renamed it the MyCode Community Health Initiative to distinguish it from the biorepository
- Inherent in this are educational efforts directed at participants, providers, payers, administrators and other stakeholders
- This is endorsed at the highest level of the organization as a strategic initiative

What is a Learning Healthcare System?

The Institute of Medicine has defined this as a healthcare system:

- *'that is designed to generate and apply the best evidence for the collaborative healthcare choices of each patient and provider;*
- *to drive the process of discovery as a natural outgrowth of patient care;*
- *and to ensure innovation, quality, safety, and value in health care.'*





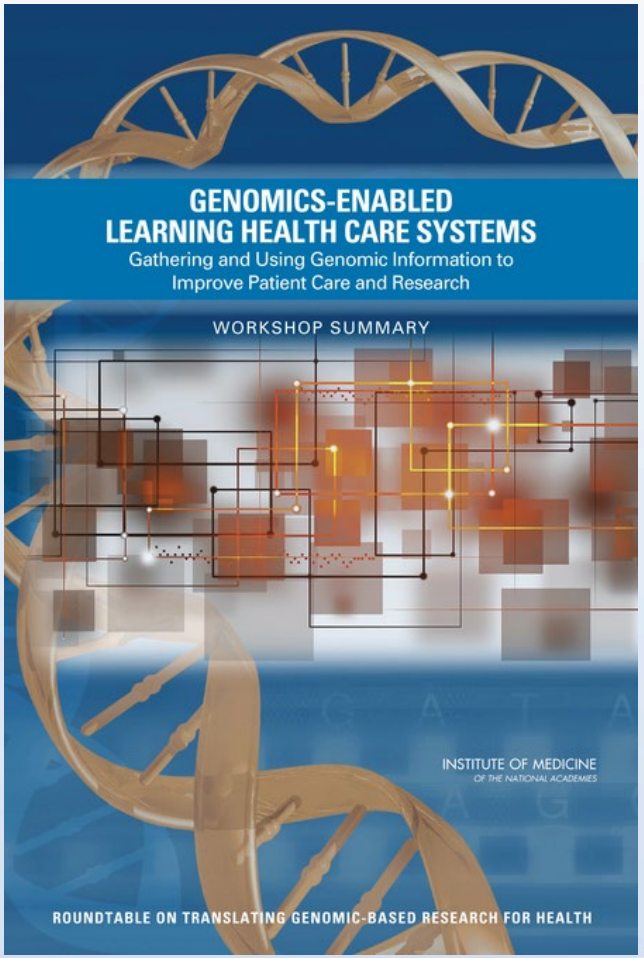
Learning Healthcare System-Goal

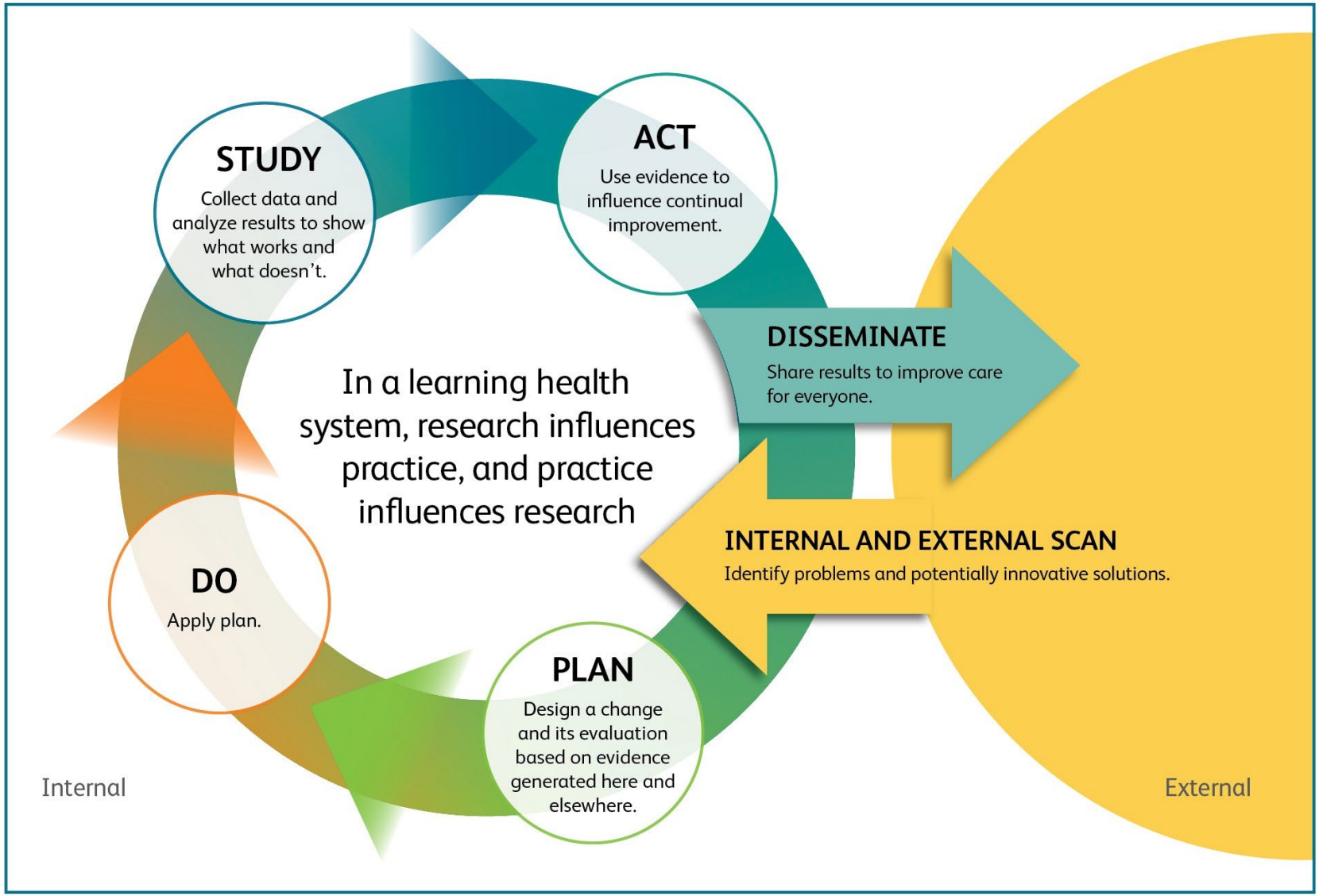
"Science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience."

2015

Page 19

"A health care system in which an infrastructure supports complete learning cycles that encompass both the analysis of data to produce results, and the use of those results to develop changes in clinical practices is a system that will allow for optimal learning." (Friedman)





Geisinger

Source: KP Washington Health Research Institute

Geneticists know how to do this

PCHR INSERT FOR BABIES BORN WITH ACHONDROPLASIA

First Edition, July 2007

These are extra pages for your child's Personal Health Record. They have been created especially for babies and young children with Achondroplasia. They contain background information for families and health care professionals, and guidelines and checklists for growth and development.

Children with Achondroplasia

guidance for parents and health care professionals

Image reproduced with kind permission from the Dwarf Athletic Association United Kingdom

Document Version: PHR11-Achon-boy
Created: 24/06/06
Amended: 27/01/10

This project has been funded by a Department of Health Grant with additional support from Nowgen

North West Regional Genetics Service: 0161 276 6506 www.mangen.co.uk

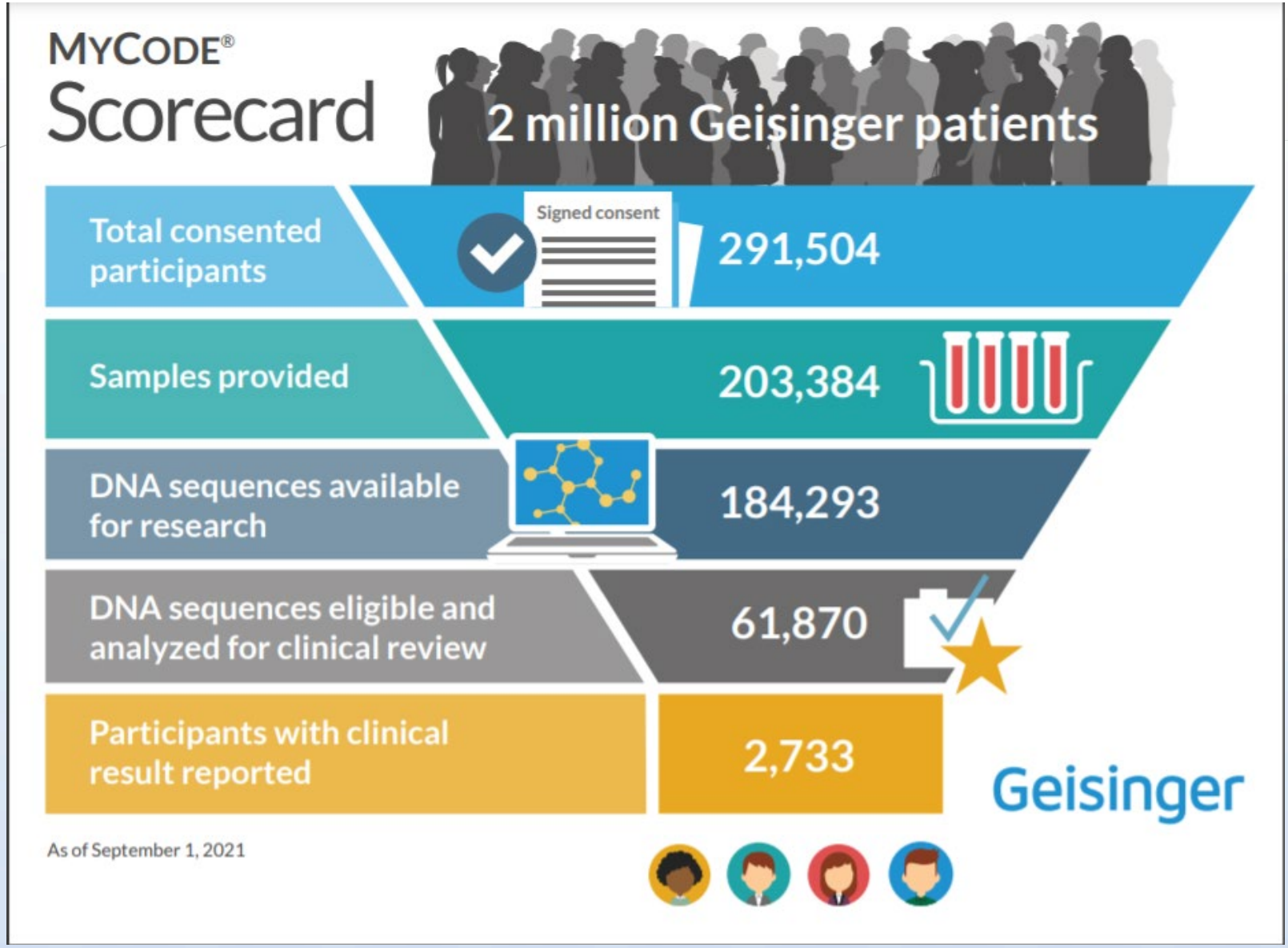
Central Manchester University Hospitals NHS

Genomics at scale

Geisinger

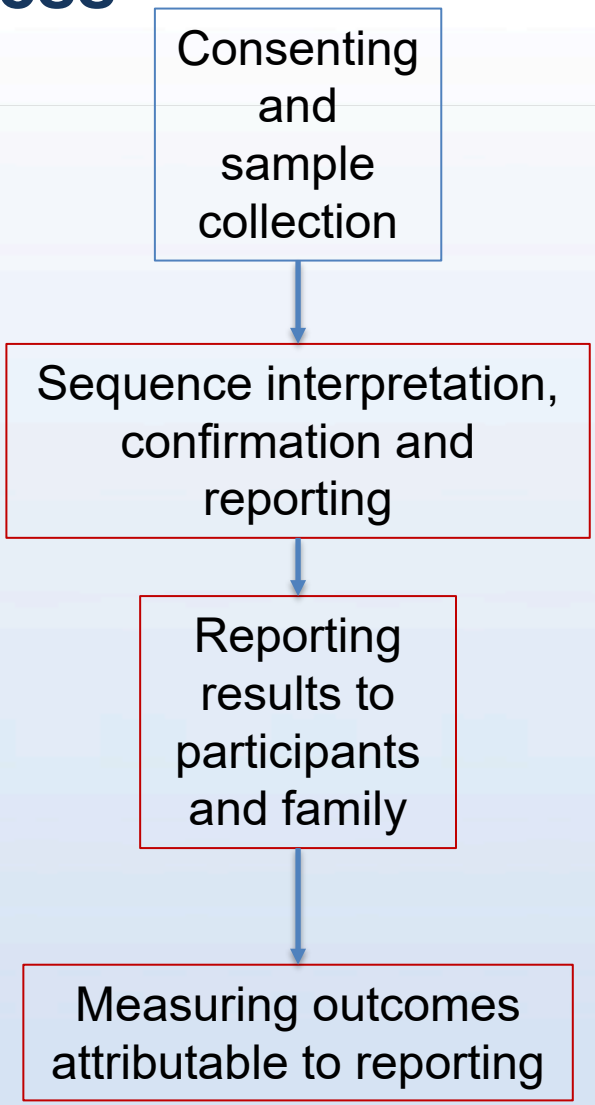
GenomeFIRST™ Return of Results

- 250,000+ Geisinger Patients Will Have Their Exomes Sequenced.
- We will Look For Medically Actionable Results In That Data And Then Return Results To Patients And Providers.
- We will support the patients and providers in the follow-up to the results and long-term management planning.
- We will be Operationalizing A Scalable Genomic Return Of Results Infrastructure In A Large Integrated Healthcare System



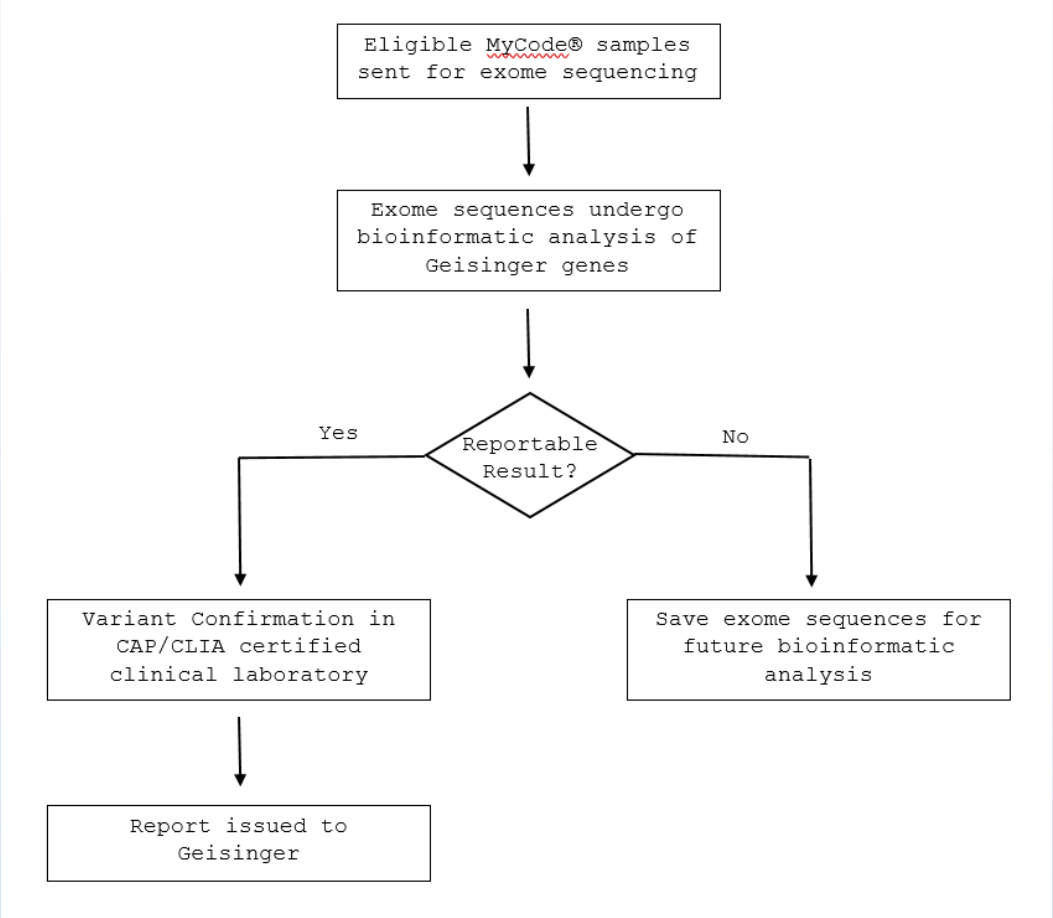
Geisinger https://www.geisinger.org/-/media/OneGeisinger/pdfs/ghs/research/mycode/mycode-scorecard.pdf?la=en

High Level Process



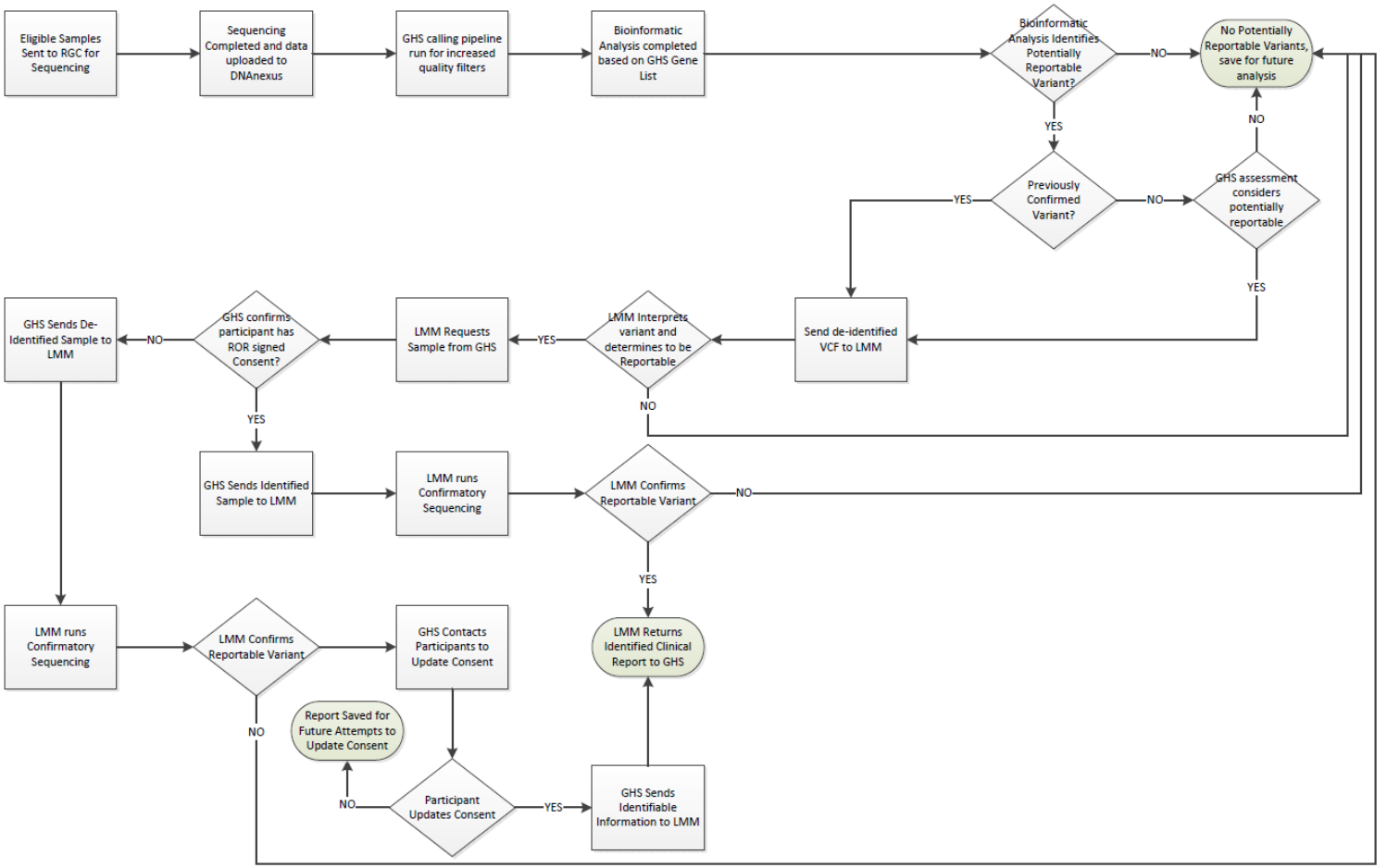
Geisinger

Sequencing, confirmation, and reporting- In theory



Geisinger

Sequence Analysis-in practice



Geisinger

Challenges to Scale

- Standardization of Genetic Phenotypes
- Getting Discrete Data from the Lab to the EHR
- Address the Role of the LIS in the process
- Discordance between HL7 genomic report and FHIR molecular sequence resource
- Integration with existing maintenance guidelines
- Inability to represent variant level data for PGx (* system unique to PGx)
- Overall lack of standards and standard approaches for each step in the process

Reporting Results to Participants and Families

Geisinger

How are results disclosed and discussed?

Primary care provider notified of a patient's result

- Electronic health record communication
- Option for PCP to disclose

Genetic counselor discloses result by phone

- Often unanticipated call
- May not be related to acute concerns

Brief description of risk and specific gene

- Gene causes risk for heart disease, early cancer…
- Screening and prevention may include…

Recommend discussion with genetic counselor

- Service provided at no charge
- Refer to other appropriate healthcare provider

Recommend discussing result with family members

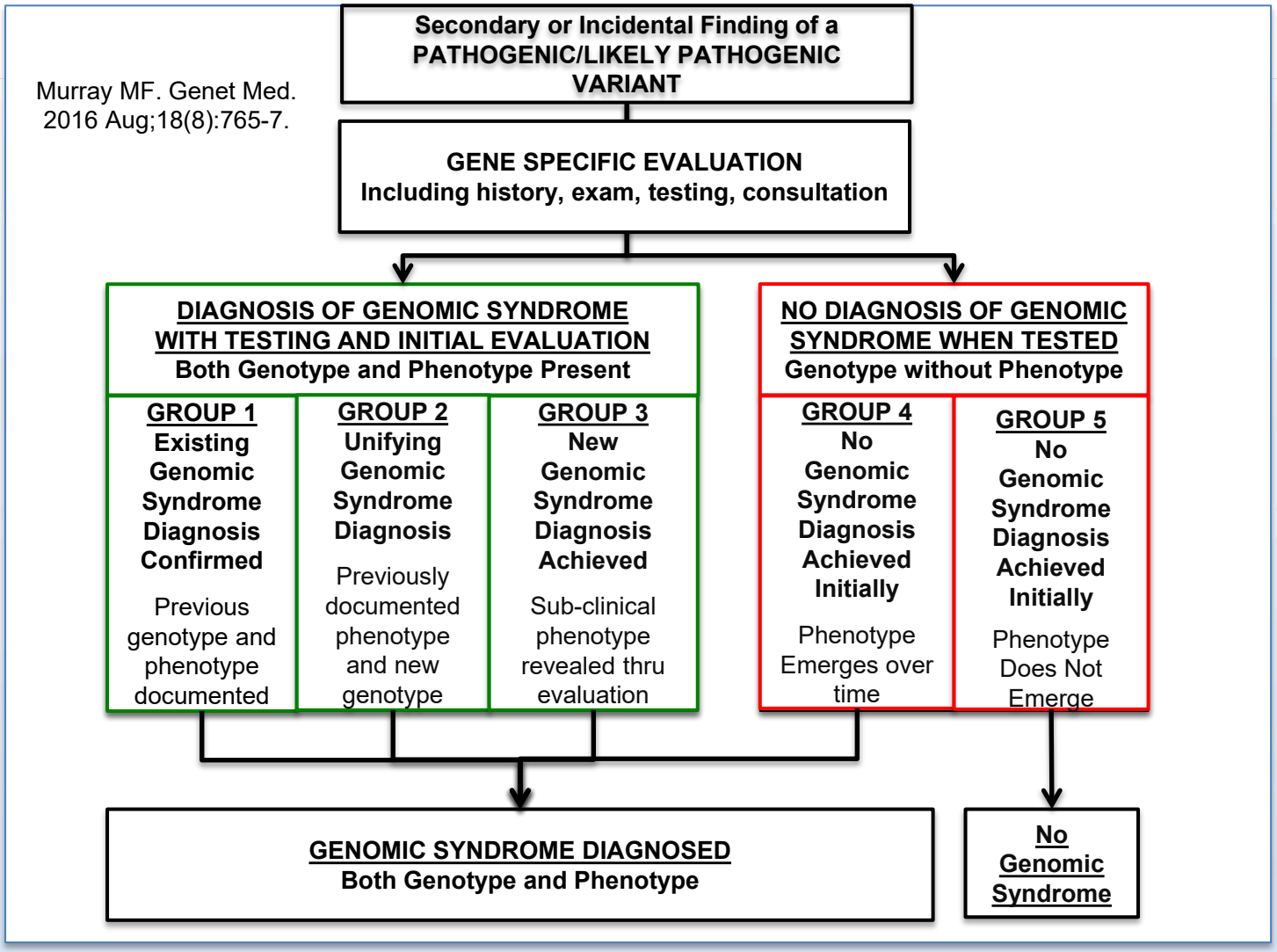
- Program provides letters and resources to help with this communication

Challenges to Scale

- Lack of standard resources for patient/provider information
  - ACMG ACT sheets for secondary findings
- Creation and maintenance of clinical decision support
  - Need structured data to run CDS rules
  - Standard CDS format to enhance generalizability (e.g. CDSHooks)
  - Reuseable CDS rules (CDSKB)
    - Currently only narrative and flow chart—no code
- Different perceptions of discrete genomic data versus scanned report
- Gaps in current proposed standards
  - Inability to handle recessive conditions with compound heterozygotes

Measuring Outcomes Attributable to Reporting

Murray MF. Genet Med. 2016 Aug;18(8):765-7.

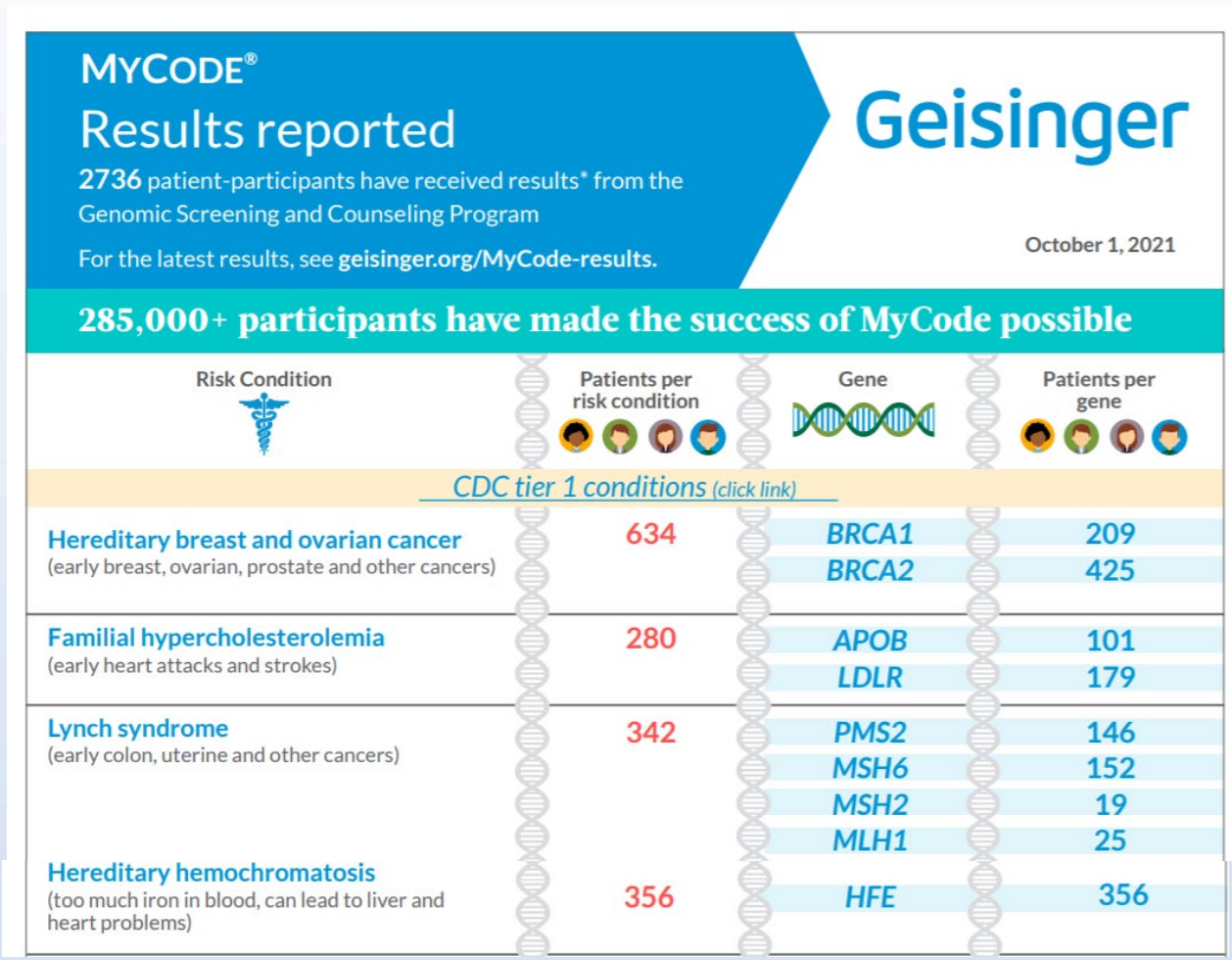


Geisinger

Opportunities

GENOMIC CONDITION	POPULATION PREVALENCE	CLINICAL RISK	DISEASE-ALTERING INTERVENTION
Familial Hypercholesterolemia (*LDLR, APOB,PCSK9)*	1 in 222	Early-onset Coronary Artery Disease and Stroke	Targeted screening and aggressive medical management
Hereditary Breast and Ovarian Cancer Syndrome (*BRCA1, BRCA2)*	1 in 400	Early-onset Breast, Ovarian, and Prostate Cancers	Targeted screening with prophylactic medical and surgical intervention
Lynch Syndrome (*MLH1,MSH2,MSH6,PMS2)*	1 in 440	Early-onset Colon and Uterine Cancers	Targeted screening and management of pre-cancerous changes
TOTAL	**~ 1 in 100**	**Multiple Cancers and Cardiovascular Diseases**	**Life-saving screening and intervention before development of disease**

Progress to date



MYCODE®

Results reported

2736 patient-participants have received results* from the Genomic Screening and Counseling Program

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

Geisinger

October 1, 2021

285,000+ participants have made the success of MyCode possible

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)	634	*BRCA1*	209
		BRCA2	425
Familial hypercholesterolemia (early heart attacks and strokes)	280	*APOB*	101
		LDLR	179
Lynch syndrome (early colon, uterine and other cancers)	342	*PMS2*	146
		MSH6	152
		MSH2	19
		MLH1	25
Hereditary hemochromatosis (too much iron in blood, can lead to liver and heart problems)	356	*HFE*	356

Outcomes

Outcome Type	Description	Examples
Process	These measures are the specific steps in a process that lead — either positively or negatively — to a particular health outcome	Lipid profile performed after return of a pathogenic variant in LDLR a gene associated with familial hypercholesterolemia
Intermediate	A biomarker associated — either positively or negatively — to a particular health outcome	An LDL cholesterol level at or below the target level of 100 mg/dl in response to interventions recommended based on presences of a pathogenic variant in LDLR
Health	Change in the health of an individual, group of people or population which is attributable to an intervention or series of interventions	Decrease in myocardial infarction, or cardiac revascularization procedures in response to interventions recommended based on presences of a pathogenic variant in LDLR
Cost	Standard costs associated with the interventions and health states experienced by the patient. Can also include costs associated with patient report outcomes from self-reported health state and life disruption.	Cost of sequencing Cost of genomics results delivery infrastructure Direct costs of care related to return of genomic information Utilization
Behavioral	Change in patient or provider behavior attributable to genomic information	Improved adherence to medication Modification of care based on condition-specific recommendations
Patient-reported	Report of the status of a patient's health condition, knowledge, or service outcomes that comes directly from the patient, without interpretation of the patient's response	Satisfaction with service Engagement with self-care Knowledge about gene and disease Access to recommended care Self-assessed well being Family communication of genomic risk result and uptake of cascade testing

Geisinger

System Outcomes

- Costs incurred/avoided
- Utilization
- Visibility/reputation
- Patient experience

Measuring Outcomes Attributable to Reporting

- Define outcomes to be collected
- Implement systems to capture outcomes

- Determination of attribution not standardized
- Reliance on manual collection
- Patient self-reported data necessary (and desirable in some cases)
- Outcomes not harmonized across different projects
- Standardized outcomes not available for the most part
  - PROMIS for patient reported outcomes

Geisinger

What is Value?

- Crudely can be thought of as a relationship between outcomes and cost of care
- Patient centered outcomes would include
  - Medical outcomes (treatment, prevention, safety)
  - Service outcomes (number of visits, disruption of life routine)
  - Information?
    - Highly valued in genetics
    - Difficult to value economically
    - Personal utility vs. control of health care costs
- In general we do a poor job measuring cost of services

Value Plot

Medical and/or Service Outcomes	Cost of care decreased	Cost of care unchanged	Cost of care increased
Improved			
Unchanged			
Worsened			

Geisinger

Genomic LHS in action

JAMA Network | Open

Original Investigation | Genetics and Genomics

Exome Sequencing–Based Screening for *BRCA1/2* Expected Pathogenic Variants Among Adult Biobank Participants

Kandamurugu Manickam, MD, MPH; Adam H. Buchanan, MS, MPH; Marci L. B. Schwartz, ScM; Miranda L. G. Hallquist, MSc; Janet L. Williams, MS; Alanna Kulchak Rahm, PhD, MS; Heather Rocha, MS; Juliann M. Savatt, MS; Alyson E. Evans, BS; Loren M. Butry, MS; Amanda L. Lazzeri, BS; D'Andra M. Lindbuchler, MSN; Carroll N. Flansburg, MPH; Rosemary Leeming, MD, MHCM; Victor G. Vogel, MD, MHS; Matthew S. Lebo, PhD; Heather M. Mason-Suares, PhD; Derick C. Hoskinson, PhD; Noura S. Abul-Husn, MD, PhD; Frederick E. Dewey, MD; John D. Overton, PhD; Jeffrey G. Reid, PhD; Aris Baras, MD; Huntington F. Willard, PhD; Cara Z. McCormick, MPH; Sarath B. Krishnamurthy, PhD; Dustin N. Hartzel, BS; Korey A. Kost, BS; Daniel R. Lavage, BS; Amy C. Sturm, MS; Lauren R. Frisbie, BS; T. Nate Person, MS; Raghu P. Metpally, PhD; Monica A. Giovanni, MS; Lacy E. Lowry, MD; Joseph B. Leader, BA; Marylyn D. Ritchie, PhD; David J. Carey, PhD; Anne E. Justice, PhD; H. Lester Kirchner, PhD; W. Andrew Faucett, MS; Marc S. Williams, MD; David H. Ledbetter, PhD; Michael F. Murray, MD

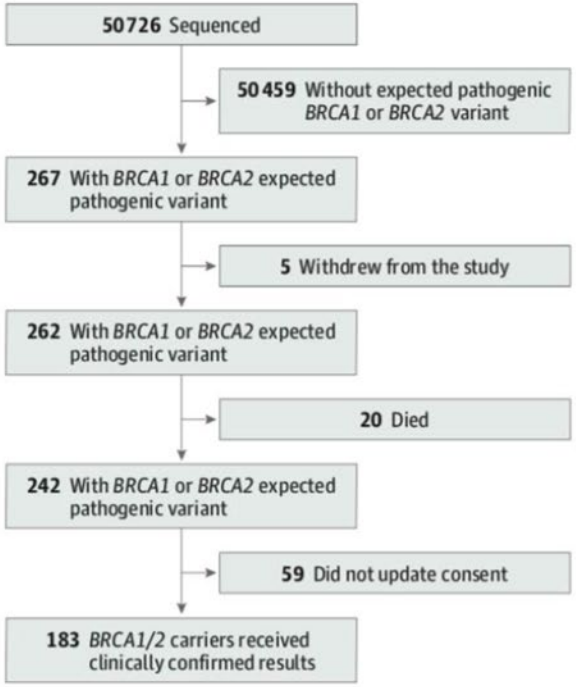
- Identify pathogenic & likely pathogenic (P/LP) *BRCA1/2* variants in unselected research cohort
- Characterize features associated with P/LP variants

Manickam K et al. *JAMA Network Open* 1.5 (2018): e182140-e182140

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2703131

Results – prevalence & genetic testing history

- 36% *BRCA1* (n=95), 64% *BRCA2* (n=172)
- Prevalence: 1:180 (corrected for relatedness)
- **Only 18% had prior clinical *BRCA1/2* testing**
- ~50% of those without prior testing did not meet NCCN genetic testing criteria
- *BRCA*-associated cancers more common in cases vs. controls



Manickam K et al. *JAMA Network Open* 1.5 (2018): e182140-e182140

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2703131

‘Tier 1’ Outcomes Paper

What is clinical utility of genomic screening program among MyCode patients with a ‘CDC Tier 1’ genomic condition?

- 350 patients with HBOC, Lynch, or FH result (May 2015-February 2018)
  - Double-coded chart review performed by clinicians in June-Dec 2018
  - Median follow-up window: 21.8 months (inter-quartile range 15-31 months)

Buchanan AH, et al. Clinical outcomes of a genomic screening program for actionable genetic conditions. Genet Med (2020). https://doi.org/10.1038/s41436-020-0876-4

Results, Conclusions

Majority of patients in genomic screening program:

Previously unaware of their Tier 1 variant (87%)	Eligible to perform risk management (86%)	Performed *some* management post-disclosure (68%)

Ascertainment of genomic risk led to relevant disease diagnoses during follow-up period (13%)

Supports effectiveness of genomic screening programs in identifying previously undetected individuals at risk for preventable cancers and heart disease

Value Plot

Medical and/or Service Outcomes	Cost of care decreased	Cost of care unchanged	Cost of care increased
Improved			??
Unchanged			
Worsened			

Geisinger

Selected Active and Future Studies

Additional clinical utility questions

- Clinical outcomes for Tier 1 & non-Tier 1 genes/conditions
- Risk management performance & post-disclosure disease diagnosis in *HFE* C282Y homozygote

Assessment of intermediate health outcomes

- Lipid levels at goal, high-intensity statin initiated

Penetrance

- Understanding phenotypic burden, link with exercise and penetrance and subtle cardiac phenotypes in ARVC

Family Member Testing

- Uptake of cascade testing among first-degree relatives

A face of our project

Found to have a pathogenic variant in *BRCA1*

Result returned and she proceeded to have a mammogram which was normal

Counseled per guidelines

NCCN Guidelines: Medical Management

- Annual mammogram and breast MRI (alternate 6 months)
- Consider RRM and RRSO
- Clinical Breast Exam every 6-12 months
- Encourage Breast awareness
- Consider risk reduction agents and investigational imaging trials

A face of our project

After several months elected to pursue BSO

"I need to be around for my grandchildren"

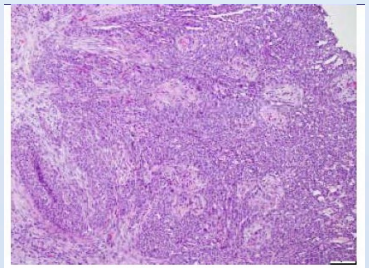
A face of our program

Had bilateral salphingo-oopherectomy in August 2016

No complications from surgery

Follow up pathology by serial sectioning showed: right fallopian tube high grade serous carcinoma 1.4 cm with stromal invasion

Pre-surgical ovarian ultrasound did not detect and CA-125 was normal



Invasive carcinoma

A face of our program

- Pelvic washing also positive- Stage 1C (though could easily be up-staged to 2C because of nature of this tumor)
- Started chemotherapy less than month later: Carboplatin and Taxol
- Stopped Crohn's disease treatment because of immunosuppression and risk with biological agents (2 years post treatment can be restarted)

Stage	Relative 5-Year Survival Rate
I	89%
IA	94%
IB	91%
IC	80%

Stage	Relative 5-Year Survival Rate
II	66%
IIA	76%
IIB	67%
IIC	57%

8 faces of our program

- As a result of surveillance recommended by return of *BRCA1/2* pathogenic variants we identified:
  - 3 Breast cancers (1 bilateral DCIS)
  - 3 Prostate cancers
  - 1 Fallopian tube carcinoma (discussed)
  - 1 carcinoma Ampulla of Vater
- All were stage 2 or earler

Takeaways

- Implementation of genomic medicine using LHS model can be used to develop evidence-based best practices
- Significant care gaps exist for patients with genetic conditions
- Successful delivery models must be studied to allow replication and rapid dissemination
- Understanding the value proposition from the organizational perspective is essential for success
- We can’t forget that at the end of the day this is impacting the lives of our patients

Acknowledgements

Thank you to:

Our MyCode patient-participants, Geisinger Providers and Staff, and the MyCode Research Team

Geisinger Executive Committee
David H. Ledbetter, PhD
Christa Lese Martin, PhD
Amy Sturm, MS
Daniel Davis, PhD
David Rolston, MD

Regeneron Genetics Center
Aris Baras, MD, PhD
Jeff Reid, PhD
John Overton, PhD

Funding from:
Geisinger
Regeneron Pharmaceuticals

Genomic Screening & Counseling program:

Amy Sturm, MS
Adam Buchanan, MS, MPH
Marc Williams, MD
Cara McCormick, MPH
Amanda Lazzeri, BS
Gary Bellus, MD
Nephi Walton, MD
Laney K Jones, MPH, PharmD
Marci Schwartz, ScM
Heather Rocha, MS
Tara Schmidlen, MS
Miranda Hallquist, MSc
Megan Betts, MS
Rachel Schwiter, MGC
Nicole Deckard, MS
Gretchen Thone, MS
Kerrianne Fry, MS
Missie Kelly, MS
Claire Jones, BS
Sarah Sturm, BS
Dan Brennsteiner, BS
Kristy DiLoreto, BS
Krista Zimmerman, BS

Further Reading

PRECISION MEDICINE

By Marc S. Williams, Adam H. Buchanan, F. Daniel Davis, W. Andrew Faucett, Miranda L. G. Hallquist, Joseph B. Leader, Christa L. Martin, Cara Z. McCormick, Michelle N. Meyer, Michael F. Murray, Alanna K. Rahm, Marci L. B. Schwartz, Amy C. Sturm, Jennifer K. Wagner, Janet L. Williams, Huntington F. Willard, and David H. Ledbetter

Patient-Centered Precision Health In A Learning Health Care System: Geisinger's Genomic Medicine Experience

DOI: 10.1377/hlthaff.2017.1557
HEALTH AFFAIRS 37,
NO. 5 (2018): 757–764