Caring

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A Clinical Imperative: **Genomics, Population Health, and Precision Health at Geisinger**

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NHGRI Council
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Geisinger and Precision Health: Our Vision Statement

Universal genomic sequencing will become a routine part of public health and medicine, to improve **individual health and well-being**, while optimizing the cost of healthcare over the lifespan.

To do this, we strive to **demonstrate the clinical utility and personal value** of genomic information at the **individual and community level**….

Geisinger is the ideal "healthcare laboratory" for implementation of genomic precision health.

Not just someday, but *today.*

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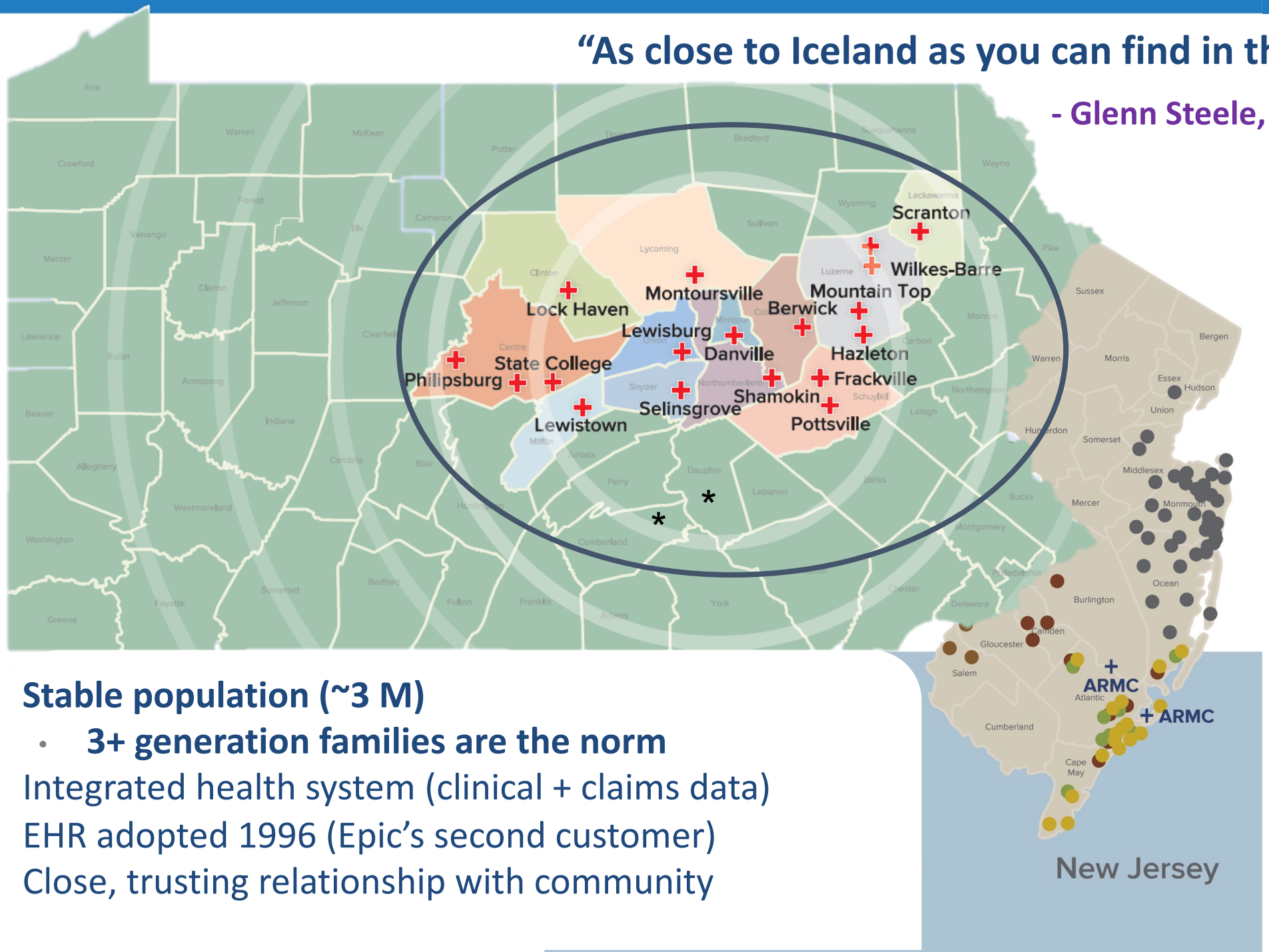
“As close to Iceland as you can find in the U.S.”

- Glenn Steele, MD, PhD



- **Stable population (~3 M)**
  - **3+ generation families are the norm**
- Integrated health system (clinical + claims data)
- EHR adopted 1996 (Epic’s second customer)
- Close, trusting relationship with community

Genetics in Medicine

- Broad impact of genetic variants/mutations on essentially *every* aspect of medicine, from lab values to inherited conditions to birth defects to risk of common adult disorders
- Mendelian disorders and polygenic common disorders: a continuum, not a dichotomy
- Viewed differently because impact of individual genomic variants varies
- Mendelian conditions seem like the most straightforward place to start **broad clinical implementation**: predictable and actionable

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Genomics in Medicine

- Any two genomes will differ at **millions** of positions among the 3 billion base pairs that comprise the human genome
- Any two exomes will differ at ~35,000 positions in the coding regions of the estimated 20,000 genes that encode proteins
- Great variability among populations worldwide (much of which has not yet been detected or catalogued)
- So **the question in medicine becomes**: how do we find, interpret, and use which or how many of those variants 'matter' clinically in any given individual? Both today and in the future?

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If we know all this, then why are we not doing it yet?

- Average ~20-year lag from **discovery to implementation**
- Need to change thinking about the impact of genetics on medicine, from **rare and highly specialized** to **essential and ubiquitous**
- Ownership issues: “you take the heart, **we’ll take the genome**”
- Genetic ‘exceptionalism’: **unsolvable and scary** ethical, social, policy dilemmas
- Uncertain finish line: we don’t know enough yet, so **wait**

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THE GEISINGER JOURNEY:

Genomic Sequencing to Precision Health

INSTITUTIONAL COMMITMENTS:

- Patients first
- Time and effort
- Financial
- Clinical urgency, *today*

SPONSORSHIP:

- Leadership
- Throughout the System
- Driven by clinical leaders

KEY LESSONS:

- Engage community and consumers
- Engage providers
- Align research/clinical missions
- Be nimble and evolve
- Make it easy, not a burden

A CLINICAL IMPERATIVE:

Research and Clinical Pathways to Precision Health

MyCode Community Health Initiative



- High research consent rate (~65-85%)
- In person (clinics) and online (MyGeisinger)
- >225,000 patients consented to date
- >150,000 samples provided to date

- Goal: >250,000 exomes
- 92,000 research WES to date
- ~50,000 in Regeneron sequencing queue (early 2019)

How many genes ‘cause’ Mendelian disease?

- **20,376** coding genes annotated to date
- 50 YEARS OMIM Human Genetics Knowledge for the World

  5,260 phenotypes due to single-gene mutations

  3,621 genes with phenotype-causing mutation(s)

  The ’Clinical Genome’ or ’Mendelome’…
- ClinGen Clinical Genome Resource

  ~1,600 genes clinically annotated to date

  >**7,000 different variants** ranked as ‘Pathogenic’ or ‘Likely Pathogenic’

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mycode Clinical Reporting

- **65,000 DNA sequences available** for clinical reporting of results
- Have reported **medically actionable results to ~1100 patients**
- Data to date: **~1.5-2%** of Geisinger patient population have positive results in a subset of genes that can directly impact care and anticipate/prevent disease
- Will increase over time as new genes and new variants added and as we better define “medical actionability”

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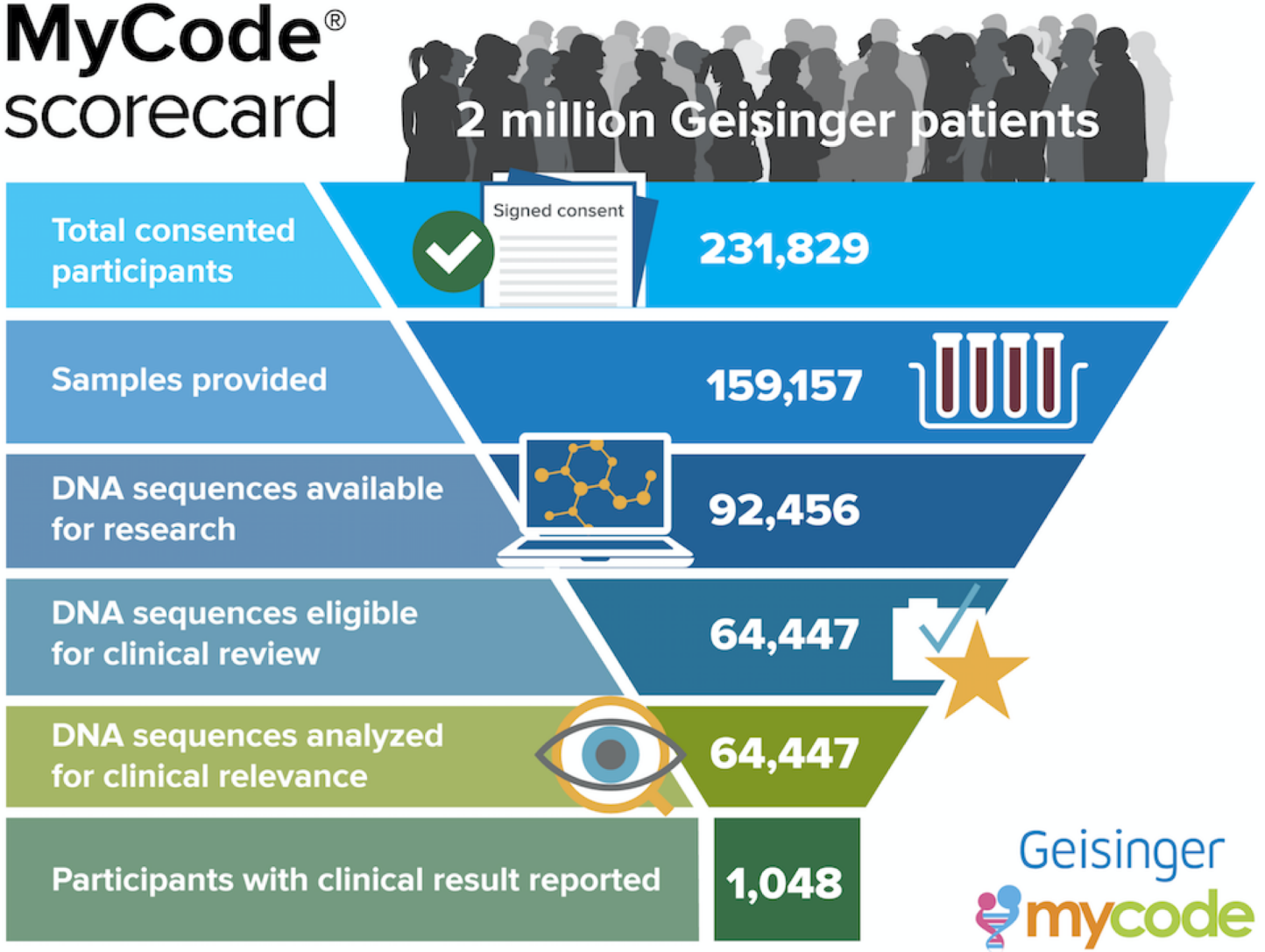
MyCode® scorecard



Geisinger mycode

mycode

- 3 conditions account for ~50% of cases (Breast/Ovarian cancer, FH, Lynch syndrome)
- In total, results have engaged **>300 different PCPs** and specialists from at least **14 medical specialties**

As of February 2019

So, why does this work at Geisinger?

- We were determined to make it easy, not burdensome
- We committed to genomics early, and we engaged the community and our primary care physicians from the very beginning
- We committed to helping our doctors and being viewed as enabling partners, not competitors
- We committed to fitting into existing care paths and workflows

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- But…
- It's fundamentally a research project and **lacks clinical urgency**

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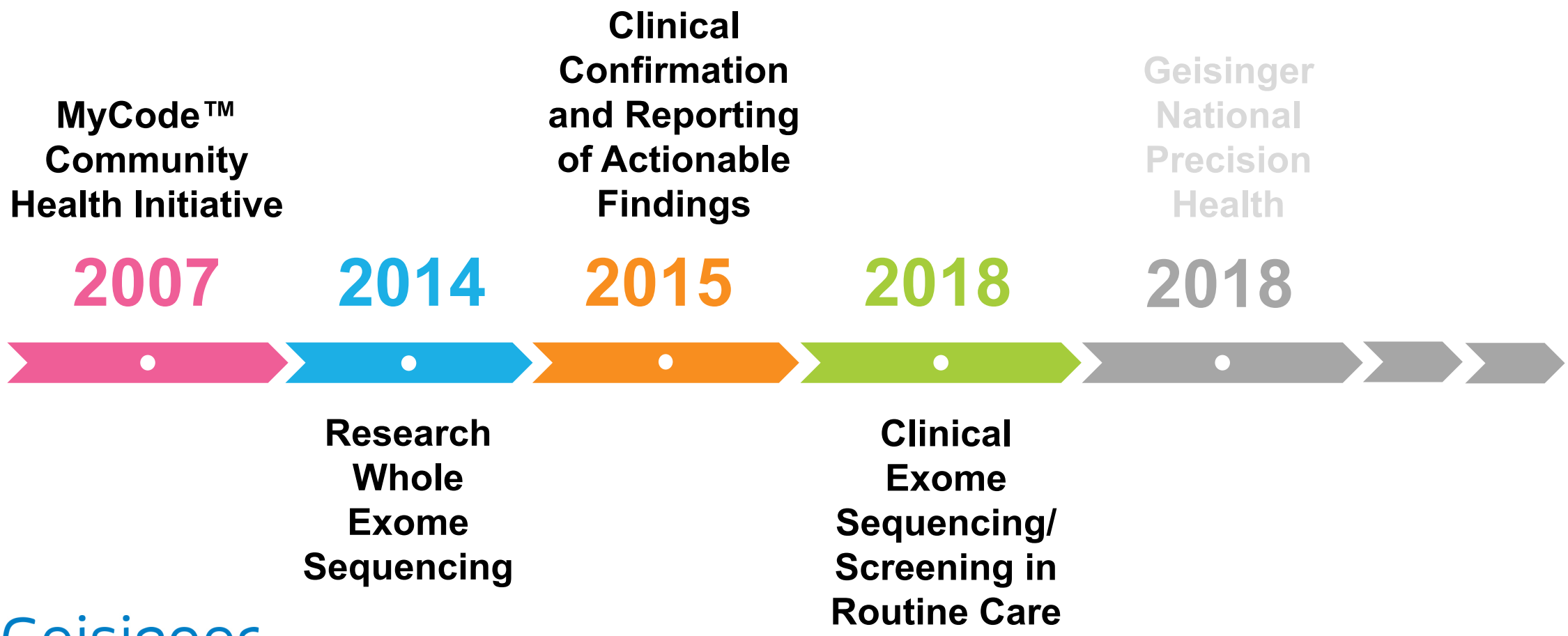
USING GENOMICS TO IMPROVE PATIENT CARE:

The Evolution of Geisinger Genomic Precision Health



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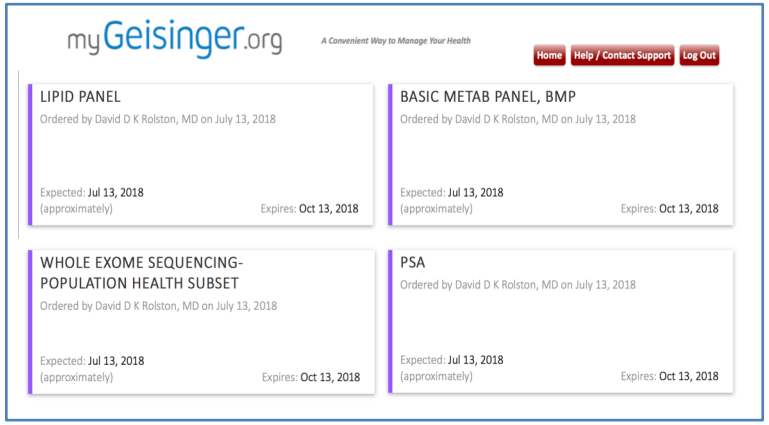
A CLINICAL IMPERATIVE:

Research and Clinical Pathways to Precision Health

Clinical Exome Sequencing in Routine Care



- **Launched July 2018, ~60 genes**
- **Verbal consent during clinic visit**
- **250+ patients consented to date**
- ***Goal*: all interested patients**
- **~150 clinical WES to date (2-3 wk TAT)**
- **6 positives thus far** (*MSH2, RET, BRCA2, MYH7, RYR1*)
- → **Family cascade testing**
- **Learning laboratory for process improvements**

Population Health Screening

- Fully incorporated into routine healthcare visits
- Minimal time required by provider – not different from any other screening test offered
- PCPs informed of all positive results, with an automatic referral to genetic counseling
- *Goal:* keep our patients healthy rather then treating them only after they get sick

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Primary Care Clinical Model

Testing offered to all adults by Primary Care Physician

PCP will discuss information about the test, get verbal consent to do testing, and order the test.

Blood sample collected

Sample shipped to the clinical sequencing lab

Genomic data are analyzed

Report sent to PCP and entered into EHR

Automated referral to Genetic Counselor to discuss results and recommendations

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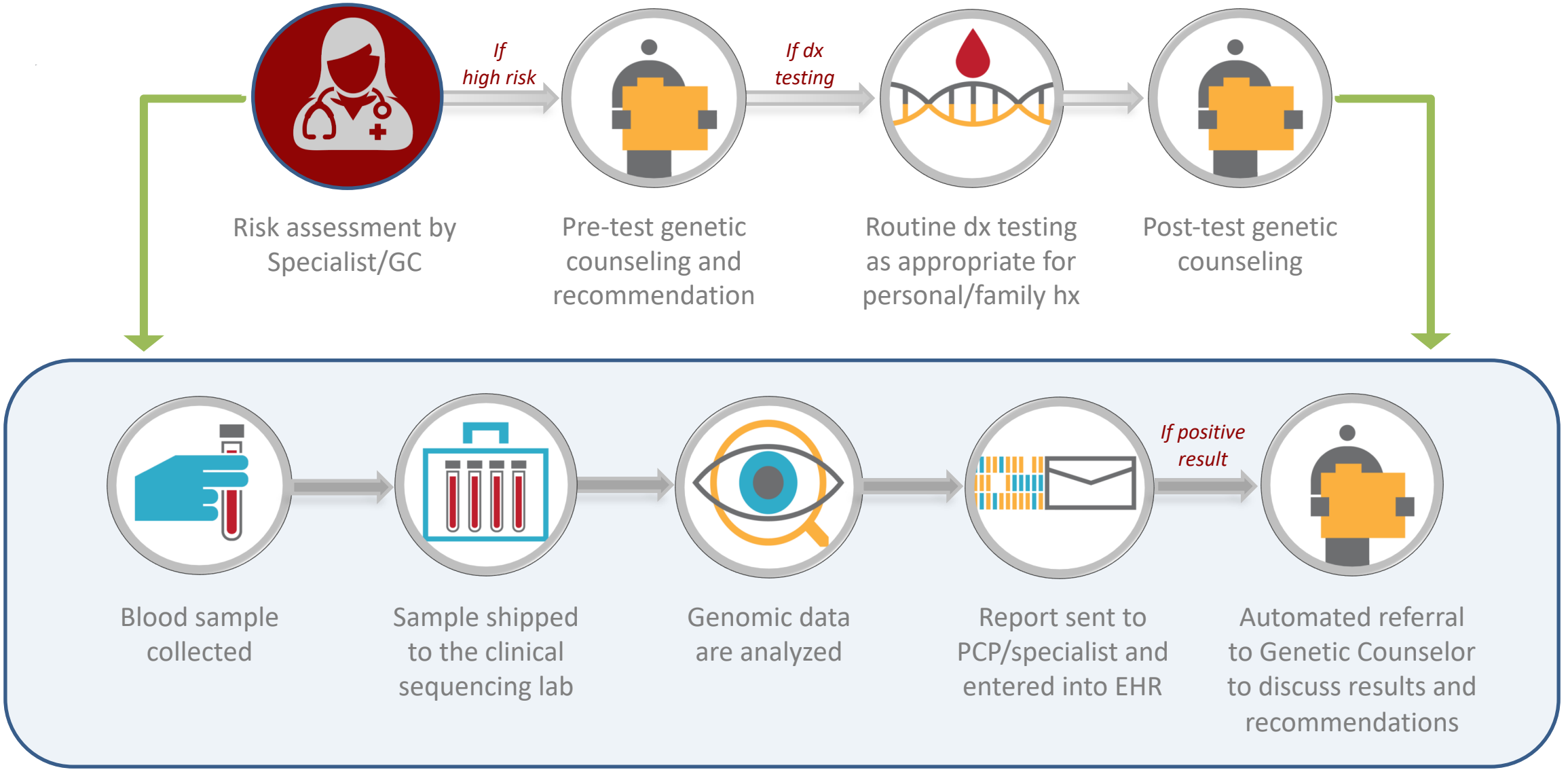
Specialty Care Clinical Model



Just-in-Time Physician Education

What you need to know.

When you need to know.

All in one page.

Pathogenic/Likely Pathogenic *BRCA1* Variant: Clinical Next Steps

Patient has increased risk for associated cancers – breast, ovarian, pancreatic, prostate

1. Evaluate patient for history and symptoms of associated cancers
2. Manage risk according to clinical evaluation and published guidelines summarized below[1]
3. Encourage patient to share result with at-risk relatives
    - First-degree relatives (parents, siblings, children) have 50% risk of inheriting familial *BRCA1* variant

Clinical resources at Geisinger

- Clinical Genomics (XX referral and contact info for on-call genetic counselor)
- Inherited Risk Breast Clinic (XX referral and contact info)

Cancer Risks[2,3,4]

Cancer Type	*BRCA1*-Associated Cancer Risk	General Population Risk
Female breast	46%-79%	12%
2nd primary breast	21% within 10 years	2% within 5 years
Ovarian	39%-53%	1%-2%
Pancreatic	1%-3%	0.5%
Male breast	1%-2%	0.1%
Prostate	Up to 33%	11%

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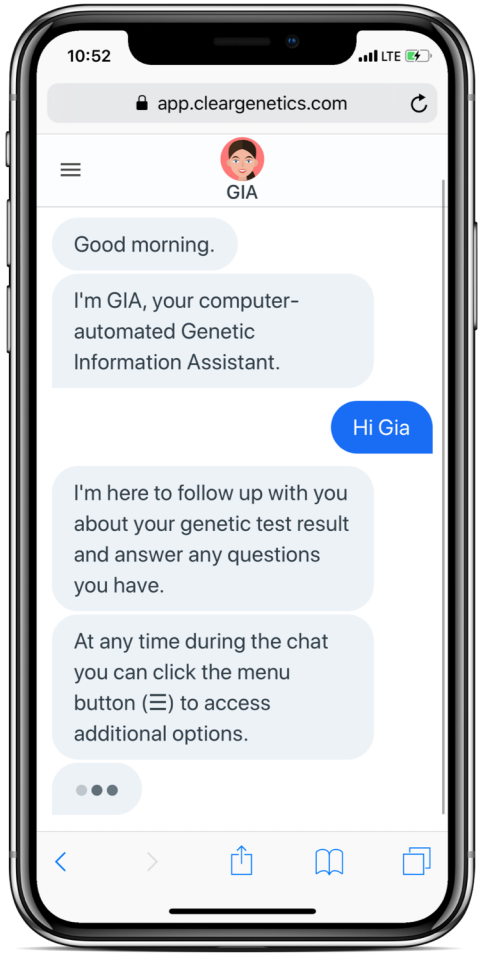
Chatbots for Scaling Consenting & Genomic Counseling

(co-development project with Clear Genetics, Inc.)

In some routine settings, can reduce need for human expert GC by 90%.



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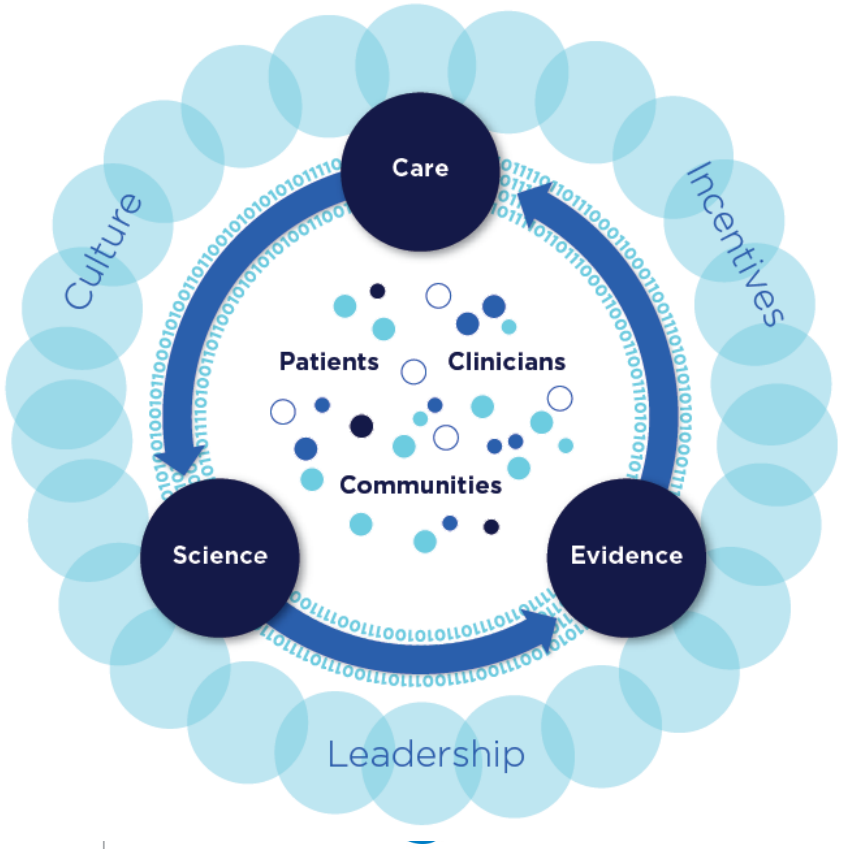
FOUR KEY LESSONS LEARNED:

Research and Clinical Care in a Learning Healthcare System

We do ***not*** have to wait until we understand everything; that's an unachievable and unthinkable goal. It does not serve our patients well.



Research and clinical care should not be separate. It's an endless and virtuous cycle.

Focus research enterprise on how it can best impact health care. The first patient a doctor sees benefiting from research will change attitudes.

Advanced EHR/clinical data warehouses offer opportunities for phenotype/genotype research with massive amounts of data that should be open to all.

What have we learned at Geisinger over the past 11 years?

Healthcare should focus on the end point, where one can make a difference and have impact

- Our patients count on this

Let *clinical* sequencing lead

- Research will benefit at its own pace, but patients are waiting

Do the whole exome, not just panels

- Today's expediency will be tomorrow's mistake

Serve our patients today. But prepare for tomorrow

- We do not have to know everything, but we have to be willing to start

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What have we learned at Geisinger over the past 11 years?

Current clinical guidelines are inadequate

- Miss up to 50% of at-risk individuals in population
- Population health screening misses none of them

Overall population incidence of pathogenic variants

- Higher than predicted clinically (often much higher)
- ? Incomplete penetrance / variable expressivity
- ? Polygenic inheritance / modifiers of risk

Population screening informs cascade testing

- Every 1 case leads to 6 first-degree relatives on average

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COMPLEXITY OF GENETIC DISEASE:

Genomics in Medicine

CLINICAL

- OMIM: **3,600** genes with phenotype—causing mutation(s)

  The 'Clinical Genome' or 'Mendelome'…

- More genes and variant reclassification over time

  Iterative reevaluation and updated clinical reports

RESEARCH

- Polygenic complex disease and Polygenic Scores
  - Heart disease, cancer, diabetes, neurodevelopment, neurodegeneration, obesity, neuropsychiatric conditions
  - Other 'omics (RNA, protein, microbiome, epigenetics….)
  - Somatic genomes, single-cell genomes

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Genomics and Precision Health: Our Commitment

This is not primarily a matter of technology and science, nor just of economic models

This reflects our commitment to community partnerships and an **investment in the health and well-being** of our neighbors

Geisinger is the trusted healthcare partner for implementation of genomic and precision health

Not just someday. ***Today.***

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THE PLAN:

Genomic Precision Health on a National Scale

A Partnership of 'First-Movers' for Implementation of Precision Health

Like-minded health systems committed to the vision of genome-based population health screening to improve patients' health and healthcare over the lifespan

- Offer clinical genomic sequencing as part of **routine clinical care *today***
- Combine and share data to **accelerate research and improve healthcare *tomorrow***

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GEISINGER MODEL OF PRECISION HEALTH:

Genetic Code & ZIP Code

- **Anticipatory medicine**
  - Disease prevention
- **Earlier detection** of disease
  - Better management of risk
- Based on variability in **genes, environment, and lifestyle** *in each individual*

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