Caring

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Leveraging Informatics to Improve Health Outcomes and Value

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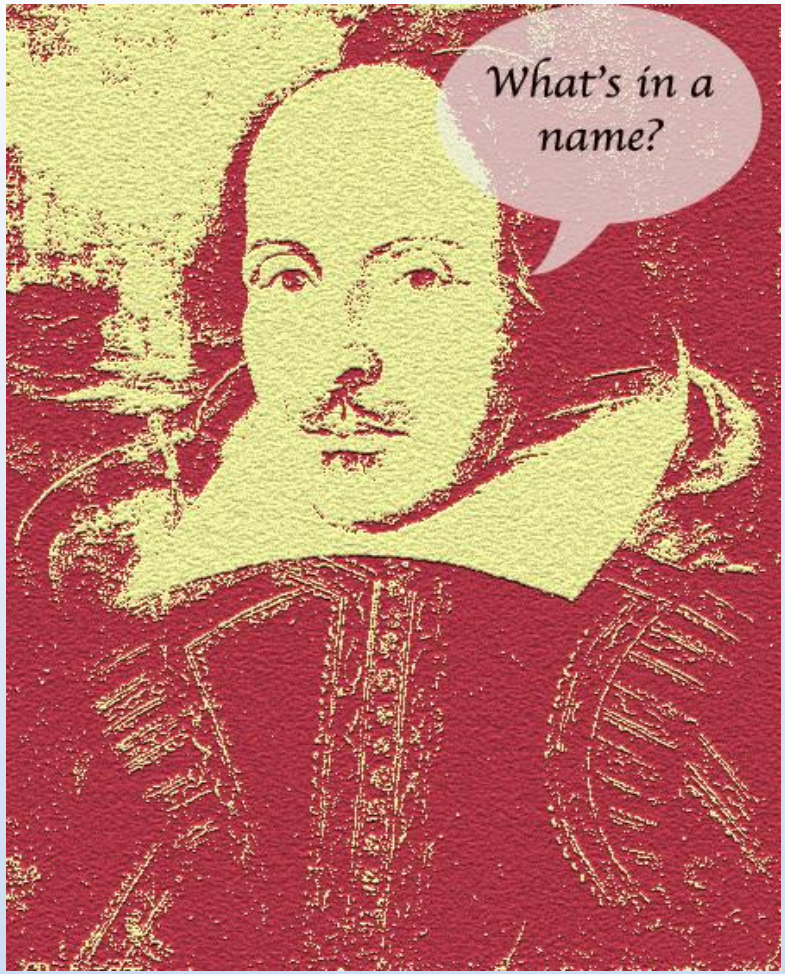
Topic Perspective

Genomic Medicine

Personalized Medicine

Individualized Medicine

Precision Medicine



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

Personalized Medicine-Definition

"…use of information and data from a patient's genotype, or level of gene expression to stratify disease, select a medication, provide a therapy, or initiate a preventative measure that is particularly suited to that patient at the time of administration"

– Wikipedia

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."

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

Personalized vs. Precision Medicine

- Clinicians practice personalized medicine (and always have)
- 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

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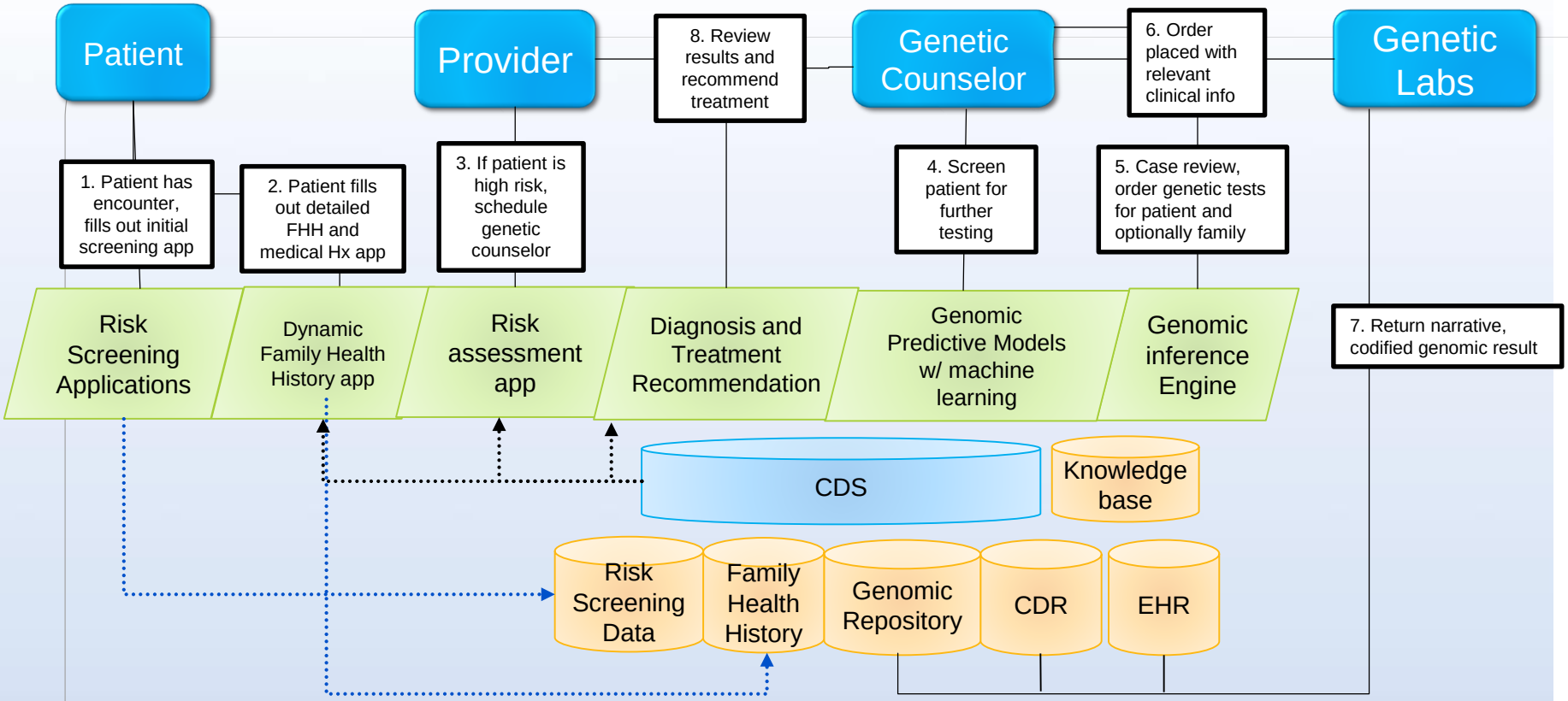
Adapted from The Innovator’s Prescription A Disruptive Solution for Healthcare. Christensen , Grossman and Hwang, 2009

GenomeFIRST™ A New Paradigm for Return of Genomic Results



The Current Approach—'Phenome First' Ideal

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mycode

- GHS Biorepository started in 2007
  - Followed extensive consultation with GHS patients and other stakeholders that informed design of project
  - Defined as Community Health Initiative as opposed to biorepository
- Participants sign broad consent to combine EHR data (prospective, de-identified) and biospecimens
- Consent includes the ability to re-contact participants for future projects and communicate medically actionable results
- Exome sequencing on participants (~53,000)

GenomeFIRST ™

The prompt for the clinical encounter is the DNA variant

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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

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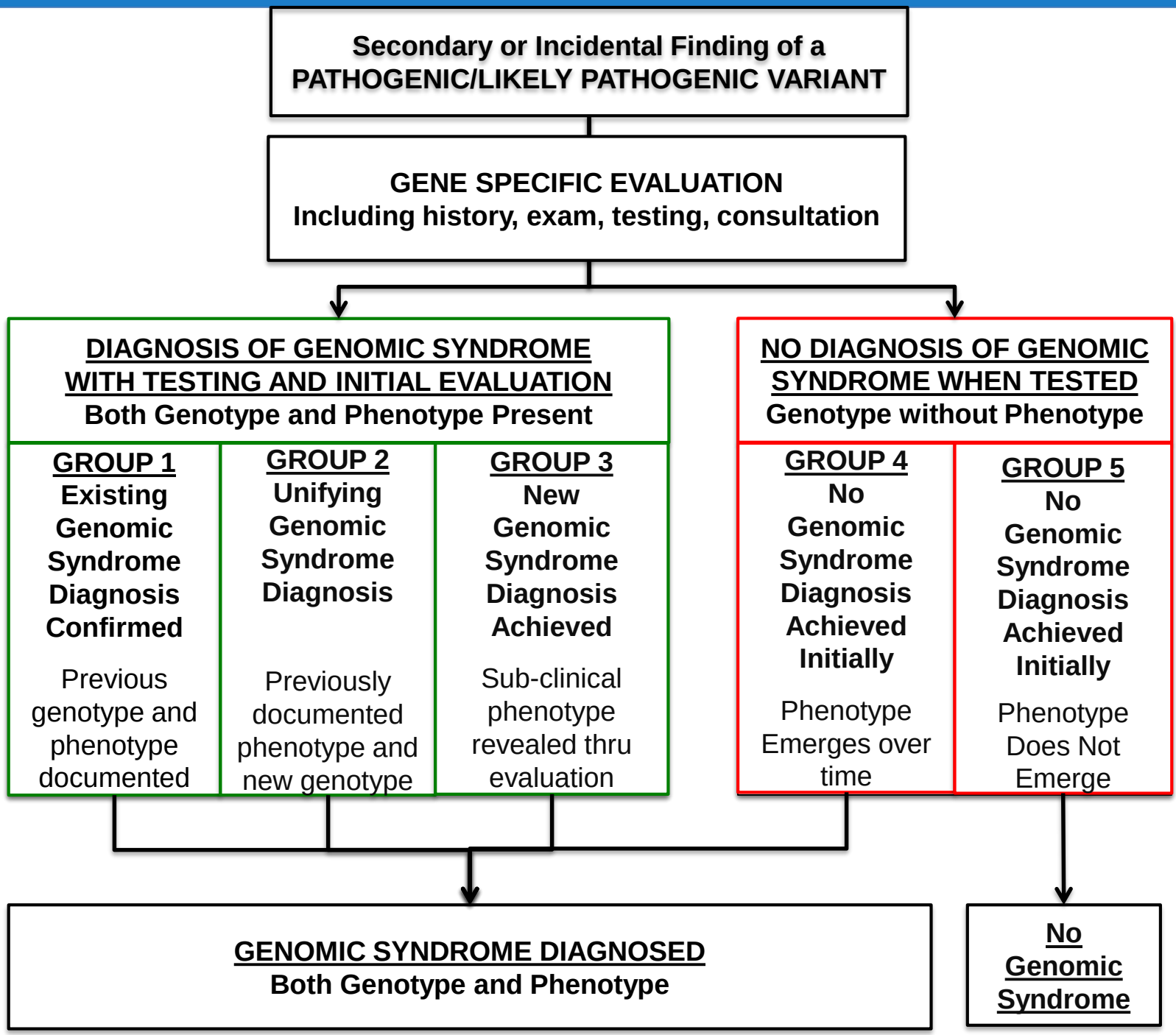
GenomicFIRST™ Return of Results

The Geisinger 76 (G76)

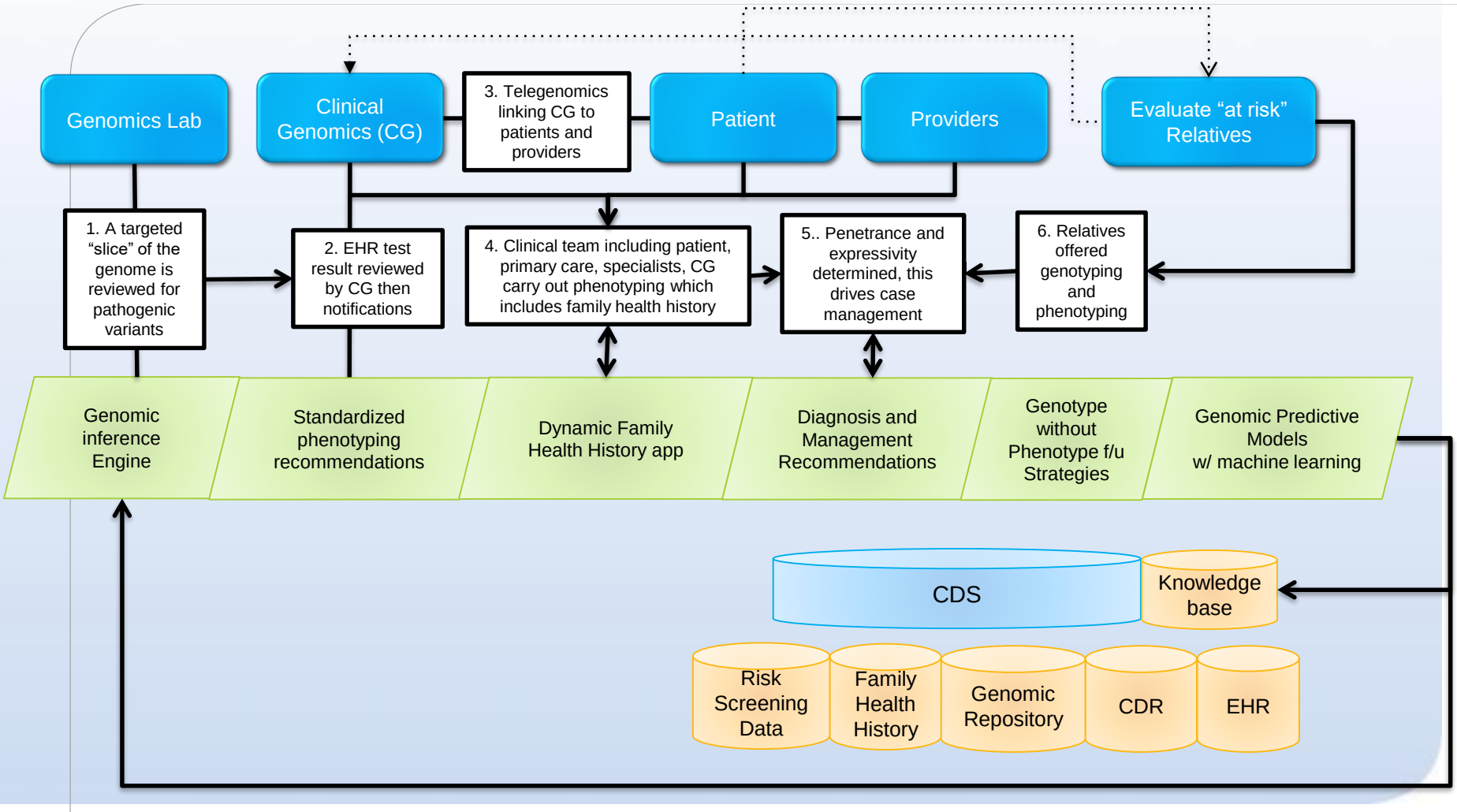
- Focus on 27 conditions (76 genes)
- Builds on the ACMG Incidental Findings List (published 2013)
- Cancer predisposition (e.g. *BRCA1* and *BRCA2*)
- Cardiovascular disease (e.g. FH)
- Malignant Hyperthermia
- Hereditary Hemorrhagic Telangiectasia
- Ornithine Transcarbamylase (OTC) deficiency

Three Most Prevalent Conditions Half of those Returned

GENOMIC CONDITION	POPULATION PREVALENCE	CLINICAL RISK	DISEASE-ALTERING INTERVENTION
Familial Hypercholesterolemia (*LDLR, APOB,PCSK9)*	1 in 175	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**


Secondary or Incidental Finding of a PATHOGENIC/LIKELY PATHOGENIC VARIANT
GENE SPECIFIC EVALUATION
Including history, exam, testing, consultation
DIAGNOSIS OF GENOMIC SYNDROME WITH TESTING AND INITIAL EVALUATION
Both Genotype and Phenotype Present
NO DIAGNOSIS OF GENOMIC SYNDROME WHEN TESTED
Genotype without Phenotype
GROUP 1
Existing Genomic Syndrome Diagnosis Confirmed
Previous genotype and phenotype documented
GROUP 2
Unifying Genomic Syndrome Diagnosis
Previously documented phenotype and new genotype
GROUP 3
New Genomic Syndrome Diagnosis Achieved
Sub-clinical phenotype revealed thru evaluation
GROUP 4
No Genomic Syndrome Diagnosis Achieved Initially
Phenotype Emerges over time
GROUP 5
No Genomic Syndrome Diagnosis Achieved Initially
Phenotype Does Not Emerge
GENOMIC SYNDROME DIAGNOSED
Both Genotype and Phenotype
No Genomic Syndrome

Geisinger GenomeFIRST™ Clinical Workflow



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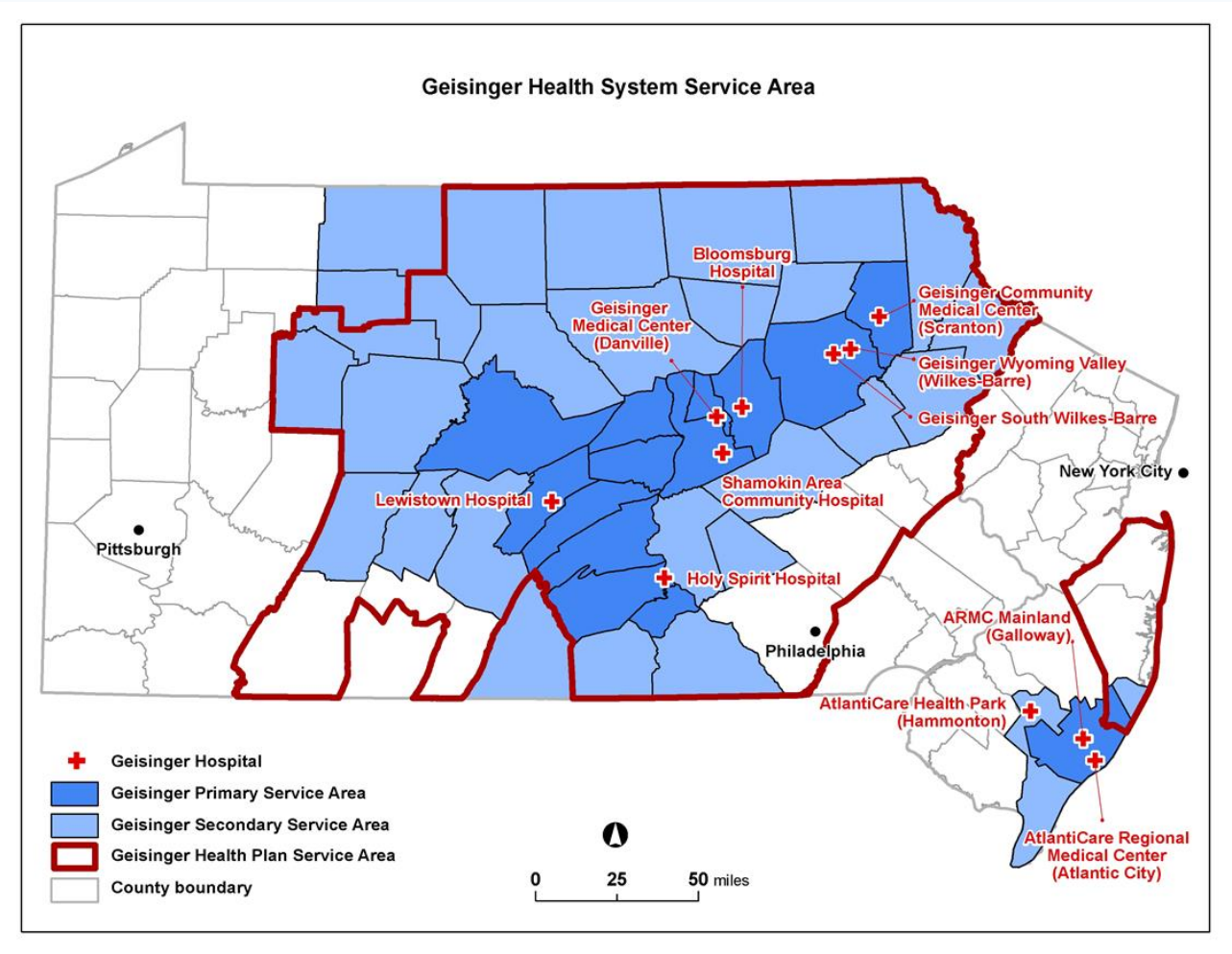
Implementation Barriers

- System leadership
  - Genomic medicine is represented in both the system and research strategic plans
- Clinicians
  - Presentations at system-wide and department level business meetings and conferences
  - Identifying clinician champions in relevant areas
  - Take advantage of existing infrastructure
    - Multidisciplinary hereditary cancer clinics
    - Lipid Clinic
- Education and support for providers and patients
  - Goals courses (CME available)
  - Provider and patient facing genome reports
  - Genomic Medicine Consultants
- Informatics systems

Measuring Value

- Define outcomes for GenomeFIRST program
  - Health Outcomes
    - Process
    - Intermediate
    - Disease/Health
  - Patient-Centered Outcomes
    - Satisfaction
    - Engagement
    - Information
    - Access
    - Self-assessed well being
  - System Outcomes
    - Costs incurred/avoided
    - Utilization
    - Patient experience
    - Visibility/reputation

Value from the Health System Perspective



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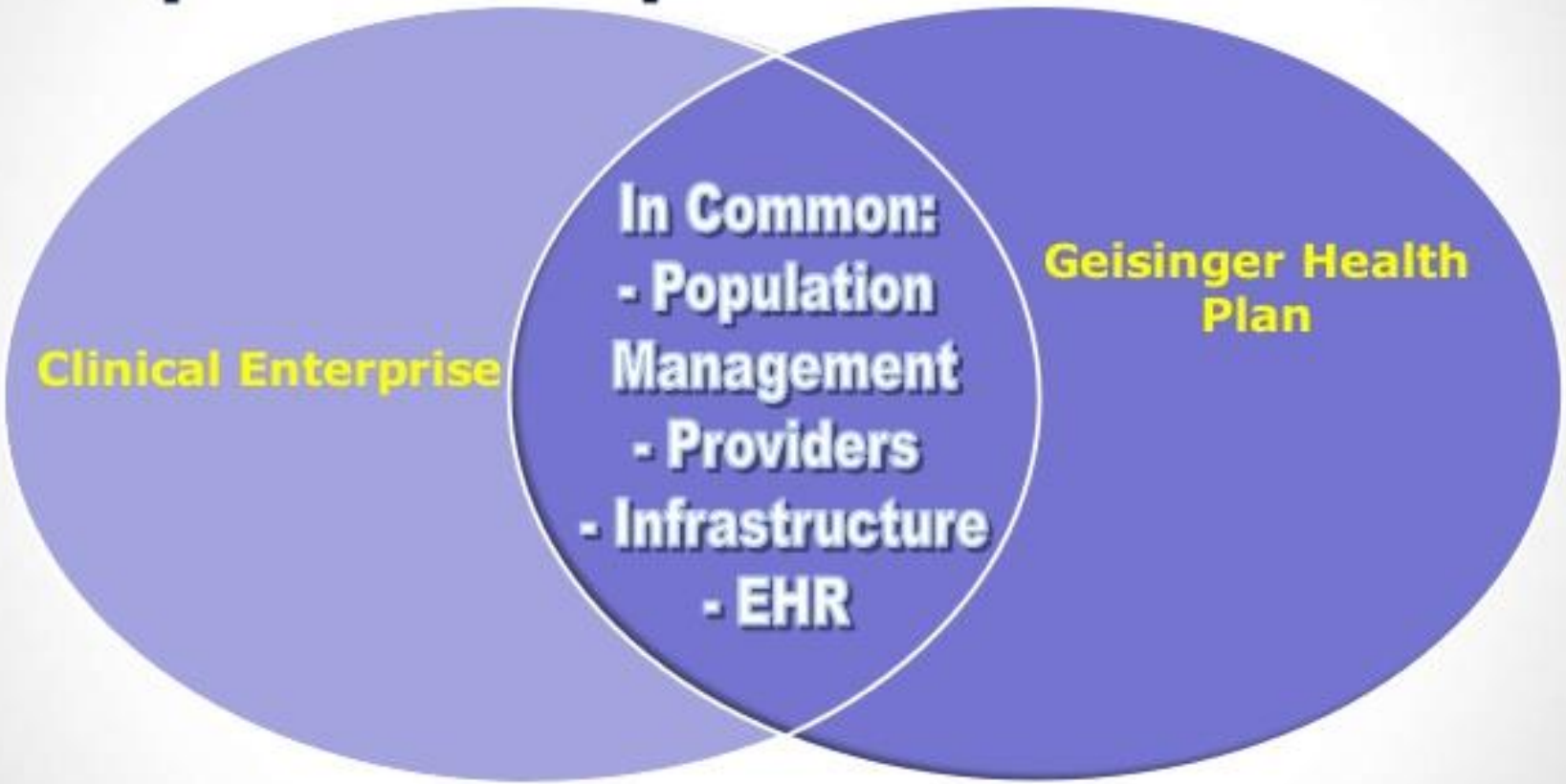
The Sweet Spot: Our realm of partnership and innovation



Aligned objectives for the greatest impact

Value: Genomics over the Lifespan

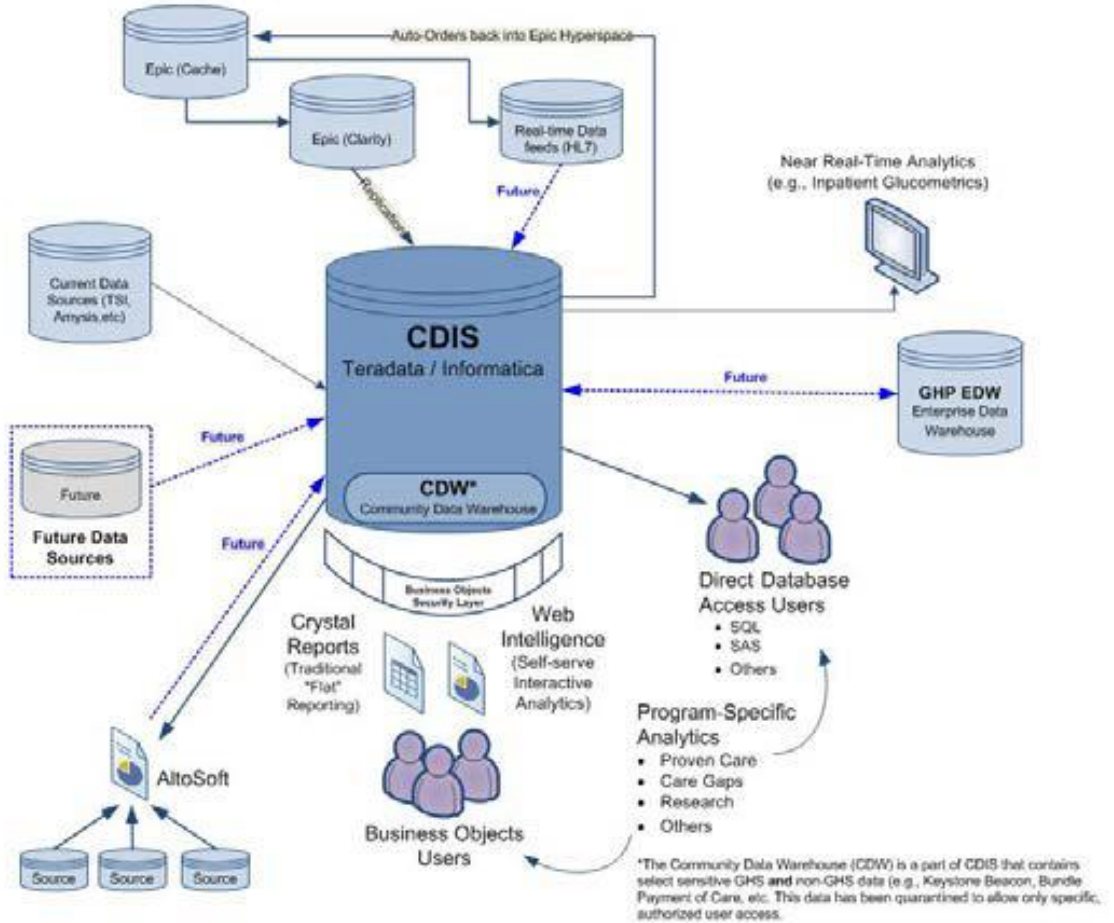
Advantages

- Cost spread out over lifetime of care
- Avoids need to repeat testing
- Information can be used as soon as it is needed
- More precise pharmacologic therapy
  - Avoid adverse events
  - Choose best tolerated most effective therapy

Questions

- Storage of information
- Presentation of information when needed at point of care
- Information available wherever patient receives care
- Evidence of benefit (or lack thereof)
- Updating information
- Discrimination
- Health Disparities

Storage



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Information at point of care

- Focus on passive clinical decision support
- Highlight Clinical Genome Resource (ClinGen)

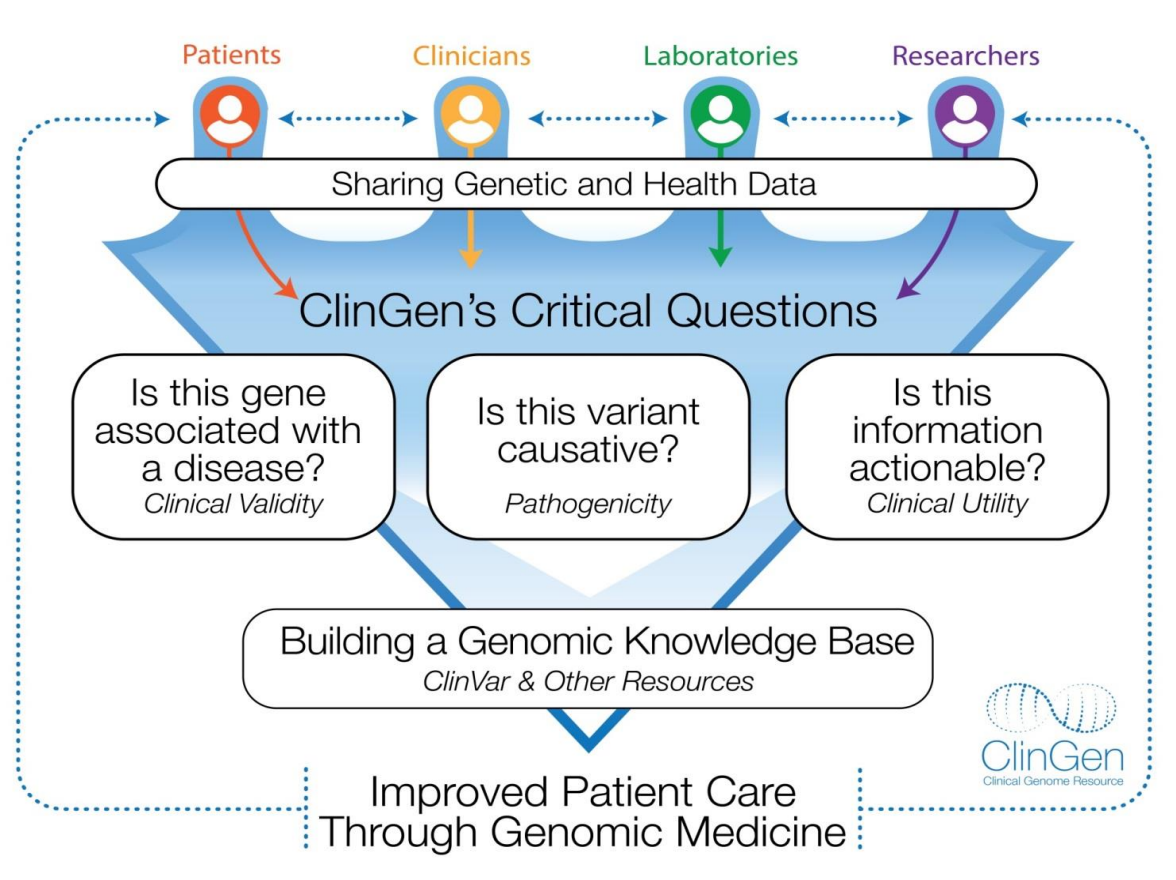
ClinGen

The Clinical Genome Resource (ClinGen) aims to create an authoritative resource that defines the clinical relevance of genes and variants for use in precision medicine and research.

NHGRI-funded program launched Sept. 2013

- FY13-FY16 = $28M Total Costs
- 3 U grants, working closely with NCBI's ClinVar
- Co-funding from NICHD and NCI
- > 350 researchers & clinicians from 90 institutions

Building a genomic knowledge base to improve patient care



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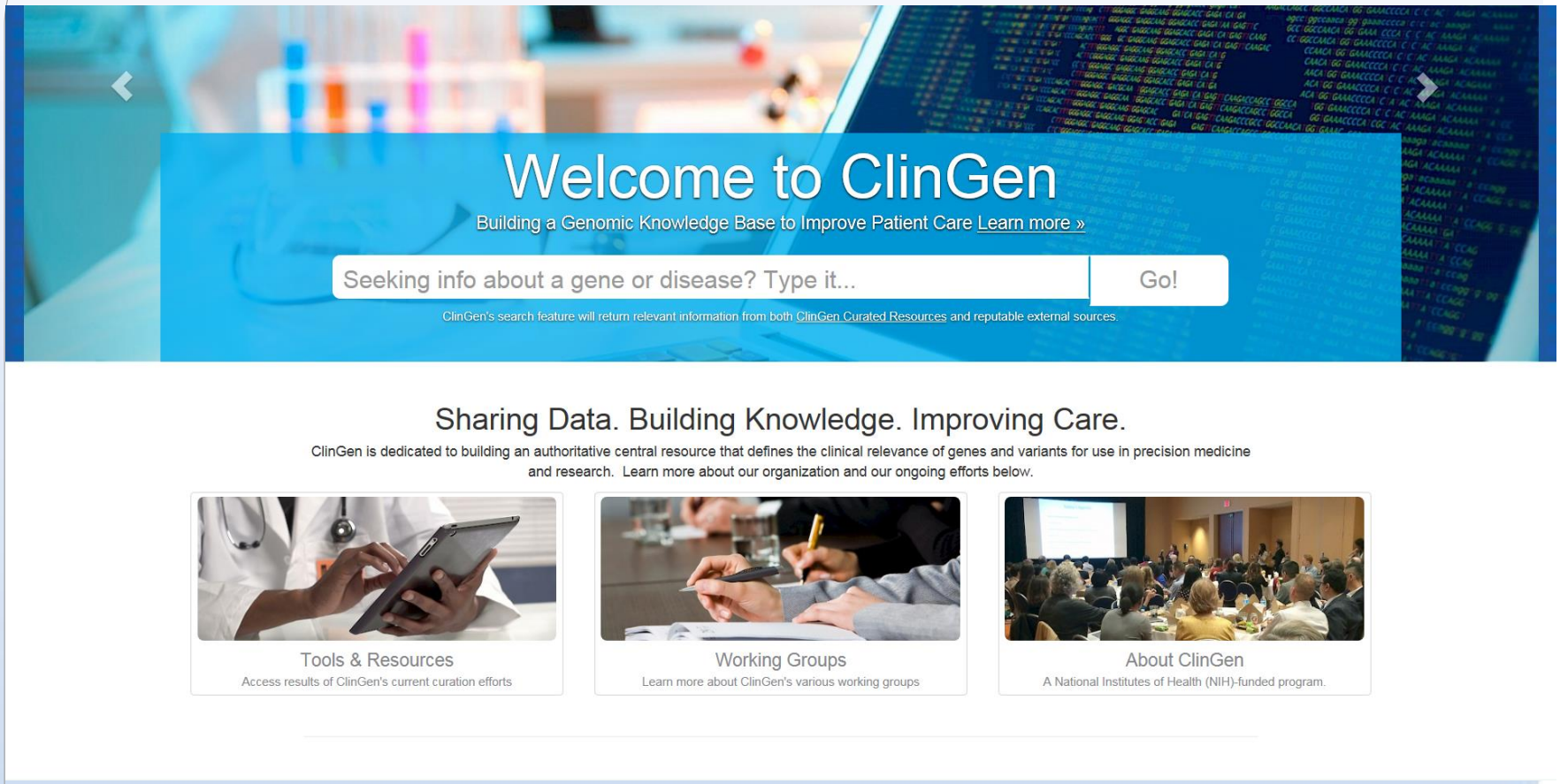
Initial Solution



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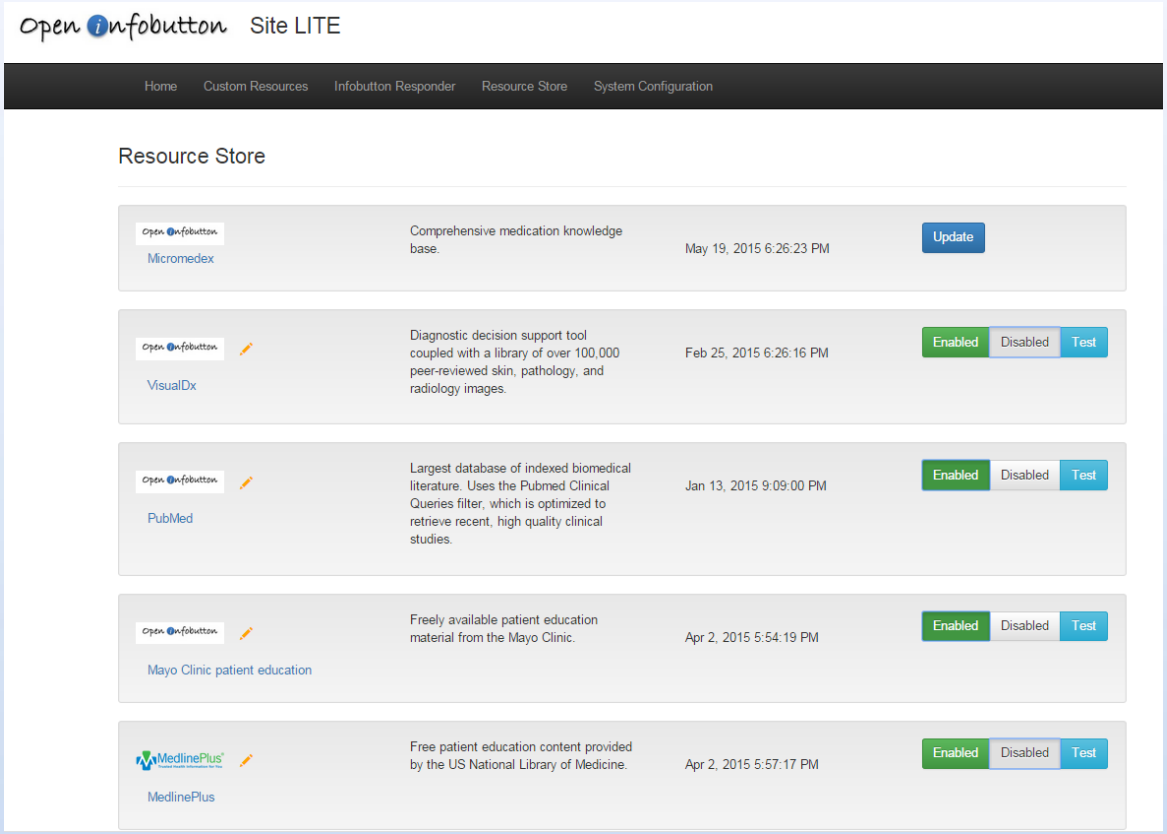
https://www.clinicalgenome.org/

Access to ClinGen resource from any OpenInfobutton compliant EHR system

http://service.oib.utah.edu:8000/app/#/home



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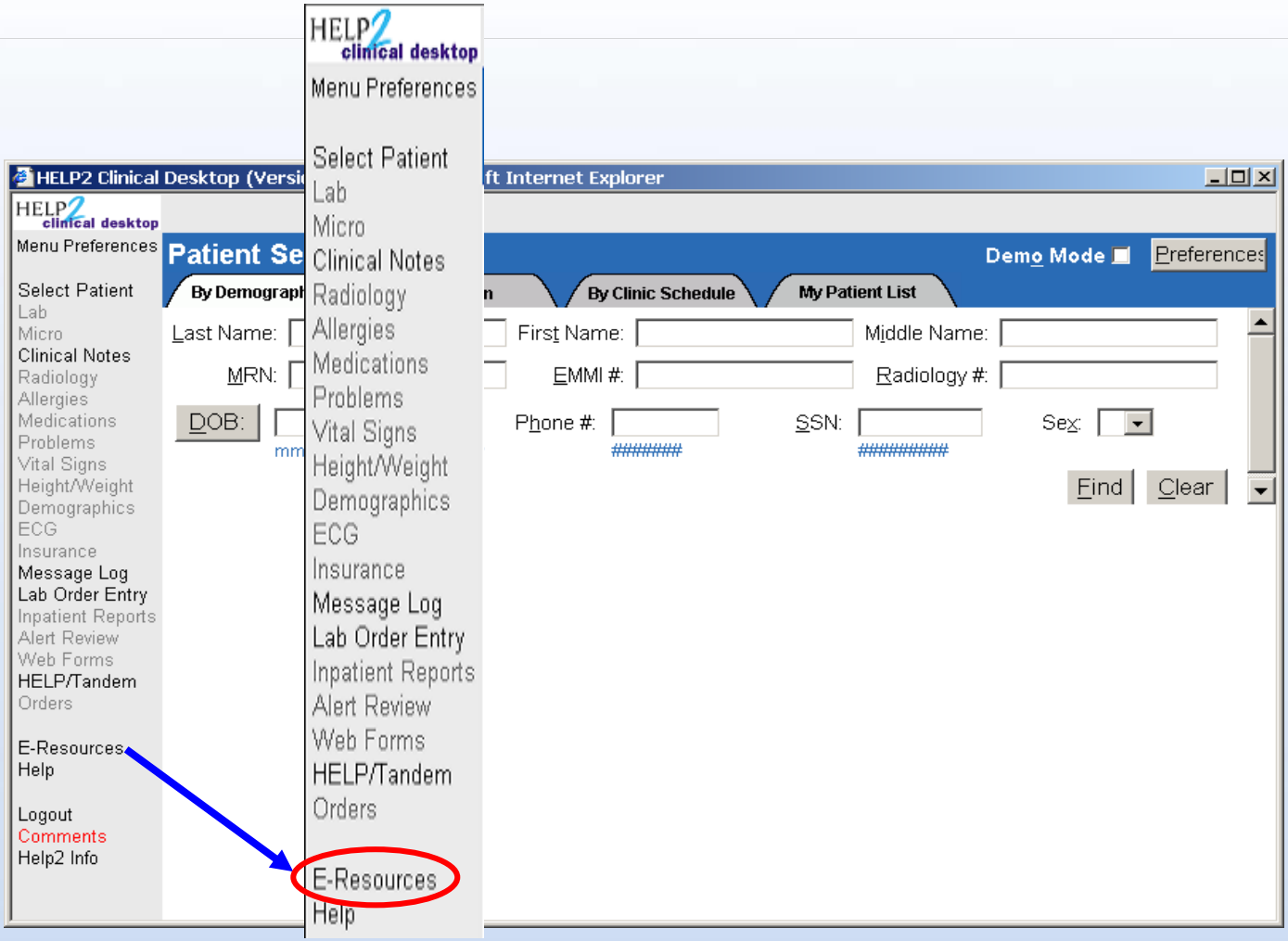
e-Resources



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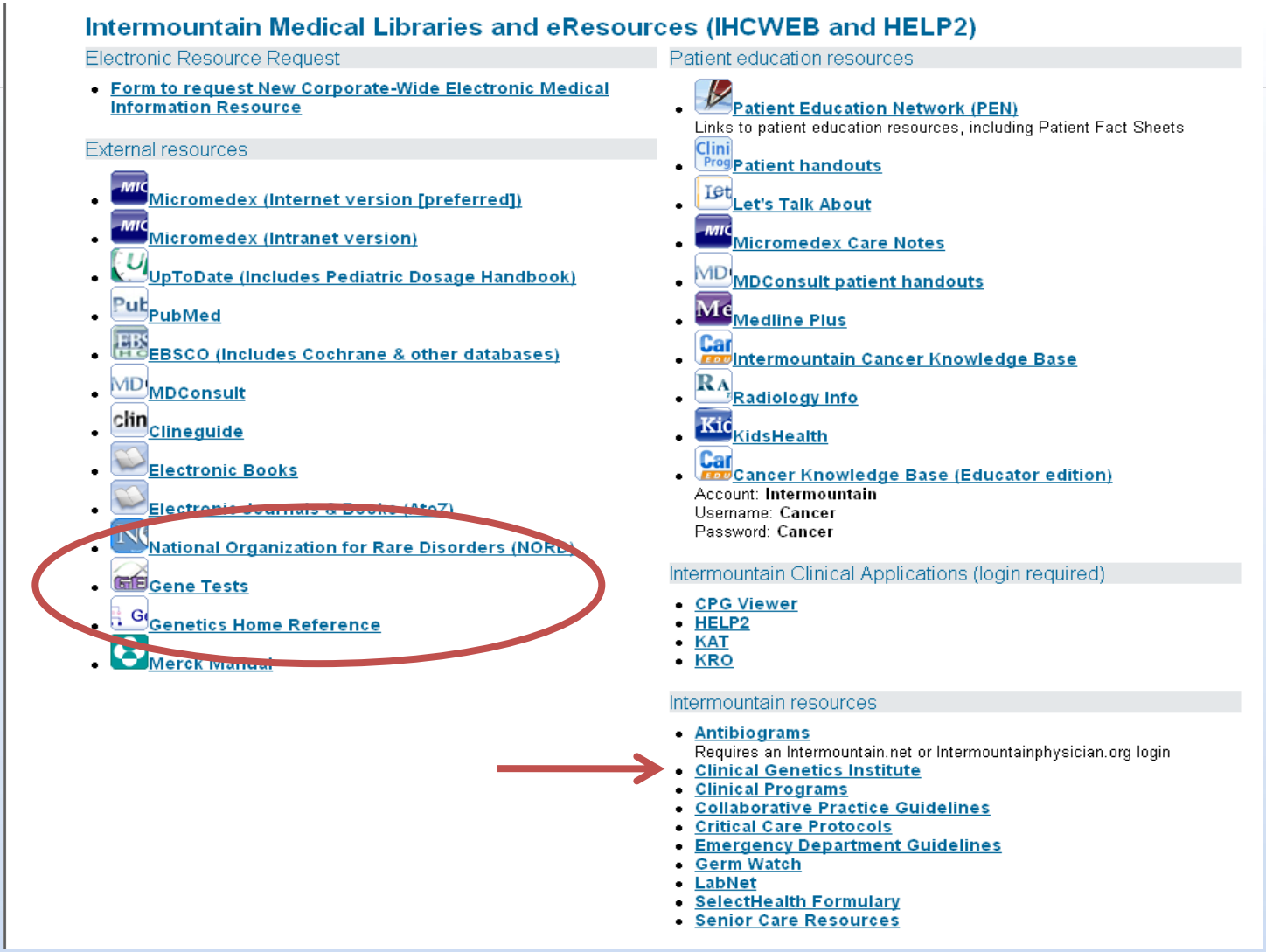


Intermountain Medical Libraries and eResources (IHCWEB and HELP2)

Electronic Resource Request

- Form to request New Corporate-Wide Electronic Medical Information Resource

External resources

- Micromedex (Internet version [preferred])
- Micromedex (Intranet version)
- UpToDate (Includes Pediatric Dosage Handbook)
- PubMed
- EBSCO (Includes Cochrane & other databases)
- MDConsult
- Clineguide
- Electronic Books
- Electronic Journals & Books (AtoZ)
- National Organization for Rare Disorders (NORD)
- Gene Tests
- Genetics Home Reference
- Merck Manual

Patient education resources

- Patient Education Network (PEN)
  Links to patient education resources, including Patient Fact Sheets
- Patient handouts
- Let's Talk About
- Micromedex Care Notes
- MDConsult patient handouts
- Medline Plus
- Intermountain Cancer Knowledge Base
- Radiology Info
- KidsHealth
- Cancer Knowledge Base (Educator edition)
  Account: **Intermountain**
  Username: **Cancer**
  Password: **Cancer**

Intermountain Clinical Applications (login required)

- CPG Viewer
- HELP2
- KAT
- KRO

Intermountain resources

- Antibiograms
  Requires an Intermountain.net or Intermountainphysician.org login
- Clinical Genetics Institute
- Clinical Programs
- Collaborative Practice Guidelines
- Critical Care Protocols
- Emergency Department Guidelines
- Germ Watch
- LabNet
- SelectHealth Formulary
- Senior Care Resources

Add ClinGen to your e-Resources

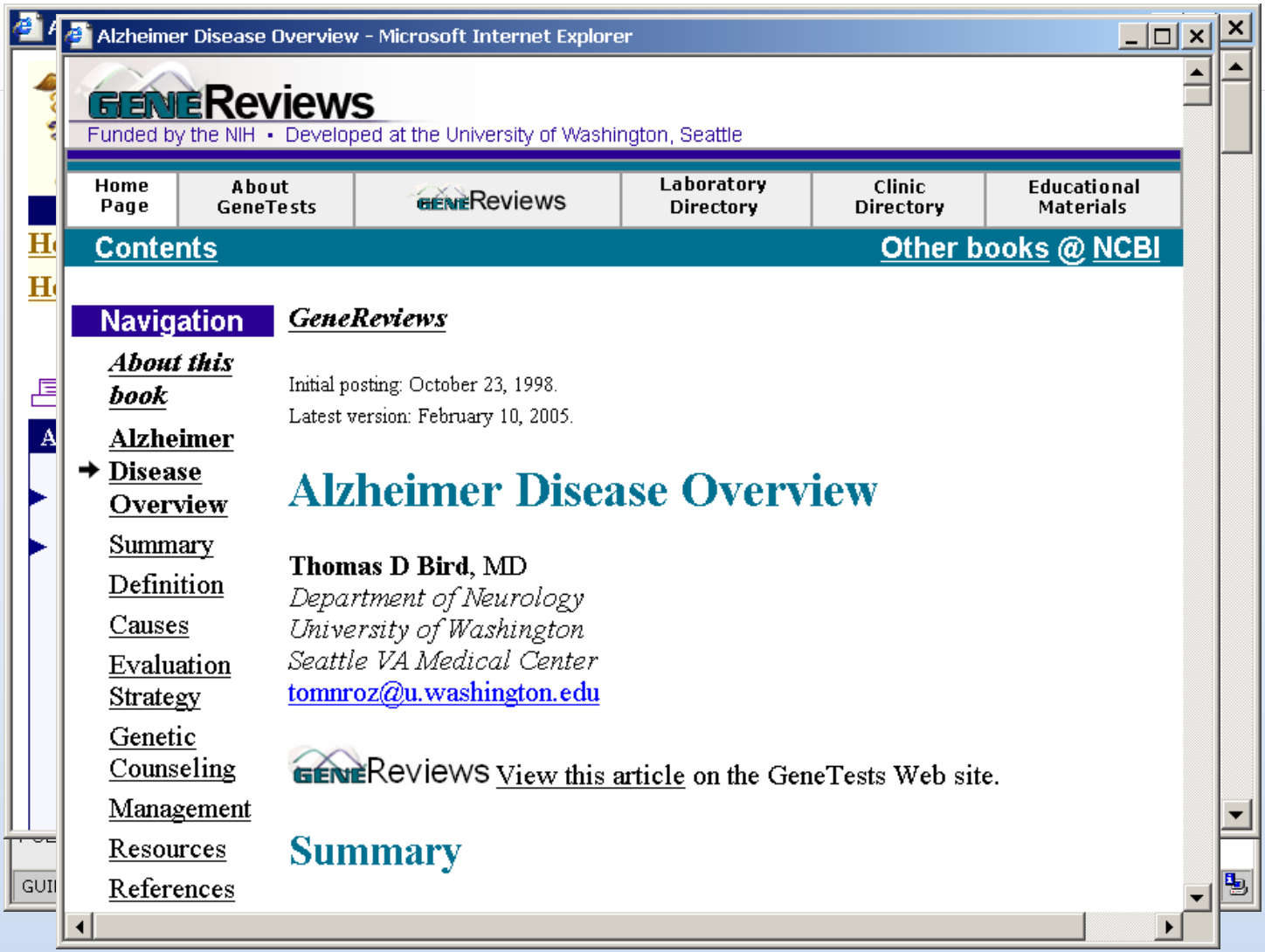
We can create a unique link for your institution so you can add to your own e-resources collection

InfoButtons

- Uses a Health Data Dictionary (HDD), InfoButtons build and run queries against e-Resources based on **patient data** and **clinical context**
- Take user to the most appropriate section(s) within a content collection
- Minimum number of mouse clicks

InfoButtons

	Resource	Terminologies (all use the HDD)
Lab results	Clineguide	LOINC codes, free-text search
Medications	UpToDate, Micromedex, Clineguide	RxNORM, NDC codes, free-text search
Problem list	UpToDate, MDConsult, Clineguide, PubMed	ICD-10-CM codes, free text search


Alzheimer Disease Overview - Microsoft Internet Explorer
GENEReviews
Funded by the NIH • Developed at the University of Washington, Seattle
Home Page
About GeneTests
GENEReviews
Laboratory Directory
Clinic Directory
Educational Materials
Contents
Other books @ NCBI
Navigation
About this book
Alzheimer Disease Overview
Summary
Definition
Causes
Evaluation Strategy
Genetic Counseling
Management
Resources
References
GeneReviews
Initial posting: October 23, 1998.
Latest version: February 10, 2005.
Alzheimer Disease Overview
Thomas D Bird, MD
Department of Neurology
University of Washington
Seattle VA Medical Center
tomnroz@u.washington.edu
GENEReviews View this article on the GeneTests Web site.
Summary

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Future Plans

Pursuing full integration with open infobutton

Add variant level searching

Solicit input from end users (that is you!!)

- Encourage your member to go to:
  - https://www.clinicalgenome.org/
- Enter diseases, genes and/or medications into the search box on the home page. It may help to generate a question or questions you may want to try and answer (examples could be: does this medication have pharmacogenomics information; does this disease have a genetic cause; what diseases are associated with this gene; are there interventions for this genetic disease)
- Navigate the content collections that appear as part of the search result
- Identify suggestions for improvement of the site, the search function and/or improving your user experience

Send suggestions to Marc Williams mswilliams1@geisinger.edu, or use the contact button on the website to reach our webmaster

Patient's information travels with them

- US healthcare system is 'dis-integrated'
- Few solutions for interoperability have been broadly implemented
- Patient is the only common actor in the system

β5

Patient-Centered Outcomes Research Institute

- Communication and Dissemination funding opportunity
- To design patient-facing laboratory reports
- To design a provider-facing genomic report
- To improve communication around the results of genomic tests for rare diseases

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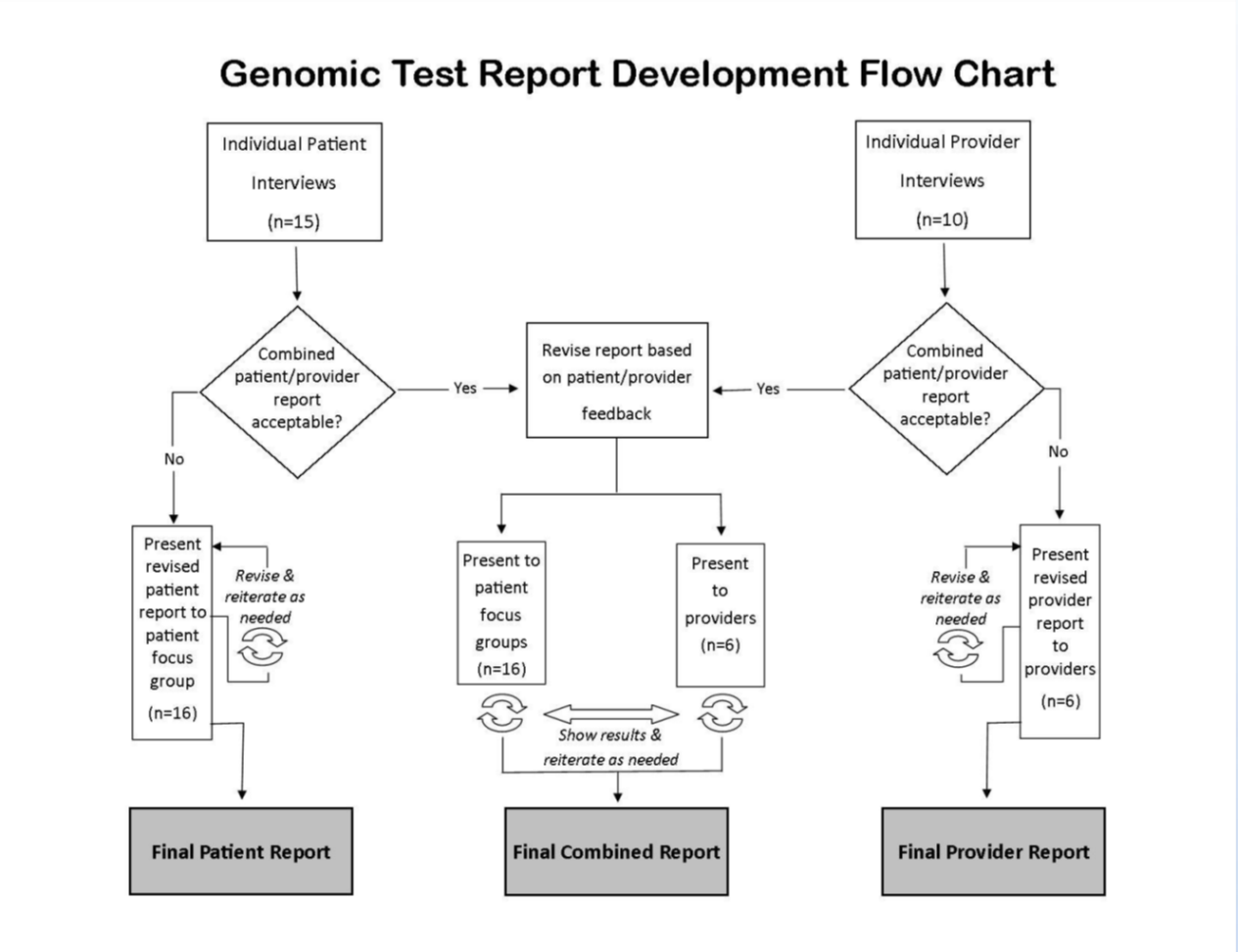
Development and Testing



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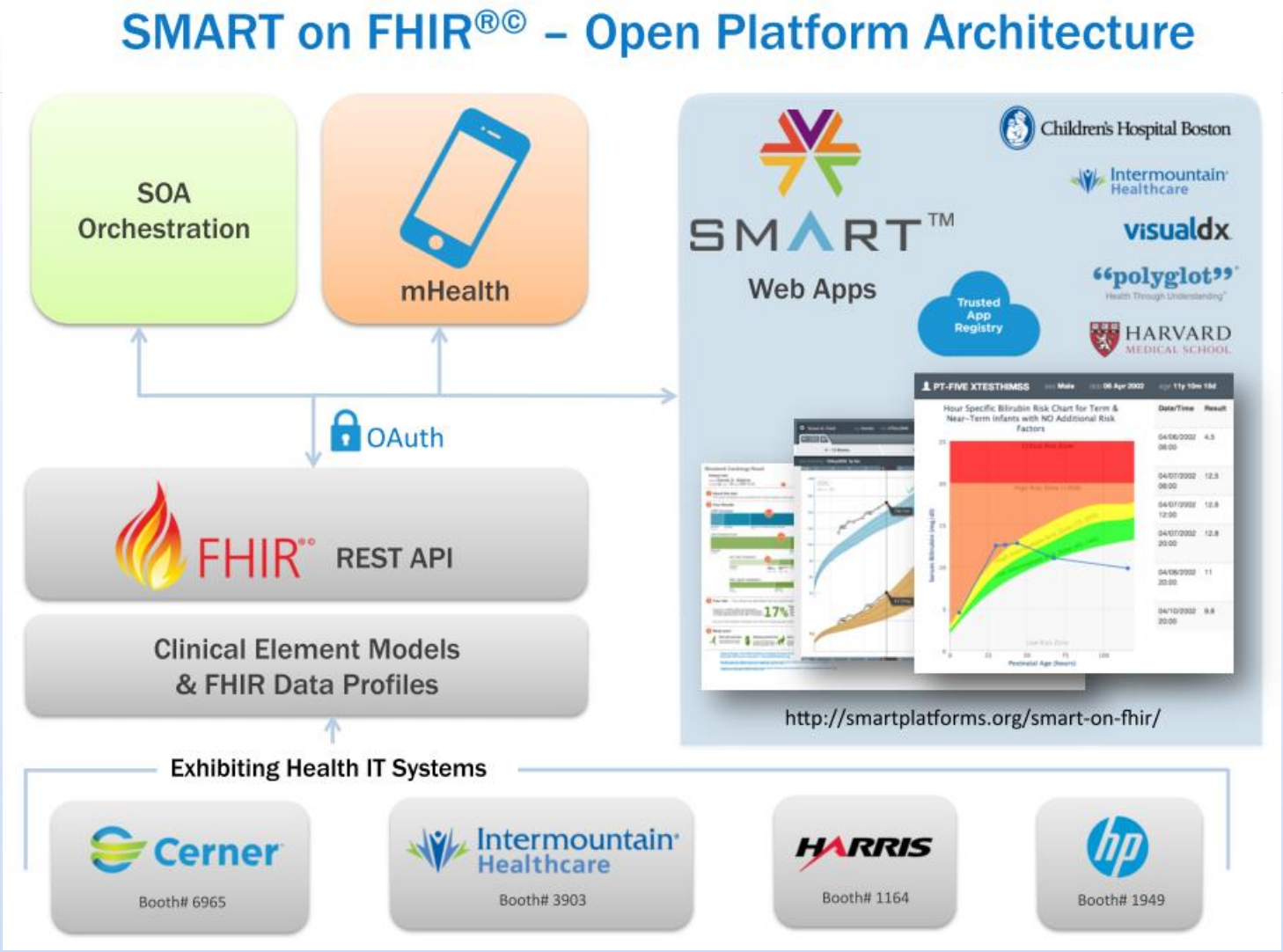
Methods: Report Development

- Preliminary report designed by the team
- Referenced published laboratory standards
- Input from patient co-investigator
- Input from consumer education/advocacy expert
- Reviewed and revised by health literacy expert
- Provided to parents prior to in-person interviews

Inter-APP-able: SMArt Platform



Mandl et al – details at http://smartplatform.org

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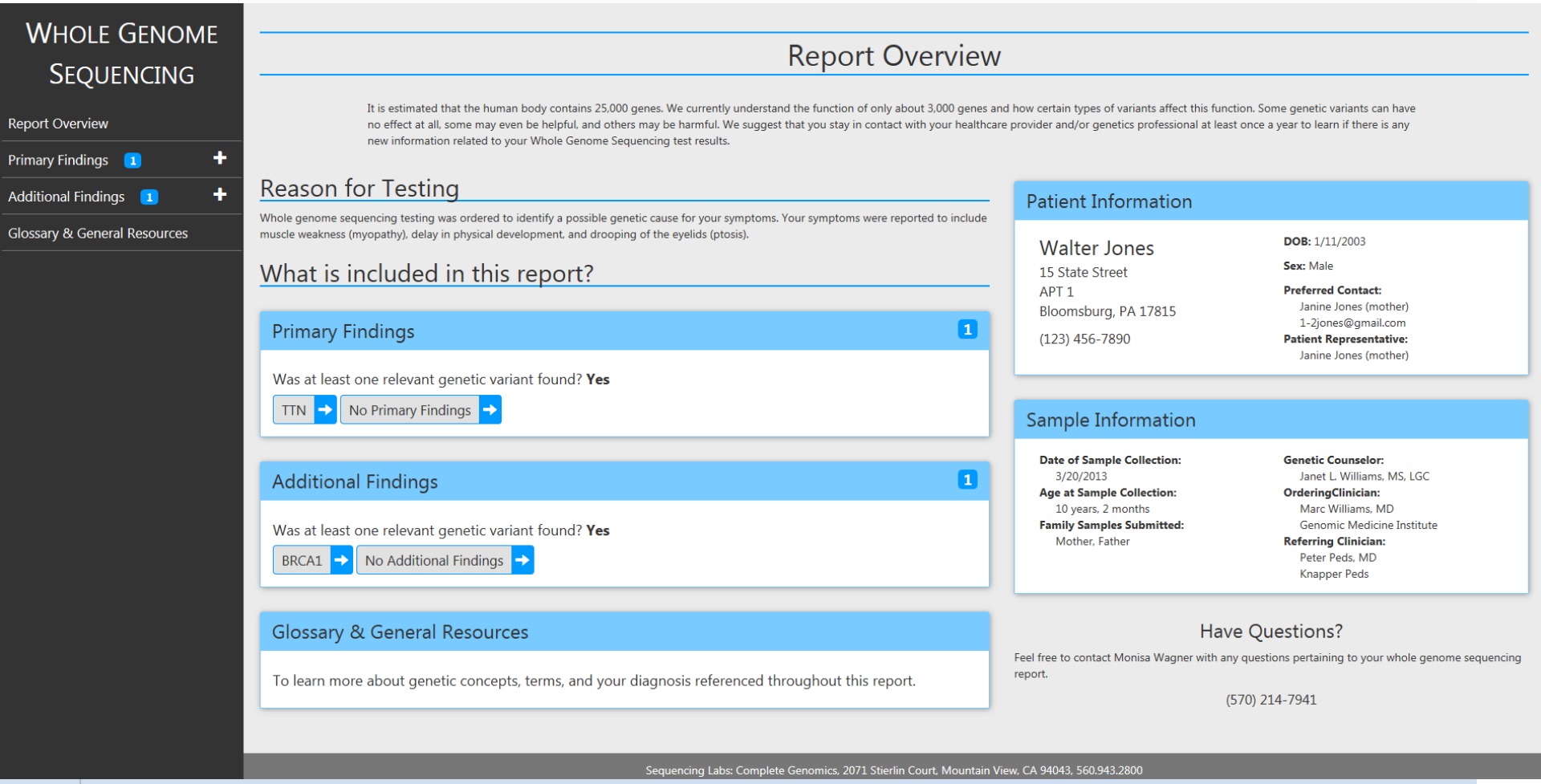
Compass Genome Report Primary Findings



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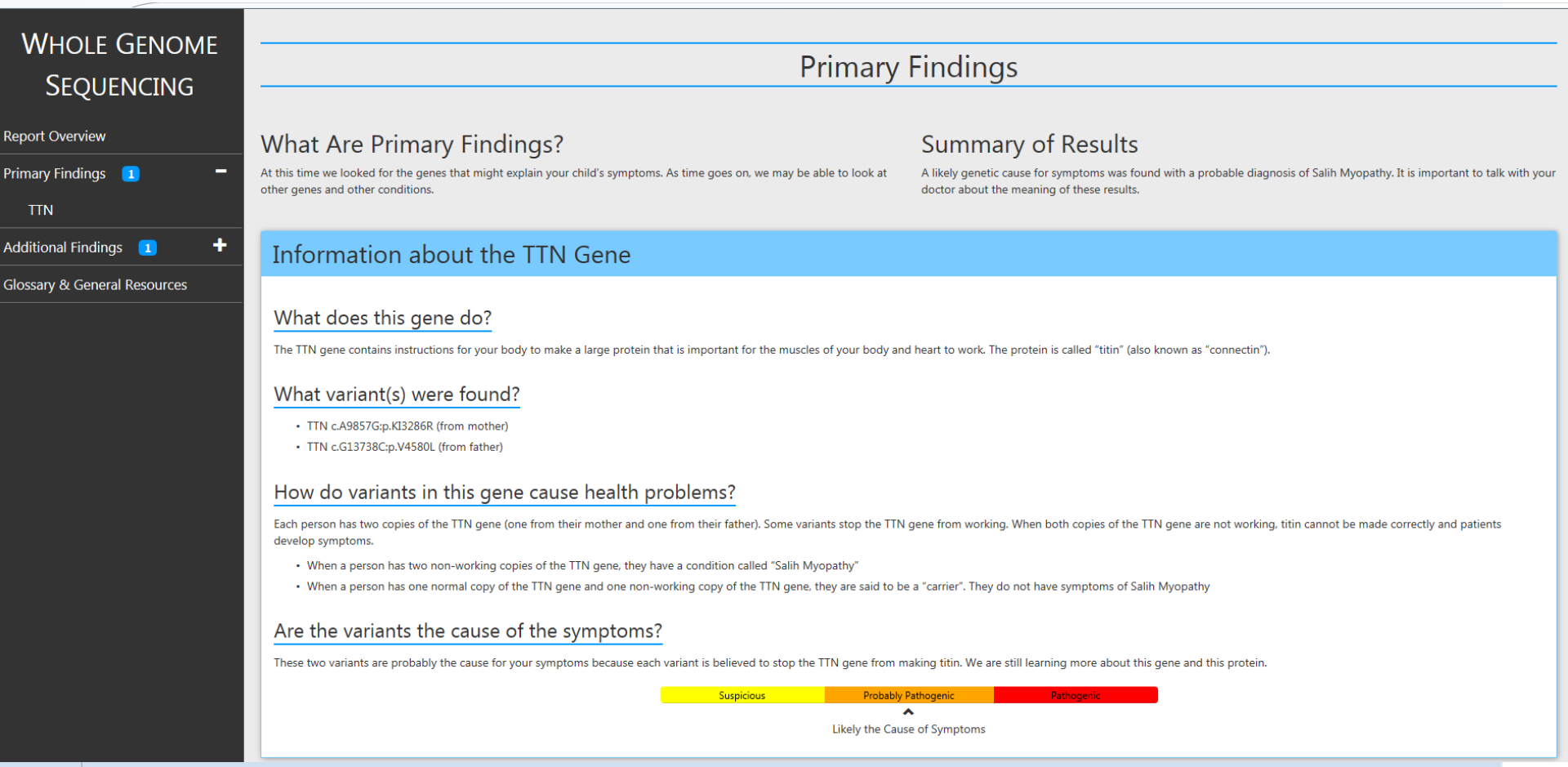
REDEFINING BOUNDARIES

Compass Genome Report Primary Findings



Compass Genome Report Primary Findings

Understanding the Diagnosis

This table summarizes the most common and medically important symptoms associated with Mowat-Wilson syndrome. There are a range of symptoms associated with this condition. Each child with Mowat-Wilson syndrome will have his or her own unique combination of the symptoms listed. Some symptoms are more common than others and are indicated this way:

How many children with Mowat-Wilson Syndrome are expected to have this symptom?

Also, keep in mind that our understanding and management of Mowat-Wilson syndrome will change as researchers continue to study this condition. It is not possible to predict what new types of treatments and interventions will be available in the future through advances in medical science.

Key	Most	Some	Few	NA

	By what age do most children with Mowat-Wilson Syndrome have this symptom?								
Symptom:	**At birth**	**1 month**	**3 months**	**6 months**	**1 year**	**3 years**	**6 years**	**10 year**	**15 years**
ZEB2 gene mutation or deletion	Most	Most	Most	Most	Most	Most	Most	Most	Most
Developmental delay / Intellectual disability	NA	NA	Few	Some	Most	Most	Most	Most	Most
Motor developmental delay	Few	Few	Few	Most	Most	Most	Most	Most	Most
Head size is smaller than typical ("Microcephaly")	Few	Some	Some	Some	Most	Most	Most	Most	Most
Seizures	Few	Few	Few	Few	Some	Some	Some	Most	Most
Sparse hair growth	Some	Some	Some	Some	Some	Some	Some	Some	Some
Intestinal obstruction	Few	Some	Some	Some	Some	Some	Some	Some	Some
Eye movement problems (side-to-side)	Few	Some	Some	Some	Some	Some	Some	Some	Some
"Wide-based gait", an altered walking pattern where the legs are kept extended out to the sides	NA	NA	NA	NA	Few	Some	Some	Some	Some
Elbows held in flexed position	NA	NA	NA	NA	Few	Some	Some	Some	Some
Foot is flexed upwards and towards the front of the leg ("Calcaneovalgus")	Some	Some	Some	Some	Some	Some	Some	Some	Some
Gastroesophageal (GE) reflux	Some	Some	Some	Some	Some	Some	Some	Some	Some
Weight problems – low weight or a tendency to lose weight	Few	Some	Some	Some	Some	Some	Some	Some	Some
Unusual, repetitive movements and behaviors ("Stereotypies")	NA	NA	NA	Few	Few	Some	Some	Some	Some
Short stature	Few	Few	Few	Few	Few	Some	Some	Some	Some
Overly happy demeanor ("inappropriately happy affect")	NA	NA	Few	Few	Few	Few	Some	Some	Some
Symptoms that can be detected only by a special test:									
Electroencephalogram (EEG) – Electrical activity of the brain is measured found to be abnormally slower	Few	Few	Few	Few	Some	Some	Some	Some	Some
Echocardiogram (ECG): This test produces images of the heart's structure and may detect a heart defect ("cardiac anomaly")	Some	Some	Some	Some	Some	Some	Some	Some	Some

Compass Genome Report Primary Findings

Specific Issues to Discuss with Your Doctor

Treatment options and current care

- There are no overall treatment options that change as a result of the diagnosis of Mowat-Wilson
- Some of the symptoms may be managed through various treatments

Lifestyle changes

- Most children with this diagnosis will show delay in their motor milestones meaning that they are slow to roll over, or slow to sit and crawl and in their thinking skills.
- Most of these children will need support services into adulthood.
- Roughly one-third of children with this disease find their symptoms worsen with heat (as well as a fever or infection). Avoiding exposure to very hot conditions may be helpful.

Support services

- Birth to Three developmental school-based program
- Speech & Language
- Physical Therapy
- Vision Aides
- Alternative Communication Devices

Monitoring

- **Seizures:** Because the types of seizures may be different in different children, the choice of seizure medications will be specific to the type of seizure not the overall condition.
- **Anxiety or aggression** may develop in early childhood in about one-third of children with this condition, and if so, your child should be seen by a developmental neurologist/pediatrician
- **Vision problems**, including various abnormalities and decreased vision, rapid eye movement back and forth, occasionally blind or low vision from birth. These indicate the need for annual eye examinations in childhood to monitor for strabismus and the strength of the lenses (refractive errors)
- **Heart defects:** Many children will have heart defects at birth, but not all may be detected immediately. If testing shows none present, then such symptoms will not develop over time.
- **Constipation / Intestinal obstruction / Hirshsprung's Disease:** More than half of children with this diagnosis will have constipation, reflux, failure to gain weight ("thrive") or weight loss. In a few children, the nerves in the colon are not properly formed and the colon does not work.

Additional medical specialists that may be relevant

- Developmental Neurologist/Pediatrician
- Ophthalmologist
- Cardiologist
- Pediatric Gastroenterologist

Evaluation of relatives at risk

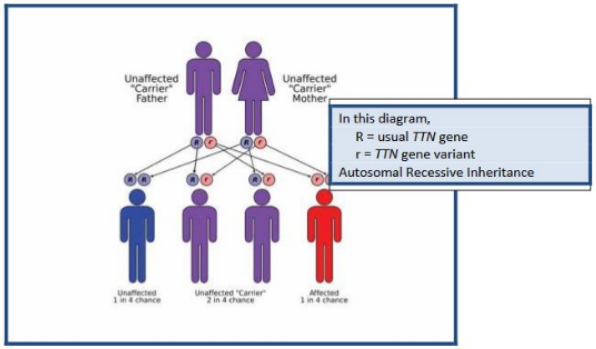
Early diagnosis of at-risk sibs by clinical examination and/or molecular genetic testing is important in order to monitor motor development and cardiac function so that treatment can be instituted early. If a fetus is diagnosed prenatally to have Salih myopathy, special considerations are needed at and following delivery since muscle weakness may manifest during the neonatal period.

Compass Genome Report Primary Findings

How This Might Affect Family Members

How is this passed on in families?

This condition is caused because you have two copies of the TTN genes that do not work correctly. One TTN gene came from Mom and one came from Dad. We know that each of you must have one copy of the TTN gene that works correctly and one copy that is not working. People who have at least one working TTN gene, do not have myopathy. Copies of the TTN gene that do not work have a change in the structure that is called a "mutation". Inheritance that is caused by two copies of non-working genes is called autosomal recessive inheritance.



Could your siblings also have this condition?

This condition is identified early in infancy. We would know already whether or not your siblings have myopathy. Other children in the family may carry a single non-working copy of the TTN gene. They are not at risk for health problems for themselves. Any of your siblings could have testing to find out if they carry one or the other of the TTN gene changes.

Could your children also have this condition?

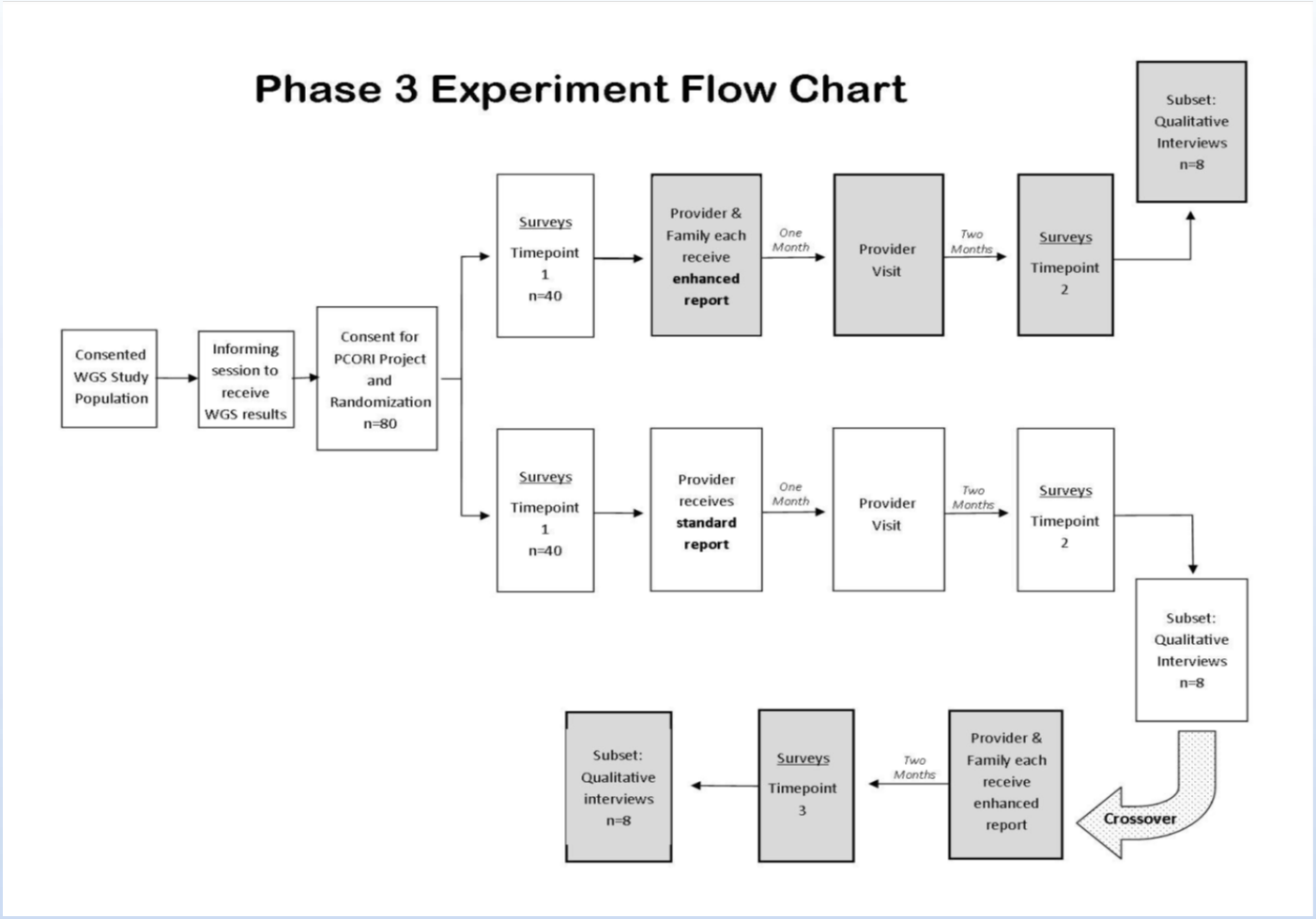
You have a 1 in 4 chance or a 25% chance with each pregnancy that each child could inherit two non-working copies of the same gene. There are 3 out of 4 chances or 75% chance that each child in the future would not have this myopathy. If you are thinking about children in the future we can talk about possible testing options before or during pregnancy.

Genetic testing for family members

TTN Resources

- **Children's Hospital:** https://www.childrenshospital.org/research-and-innovation/research-labs/beggs-laboratory/recent-developments/nemaline-animation
- **Jashua Frase:** http://www.joshuafrase.org/life-with-cnm-mtm/the-disorder.php
- **Myopathy Support Group:** A support group that focuses on myopathy may also be helpful. http://www.childrenscardiomyopathy.org/

Comparative Effectiveness Trial



Conclusions

- Genomics as an emerging technology must be able to demonstrate improved value in the health care delivery setting before it will be adopted
- Implementation is complex and requires a systematic approach of engagement, education, evidence and evaluation
- Outcomes must defined and systems built to support measurement to determine which services add value