Leveraging Informatics to Improve Health Outcomes and Value

Marc S. Williams, MD
Director, Genomic Medicine Institute
Geisinger Health System Danville, PA
Topic Perspective

Genomic Medicine
Personalized Medicine
Individualized Medicine
Precision Medicine

What’s in a name?
Genomic Medicine

• Includes
  o Traditional single gene disorders (genetics)
  o Analysis of the whole genome (genomics)
  o Analysis of subsets of the whole genome
    ▪ Exome sequencing
    ▪ Pharmacogenomics
  o 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.”

• Clinicians practice personalized medicine (and always have)
• Currently—Intuitive medicine
  o 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.
  o Empiric ‘trial and error’
• Future—Precision medicine
  o 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.
  o 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
GenomeFIRST™ A NEW PARADIGM FOR RETURN OF GENOMIC RESULTS
The Current Approach—‘Phenome First’ Ideal

1. Patient has encounter, fills out initial screening app
2. Patient fills out detailed FHH and medical Hx app
3. If patient is high risk, schedule genetic counselor
4. Screen patient for further testing
5. Case review, order genetic tests for patient and optionally family
6. Order placed with relevant clinical info
7. Return narrative, codified genomic result

- Patient
- Provider
- Genetic Counselor
- Genetic Labs

Risk Screening Applications
Dynamic Family Health History app
Risk assessment app
Diagnosis and Treatment Recommendation
Genomic Predictive Models w/ machine learning
Genomic inference Engine

CDS Knowledge base
Risk Screening Data Family Health History Genomic Repository CDR EHR

Geisinger
• 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)
The prompt for the clinical encounter is the DNA variant
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
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

<table>
<thead>
<tr>
<th>GENOMIC CONDITION</th>
<th>POPULATION PREVALENCE</th>
<th>CLINICAL RISK</th>
<th>DISEASE-ALTERING INTERVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Hypercholesterolemia (<em>LDLR, APOB, PCSK9</em>)</td>
<td>1 in 175</td>
<td>Early-onset Coronary Artery Disease and Stroke</td>
<td>Targeted screening and aggressive medical management</td>
</tr>
<tr>
<td>Hereditary Breast and Ovarian Cancer Syndrome (<em>BRCA1, BRCA2</em>)</td>
<td>1 in 400</td>
<td>Early-onset Breast, Ovarian, and Prostate Cancers</td>
<td>Targeted screening with prophylactic medical and surgical intervention</td>
</tr>
<tr>
<td>Lynch Syndrome (<em>MLH1, MSH2, MSH6, PMS2</em>)</td>
<td>1 in 440</td>
<td>Early-onset Colon and Uterine Cancers</td>
<td>Targeted screening and management of pre-cancerous changes</td>
</tr>
<tr>
<td>TOTAL</td>
<td>&gt; 1 in 100</td>
<td>Multiple Cancers and Cardiovascular Diseases</td>
<td>Life-saving screening and intervention before development of disease</td>
</tr>
</tbody>
</table>
Secondary or Incidental Finding of a PATHOGENIC/LIKELY PATHOGENIC VARIANT

GENE SPECIFIC EVALUATION
Including history, exam, testing, consultation

**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

**GROUP 6**
No Genomic Syndrome

**DIAGNOSIS OF GENOMIC SYNDROME WITH TESTING AND INITIAL EVALUATION**
Both Genotype and Phenotype Present

**NO DIAGNOSIS OF GENOMIC SYNDROME WHEN TESTED**
Genotype without Phenotype

**GENOMIC SYNDROME DIAGNOSED**
Both Genotype and Phenotype
1. A targeted "slice" of the genome is reviewed for pathogenic variants

2. EHR test result reviewed by CG then notifications

3. Telegenomics linking CG to patients and providers

4. Clinical team including patient, primary care, specialists, CG carry out phenotyping which includes family health history

5. Penetrance and expressivity determined, this drives case management

6. Relatives offered genotyping and phenotyping

Genomic inference Engine

Standardized phenotyping recommendations

Dynamic Family Health History app

Diagnosis and Management Recommendations

Genotype without Phenotype f/u Strategies

Genomic Predictive Models w/ machine learning

CDS

Knowledge base

Risk Screening Data

Family Health History

Genomic Repository

CDR

EHR
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

  o Health Outcomes
    ▪ Process
    ▪ Intermediate
    ▪ Disease/Health

  o Patient-Centered Outcomes
    ▪ Satisfaction
    ▪ Engagement
    ▪ Information
    ▪ Access
    ▪ Self-assessed well being

  o System Outcomes
    ▪ Costs incurred/avoided
    ▪ Utilization
    ▪ Patient experience
    ▪ Visibility/reputation
Value from the Health System Perspective
The Sweet Spot: Our realm of partnership and innovation

Clinical Enterprise

In Common:
- Population Management
- Providers
- Infrastructure
- EHR

Geisinger Health Plan

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

The Community Data Warehouse (CDW) is a part of CDIS that contains select sensitive GHS and non-GHS data (e.g., Keystone Beacon, Bundled Payment of Care, etc.) This data has been quarantined to allow only specific, authorized user access.
Information at point of care

• Focus on passive clinical decision support
• Highlight Clinical Genome Resource (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

ClinGen’s Critical Questions:
- Is this gene associated with a disease? *Clinical Validity*
- Is this variant causative? *Pathogenicity*
- Is this information actionable? *Clinical Utility*

Building a Genomic Knowledge Base
*ClinVar & Other Resources*

Improved Patient Care Through Genomic Medicine

Geisinger
Initial Solution

Welcome to ClinGen
Building a Genomic Knowledge Base to Improve Patient Care Learn more »

Seeking info about a gene or disease? Type it... Go!

ClinGen's search feature will return relevant information from both ClinGen Curated Resources and reputable external sources.

ClinGen is dedicated to building an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research. Learn more about our organization and our ongoing efforts below.

Tools & Resources
Access results of ClinGen's current curation efforts.

Working Groups
Learn more about ClinGen's various working groups.

About ClinGen
A National Institutes of Health (NIH)-funded program.

https://www.clinicalgenome.org/
Access to ClinGen resource from any OpenInfobutton compliant EHR system

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

<table>
<thead>
<tr>
<th>Resource Store</th>
<th>Description</th>
<th>Date Update</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micromedex</td>
<td>Comprehensive medication knowledge base.</td>
<td>May 19, 2015 6:26:23 PM</td>
<td>Update</td>
</tr>
<tr>
<td>VisualDx</td>
<td>Diagnostic decision support tool coupled with a library of over 100,000 peer-reviewed skin, pathology, and radiology images.</td>
<td>Feb 25, 2015 6:26:16 PM</td>
<td>Enabled</td>
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<tr>
<td>Pubmed</td>
<td>Largest database of indexed biomedical literature. Uses the PubMed Clinical Query filter, which is optimized to retrieve recent, high-quality clinical studies.</td>
<td>Jan 13, 2015 9:09:00 PM</td>
<td>Enabled</td>
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<tr>
<td>Mayo Clinic patient education</td>
<td>Freely available patient education material from the Mayo Clinic.</td>
<td>Apr 2, 2015 5:54:19 PM</td>
<td>Enabled</td>
</tr>
<tr>
<td>MedicinePlus</td>
<td>Free patient education content provided by the US National Library of Medicine.</td>
<td>Apr 2, 2015 5:57:17 PM</td>
<td>Enabled</td>
</tr>
</tbody>
</table>
# Intermountain Medical Libraries and eResources (IHCWEB and HELP2)

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

## Patient Education Resources
- Patient Education Network (PEN)
  Links to patient education resources, including Patient Fact Sheets
- Let's Talk About
- Micromedex Care Notes
- MDConsult patient handouts
- Medline Plus
- Intermountain Cancer Knowledge Base
- Radiology Info
- KidsHealth

## 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 Curriculum & Books (ACE)
- National Organization for Rare Disorders (NORD)
- Gene Tests
- Genetics Home Reference
- Merck Manual

## Intermountain Clinical Applications (login required)
- CPG Viewer
- HELP2
- KAT
- KRO

## Intermountain resources
- Antibiotics
  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

<table>
<thead>
<tr>
<th>Category</th>
<th>Resource</th>
<th>Terminologies (all use the HDD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab results</td>
<td>Clineguide</td>
<td>LOINC codes, free-text search</td>
</tr>
<tr>
<td>Medications</td>
<td>UpToDate, Micromedex, Clineguide</td>
<td>RxNORM, NDC codes, free-text search</td>
</tr>
<tr>
<td>Problem list</td>
<td>UpToDate, MDConsult, Clineguide, PubMed</td>
<td>ICD-10-CM codes, free text search</td>
</tr>
</tbody>
</table>
Alzheimer Disease Overview

Thomas D Bird, MD
Department of Neurology
University of Washington
Seattle VA Medical Center
tomproz@u.washington.edu

Summary

View this article on the GeneTests Web site.
Future Plans

Pursuing full integration with open info button
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
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
Development and Testing
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

SMART on FHIR® – Open Platform Architecture

SOA Orchestration
mHealth
OAuth
FHIR® REST API
Clinical Element Models & FHIR Data Profiles
Exhibiting Health IT Systems

http://smartplatforms.org/smart-on-fhir/

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

Geisinger
Compass Genome Report Primary Findings

Reason for Testing
Whole genome sequencing testing was ordered to identify a possible genetic cause for your symptoms. Your symptoms were reported to include muscle weakness (myopathy), delay in physical development, and drooping of the eyelids (ptosis).

What is included in this report?

Primary Findings
Was at least one relevant genetic variant found? Yes

Additional Findings
Was at least one relevant genetic variant found? Yes

Glossary & General Resources
To learn more about genetic concepts, terms, and your diagnosis referenced throughout this report.

Patient Information
Walter Jones
15 State Street
APT 1
Bloomsburg, PA 17815
(123) 456-7890
DOB: 1/11/2001
Sex: Male
Preferred Contact: Janine Jones (mother)
j1jones@gmail.com
Patient Representative: Janine Jones (mother)

Sample Information
Date of Sample Collection: 3/20/2013
Age at Sample Collection: 10 years, 2 months
Family Samples Submitted: Mother, Father

Have Questions?
Feel free to contact Monica Wagner with any questions pertaining to your whole genome sequencing report.

(570) 214-7941

Sequencing Labs: Complete Genomics, 2071 Storin Court, Mountain View, CA 94043, 560/943-2800
Primary Findings

What Are Primary Findings?
At this time we looked for the genes that might explain your child’s symptoms. As time goes on, we may be able to look at other genes and other conditions.

Summary of Results
A likely genetic cause for symptoms was found with a probable diagnosis of Salih Myopathy. It is important to talk with your doctor about the meaning of these results.

Information about the TTN Gene

What does this gene do?
The TTN gene contains instructions for your body to make a large protein that is important for the muscles of your body and heart to work. The protein is called “titin” (also known as “connectin”).

What variant(s) were found?
- TTN c.G13738C:p.V4580L (from father)

How do variants in this gene cause health problems?
Each person has two copies of the TTN gene (one from their mother and one from their father). Some variants stop the TTN gene from working. When both copies of the TTN gene are not working, titin cannot be made correctly and patients develop symptoms.
- When a person has two non-working copies of the TTN gene, they have a condition called “Salih Myopathy”
- When a person has one normal copy of the TTN gene and one non-working copy of the TTN gene, they are said to be a “carrier”. They do not have symptoms of Salih Myopathy

Are the variants the cause of the symptoms?
These two variants are probably the cause for your symptoms because each variant is believed to stop the TTN gene from making titin. We are still learning more about this gene and this protein.

[Status of variants: Suspicious, Probably Pathogenic, Pathogenic]

Likely the Cause of Symptoms
**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.

<table>
<thead>
<tr>
<th>Key</th>
<th>Most</th>
<th>Some</th>
<th>Few</th>
<th>NA</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Symptom</th>
<th>At birth</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>1 year</th>
<th>3 years</th>
<th>6 years</th>
<th>10 year</th>
<th>25 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZES2 gene mutation or deletion</td>
<td>Most</td>
<td>Most</td>
<td>Most</td>
<td>Most</td>
<td>Most</td>
<td>Most</td>
<td>Most</td>
<td>Most</td>
<td></td>
</tr>
<tr>
<td>Developmental delay/intellectual disability</td>
<td>NA</td>
<td>NA</td>
<td>Few</td>
<td>Some</td>
<td>Most</td>
<td>Most</td>
<td>Most</td>
<td>Most</td>
<td>Most</td>
</tr>
<tr>
<td>Motor developmental delay</td>
<td>Few</td>
<td>Few</td>
<td>Few</td>
<td>Most</td>
<td>Most</td>
<td>Most</td>
<td>Most</td>
<td>Most</td>
<td>Most</td>
</tr>
<tr>
<td>Head size is smaller than typical (“Microcephaly”)</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
</tr>
<tr>
<td>Seizures</td>
<td>Few</td>
<td>Few</td>
<td>Few</td>
<td>Few</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
</tr>
<tr>
<td>Sparse hair growth</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td>Few</td>
<td>Few</td>
<td>Few</td>
<td>Few</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
</tr>
<tr>
<td>Eye movement problems (side-to-side)</td>
<td>Few</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
</tr>
<tr>
<td>&quot;Wide-based gait&quot;, an altered walking pattern where the legs are kept extended out to the sides</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Few</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
</tr>
<tr>
<td>Elbow held in flexed position</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Few</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
</tr>
<tr>
<td>Foot is flexed upwards and towards the front of the leg (&quot;Calcaneovalgus&quot;)</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
</tr>
<tr>
<td>Ventriculomegaly (CE) reflux</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
</tr>
<tr>
<td>Weight problems – low weight or a tendency to slow weight</td>
<td>Few</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
</tr>
<tr>
<td>Unusual, repetitive movements and behaviors (&quot;Stereotypies&quot;)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Few</td>
<td>Few</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
</tr>
<tr>
<td>Short stature</td>
<td>Few</td>
<td>Few</td>
<td>Few</td>
<td>Few</td>
<td>Few</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
</tr>
<tr>
<td>Overly happy demeanor (&quot;inappropriately happy affect&quot;)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Few</td>
<td>Few</td>
<td>Few</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
</tr>
</tbody>
</table>

**By what age do most children with Mowat-Wilson Syndrome have this symptom?**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>At birth</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>1 year</th>
<th>3 years</th>
<th>6 years</th>
<th>10 year</th>
<th>25 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electroencephalogram (EEG) – Electrical activity of the brain is measured found to be abnormally slow</td>
<td>Few</td>
<td>Few</td>
<td>Few</td>
<td>Few</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
</tr>
<tr>
<td>Cardiac ultrasound (ECHO) – This test produces images of the heart’s structure and may detect a heart defect (&quot;cardiac anomaly&quot;)</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
<td>Some</td>
</tr>
</tbody>
</table>
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 / Hirschsprung’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

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 2 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
- Myopathy Support Group: A support group that focuses on myopathy may also be helpful. http://www.childrenscardiomyopathy.org/
Comparative Effectiveness Trial

Phase 3 Experiment Flow Chart

Consented WGS Study Population

Informing session to receive WGS results

Consent for PCORI Project and Randomization n=80

Surveys Timepoint 1 n=40

Provider & Family each receive enhanced report

One Month

Provider Visit

Surveys Timepoint 2

Provider Visit

Two Months

Surveys Timepoint 3

Provider & Family each receive enhanced report

Two Months

Subset: Qualitative Interviews n=8

Crossover

Subset: Qualitative Interviews n=8
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