Beyond the Diagnosis: Looking to the Future

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Disclaimers/Disclosures

- My Journey and My Blessings
- Texas State University
- Growing Places Therapy Services and Creative Therapy Solutions
- Bobcat Babies
- My research, practice and passion are married by my work at U.R. Our Hope.

Objectives

- Discuss genetic changes that are beyond basic mutations in our DNA
- Review complex disorders that may be difficult to diagnose
- Investigate new options for exploring our DNA
- Explore new options for diagnosis and treatment of genetic disorders

THE HIDDEN EPIDEMIC

LIFE WITH AN UNDIAGNOSED OR RARE DISORDER

LIFE UNDIAGNOSED

30-40%

OF CHILDREN WITH SPECIAL NEEDS **DO NOT** HAVE A DIAGNOSIS[3]

IT CAN TAKE UP TO **SEVEN YEARS** TO FIND A DIAGNOSIS[4]

PATIENTS SEE UP TO **8 SPECIALISTS** BEFORE RECEIVING A **PROPER DIAGNOSIS**[4]

THERE ARE OFTEN **2-3 MISDIAGNOSES**[4]

83% OF PHYSICIANS SAY GENETIC TESTING IS USEFUL IN FINDING A DIAGNOSIS[5]

BUT, GENETIC TESTING IS **NOT COVERED** BY MANY INSURANCE COMPANIES TESTING IS ELECTIVE OR EXPERIMENTAL

GENETIC TESTING CAN COST **$10,000 OR MORE**

60% OF PATIENTS EXPERIENCE UNEXPECTED **FINANCIAL BURDEN**[5]

29% GO INTO DEBT[5]

39% PAY FOR **INEFFECTIVE TREATMENTS** DUE TO LACK OF OR IMPROPER DIAGNOSIS[5]

HIDDEN COSTS

TIME OFF WORK | PARKING FEES
SPECIALIZED CHILD CARE | GAS
LOSS OF INSURANCE COVERAGE
NO ACCESS TO SOCIAL SERVICES
INEFFECTIVE TREATMENTS

30 MILLION PEOPLE IN THE U.S. AFFECTED BY RARE DISEASE

WHICH MEANS **1 IN 10 AMERICANS** LIVING WITH RARE DISEASE[1]

IN THE UNITED STATES, A RARE DISEASE IS A CONDITION THAT AFFECTS **LESS THAN 200,000 PEOPLE**[1]

TWO-THIRDS OF RARE DISEASE PATIENTS **ARE CHILDREN**[1]

30% OF CHILDREN WITH A RARE DISEASE **DO NOT LIVE** TO SEE THEIR **5TH BIRTHDAY**[1]

35% OF DEATHS IN THE FIRST YEAR ARE CAUSED BY RARE DISEASE

THERE ARE CURRENTLY **7,000 IDENTIFIED RARE DISEASES**[1]

95% DO NOT HAVE AN **FDA APPROVED TREATMENT**[2]

CURRENTLY, ONLY **350 OUT OF 7,000** HAVE FDA APPROVED TREATMENTS

50% 50% OF RARE DIAGNOSES **DO NOT** HAVE A DISEASE SPECIFIC FOUNDATION DEDICATED TO SUPPORTING OR ADVANCING RESEARCH[2]

HOW U.R. OUR HOPE IS MAKING AN IMPACT

ONE OF THE ONLY ORGANIZATIONS DEDICATED TO UNDIAGNOSED AND RARE DISEASE, SO OUR PATIENTS ARE FROM ALL OVER THE WORLD

OVER 75 ACTIVE FAMILIES AND COUNTING

CURRENTLY HELPING FAMILIES IN **10** DIFFERENT STATES
MOST ARE IN CENTRAL TEXAS

4 DIFFERENT COUNTRIES

WE PROVIDE

GAS/MEAL CARDS TO THOSE TRAVELING OUT OF TOWN FOR MEDICAL VISITS

PROVIDE MEALS DURING HOSPITALIZATIONS OR DURING TIMES OF CRISIS

CONNECT FAMILIES WITH RESEARCH PROGRAMS, MEDICAL RESOURCES, GRANTS

OUR NEWEST PROJECT AIMS TO **HELP FAMILIES COVER THE COSTS** OF GENETIC TESTING IN HOPES OF FINDING A PROPER DIAGNOSIS

HOW YOU CAN HELP

MAKE A **DONATION TODAY** WITH ONE OF OUR LOCAL PARTNERS OR ON OUR WEBSITE

LEARN MORE AT **WWW.UROURHOPE.ORG**
& JOIN US AT UPCOMING EVENTS!

JOIN THE CONVERSATION
U.R. Our Hope
@UROURHOPE
@UROURHOPE

SOURCES: 1. rarediseases.org ; 2. globalgenes.org ; 3. files.eric.ed.gov/fulltext/EJ828952.pdf ; 4. sireninteractive.com ; 5. Gandomi SK and Esplin ED. Rare Disease Diagnosis Obstacles: Patient Perspective and Physician Findings; Presented at ACMG Annual Meeting, 2016

TEXAS PHYSICAL THERAPY SPECIALISTS

AND OUR PARTNERS
Confluent HEALTH
BreakThrough Physical Therapy · Evidence in Motion · Fit for Work · Physical Therapy · ProRehab

PROUDLY SUPPORT
U.R. Our Hope
www.UROurHope.org

Beyond…

- Changes in our DNA that are beyond the “basic”

1. Mosaicism
2. Chimerism
3. Epigenetics
4. Synergistic Heterozygocity

CLOVES as an example

- E.g., CLOVES Syndrome
- CLO- congenital lipomatous overgrowth
- V- vascular malformations
- E- epidermal nevi
- S- scoliosis/skeletal/spinal anomalies
- Mutation in PIK3CA gene which is a growth regulatory gene

But, there is HOPE!

Wednesday 13 June 2018

Press Release

A medical first: CLOVES Syndrome and overgrowth syndromes: remarkable improvement in the health of 19 paediatric and adult patients using a new therapeutic strategy

Dr Guillaume Canaud at the Necker-Enfants Malades Hospital – AP-HP, the Paris Descartes University, Inserm (INEM Institute Necker Enfants Malades – Centre for Molecular Medicine) and his team recently demonstrated the efficacy of a novel medication, a specific inhibitor called BYL719, in a cohort of 19 patients treated at the Necker-Enfants Malades Hospital – AP-HP and suffering from CLOVES Syndrome (Congenital Lipomatous Overgrowth, Vascular Malformation, Epidermal Naevi) or similar disorders. This medication is currently undergoing therapeutic oncology trials (phase I/II). No significant side effects have been observed 18 months after commencement of treatment. This study, published in the journal *Nature*, is an example of precision medicine and demonstrates the major benefits of this therapeutic strategy for these patients, who have seen their health and quality of life improve significantly.

Recent article

NYTIMES.COM

Every Cell in Your Body Has the Same DNA. Except It Doesn't.

The genome obviously varies from person to person. But it can also vary from...

Chimerism (Chimera)

- An organism made up of cells from 2 zygotes
- Can be acquired through blood transfusion or organ transplant

Epigenetics

- Dr. Arthur Beaudet defined epigenetics as a change in the '*the* word processing *font* OF the **genetic** code.'
- '…heritable changes in gene expression that occur without changes in the DNA sequence…'
- DNA methylation
- Histone acetylation

Rangel and Lewis, 2006

Synergistic Heterozygocity

- First identified in the literature by Vockley et al., 2000
- Occurs when partial defects in a metabolic pathways work together to cause disease
- An individual may have 2 or more heterozygous mutations that alone would not cause issues, but together cause disease
- Mitochondrial disorders are an example
- Implications for diabetes and obesity, Vockley, 2008

Getting to the truth…

Examples of “Dump Diagnoses”

- Some may surprise you

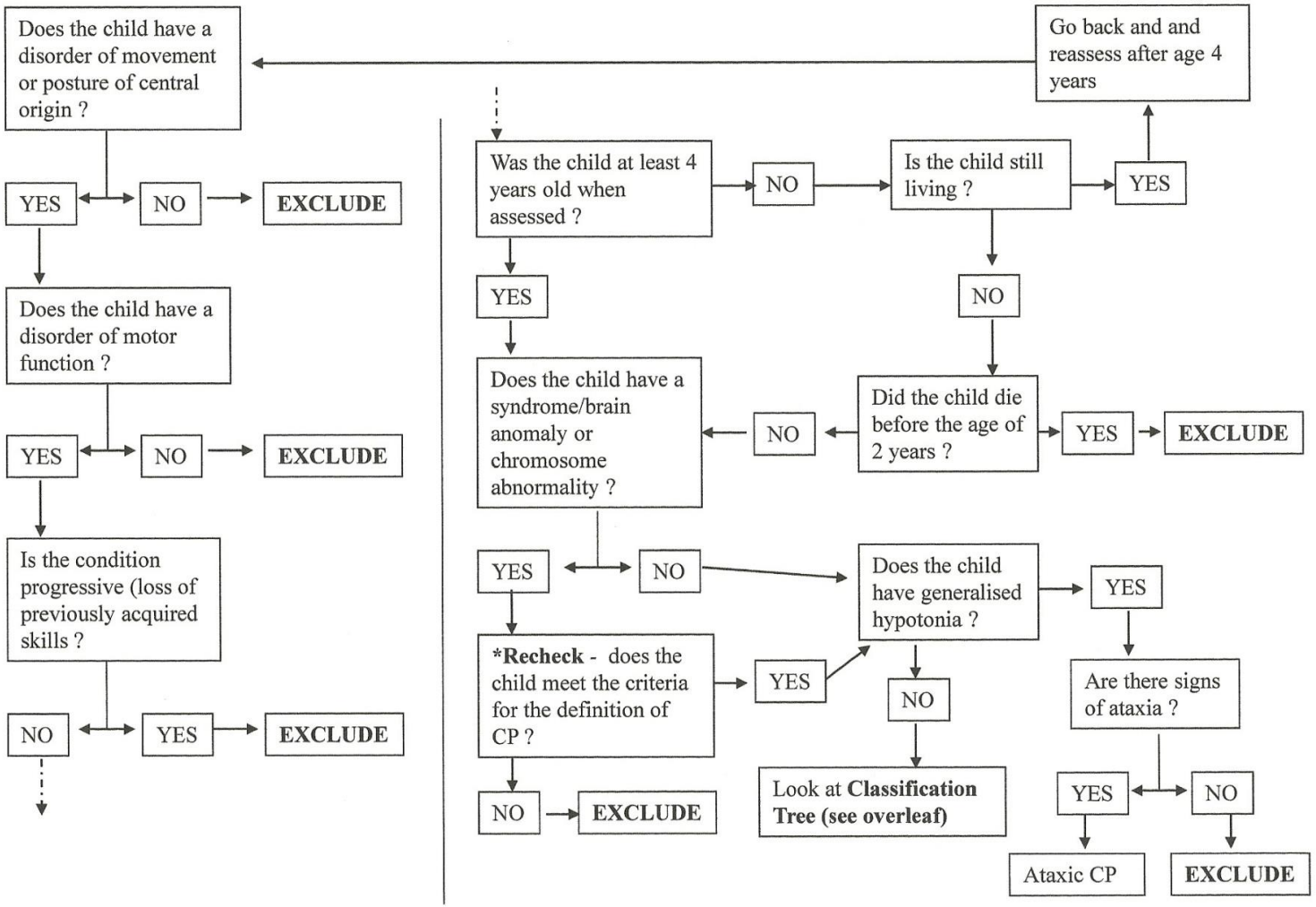
A List of a Few “Dump Diagnoses”

- Failure to thrive (FTT)
- PDD-NOS (or as MEP calls it, **p**hysician **d**oes not **d**iagnose)
- Autism
- Cerebral palsy

A Tool to Assist with the Diagnosis of CP

- Surveillance of Cerebral Palsy in Europe (SCPE)
- Over 1000 cases reviewed
- A set of flow charts to assist with diagnosis
- Ruling out disorders related to genetic mutations and disorders such as Rett syndrome or leukodystrophies where regression is a key clinical indicator

SCPE Decision tree for Cerebral Palsy



SCPE Collaborative Group, Surveillance of Cerebral Palsy in Europe: A collaboration of cerebral palsy surveys and registers.

Dev Med Child Neurol 2000, 42:816-24

The Sneaky Disorders

Mitochondrial Disorders

- Mitochondria are the energy producing parts of our cells
- Highly glucose dependent
- It is estimated that every 30 minutes a child is born who will develop a mitochondrial disorder by the age of 10
- Heterogeneous nature
- Maternally inherited or Mendelian genetics
- More that 3 organ systems involved
- Typical disease with atypical presentation

Lysosomal Storage Disorders

- Lysosomes are the vacuums of our cells

Congenital Disorders of Glycosylation

- Body cannot process sugar correctly, affects the relationship of protein to sugar
- Hypotonia, developmental delay, FTT, seizures, and multiple system involvement
- Autosomal recessive inheritance (in most cases)
- Differential diagnosis: Prader-Willi syndrome, MD, mitochondrial disorders, CP (MEP)
- Refer to SCPE Criteria

Case for Review

Take Home Message…

- If it does not walk like a duck, and quack like a duck…
- Multisystem disorders point to more complex diseases

- IS THIS A DUCK?

Let’s look at Ehlers-Danlos syndrome

- First described by Hippocrates in 400 B.C.
- Multiple presentations
- Hallmark is joint hypermobility
- BUT, many other issues…including some forms that manifest with postural orthostatic tachycardia syndrome (POTS), chronic pain, and gastrointestinal dysfunction
- Mast cell activation disorders (MCADS)
- https://www.ehlers-danlos.com/eds-types/#chart

EDS Diagnosis and Beyond

- “Difficult” to diagnose
- Multiple genes affecting collagen production
- Marfan/TAAD Panel available

What is Ehlers Danlos Syndrome?

Individuals with EDS have a defect in their connective tissue, the tissue that provides support to many body parts such as the skin, muscles and ligaments. The fragile skin and unstable joints found in EDS are the result of faulty collagen. Collagen is a protein, which acts as a "glue" in the body, adding strength and elasticity to connective tissue

Signs & Symptoms

Symptoms vary widely based on which type of EDS the patient has. In each case, however, the symptoms are ultimately due to faulty or reduced amounts of collagen. EDS typically affects the joints, skin, and blood vessels.

Pain
Dislocations
Subluxations
Hypermobility
Osteoarthritis
Osteoporosis
Skin Tearing
Stretchy skin
Soft skin
Mitral Valve Prolapse
Easy bruising

Fatigue
Chiari
Sprains
Gastrointestinal issues
Atrophic scarring
Muscle spasms
Poor healing
TMJ
POTS
Organ rupture
Aneurysms

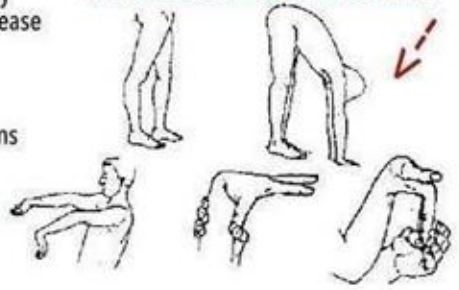
Prolapse
Preterm labor
IBS
Dysautonomia
Flat feet
Swan neck deformity
Degenerative Joint Disease
Gastritis
Arthralgia
Myalgia
Surgical complications

FB you know you have EDS when

AND YOUR BODY EXPERIENCES ANY OF THE ABOVE

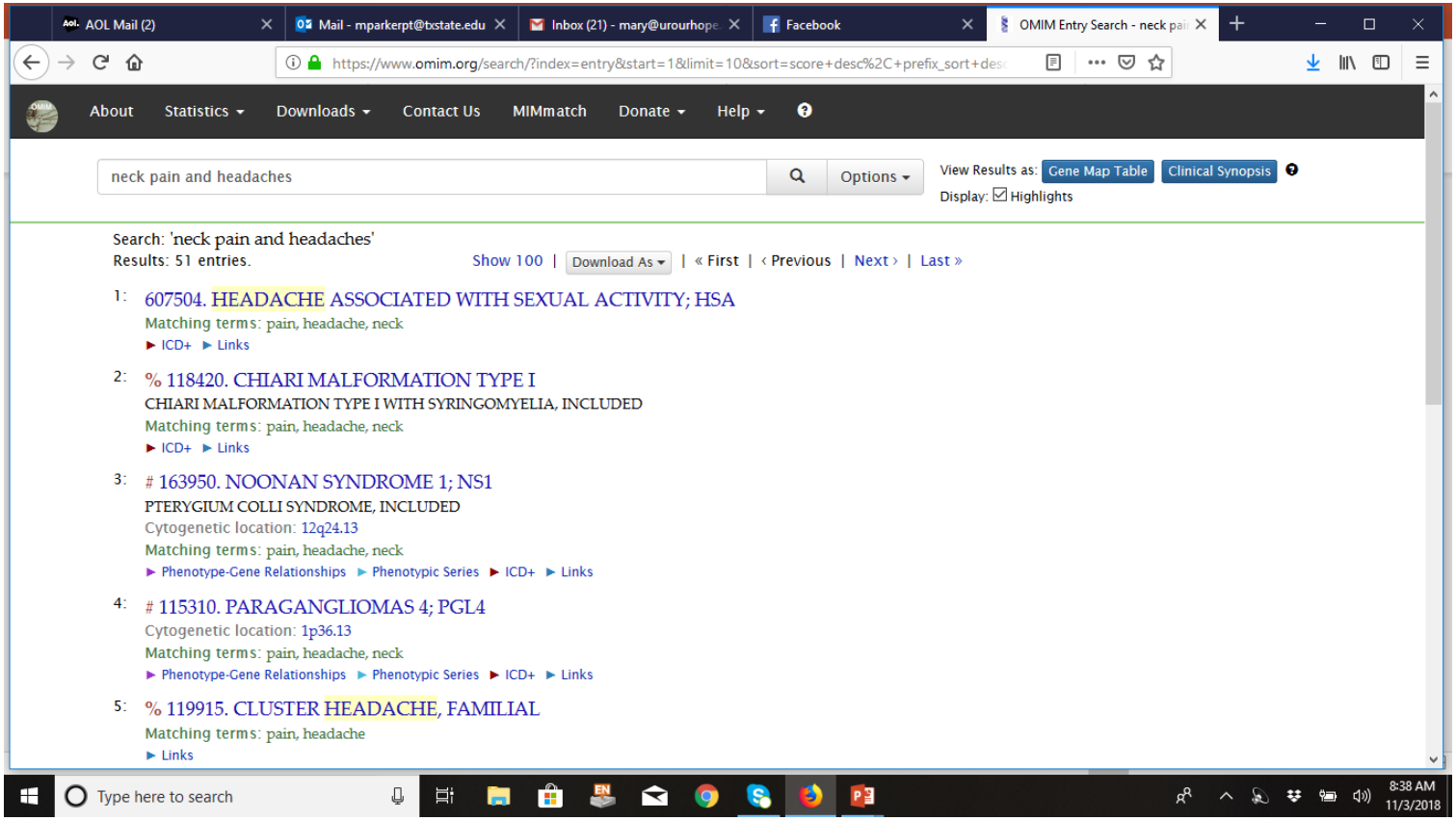
You should ask your doctor about genetic testing for Ehlers-Danlos Syndrome!

IF YOUR JOINTS CAN DO THIS:



A tool to use and share…

Online Mendelian Inheritance in Man (OMIM)



Our challenge…

Resources


U.R. Our Hope


RareConnect.ORG
A PARTNERSHIP OF EURORDIS AND NORD


NORD


CrowdMed


GeneDx
DNA DIAGNOSTIC EXPERTS


rare
genomes
project

Exploring and sharing your own DNA…

Ancestry.com

MyGene2

23andme

FamilyTreeDNA

Genome Connect

Participate

By Lena Huang

GenomeConnect

Help advance research by donating your genetic information.

What is it?
GenomeConnect is a secure patient portal, or registry, where patients voluntarily share and store health information. The information is available to healthcare providers and researchers who are interested in studying certain conditions and in learning more about human health.

Who can participate?
GenomeConnect is open to anyone age 18 and older, and to minors under the age of 18 who have consent from a parent or legal guardian. The participant must have had genetic testing, be considering genetic testing, or have family members who have had genetic testing.

Who sponsors GenomeConnect?
GenomeConnect is a project of the Clinical Genome Resource (ClinGen), a National Institutes of Health-funded organization dedicated to building a central resource of clinically relevant genomic variants to be used in precision medicine and research that improves patient care.

Why participate?
There are many reasons to participate. Individuals with rare conditions may want to join the registry to connect with other individuals or families like themselves to share information and offer support. Researchers use registries to identify people who have certain conditions or gene variants that the researchers may want to study. Bringing together information and large amounts of data from patients helps researchers advance the medical care of patients with rare diseases.

How do I participate?
Sign up at GenomeConnect.org to create a personal portal account. You will be provided with details on what information is collected and what information others can access. You will be asked to sign an electronic consent form. Once you've completed it, you can upload your genetic testing reports and complete health information surveys. GenomeConnect will not release any personal information about you without your permission.

ILLUSTRATION BY BETHANY WALROND

Atlas of Human Malformation Syndromes in Diverse Populations

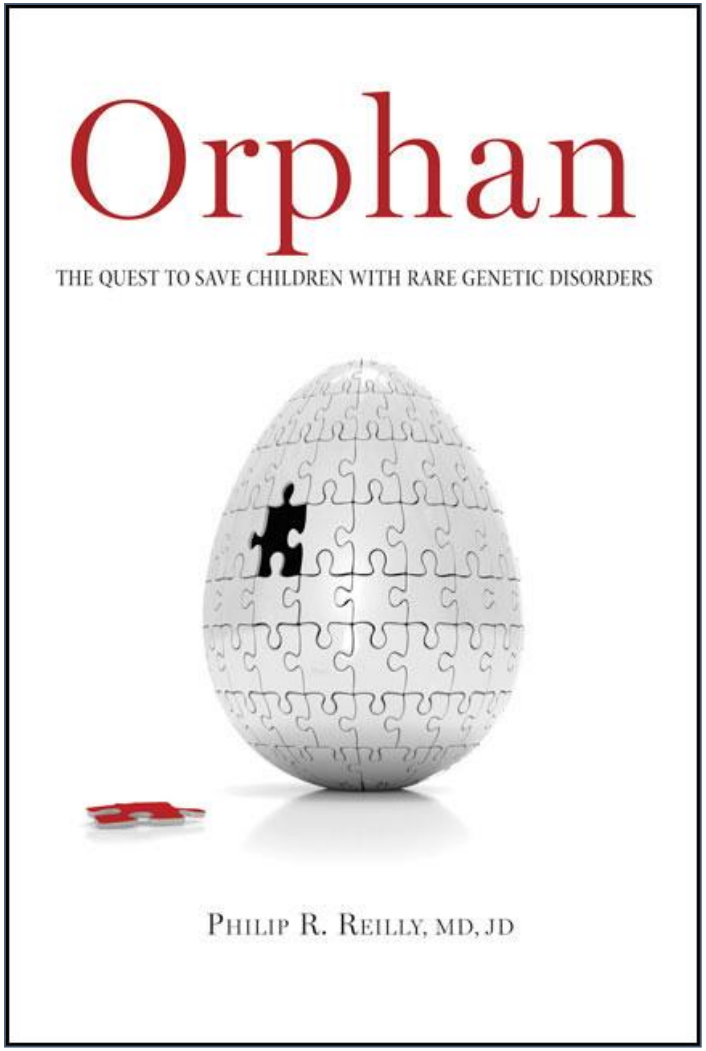
An international group of clinical geneticists, dysmorphologists, and other medical specialist have come together to create an atlas of human malformation syndromes in diverse populations. The purpose of this website is to provide a tool that is easy to use and helpful for the clinician in diagnosing syndromic disorders across varied populations. Photographs of the face and other relevant body areas are the main focus of the website. The website will include photographs and the molecular diagnoses of individuals from geographically diverse locations including multiple locations in Asia, the Indian subcontinent, the Middle-East, South America, and sub-Saharan Africa. We anticipate that our electronic atlas will assist clinicians in associating congenital malformations with syndromes, allowing for earlier diagnosis and addressing the potential multiple associated medical issues.

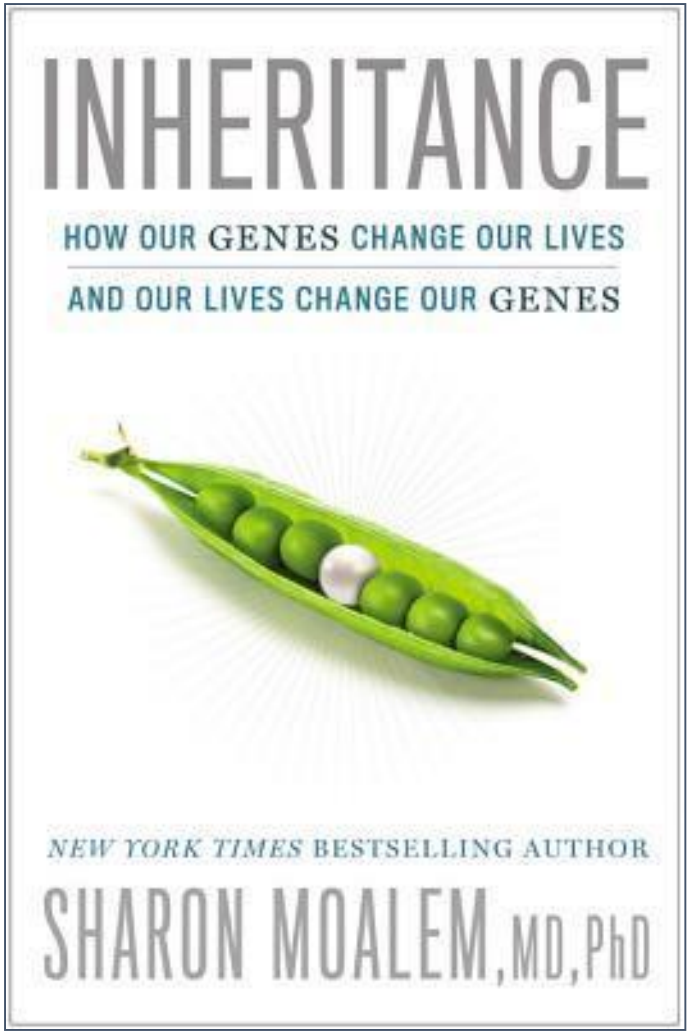
Birth defects remain a leading cause of infant mortality and childhood morbidity throughout the world. An accurate and early syndromic diagnosis is paramount, as late diagnosis can result in a delay in intervention and treatment of accompanying anomalies such as congenital heart defects or endocrine disorders. In 2010, the World Health Organization began a focus on congenital malformations and announced support for public health policy directed at preventing congenital malformations through various measures and recognizing birth defects as a public health priority. As laboratory sequencing technologies become more available, recognition of malformation syndromes will become increasing important in all parts of the globe. Recognizing the global importance of congenital malformations and that most clinicians have trained with clinical genetic resources that used patients of northern European descent as the standard of reference, in this website we present patients from other parts of the world.

There is no identifying personal information on this website. There is a remote chance that one's private gene mutation could function as a unique identifying piece of information; and, it will not be possible to obscure facial features because facial features are crucial to the diagnosis. This implies that a specific patient is potentially identifiable. However, this practice is no different from what currently occurs in textbooks of clinical genetics and malformation syndromes.

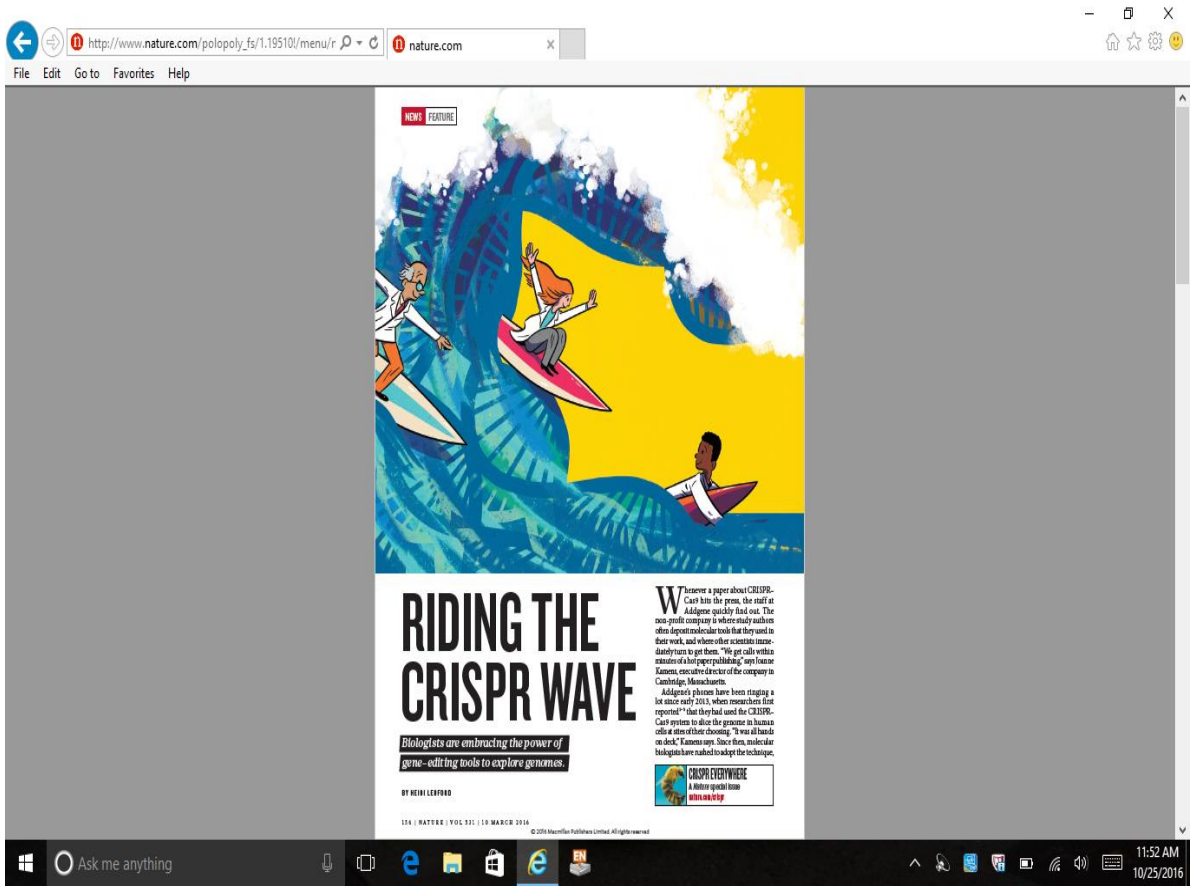
We foresee that this tool for evaluating dysmorphic patients from diverse populations will be used extensively by physicians, genetic counselors, and trainees throughout the world. Web resources are slowly becoming more popular than paper textbooks amongst medical providers as they can be used at the point of care with only a cell phone. This tool, while not replacing superior clinical skills, is intended to broaden the phenotype of syndromes to diverse populations and assist trained clinicians to make diagnoses in these populations. Variance in expression is a common finding in malformation syndromes, thus when possible, this website will attempt to show multiple

Good reads…


Orphan
THE QUEST TO SAVE CHILDREN WITH RARE GENETIC DISORDERS
PHILIP R. REILLY, MD, JD


INHERITANCE
HOW OUR GENES CHANGE OUR LIVES
AND OUR LIVES CHANGE OUR GENES
NEW YORK TIMES BESTSELLING AUTHOR
SHARON MOALEM, MD, PhD

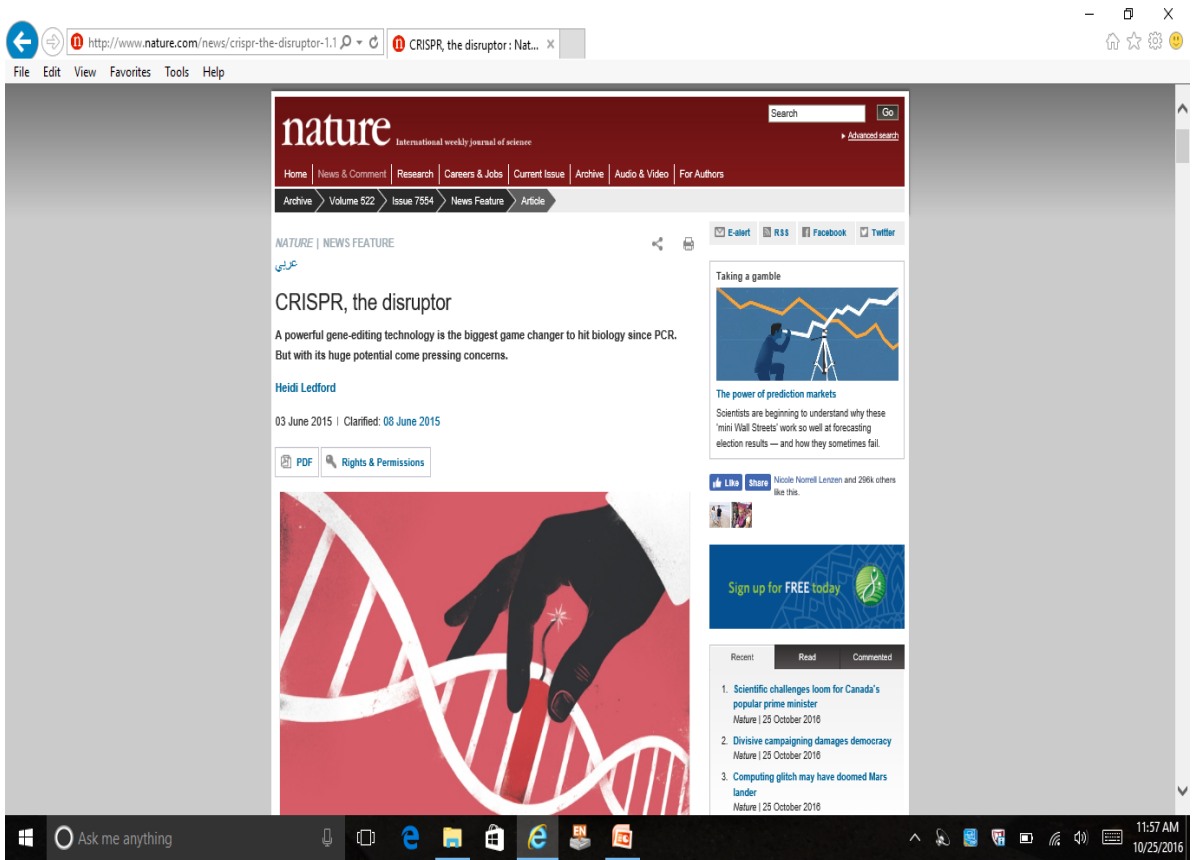
CRISPR-Cas9- Editing our DNA



Looking to the future…

CRISPR-Cas9

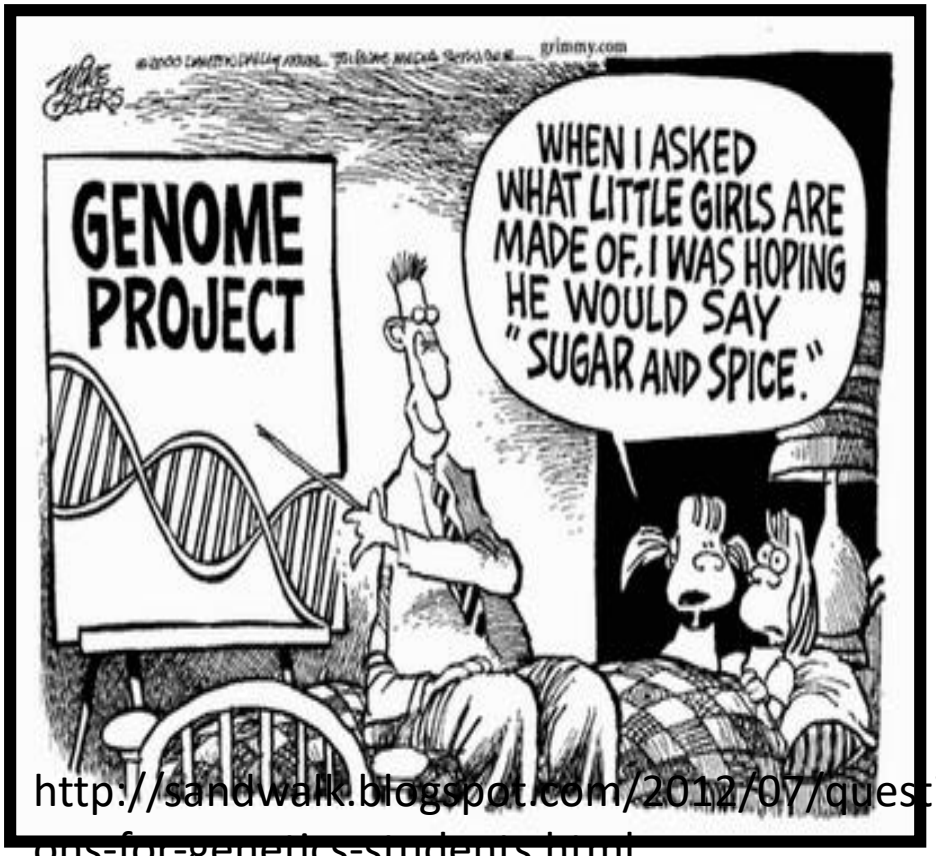
- Clustered Regularly Short Pallindromic Repeats
- https://www.youtube.com/watch?v=2pp17E4E-O8



Self-Reflection

http://health.spectator.co.uk/on-genetics-oliver-james-is-wrong-about-everything/

Questions



http://sandwalk.blogspot.com/2012/07/questions-for-genetics-students.html

Thank you for your attendance and attention!

- References available by request

"Two roads diverged in a wood and I-
I took the one less traveled by."
- Robert Frost