Pediatric Genomic Medicine

SHANE CORDER - SR. HPC SYSTEMS ENGINEER

CENTER FOR PEDIATRIC GENOMIC MEDICINE

Children's Mercy Hospital
Center for Pediatric Genomic Medicine

- Established Jan., 2011
  - Directed by Dr. Stephen Kingsmore
- Integrated with hospital practice
  - 25+ physicians as primary points of contact representing every specialty within hospital
  - Clinical Genetics & Counseling
  - CMH Center for Bioethics
- Application focuses
  - Exome sequencing
  - TaGSCAN CLIA lab test
  - STAT-seq Emergency Genome Sequencing
  - RNA
  - ….more?!


THE
WIZARD
OF
OZ

Newfoundland
and Labrador
Gulf of St
Lawrence
New
Brunswick
Nova
Scotia
Vermont
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Hampshire
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Rhode Island
Puerto
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The New York Times

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Obama and Romney, in First Debate, Spar Over Fixing

JUST THE FACTS? Mitt Romney and President Obama challenged each other on many issues.

Rapid Analysis of Infants' DNA Aids Diagnosis of Rare Diseases

By GINA KOLATA

From the day she was born, the girl had seizure after seizure. Doctors at Children's Mercy Hospital in Kansas City, Mo., frantically tried to keep her alive. Weeks passed and every medication failed. Finally, her family decided to let their baby go, and the medical devices were withdrawn. She was 5 weeks old.

Her doctors suspected a genetic disorder, and as it happened the hospital had just begun a study of a new technique for quickly analyzing the DNA of newborns, zeroing in on mutations that can cause disease.

This new method, published on Wednesday in the magazine Science Translational Medicine, is a proof of concept — a demonstration in four babies that it is possible to quickly scan a baby's entire DNA and pinpoint a disease-causing mutation in a couple of days instead of the more typical weeks or months. The study's investigators said the test could be one of the first practical fruits of the revolution in sequencing an individual's entire DNA.

For the baby with seizures, her doctors provided a sample of her blood. The analysis took only 50 hours and provided an answer. The baby had a mortal gene mutation so rare that it had been reported just once before.

If only, said Dr. Joshua E. Petrikin, one of the baby's doctors, the test could have been done within days of the baby's birth.

"There was no treatment, there was not anything that could have changed the outcome," Dr. Petrikin said. "But we could have more appropriately counseled the family and bypassed what had to have been intense suffering."

The baby, he explained, was

Continued on Page A3

A Clash

One Side Sees E
The Other Wan

DENVER — Somewhere
wonky blizzard of facts, stat
and studies thrown out on s
here on Wednesday night w
fundamental philosophical
about the future of America,
possibly the starkest in nearly
three decades.

As President Obama and Mitt Romney faced off for the first time, their largely zinger-free styles may have disguised a fierce clash of views not only over taxes, spending and health care, but over the very role of government in American society in a time of wrenching problems.

On one side was an incumbent who, while recognizing that government is not the solution to all problems, argued that it plays an essential part in promoting eco-
goal was to get out of th
free people and unleash
American entrepreneur
"Governor Romney h
spective that says if we
skewed towards the we
roll back regulations, th
be better off," Mr. Obam
He asked: "Are we goin
ble down on the top-dow
nomic policies that help
us into this mess or do w
brace a new economic p
that says America does
when the middle class d

Continued on Page

RESEARCH ARTICLE

DIAGNOSTICS

Rapid Whole-Genome Sequencing for Genetic Disease Diagnosis in Neonatal Intensive Care Units

Carol Jean Saunders,[1,2,3,4,5]* Neil Andrew Miller,[1,2,4]* Sarah Elizabeth Soden,[1,2,4]* Darrell Lee Dinwiddie,[1,2,3,4,5]* Aaron Noll,[1] Noor Abu Alnadi,[4] Nevene Andraws,[3] Melanie LeAnn Patterson,[1,3] Lisa Ann Krivohlavek,[1,3] Joel Fellis,[6] Sean Humphray,[6] Peter Saffrey,[6] Zoya Kingsbury,[6] Jacqueline Claire Weir,[6] Jason Betley,[6] Russell James Grocock,[6] Elliott Harrison [illegible] Joshua Erin Pet

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DECEMBER 24, 2012

Egypt Divided / Qatar's Ambition / Rot in the ANC

TIME

Top 10 Medical Breakthroughs

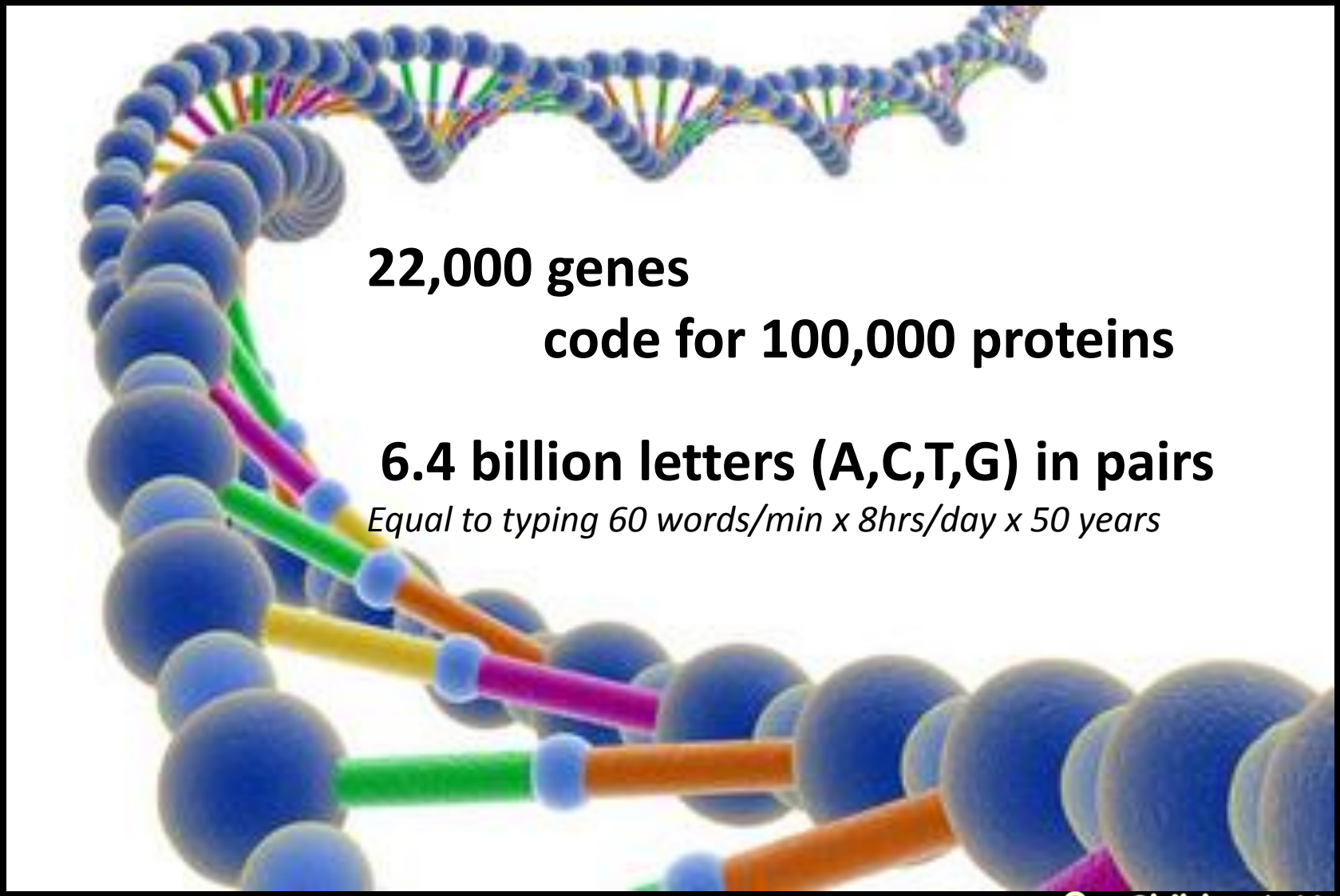
7. Speeding DNA-Based Diagnosis for Newborns

34 of 61 VIEW ALL

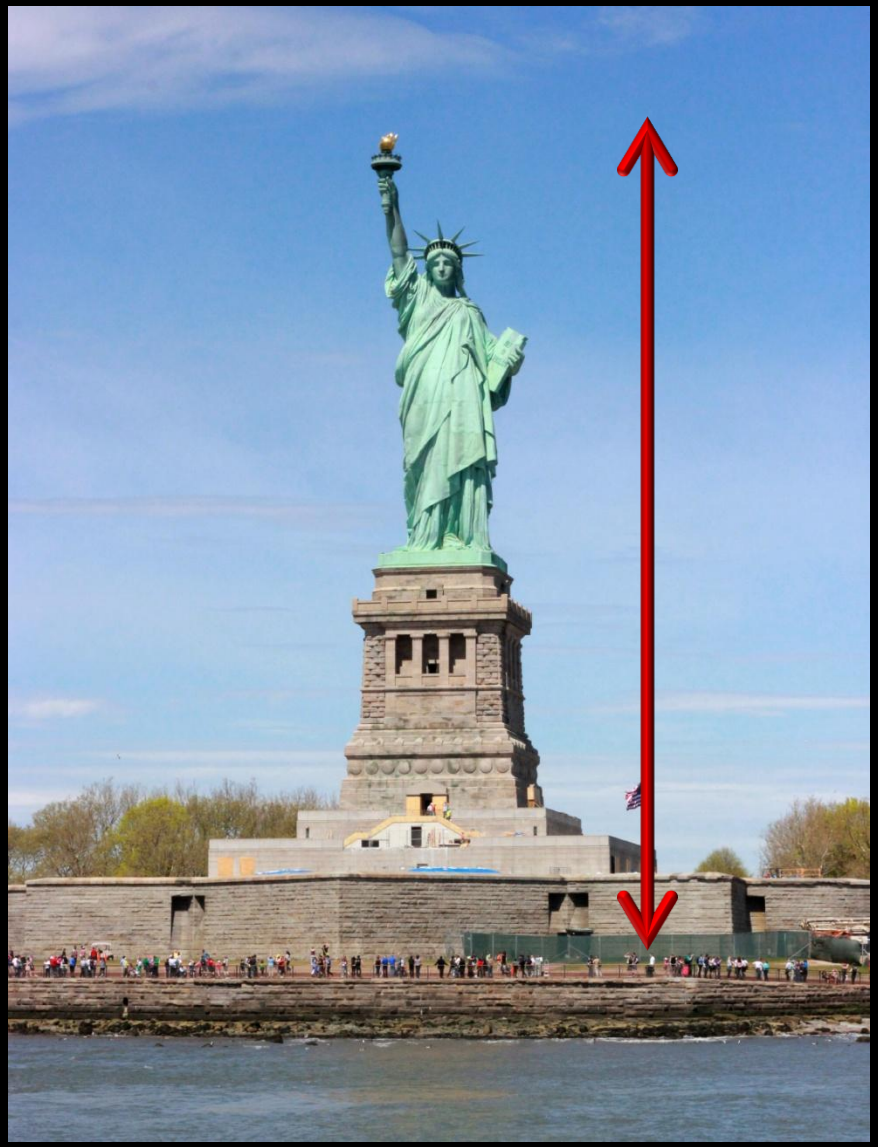
By Alice Park | Dec. 04, 2012 | Add a Comment

Fifty hours. That's how long it now takes to decode and interpret a newborn baby's genome — an undertaking that used to take weeks or even months. And those two days can mean the difference between life and death for a critically ill infant. The speedier genomic analysis is possible thanks to advances in sequencing technology as well as innovative software that links the 3,500 known genetic defects to their childhood diseases, allowing doctors to quickly decide on the right treatment that could save a baby's life. About 30% of babies admitted to the neonatal intensive care unit each year have inherited a genetic disease, and sequencing their genomes may become a critical part of improving their care in coming years — the sooner the better.

DAVID AARON TROY / GETTY IMAGES



Children's Mercy HOSPITALS & CLINICS Kansas City



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- Modest dept. Linux compute cluster
  - 40 compute nodes
  - +600 compute cores

- Isilon Storage System
  - 14 node X400 cluster
- SGI/Spectra Logic
  - SGI Infinite Storage Gateway
  - Spectra Logic T950 Library

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The Diagnostic Odyssey

- Karyotype: 46,XX $517
- Array comparative genomic hybridization $1500
- *GFAP* gene sequencing for Alexander disease $1300
- DNA testing for ataxia telangiectasia $1448
- DNA testing for Freidreich's ataxia $282
- Lactic acid level: 4.3 elevated (x2) $90
- Pyruvate: 0.23 elevated (x3) $1074
- Brain MRS $4204
- Brain MRI x2 $7784
- Urine organic acids (x2) $1188
- Acylcarnitine profile $134
- Vitamin E level $170
- AFP $177
- Urine amino acids $267
- TSH, free T4 $74
- CBC $7
- BMP $13
- Copper $149
- LFTs $9
- Ammonia (plasma) $23
- MELAS/MERRF DNA testing $864
- Pyruvate Decarboxylase Deficiency DNA testing $1600

5 yrs with no molecular diagnosis
>$23,000 in testing

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4,106 Genetic Diseases of Known Molecular Basis Affect 4 – 8 % of Children

- #1 cause of infant death (NVSR, 2010)
  - 4-yr study in Salt Lake City, UT
    - 51% of deaths age <1 year
- # 1 cause of NICU death
  - 6.7% of newborns admitted to NICU
  - 11-year study in Louisville, KY
    - 45% of NICU deaths
- Leading cause of PICU death
  - 5-yr study in Little Rock, Arkansas
    - 51 of 268 (19%) PICU deaths

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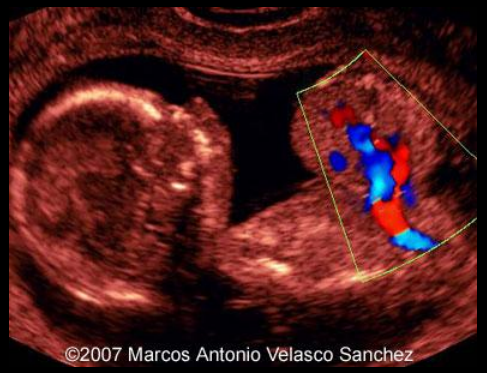
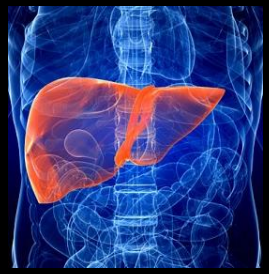
April 10th 2013, infant CMH487

- Maternal triple screen at 16 weeks ↑ α-fetoprotein
- Fetal MRI: Omphalocele, hydronephrosis, pyelectasis, hydrocele, scoliosis
- Delivery in CMH materno-fetal health center
- Admitted to NICU for treatment of ruptured omphalocele
- Acute liver failure @ 2 months of age
- Parents counseled that outcome likely to be bad





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April 10th 2013, NICU

Nomination. Genetic counseling. Consent. Symptom Entry

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April 10th 2013, NICU

Blood sample

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April 10th 2013, Genome Center Red Room

Samples to Genome Center

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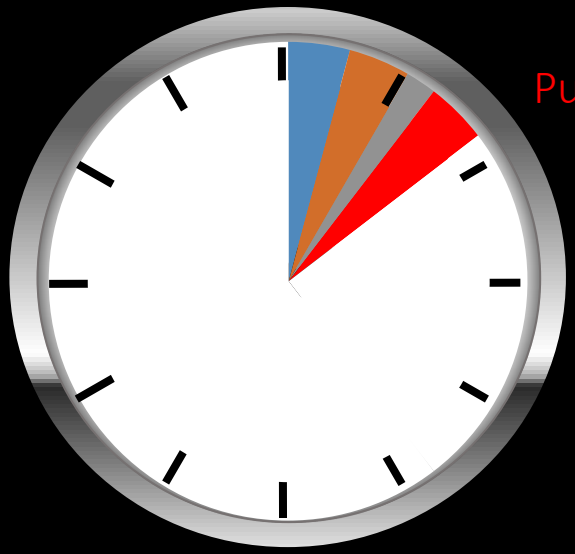
April 10th 2013, Genome Center Red Room



Purify DNA from blood

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Genome Center Yellow Room

Prepare DNA for sequencing

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Genome Center Orange Room

25-Hour Genome sequencing

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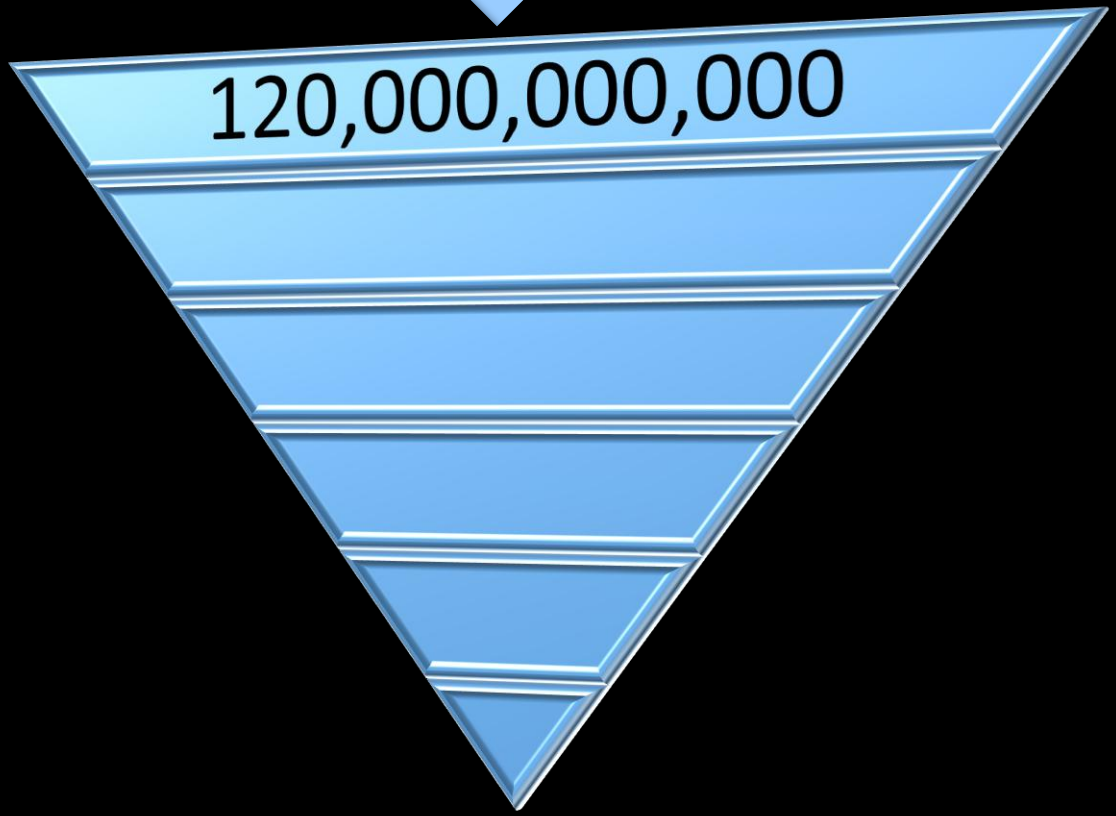
DNA from Infant CMH487

Nucleotides Sequenced



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Genome Data Center

Catalog all DNA letter changes

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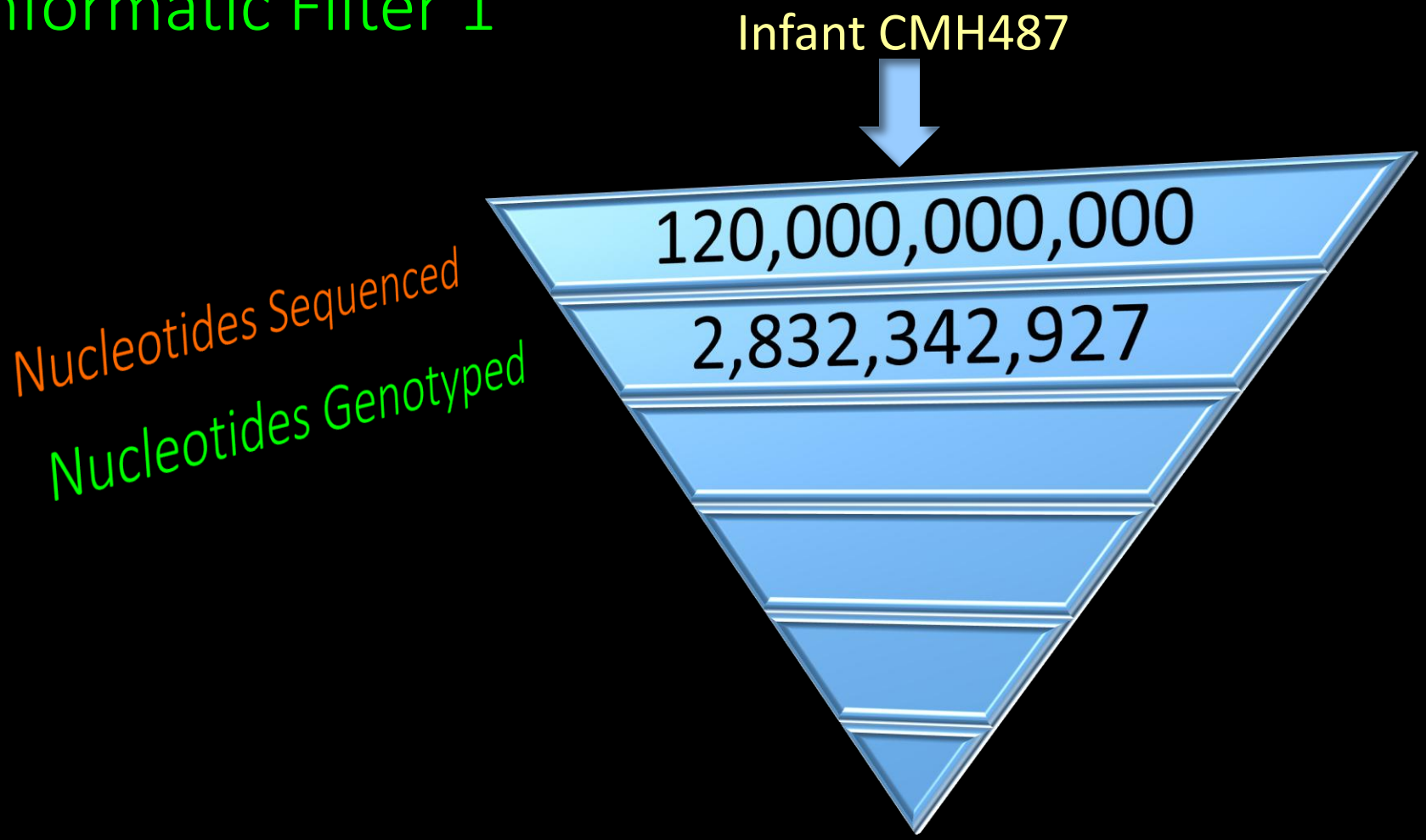
Bioinformatic Filter 1



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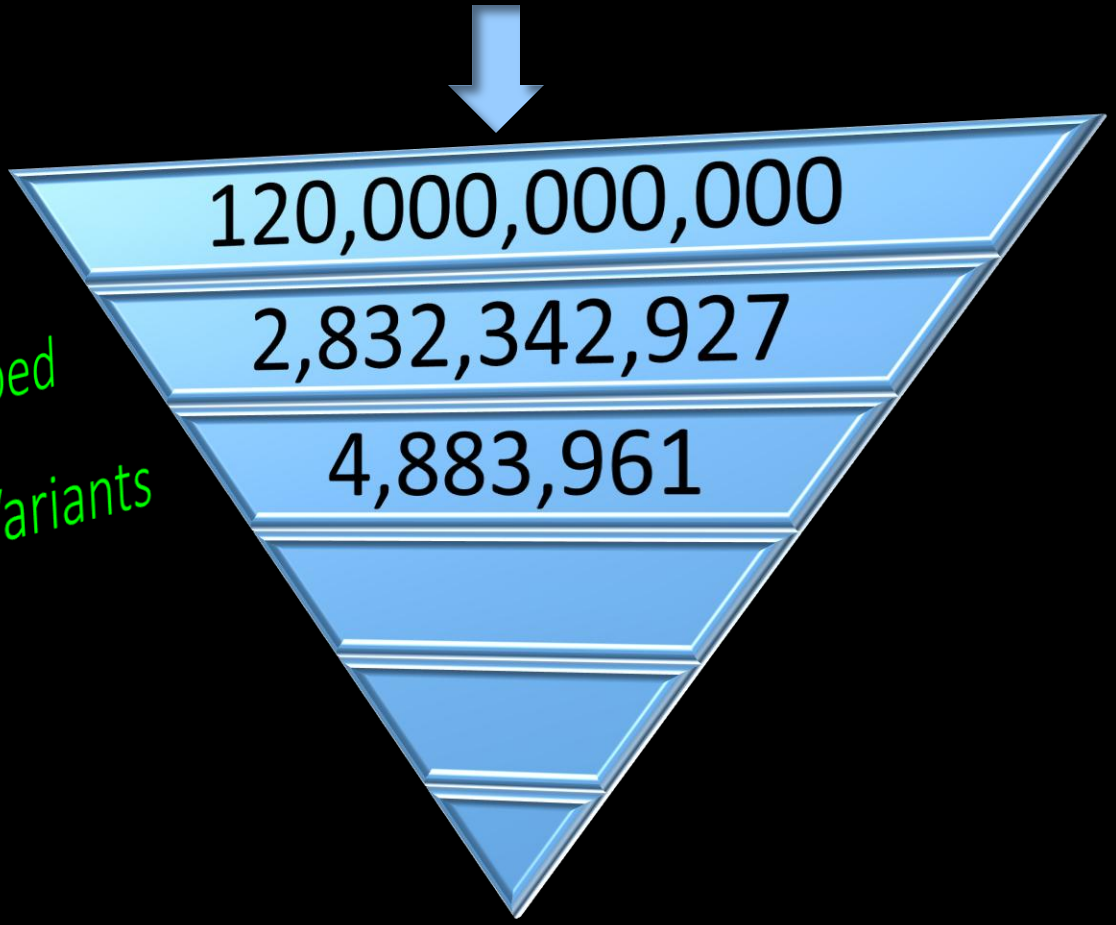
Bioinformatic Filter 2

Infant CMH487



Nucleotides Sequenced

Nucleotides Genotyped

Nucleotide Variants

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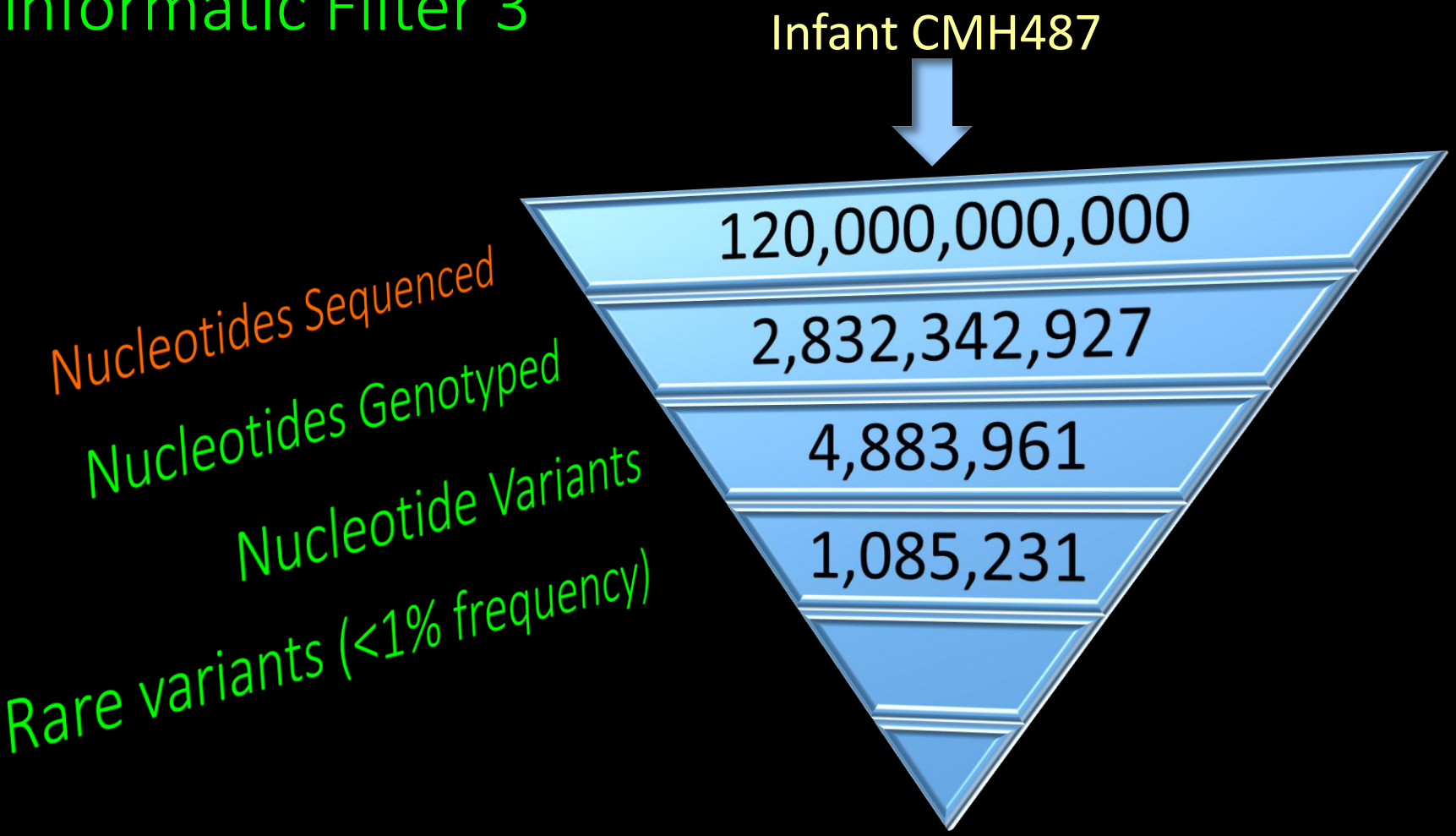
Bioinformatic Filter 3



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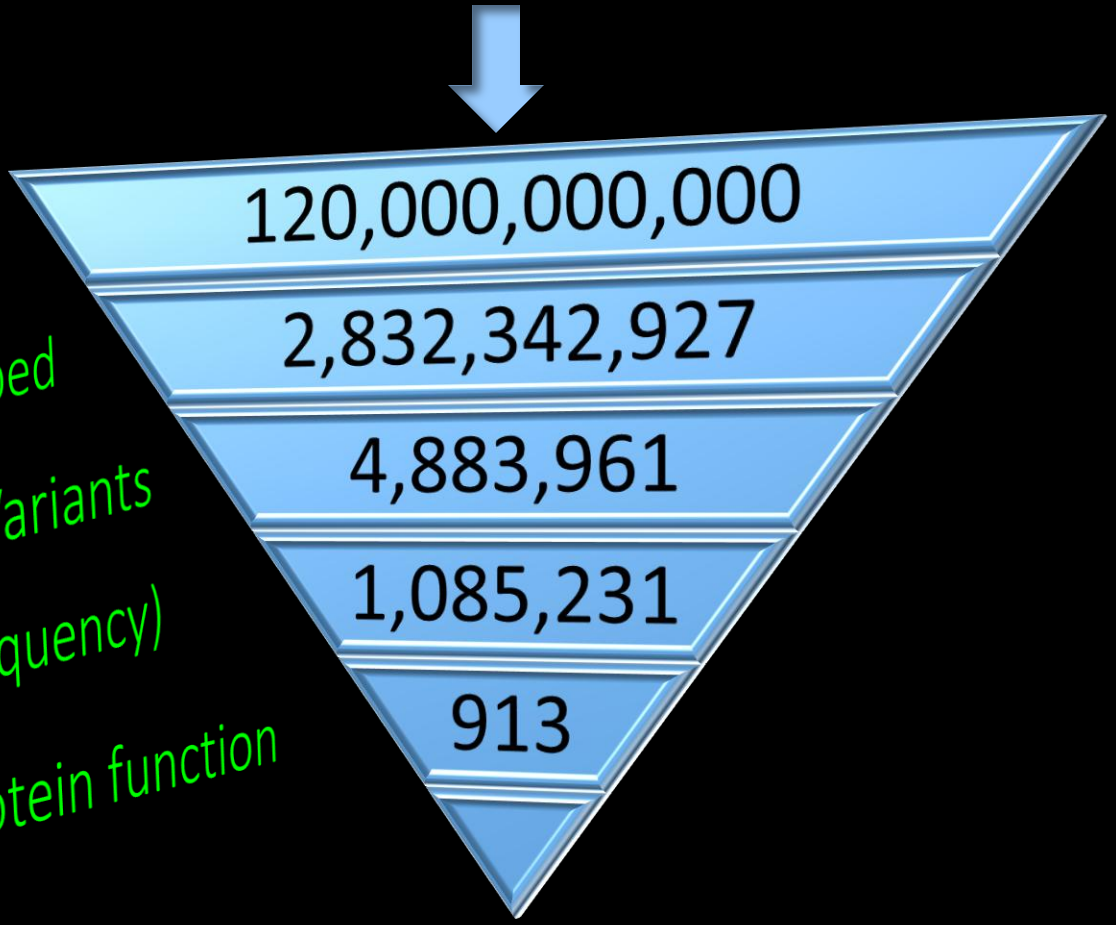
Bioinformatic Filter 4

Infant CMH487



Nucleotides Sequenced

Nucleotides Genotyped

Nucleotide Variants

Rare variants (<1% frequency)

Variants likely to alter protein function

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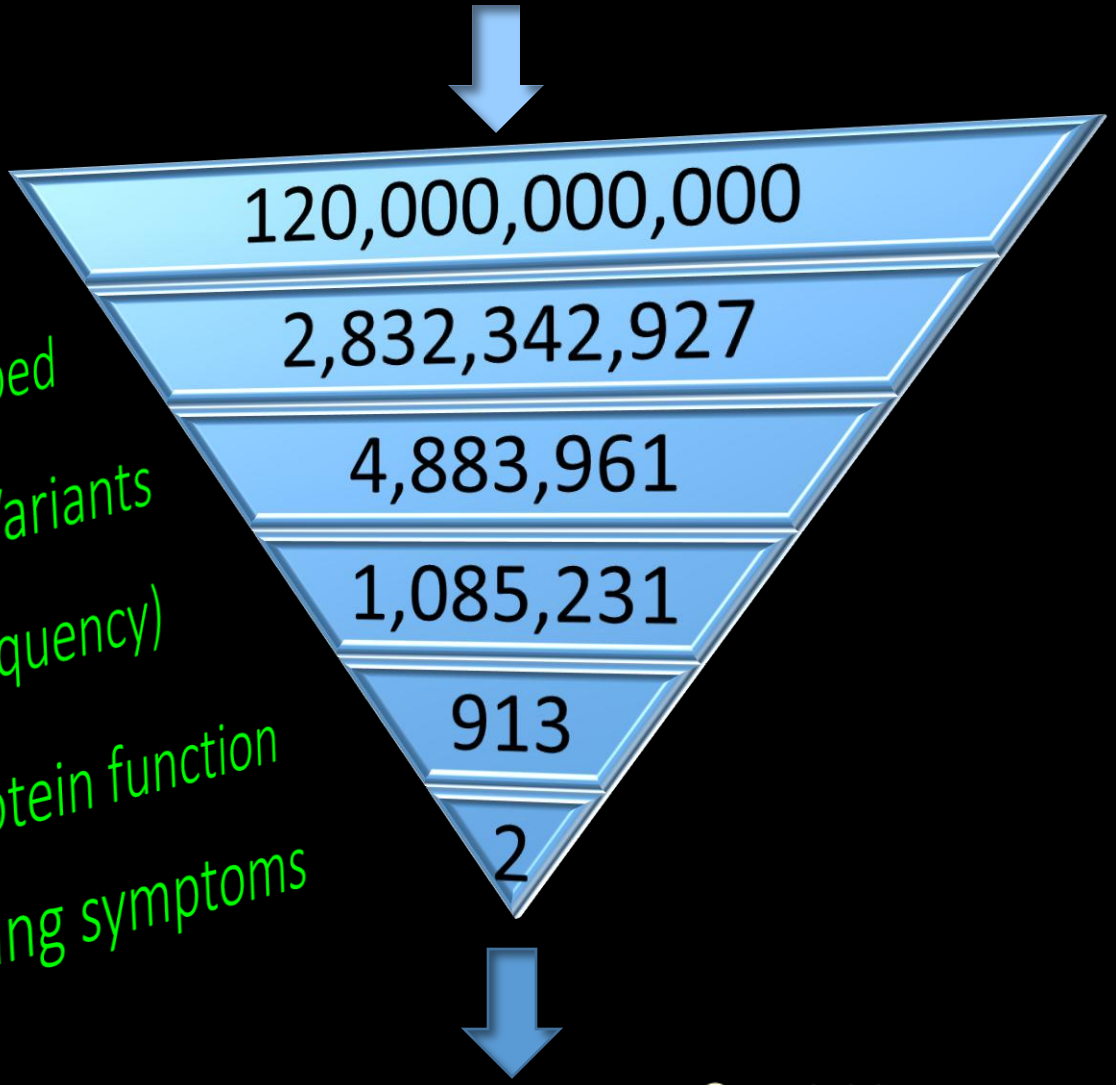
Bioinformatic Filter 5

Infant CMH487



Nucleotides Sequenced

Nucleotides Genotyped

Nucleotide Variants

Rare variants (<1% frequency)

Variants likely to alter protein function

In 341 diseases matching symptoms

Diagnosis

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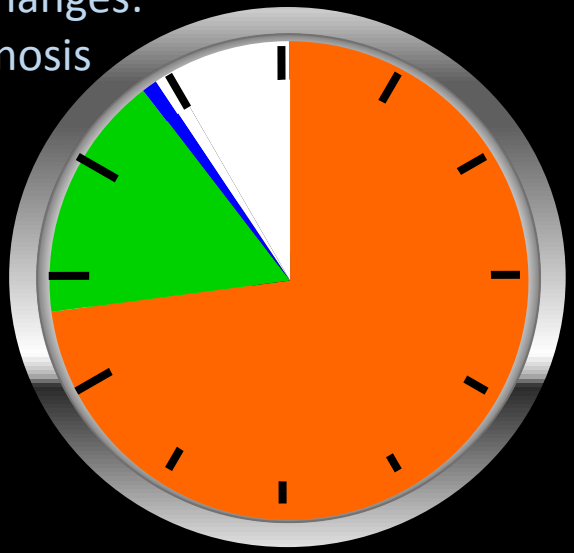
April 13th 2013, Genome Center Offices

Interpret DNA changes:
Provisional diagnosis



Two compound heterozygous variants in Perforin 1

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April 10th 2013, NICU

Confirmatory testing and treatment change: IV corticosteroids & immunoglobulin

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Today

- Liver function returned to normal
- Baby has returned home
- We did not find the genetic cause of his congenital anomalies

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Genomic Neonatology

- Using genome information in NICUs
  - Clinical diagnosis → Rx that target disease symptoms
- Genomic diagnosis
    - Rapid answers - 2 days
    - Determination of prognosis
    - Prediction of complications before they occur
    - Counseling re. risk of future affected child
- Genomic treatment
    - Early treatment
    - Rx /Dosing that target disease mechanisms

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July 25, 2013, infant CMH569

- Refractory hypoglycemia
- Transferred to CMH at 4 weeks
  - Glucoses 29, 18
  - After 30 min feed:
    glucose 19, insulin 22
- Rx: IV glucose, PO diazoxide, IV glucagon, diet change
- Breakthrough hypoglycemia

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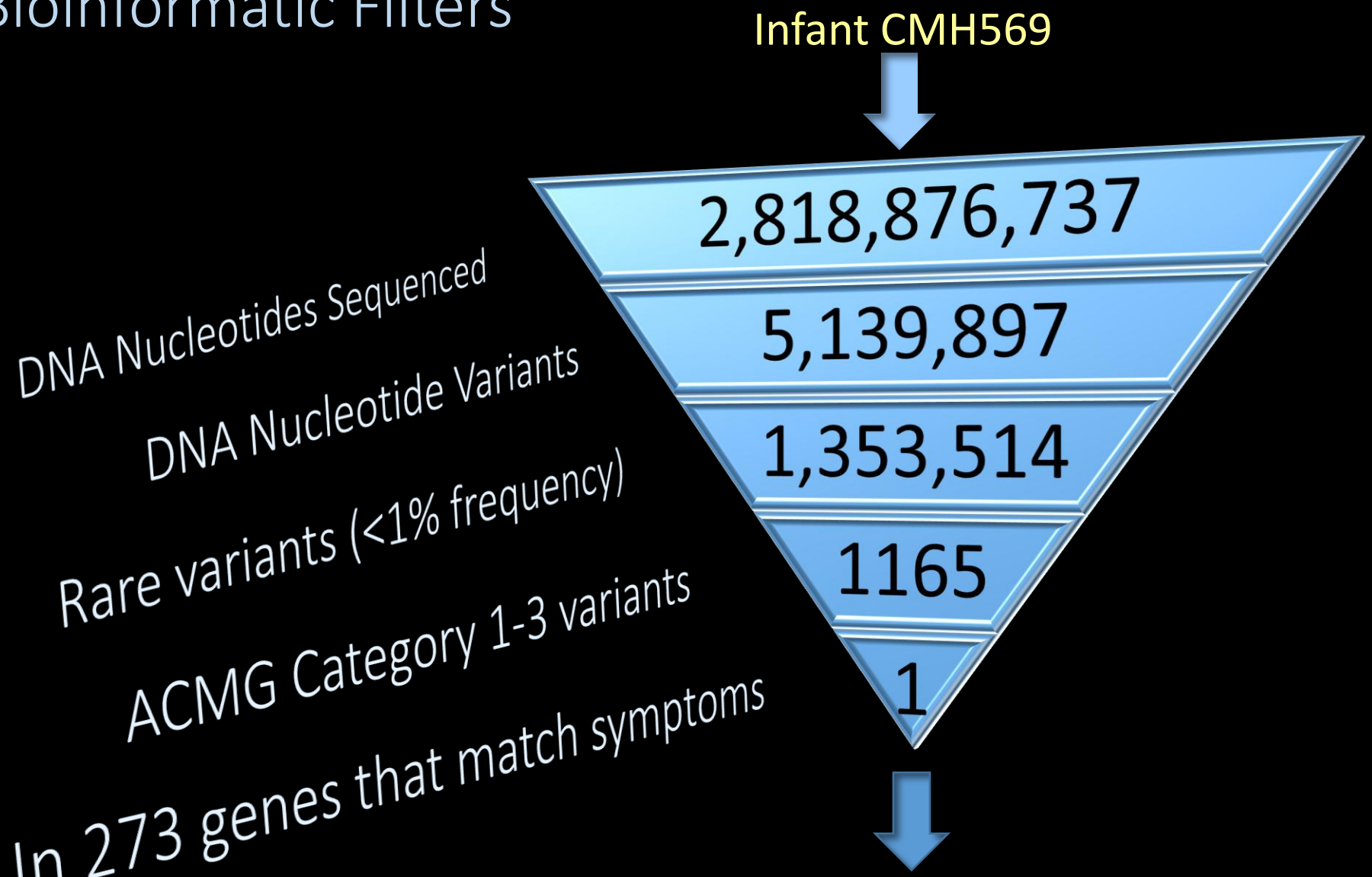
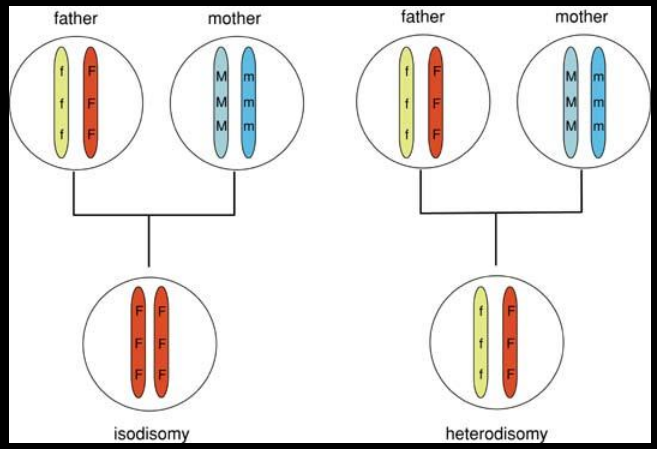
Bioinformatic Filters

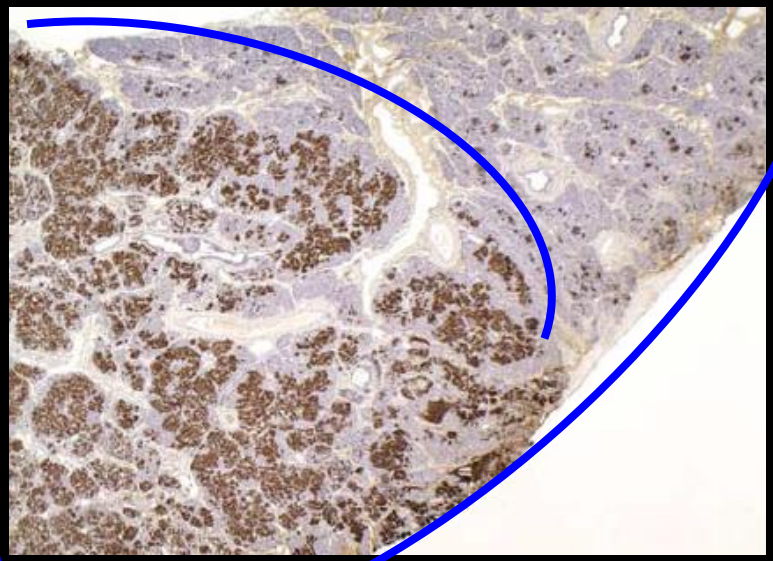


Focal *ABCC8* Congenital Hyperinsulinism: Very different treatment & outcome

- Heterozygous *ABCC8* mutation (Arg1215Trp)
- Inherited from dad
- *ABCC8*-congenital hyperinsulinism is recessive or paternal + a somatic mutation



Focal disease (paternal & somatic mutation)
40% pancreatectomy
Completely cured



Diffuse disease (2 inherited mutations)
98% pancreatectomy
Lifelong diabetes

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Experience with NICU genomic medicine

32 families, 36 affected babies
- 13 families: slamdunks
- 3 families: partial diagnosis (50%)
- 7 families: likely new disease gene
- 12 families: strikeouts (38%)

In 48%, Dx changed Rx

What about the 52%?

- Psychological benefits for parents: the power of an answer; the end of uncertainty; removal of guilt
- Ends diagnostic odyssey: avoid unnecessary testing
- Ends therapeutic odyssey: avoids unnecessary treatments
- Avoids futile continuation of intensive care
- Planning – treatment duration, bonding, good-byes, last rites
- Genetic counseling to mitigate unanticipated recurrence.

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CMH102: 1ST visit by 7 year-old boy with progressive weakness

In clinic the medical team noticed that 2 siblings also had poor muscle tone.

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Diagnosis without a muscle biopsy

- Duo exome sequencing
- Two mutations in Nebulin, 1 inherited from mom, one from dad
- Diagnosis: Autosomal recessive nemaline myopathy, type 2
- Simple confirmation in affected and unaffected siblings & parents. Muscle biopsies avoided.

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The Paradigm Shift

	Specialty visits before diagnosis	Time to Diagnosis	Prior Diagnostic Studies Billed	Impact on care
CMH001, CMH002	35	7 years	$35,349	Low cholesterol, high protein diet, CoQ10 supplements
CMH102, CMH103	1	2 months	$3,248	Cardiology eval. due to risk of cardiomyopathy

Soden et al. J. Genome Exome 2012:1 15–24

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CMH175, 20 month old boy

- Severe anemia at birth, transfused
- Brother died of anemia at 4 days old
- Hospitalized 3 times in 1st 3 months with anemia
  - Cardiac arrest with Hemoglobin 2.4
    - Normal range for age is 10 to 15 g/dl
- Has had transfusions ever since
- Usual treatments ineffective
- $30,000 work-up: no diagnosis

Diagnosis: SEC23B mutation, Type 2 Congenital Dyserythropoietic Anaemia

- Clinico-pathologic case conference: genomics, pathology, pediatrics, genetics, hematology, transplant
- 1 patient in the world had previously had hemopoietic stem cell transplantation, and was cured
- Our patient
  - Transplanted June 2012
  - Infection problems due to immunosuppression
  - Now at home and cured

Summmary: 25 families, 67 genomes, 15 diagnoses

1. 7 received altered management as a result of a genomic diagnosis
   - Unique surgery to cure disease
   - Specific treatments to prevent death, diminish disease severity, delay progression
   - N-of-1 clinical trials of experimental therapies
2. Palliative
   - Avoid future treatments, futile continuation of intensive care, unnecessary or invasive testing
3. Parental benefits
   - Psychosocial: less uncertainty
   - Planning – treatment intensity, duration, bonding, good-byes, last rites
   - Genetic counseling, recurrence risk.
4. Societal
   - Reduced NICU and lifetime cost of care

What's next for genomic medicine programs?

- Comparative effectiveness studies that lead to reimbursement
- Physician education: Master class in genomic medicine
- Genomic medicine care teams and subspecialist focus clinics
  - Function in coordination with clinical care teams and primary clinics
  - Provide thorough documentation of findings and set of recommendations to clinical care team
  - Provide consultation to families
  - Provide logistics and expertise for experimental or off label treatments for rare genetic diseases

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Our Rough 5 Year Goals

- A genomic diagnosis within a day for every baby enrolled
- An experimental treatment plan for every baby with a diagnosis for which there is no standard therapy
- A genomic diagnosis within a month for every child at CMH

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