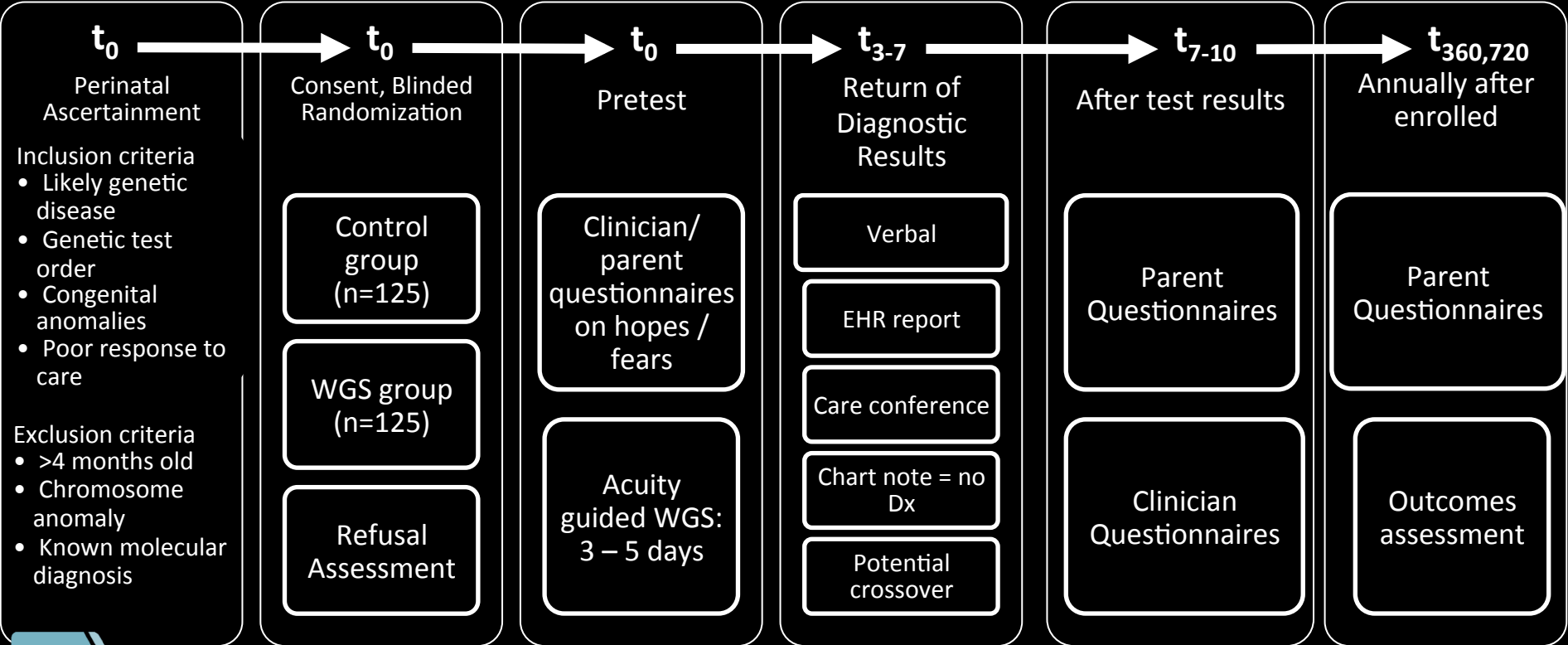


Ending the Diagnostic Odyssey

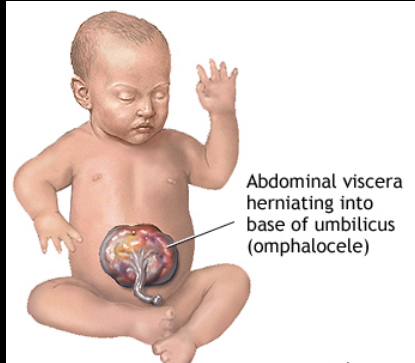
- Research to evaluate the utility of rapid genome sequencing to identify the root cause of illness in newborns
- Level IV Neonatal Intensive Care Units
 - Rady Children's Hospital, San Diego
 - Children's Mercy Hospital, Kansas City

Randomized, controlled, prospective trial of clinical utility

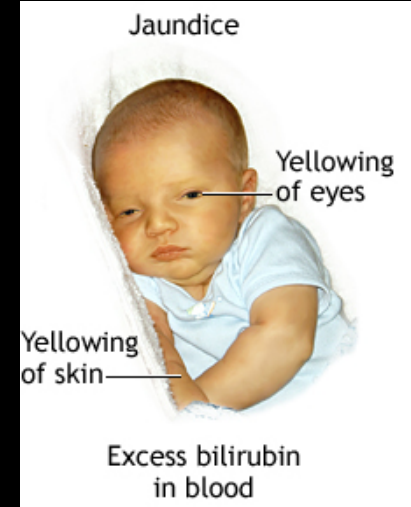


April 10, 2013

Baby CMH487



00:00



- 8,000 named diseases
- 20 more discovered each month
- Affect 1 in 25 children
- Leading cause of infant death

Solution:
Test all 8,000 Genetic Diseases
in 26 hours by WGS*

*Whole Genome Sequencing

Genetic Testing in Newborns Breakthrough

Alice Park @aliceparkny | Sept. 29, 2015

For the first time, researchers can now sequence the genomes of newborns with mystery conditions in

In every neonatal intensive care unit (NICU), about half of the residents are there because they were born prematurely and need help to breathe and get used to their new world outside the womb.

But about a third of NICU residents are there because doctors don't know what's wrong with them. They may have seizures, trouble eating or breathing, and nobody knows why.



Dr. Stephen Kingsmore (left), recently named the inaugural CEO of the genomics institute at Rady Children's Hospital, and his director of clinical services Tim Hambrich, stand near a group of genomic sequencing machines at the

Genetic screening speeds up diagnosis

New 26-hour test delivers faster diagnoses, which hold special promise for newborns

Bio-IT World

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Speed Heals: The 26-Hour Diagnostic Genome

By Allison Proffitt

September 29, 2015 | Stephen Kingsmore and his colleagues at the Center for Pediatric Genomic Diagnostics have developed a new system to quickly sequence a newborn's genome to help identify

Newsweek

Miller et al. *Genome Medicine* (2015) 7:100
DOI 10.1186/s13073-015-0221-8



METHOD

Open Access



A 26-hour system of highly sensitive whole genome sequencing for emergency management of genetic diseases

Neil A. Miller^{1†}, Emily G. Farrow^{1,2,3,4†}, Margaret Gibson¹, Laurel K. Willig^{1,2,4}, Greystone Twist¹, Byunggil Yoo¹, Tyler Marrs¹, Shane Corder¹, Lisa Krivohlavek¹, Adam Walter¹, Josh E. Petrikina^{1,2,4}, Carol J. Saunders^{1,2,3,4}, Isabelle Thiffault^{1,3}, Sarah E. Soden^{1,2,4}, Laurie D. Smith^{1,2,3,4}, Darrell L. Dinwiddie⁵, Suzanne Herd¹, Julie A. Cakici¹, Severine Catreux⁶, Mike Ruehle⁶ and Stephen F. Kingsmore^{1,2,3,4,7*}

April 10, 2013

00:20

Parents gave consent

April 10, 2013

00:40

Blood sample from mum, dad and baby

April 10, 2013

00:60

Transport to Institute

April 10, 2013

02:00

Isolate DNA



April 10, 2013

06:00

Prepare DNA
for sequencing

Each of my 37 trillion cells contains 2
genomes of 3.2 billion DNA letters

HHMI

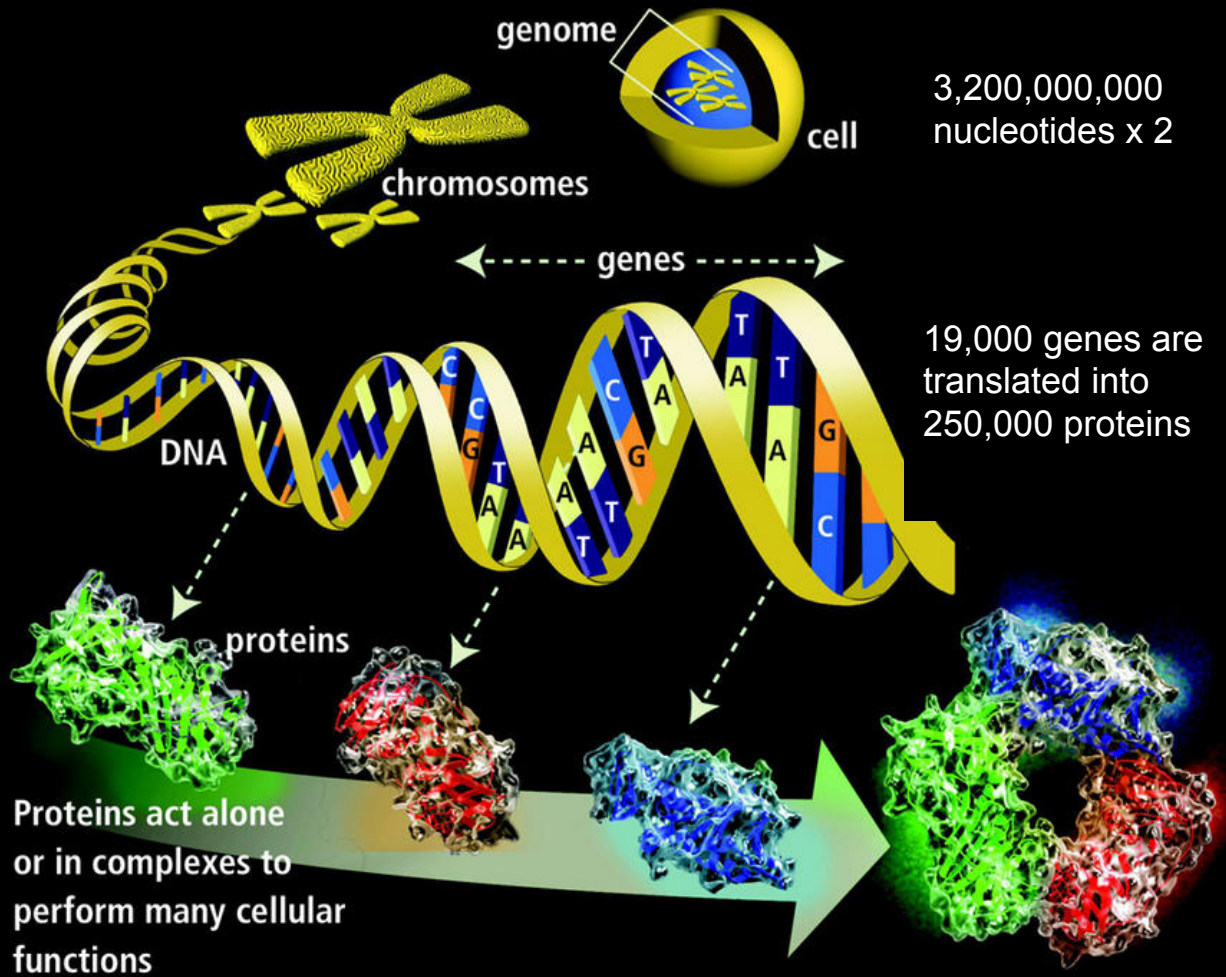
We are fearfully and wonderfully made. Psalm 139

April 10, 2013

24:30

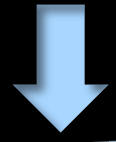
Illumina genome sequencing





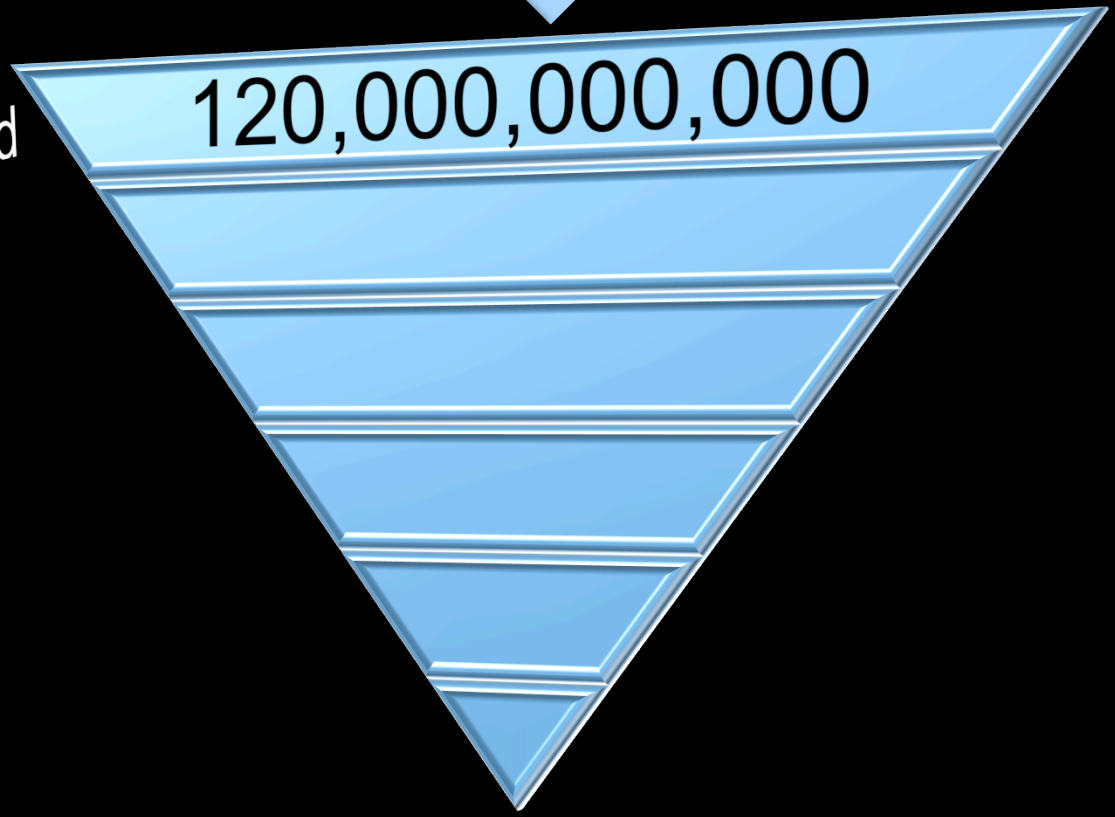
24:30

Infant CMH487



120,000,000,000

Total DNA letters detected



24:45

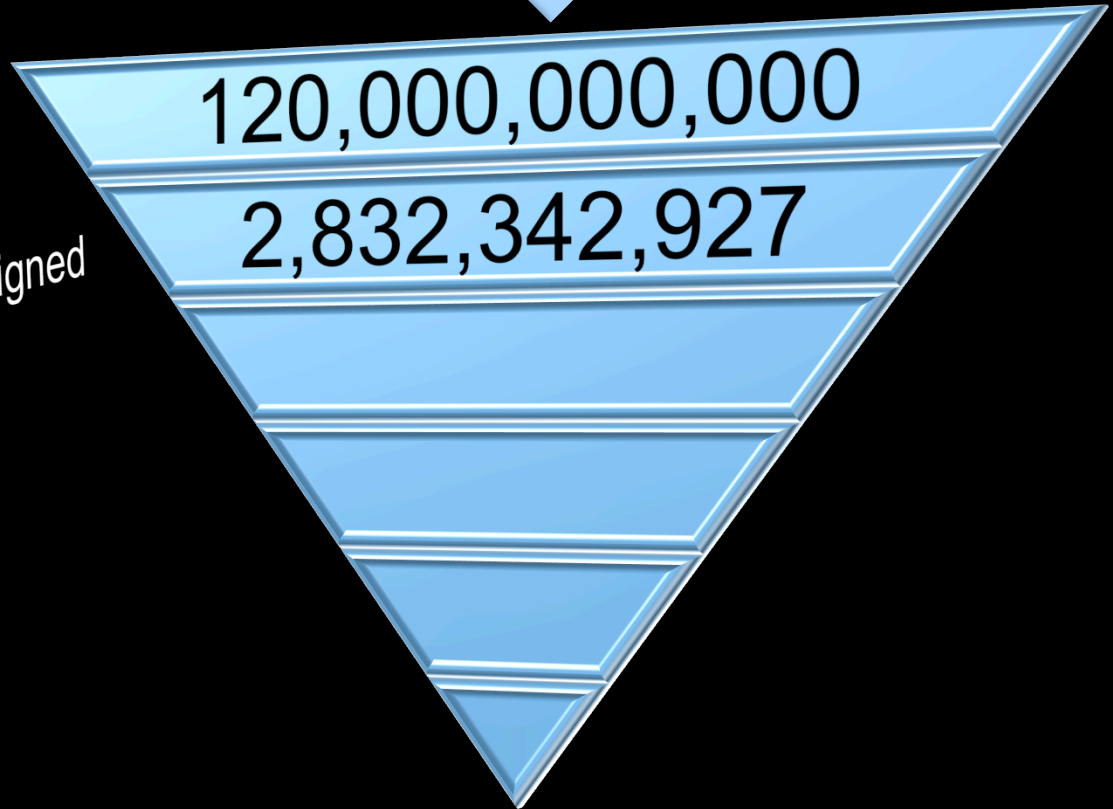
Infant CMH487



120,000,000,000

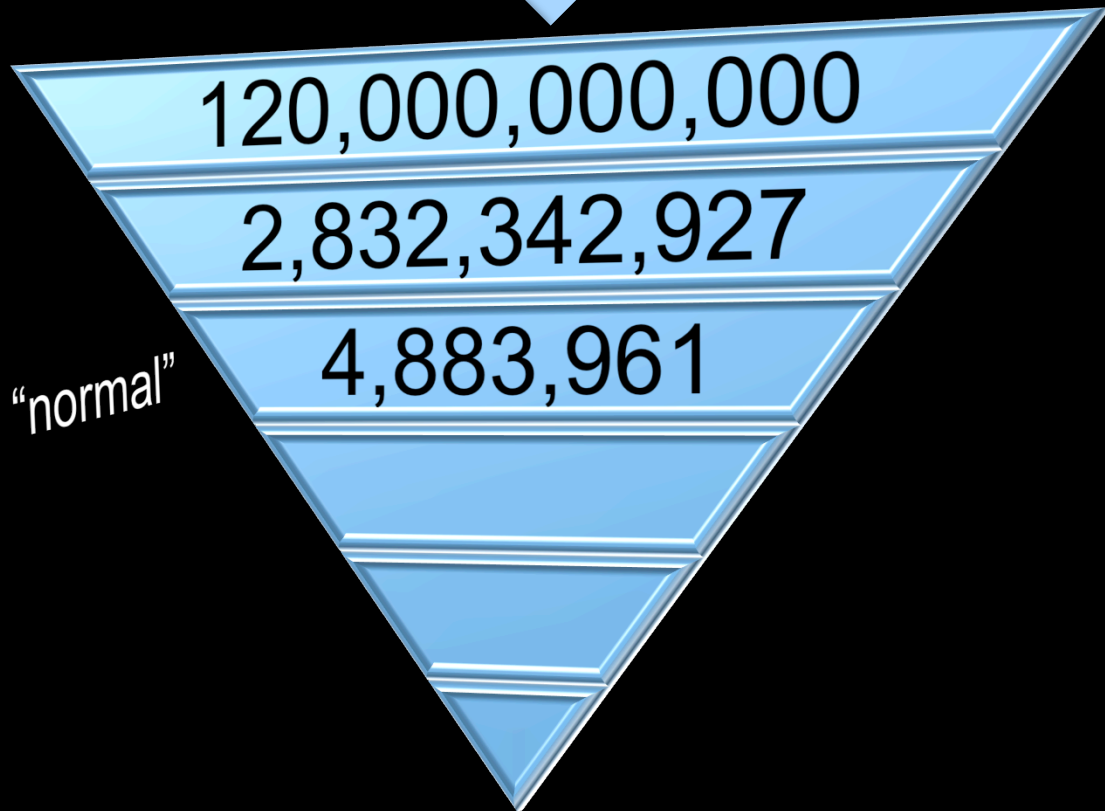
2,832,342,927

DNA letters of genome code assigned



25:00

Infant CMH487



DNA letter changes from "normal"

25:01

Infant CMH487



120,000,000,000

2,832,342,927

4,883,961

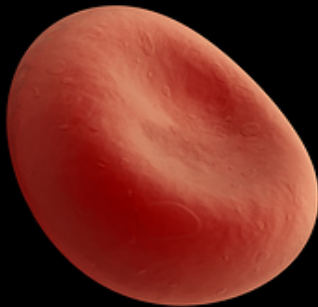
1,085,231

DNA changes present in less 1 in 100 people

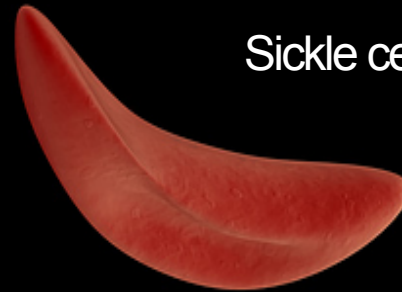
A single DNA letter change can cause a genetic disease

Hemoglobin- β
DNA code

G ₂	G ₂	T ₁	G ₂	T ₁	T ₁	G ₂	G ₂	G ₂
T ₁	T ₁	A ₁	T ₁	C ₃	C ₃	T ₁	A ₁	A ₁
A ₁	G ₂	C ₃	C ₃	A ₁	C ₃	G ₂	G ₂	A ₁



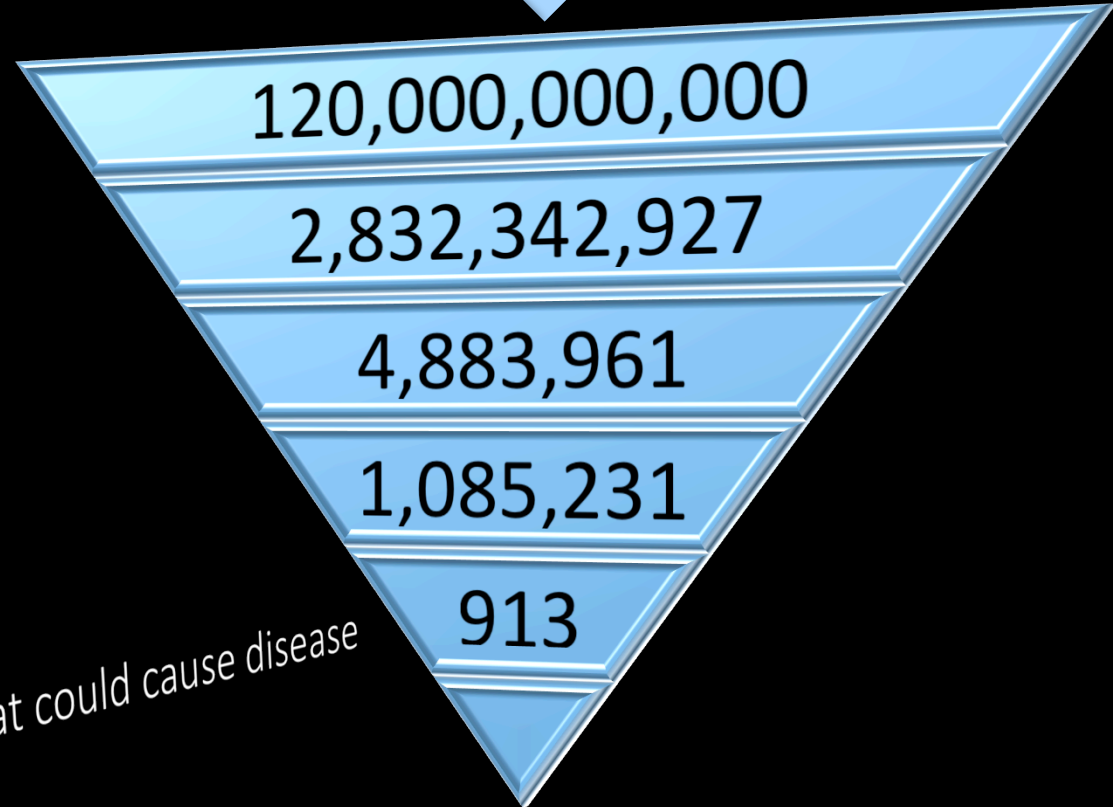
Normal red
blood cell



Sickle cell

25:41

Infant CMH487



DNA changes that could cause disease

25:42

Computer-Generated List of 341 Possible Diagnoses

The screenshot displays a medical diagnostic interface. On the left is a navigation sidebar with icons for Symptoms, Patient, Orders, and Admin. The main area is split into two panels: 'Symptoms' and 'Ontology'. The 'Symptoms' panel contains a search bar and a table of symptoms. The 'Ontology' panel shows a patient's information and a list of 341 possible diagnoses.

Symptoms Panel:

HP ID	Symptoms
HP:0001539	Omphalocele
HP:0001873	Thrombocytopenia
HP:0003645	Prolonged partial thromboplastin time
HP:0006254	Elevated alpha-fetoprotein
HP:0006583	Fatal liver failure in infancy
HP:0008151	Prolonged prothrombin time
HP:0010945	Mild fetal pyelectasis

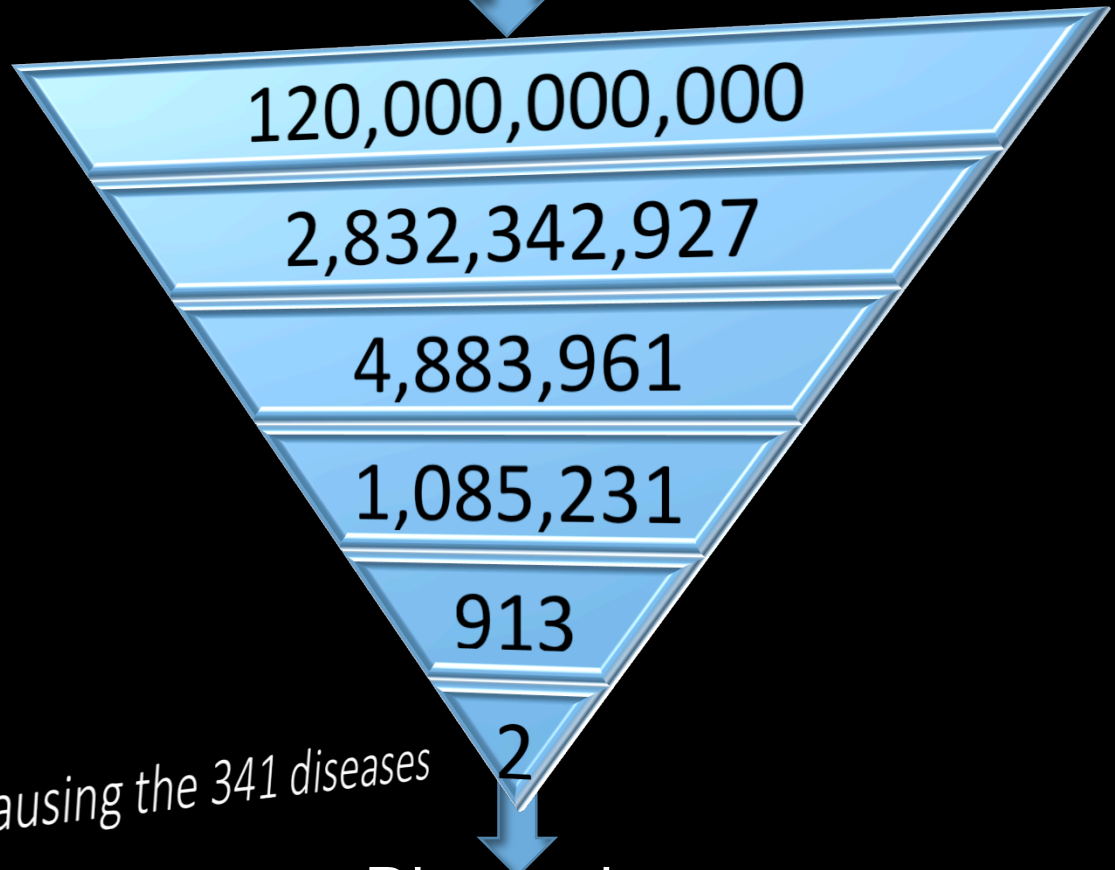
Diagnosis Panel:

Patient ID	Name	EMR ID
10	First Last	cmh000487

Symptoms	Diagnosis
<input type="checkbox"/>	Disease ID Disease Name Genes
<input type="checkbox"/>	ORPHANET:974 ADAMS-OLIVER SYNDROME RBPJ
<input type="checkbox"/>	OMIM:274000 #274000 THROMBOCYTOPENIA-ABSENT RADIUS SYNDROME; TAR; TAR SYNDRO RBM8A
<input type="checkbox"/>	OMIM:603554 #603554 OMENN SYNDROME;;RETICULOENDOTHELIOSIS, FAMILIAL, WITH EOSINOF RAG2
<input type="checkbox"/>	OMIM:603554 #603554 OMENN SYNDROME;;RETICULOENDOTHELIOSIS, FAMILIAL, WITH EOSINOF RAG1
<input type="checkbox"/>	ORPHANET:84 FANCONI ANEMIA RAD51C
<input type="checkbox"/>	OMIM:201000 #201000 CARPENTER SYNDROME 1; CRPT1;;CARPENTER SYNDROME;;ACROCEPH RAB23
<input type="checkbox"/>	OMIM:610828 HOLOPROSENCEPHALY 7 PTCH1
<input type="checkbox"/>	OMIM:610539 #610539 GAUCHER DISEASE, ATYPICAL, DUE TO SAPOSIN C DEFICIENCY PSAP
<input type="checkbox"/>	ORPHANET:1572 COMMON VARIABLE IMMUNODEFICIENCY PRKCD
<input checked="" type="checkbox"/>	OMIM:603553 #603553 HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS, FAMILIAL, 2; FHL2;;HPLH2;; PRF1
<input type="checkbox"/>	OMIM:305600 #305600 FOCAL DERMAL HYPOPLASIA; FDH;;FODH; DHOF;;GOLTZ SYNDROME;;G PORCN
<input type="checkbox"/>	OMIM:212065 #212065 CONGENITAL DISORDER OF GLYCOSYLATION, TYPE IA; CDG1A;;CDG IA; PMM2
<input type="checkbox"/>	OMIM:601709 QUEBEC PLATELET DISORDER PLAU
<input type="checkbox"/>	OMIM:601815 PHOSPHOGLYCERATE DEHYDROGENASE DEFICIENCY PHGDH
<input type="checkbox"/>	OMIM:170100 #170100 PROLIDASE DEFICIENCY PEPD
<input type="checkbox"/>	ORPHANET:1980 BILATERAL STRIOPALLIDODENTATE CALCINOSIS PDGFRB
<input type="checkbox"/>	ORPHANET:1980 BILATERAL STRIOPALLIDODENTATE CALCINOSIS PDGFB

26:00

Infant CMH487



DNA changes in genes causing the 341 diseases

Diagnosis

26:00 April 13, 2013

Interpret DNA changes: Diagnosis

- Two mutations (DNA letter changes) affecting one protein
- Diagnosis (Hemophagocytic lymphohistiocytosis type 2)

April 17, 2013

Precision medicine:

Stop non-specific treatments

Start specific treatments

Result:

Liver failure corrected within 7 days

Today

He is 31 months old

72 quality adjusted life years saved

57% diagnosis

1 st Author	Journal	Number of Subjects	Age (mean or median)	Diagnosis Rate
Soden	<i>Sci Trans Med</i>	100	7 years	47%
Srivastava	<i>Ann Neurol</i>	78	9 years	41%
Yang	<i>JAMA</i>	1756	6 years	27%
Lee	<i>JAMA</i>	814	520 <18 yr	26%
Wright	<i>Lancet</i>	1133	6 years	27%

Acute clinical utility in 65% diagnoses

Strongly favorable impact on outcome in 20%

Diagnosis Prior to Discharge	65%
Genetic Counseling Change	20%
Subspecialty Consult (non-genetic) Initiated	5%
Medication Change	20%
Procedure Change	15%
Diet Change	10%
Palliative Care Initiated	30%
Imaging Change	15%
Transferred to Another Facility	5%