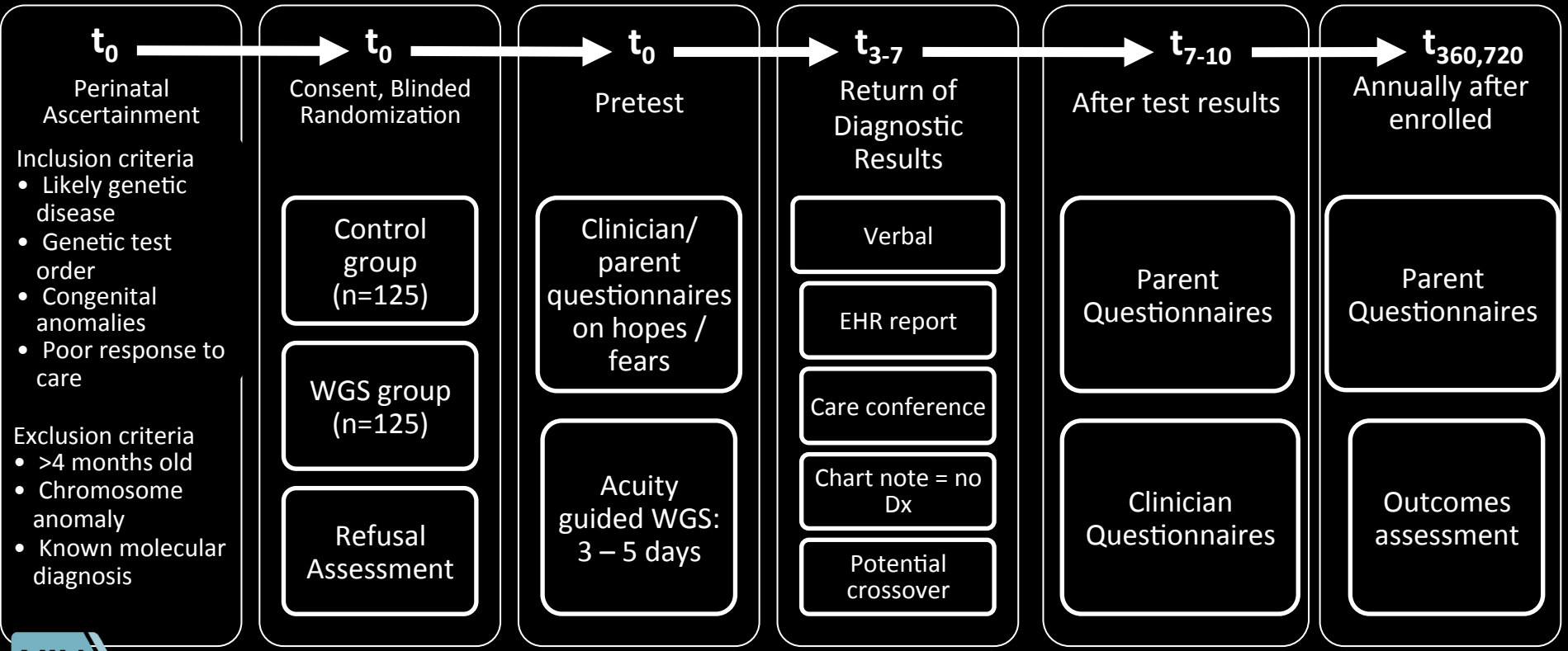
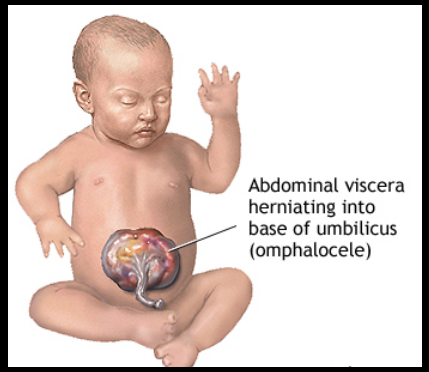
# Ending the Diagnostic Odyssey

- 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

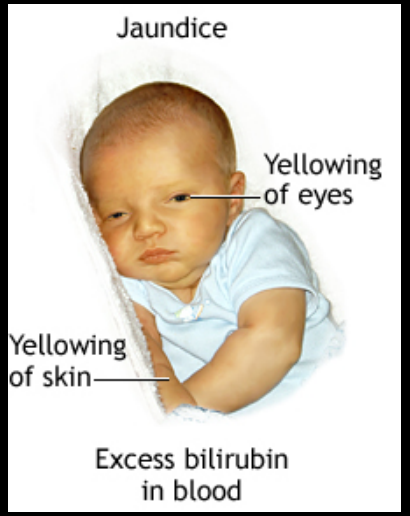
# Randomized, controlled, prospective trial of clinical utility



# 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

TIME

Health

# Genetic Testing in Newborns Breakthrough

Alice Park @aliceparkny | Sept. 29, 2015

**For the first time, res can now sequence t genomes of newbor mystery conditions i**

In every neonatal inter unit (NICU), about hal residents are there bec are born prematurely a help to breathe and ge accustomed to their ne outside the womb.

But about third of NIC there because doctors know what's wrong wi They may have seizure be eating or breathing and nobody knows wh

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sandiegouniontribune.com WEDNESDAY • SEPTEMBER 30, 2015

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

## Genetic screening speeds up

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

Speed Heals: The 26-Hour Diagnostic Genome

By Allison Proffitt

**September 29, 2015** | Stephen Kingsmore and his ...es at the Center for Pediatric Genomic ...

Newsweek

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

Genome Medicine

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 Gibson[1], Laurel K. Willig[1,2,4], Greyson Twist[1], Byunggil Yoo[1], Tyler Marrs[1], Shane Corder[1], Lisa Krivohlavek[1], Adam Walter[1], Josh E. Petrikin[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. Dinwiddie[5], Suzanne Herd[1], Julie A. Cakici[1], Severine Catreux[6], Mike Ruehle[6] 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

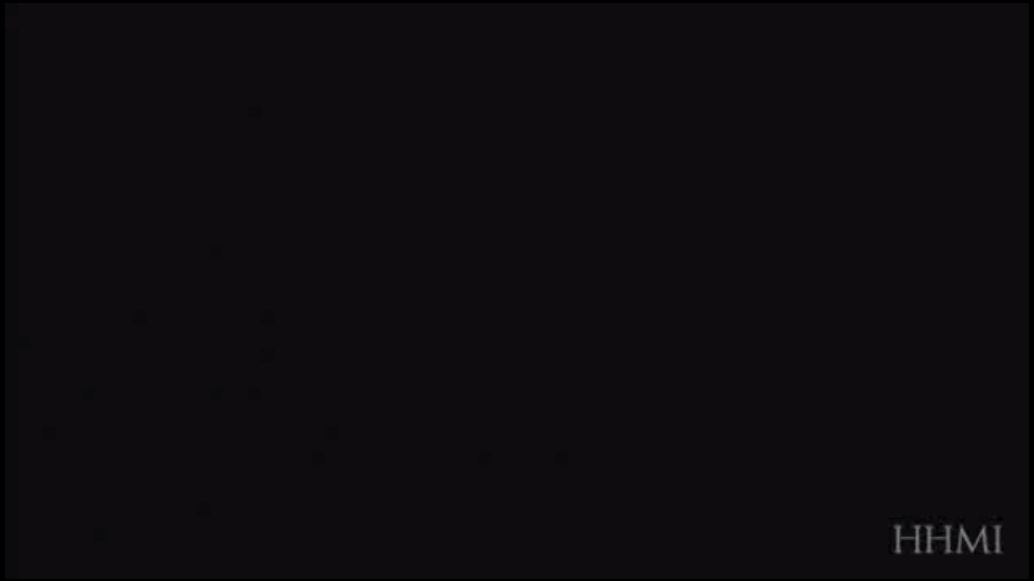
Isolate DNA

April 10, 2013

06:00

Prepare DNA
for sequencing

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

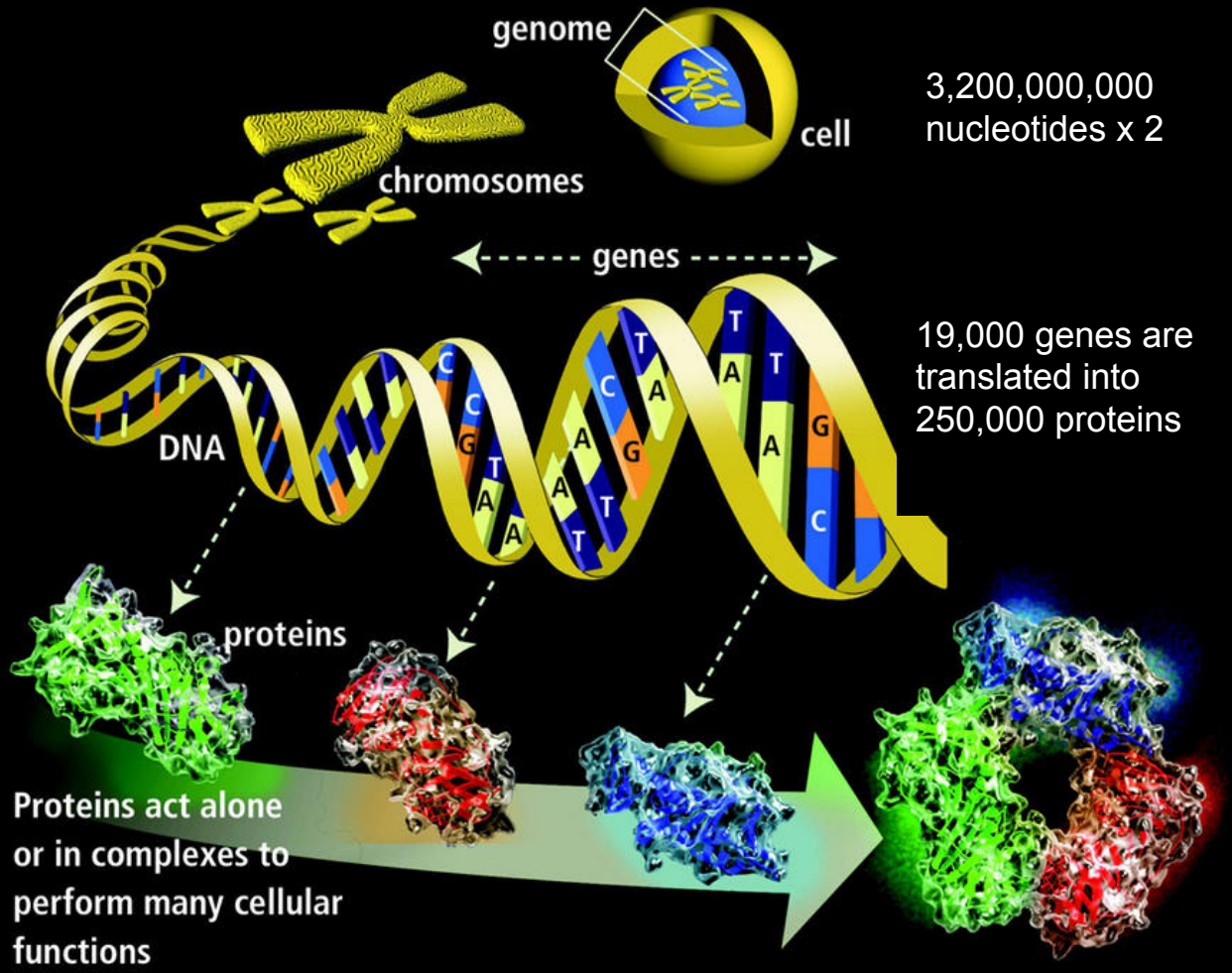



We are fearfully and wonderfully made. Psalm 139

April 10, 2013

# 24:30

Illumina genome sequencing



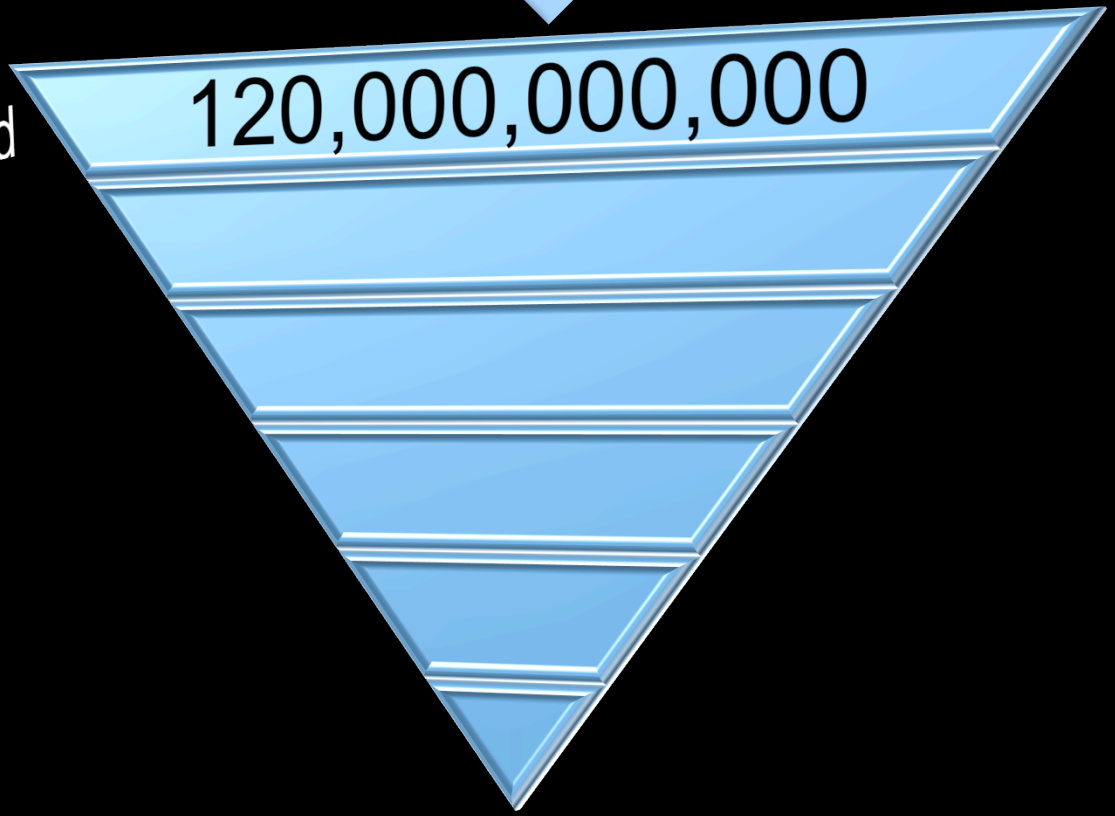

3,200,000,000 nucleotides x 2

19,000 genes are translated into 250,000 proteins

24:30

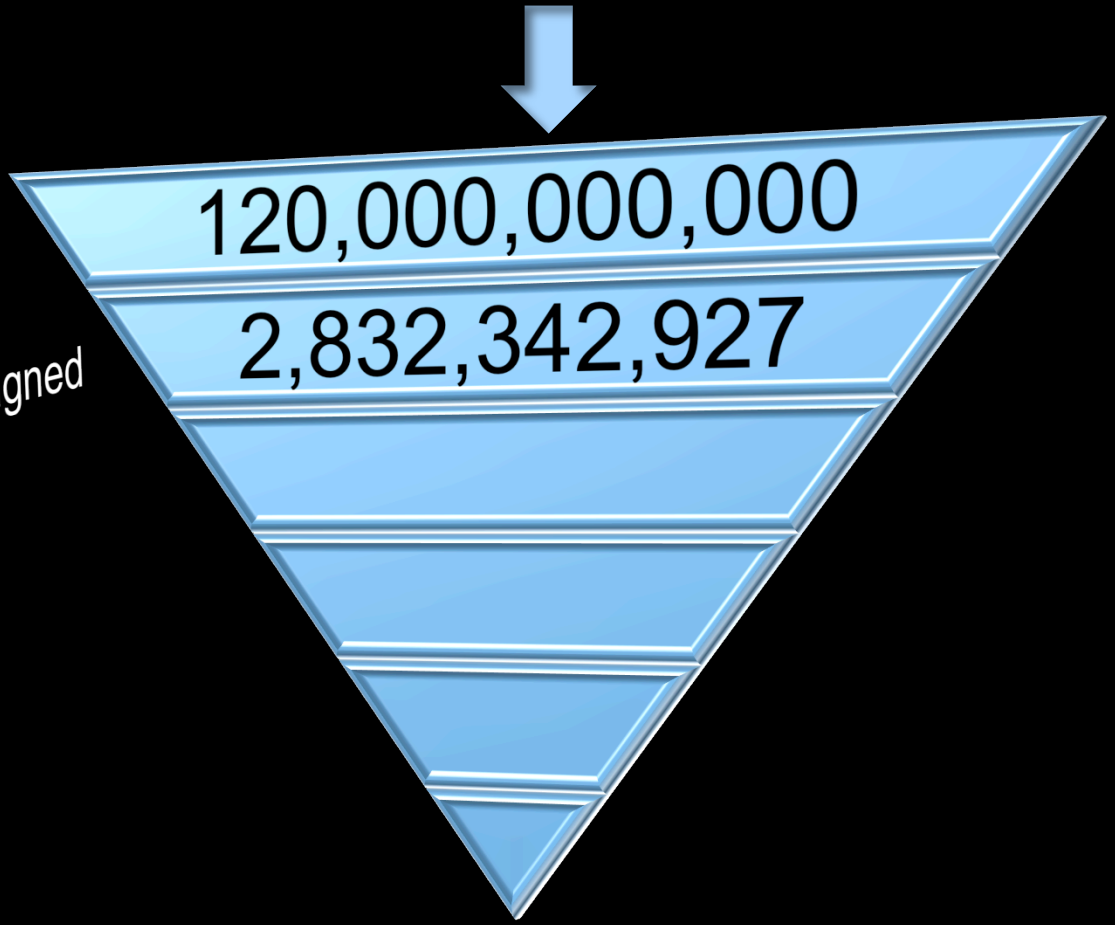
Infant CMH487

Total DNA letters detected



24:45

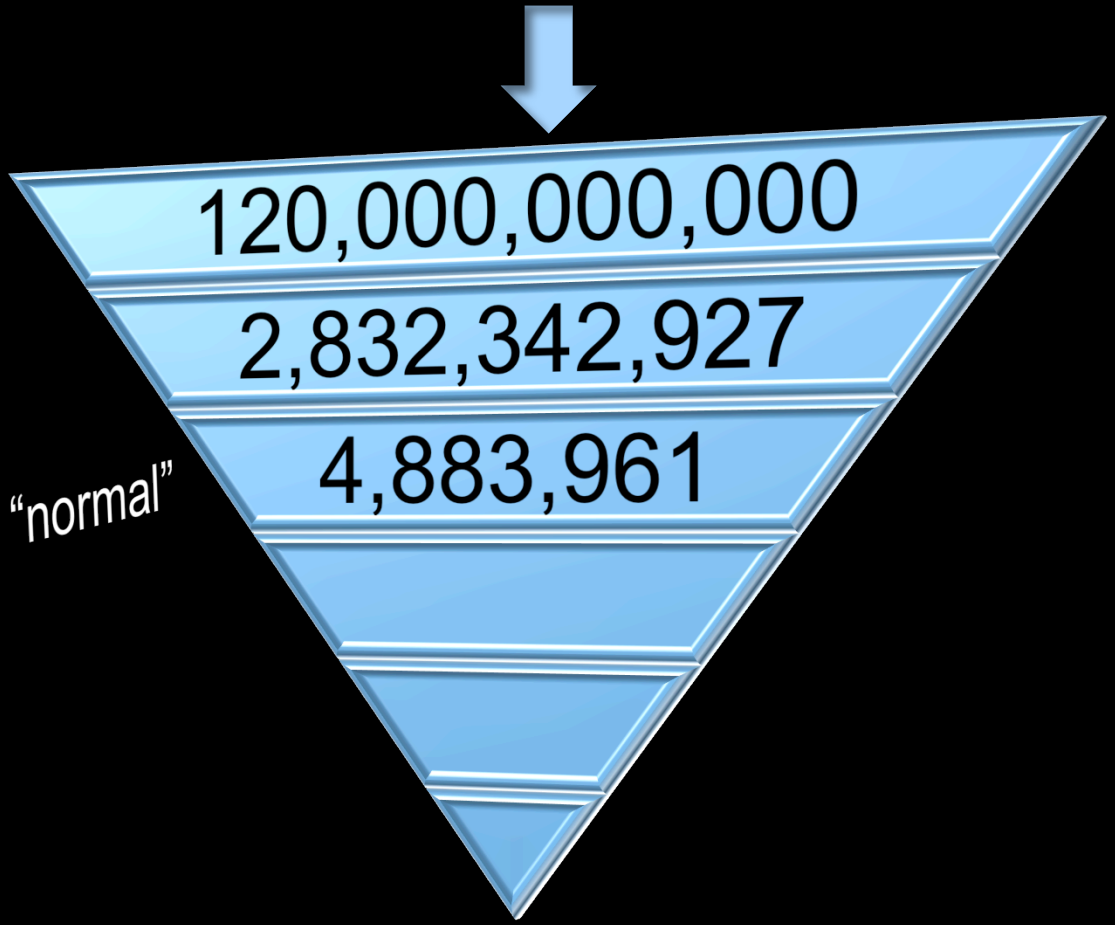
Infant CMH487




DNA letters of genome code assigned

25:00

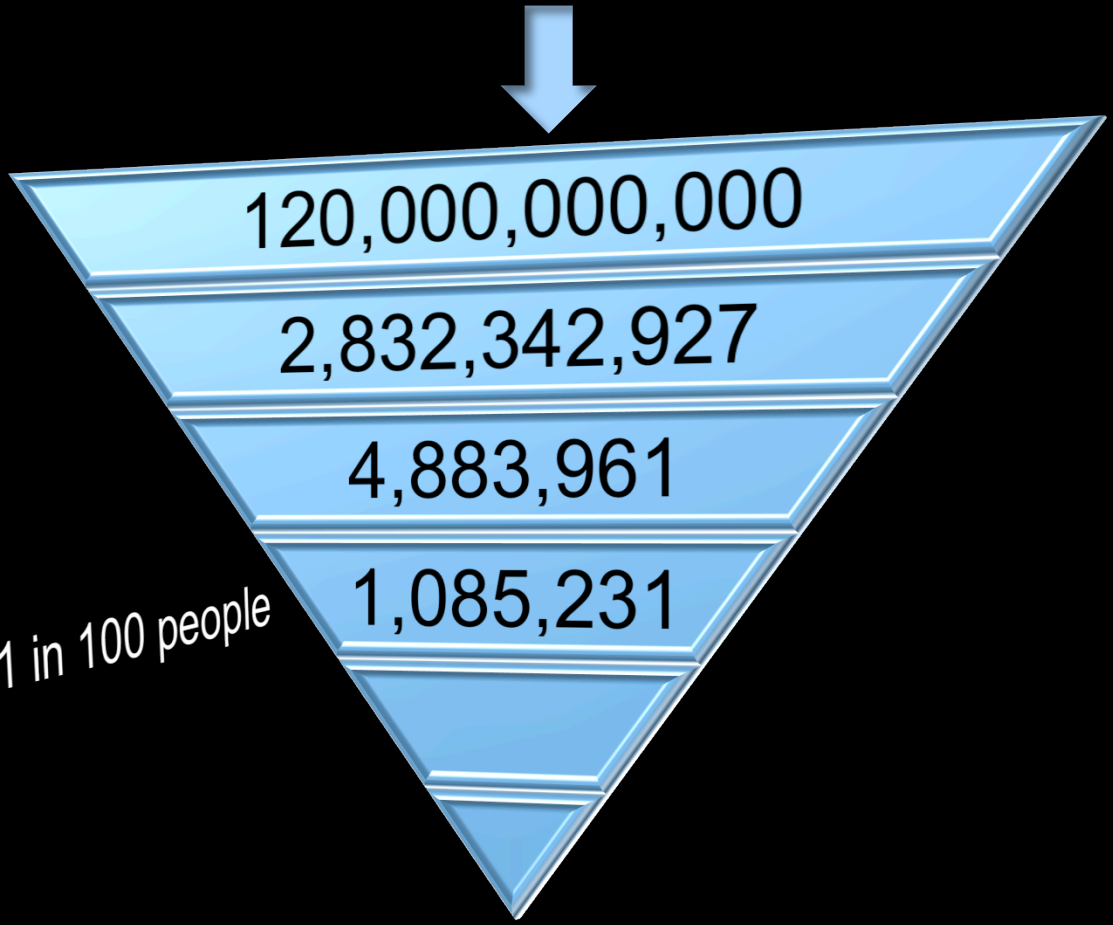
Infant CMH487




DNA letter changes from “normal”

25:01

Infant CMH487

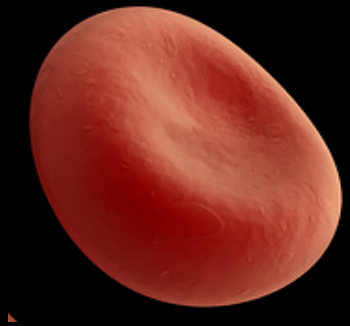



DNA changes present in less 1 in 100 people

# A single DNA letter change can cause a genetic disease

Hemoglobin-β DNA code

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| $G_2$ | $G_2$ | $T_1$ | $G_2$ | $T_1$ | $T_1$ | $G_2$ | $G_2$ | $G_2$ |
| $T_1$ | $T_1$ | $A_1$ | $T_1$ | $C_3$ | $C_3$ | $T_1$ | $A_1$ | $A_1$ |
| $A_1$ | $G_2$ | $C_3$ | $C_3$ | $A_1$ | $C_3$ | $G_2$ | $G_2$ | $A_1$ |

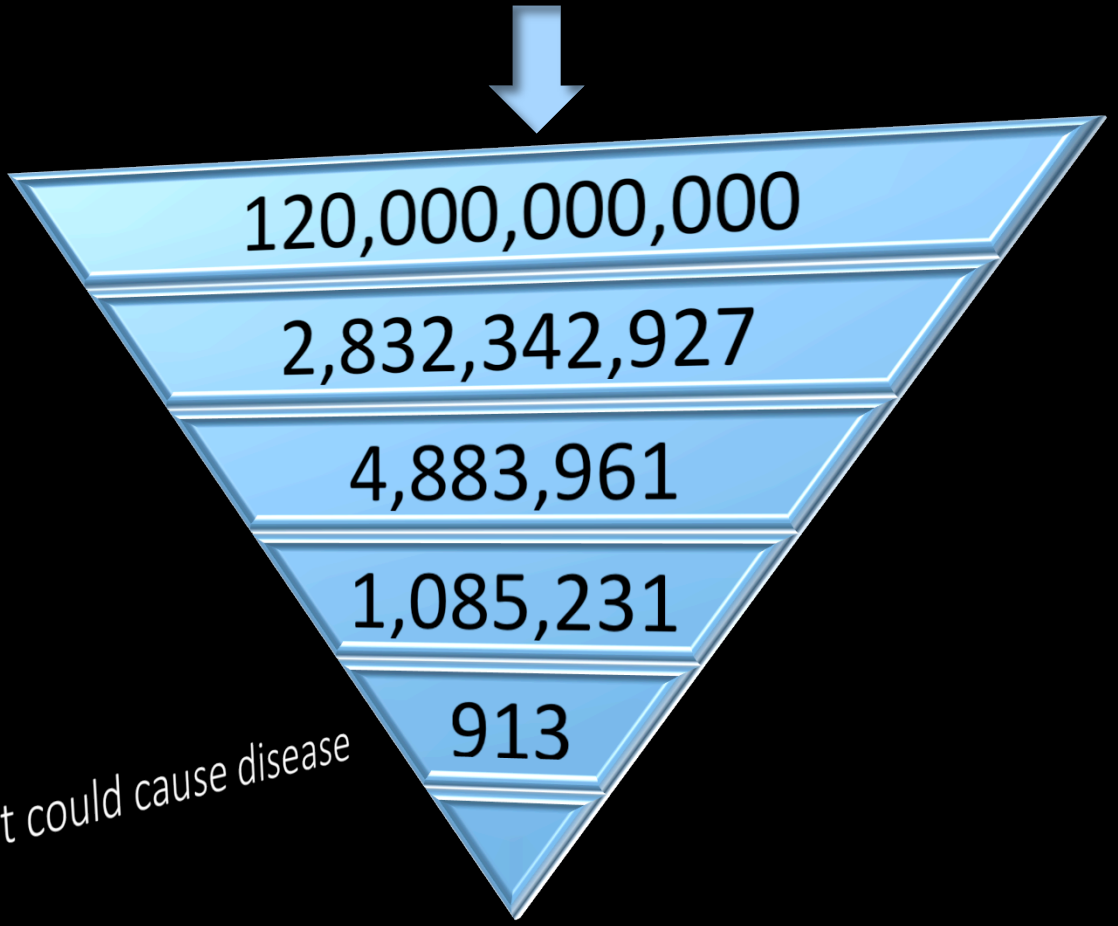


Normal red blood cell

Sickle cell

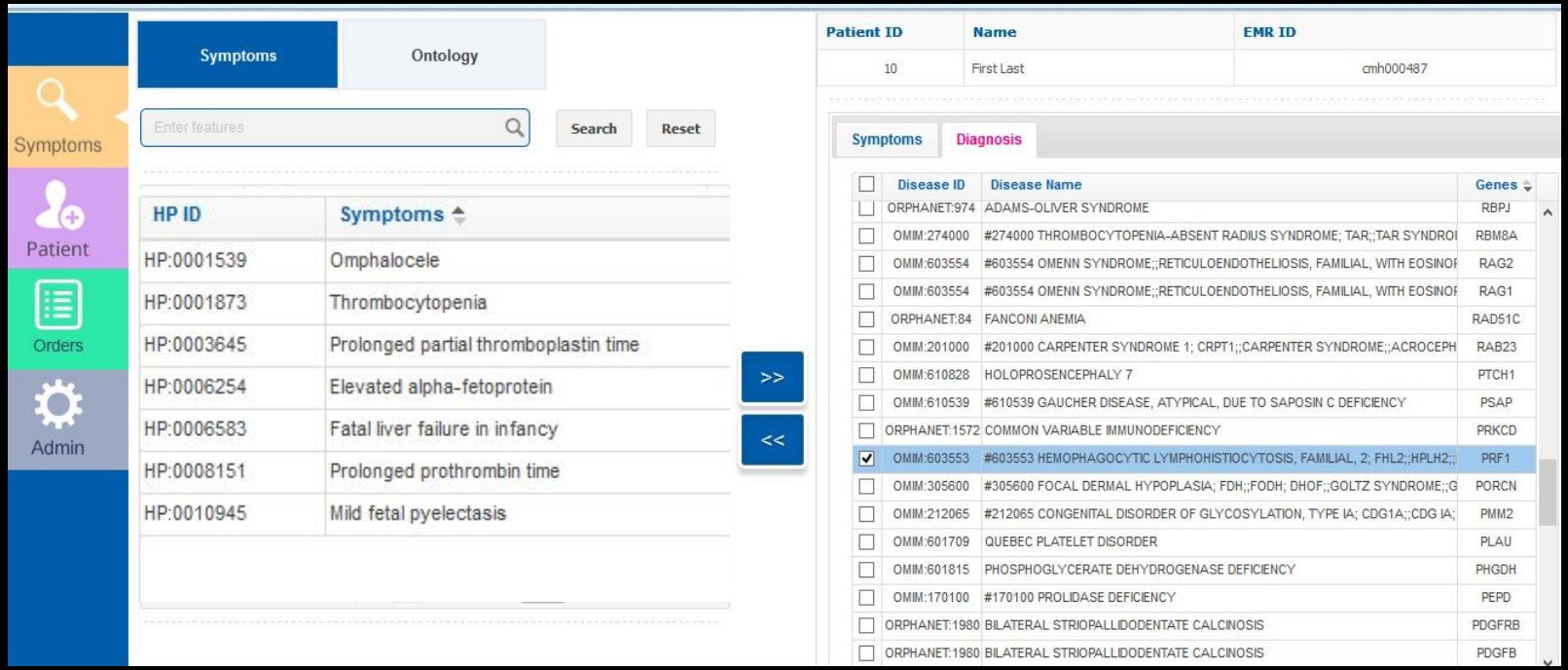
25:41

Infant CMH487

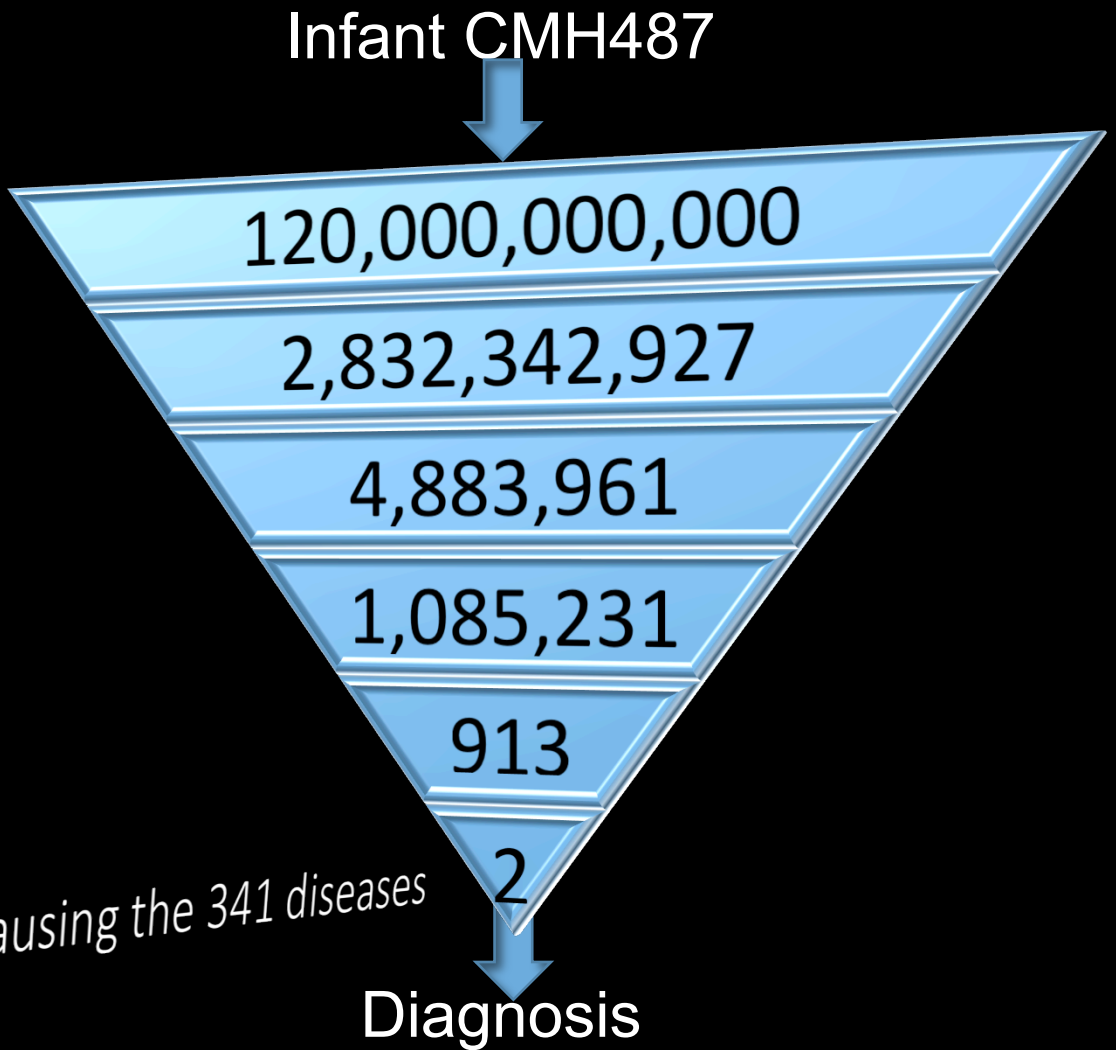


# 25:42

## Computer-Generated List of 341 Possible Diagnoses



26:00


Infant CMH487
120,000,000,000
2,832,342,927
4,883,961
1,085,231
913
2
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

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