DYING WITHOUT A DIAGNOSIS: USING GENOMIC SEQUENCING TO UNDERSTAND INFANT MORTALITY

Monica H Wojcik, MD

Division of Genetics and Genomics

Division of Newborn Medicine

3.10.2020

THE MANTON CENTER for Orphan Disease Research

BROAD INSTITUTE CENTER FOR MENDELIAN GENOMICS

Boston Children's Hospital Until every child is well

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

1

NEWBORN/GENOMIC MEDICINE

- How can we optimally apply our tools for genetic diagnosis in the neonatal intensive care unit (NICU)?
  - Infants who do not survive are likely to have genetic disorders
  - Infants with genetic disorders are more likely to not survive

2

CURRENT "UNDERSTANDING" OF THE LEADING CAUSE OF INFANT MORTALITY

TABLE 6 Deaths, Percentages of Total Deaths, and Mortality Rates for the 10 Leading Causes of Infant Death, United States, 2014 and 2013

Causes of Death and ICD-10 Codes[17]	Rank[a]	2014			2013		
		n	%	Rate[b]	n	%	Rate[b]
All causes	—	23 215	100.0	582.1	23 440	100.0	586.1
Congenital malformations, deformations, and chromosomal abnormalities (Q00–Q99)	1	4746	20.4	119.0	4758	20.3	121.0
Disorders related to short gestation and low birth weight, not elsewhere classified (P07)	2	4173	18.0	104.6	4202	17.9	106.9
Newborn affected by maternal complications of pregnancy (P01)	3	1574	6.8	39.5	1595	6.8	40.6
Sudden infant death syndrome (R95)	4	1545	6.7	38.7	1563	6.7	39.7
Accidents (unintentional injuries) (V01–X59)	5	1160	5.0	29.1	1156	4.9	29.4
Newborn affected by complications of placenta, cord, and membranes (P02)	6	965	4.2	24.2	953	4.1	24.2
Bacterial sepsis of newborn (P36)	7	544	2.3	13.6	578	2.5	14.7
Respiratory distress of newborn (P22)	8	460	2.0	11.5	522	2.2	13.3
Diseases of the circulatory system (I00–I99)	9	444	1.9	11.1	458	2.0	11.6
Neonatal hemorrhage (P50–P52, P54)	10	441	1.9	11.1	389	1.7	9.9

Data source: NCHS, National Vital Statistics System: Mortality, 2014 and 2013 (www.cdc.gov/nchs/deaths.htm). ICD-10, International Classification of Diseases, 10th Revision. —, Category not applicable.
[a] Rank is based on 2014 data.
[b] Rates are per 100 000 live births.

- But what do these mortality statistics actually represent?

Murphy, *Pediatrics*, 2017

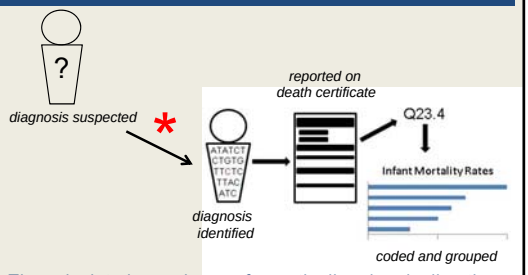
3

GENETIC DISORDERS AND MORTALITY IN THE NICU

- How many of our NICU deaths occur in the setting of a confirmed genetic diagnosis?
- Prior estimates range from 5-50% depending on definition of "genetic disorder"
  - The calculated prevalence of genetic disorders is directly related to our ability to identify them

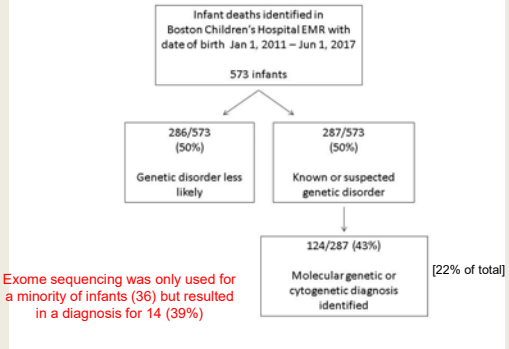
4

UNDERSTANDING INFANT MORTALITY



- The calculated prevalence of genetic disorders is directly related to our ability to identify and report them

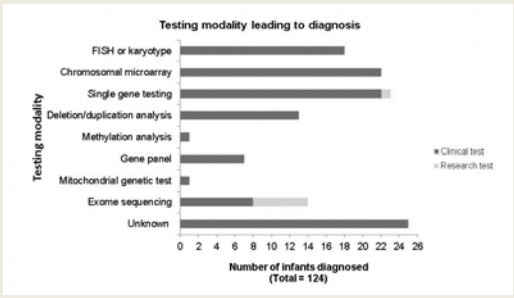
5



Exome sequencing was only used for a minority of infants (36) but resulted in a diagnosis for 14 (39%)

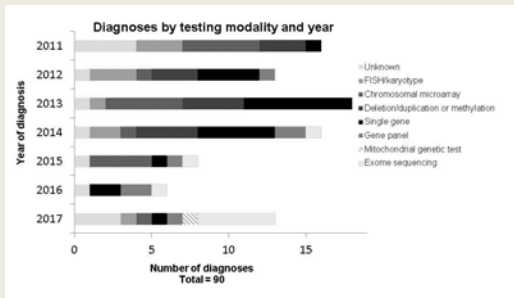
Wojcik, *J Perinatol*, 2019

6



Wojcik, *J Perinatol*, 2019

7



Wojcik, *J Perinatol*, 2019

8

THE ROLE OF THE "MOLECULAR AUTOPSY"

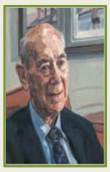
- Postmortem evaluation, including exome or genome sequencing
- Goal to identify additional diagnoses

9

MANTON CENTER FOR ORPHAN DISEASE RESEARCH

Established in 2008: One of the first Centers dedicated to rare disease research

- Gene Discovery Core
  - IRB-approved human research protocol and biobank
  - Enrollment includes:
    - Medical and family history and access to medical records
    - DNA sample from all participating family members
    - Fibroblasts, lymphoblastoid cell lines and tissue samples if available
    - Functional studies including cellular and animal (zebrafish/mouse) modeling options



Pankaj Agrawal

10

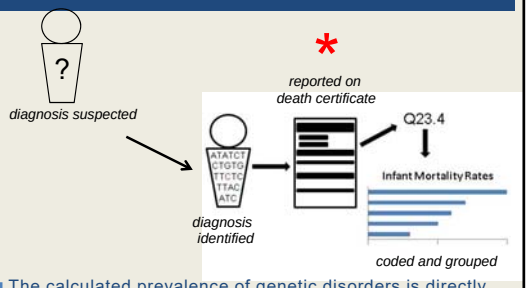
11

IDENTIFYING DIAGNOSES IN INFANTS WHO HAVE DIED…

- Allows us to better understand infant mortality
  - Ultimately improve public health
- Better understand the presentations and molecular underpinnings of severe genetic diseases
- Provide valuable information to the family

12

UNDERSTANDING INFANT MORTALITY



- The calculated prevalence of genetic disorders is directly related to our ability to identify and report them

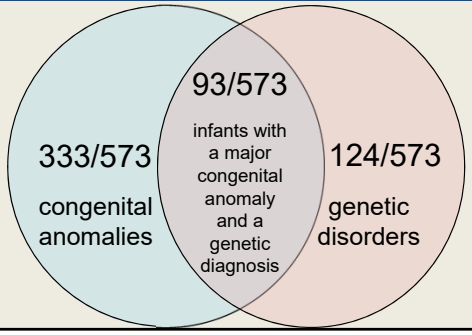
13

THE PROBLEM WITH Q00-Q99…

- Historically, identified genetic conditions were mostly chromosomal
  - Many/most had associated birth defects
- In recent years, using ES for diagnosis has been high-yield
  - 15/39, 38% in latter 2 years of infant mortality study
    - (and rising)
- We identified near-equal proportions of chromosomal and monogenic disorders
  - CHARGE syndrome, ARPKD
  - Spinal Muscular Atrophy, Inborn errors of metabolism

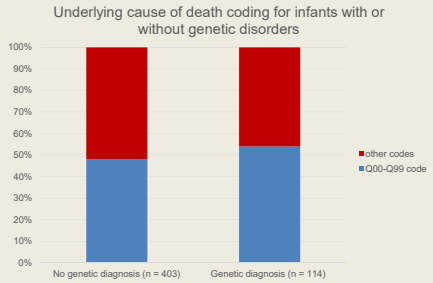
14

MANY INFANTS WITH LETHAL GENETIC DISORDERS DO NOT HAVE CONGENITAL ANOMALIES



15

MANY DECEASED INFANTS WITH GENETIC DISORDERS ARE THEREFORE NOT REFLECTED AS SUCH IN CURRENT MORTALITY STATISTICS



16

FUTURE DIRECTIONS:

- Continuing to recruit, sequence, analyze undiagnosed infant deaths
  - Improved understanding of infant mortality
    - Accurate counseling regarding the **prognosis** of rare genetic conditions
  - Provide valuable information to families
    - Formal follow-up assessment after results disclosure to families
- Deep phenotyping is critically important

17

REFERENCES

- Cuvertino S, Hartill V, Colyer A, Garner T, Nair N, Al-Gazali L et al. A restricted spectrum of missense KMT2D variants cause a multiple malformations disorder distinct from Kabuki syndrome. Genet Med. 2020 Jan 17. doi: 10.1038/s41436-019-0743-3. [Epub ahead of print]
- Flex E, Niceta M, Cecchetti S, Thiffault I, Au MG, Capuano A et al. Biallelic Mutations in TBCD, Encoding the Tubulin Folding Cofactor D, Perturb Microtubule Dynamics and Cause Early-Onset Encephalopathy. Am J Hum Genet. 2016 Oct 6;99(4):962-973.
- Hirata et al. ZC4H2 mutations are associated with arthrogryposis multiplex congenita and intellectual disability through impairment of central and peripheral synaptic plasticity. Am J Hum Genet 2013 2;92(5):681-95
- Kawame H, Hannibal MC, Hudgins L, Pagon RA. Phenotypic spectrum and management issues in Kabuki syndrome. J Pediatr. 1999 Apr;134(4):480-5.
- Miyake N, Fukai R, Ohba C, Chihara T, Miura M, Shimizu H et al. Biallelic TBCD Mutations Cause Early-Onset Neurodegenerative Encephalopathy. Am J Hum Genet. 2016 Oct 6;99(4):950-961.
- Murphy SL, Mathews TJ, Martin JA, et al. Annual Summary of Vital Statistics: 2013–2014. Pediatrics. 2017;139(6):e20163239
- Wojcik MH, Schwartz TS, Thiele KE, Paterson H, Stadelmaier R, Mullen TE, et al. Infant mortality: the contribution of genetic disorders. *J Perinatol* 2019;39(12):1611-1619.

18

THANK YOU

- Mentors/Collaborators:
  - Pankaj Agrawal
  - Ingrid Holm
  - Wen-Hann Tan
  - Richard Goldstein
  - Heidi Rehm
  - Daniel MacArthur
  - Anne O'Donnell-Luria
- Research Team
  - Casie Genetti
  - Jill Madden
  - Eleina England
  - Rachel Stadelmaier
- Division Leadership
  - Christopher Walsh
  - Stella Kourembanas
- NIH UM1HG008900
- National Death Index

19