Session IV: Guideline Development in a Rapidly Evolving field- a look ahead - geneticists perspective

Murugu Manickam, MD, MPH, FACMG
Clinical Professor
Nationwide Children's Hospital/OSU College of Medicine

NATIONWIDE CHILDREN'S®
When your child needs a hospital, everything matters.

Disclosure

- Consultant for RTI/ClinGen- population genomic screening advisory

ACMG guideline development

Genetics inMedicine | ACMG SYSTEMATIC EVIDENCE REVIEW © American College of Medical Genetics and Genomics

Systematic evidence-based review: outcomes from exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability

A full list of authors and affiliations appears at the end of the paper.

2020

Genetics inMedicine

www.nature.com/gim

Check for updates

ACMG PRACTICE GUIDELINE

Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG)

Kandamurugu Manickam[1,2], Monica R. McClain[3], Laurie A. Demmer[4], Sawona Biswas[5], Hutton M. Kearney[6], Jennifer Malinowski[7], Lauren J. Massingham[8,9], Danny Miller[10], Timothy W. Yu[11,12], Fuki M. Hisama[13] and ACMG Board of Directors[14]*

2021

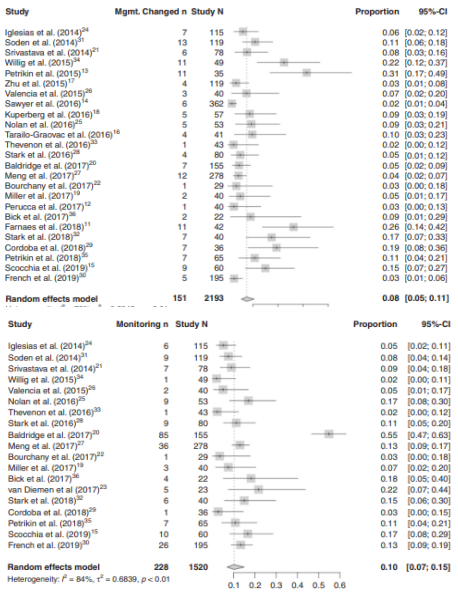


Fig. 2 Forest plot of included studies showing summation for monitoring and long-term clinical management outcomes. *CI* confidence interval.

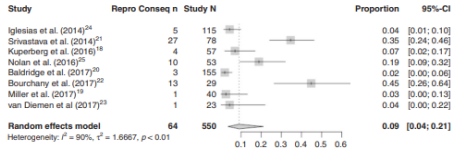
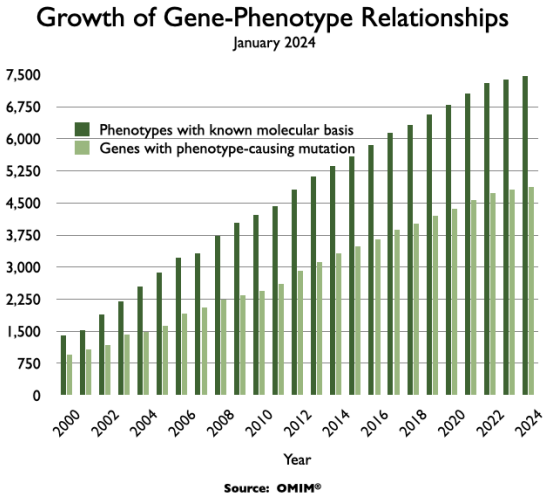


Fig. 3 Forest plot of included studies showing summation for reproductive-focused outcomes. *CI* confidence interval.

Studies from 2014-2019



OMIM: gene discovery

https://www.omim.org/statistics/paceGraph

Did not include specifically diagnostic yield as end point

Pediatric Exome Evidence-Based Guideline: Evidence catching up to practice

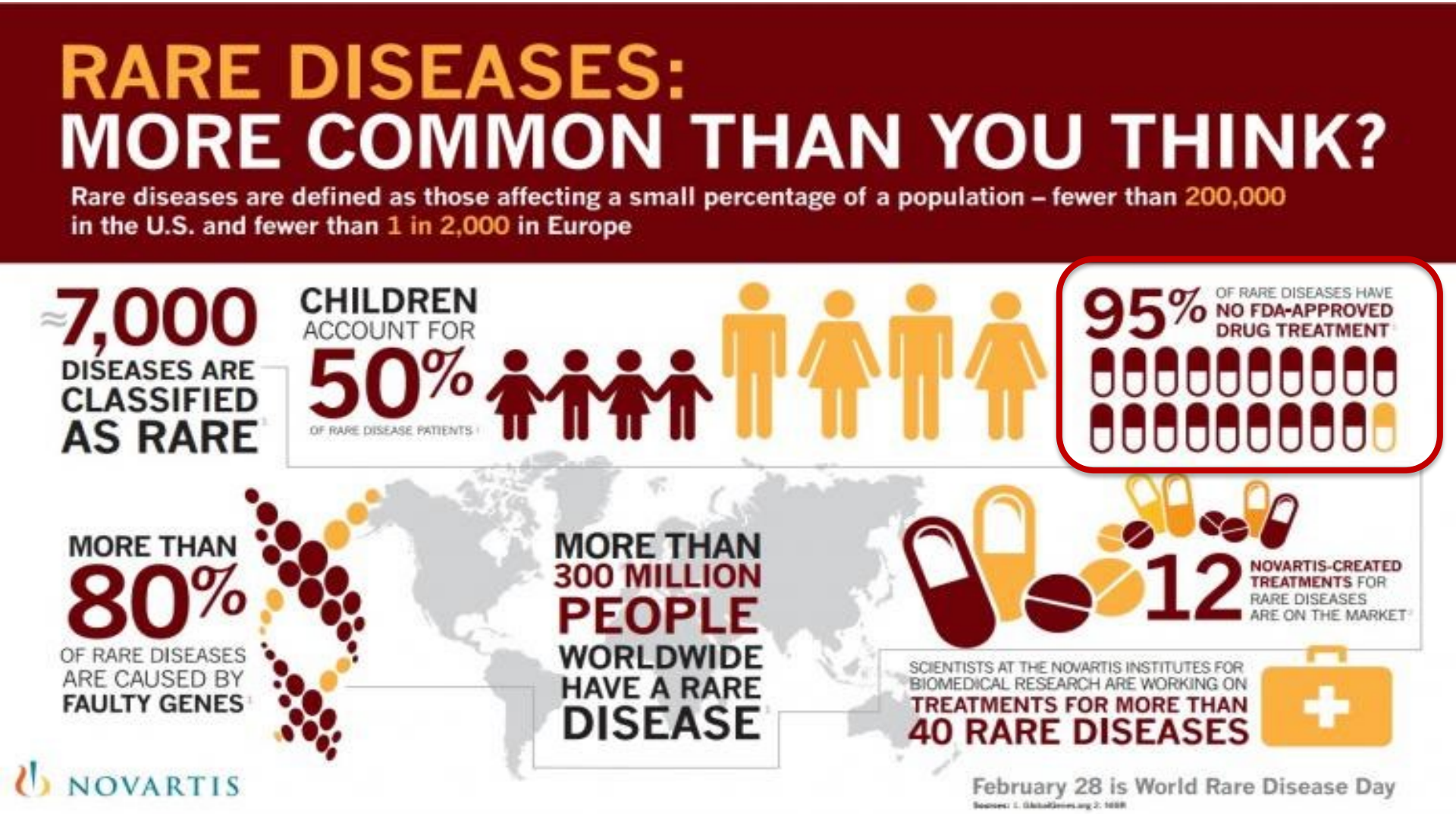
(or flying the airplane, while selling tickets, building the airplane and getting FAA approval)

Presentation at American College of Medical genetics meeting in 2023

ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

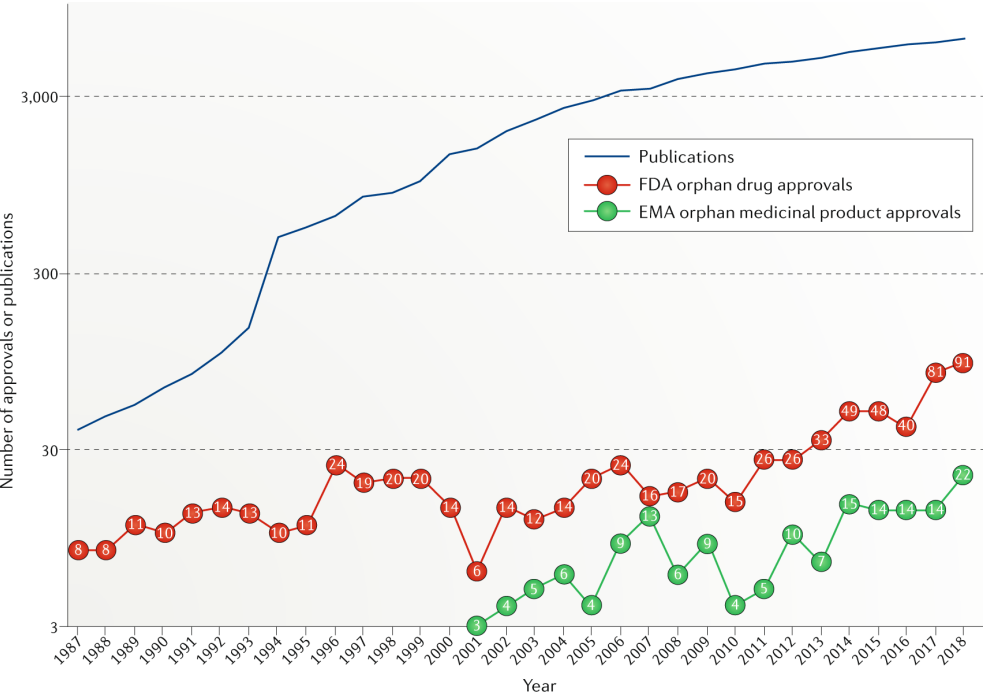
Exome (and genome sequencing) were "standards of care" in geneticists practice but could no longer be "diagnose and adios" [W. Chung]

NATIONWIDE CHILDREN'S®
When your child needs a hospital, everything matters.



Cumulatively though 1:80 will have “rare disease”

NATIONWIDE CHILDREN'S®
When your child needs a hospital, everything matters.



Tambuyzer, E., Vandendriessche, B., Austin, C.P. *et al.* Therapies for rare diseases: therapeutic modalities, progress and challenges ahead. *Nat Rev Drug Discov* **19**, 93–111 (2020). https://doi.org/10.1038/s41573-019-0049-9

- Supportive therapies
  - Palliative
  - Unnecessary procedures
  - Ending diagnostic odyssey
  - Reoccurrence risk

- Re-purposing approved medications/existing therapies
  - Small molecules
  - BMT
- Gene therapies
  - Viral vectors
  - ERT
- N=1 therapies
  - Oligonucleotides
  - RNA based

for 6650+ diseases…

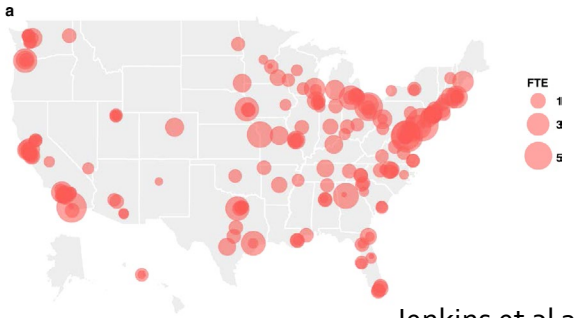
More equitable and efficient care?

- Access! Access! Access?
  - 1 practicing clinical geneticists per 500,000 in the US [1 for 6250 with a rare disorder*]

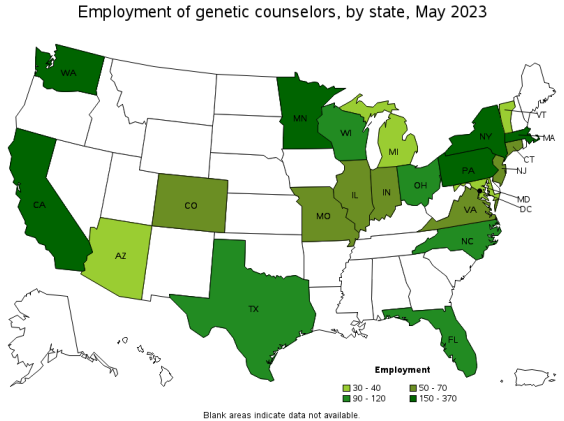
  * Majority are pediatric focused/trained

  - 1 practicing genetic counselor per 125,000 [1 for 1563 with a rare disorder**]

  * * Some working in industry/ research primarily



Jenkins et al 2019

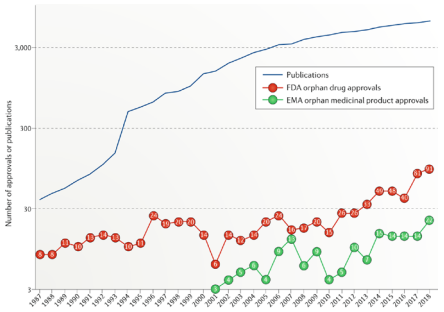


US Bureau of Labor Statistics 2023

Summary thoughts…

- If the end point is diagnosis, then continuing to refine and improve diagnostic yield (new technologies, improvement of variant interpretation, access)

- If end point is treatment, improving the 5% treatable diagnoses
  - Access to testing is first step but access to treatment will become/is more of a limiting feature



Tambuyzer, E., et al 2020