

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



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Disclosure

- Consultant for RTI/ClinGen- population genomic screening advisory

ACMG guideline development

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.

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Reliance on this SER is completely voluntary and does not necessarily assure a successful medical outcome. In determining the propriety of any specific procedure or test, the clinician should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this SER. Clinicians also are advised to take notice of the date this SER was published, and to consider other medical and scientific information that becomes available after that date.

2020

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)

Kandamurugo Manickam^{1,2}, Monica R. McClain³, Laurie A. Demmer⁴, Sawona Biswas⁵, Hutton M. Kearney⁶, Jennifer Malinowski⁷, Lauren J. Massingham⁸, Danny Miller⁹, Timothy W. Yu^{1,10,11}, Fuki M. Hisama¹² and ACMG Board of Directors¹⁴

2021

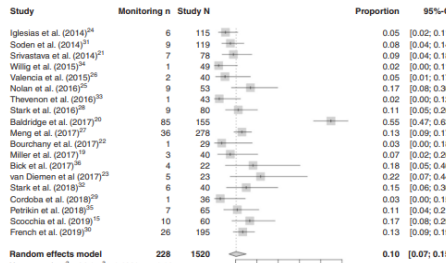
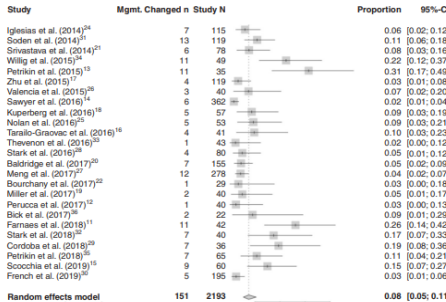


Fig. 2 Forest plot of included studies showing summation for monitoring and long-term clinical management outcomes. CI confidence interval.

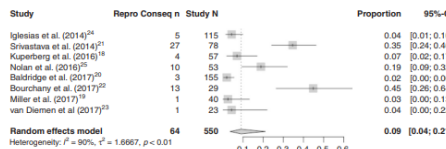
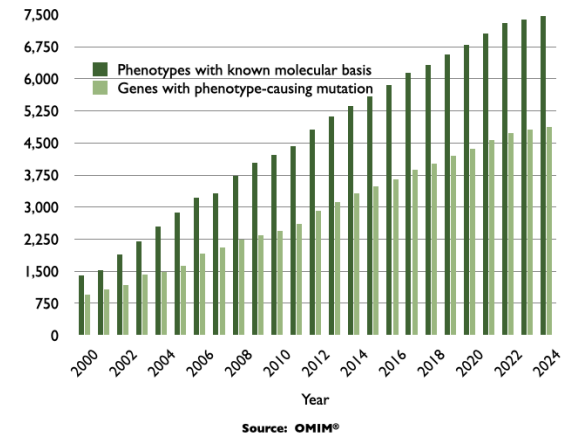


Fig. 3 Forest plot of included studies showing summation for reproductive-focused outcomes. CI confidence interval.

Studies from 2014-2019

Did not include specifically diagnostic yield as end point

Growth of Gene-Phenotype Relationships January 2024



Source: OMIM®

OMIM: gene discovery

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

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



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

RARE DISEASES: MORE COMMON THAN YOU THINK?

Rare diseases are defined as those affecting a small percentage of a population – fewer than **200,000** in the U.S. and fewer than **1 in 2,000** in Europe

≈ **7,000**
DISEASES ARE
CLASSIFIED
AS RARE

CHILDREN
ACCOUNT FOR
50%
OF RARE DISEASE PATIENTS



95% OF RARE DISEASES HAVE
NO FDA-APPROVED
DRUG TREATMENT



MORE THAN
80%
OF RARE DISEASES
ARE CAUSED BY
FAULTY GENES



MORE THAN
300 MILLION
PEOPLE
WORLDWIDE
HAVE A RARE
DISEASE



12 NOVARTIS-CREATED
TREATMENTS FOR
RARE DISEASES
ARE ON THE MARKET

SCIENTISTS AT THE NOVARTIS INSTITUTES FOR
BIOMEDICAL RESEARCH ARE WORKING ON
TREATMENTS FOR MORE THAN
40 RARE DISEASES



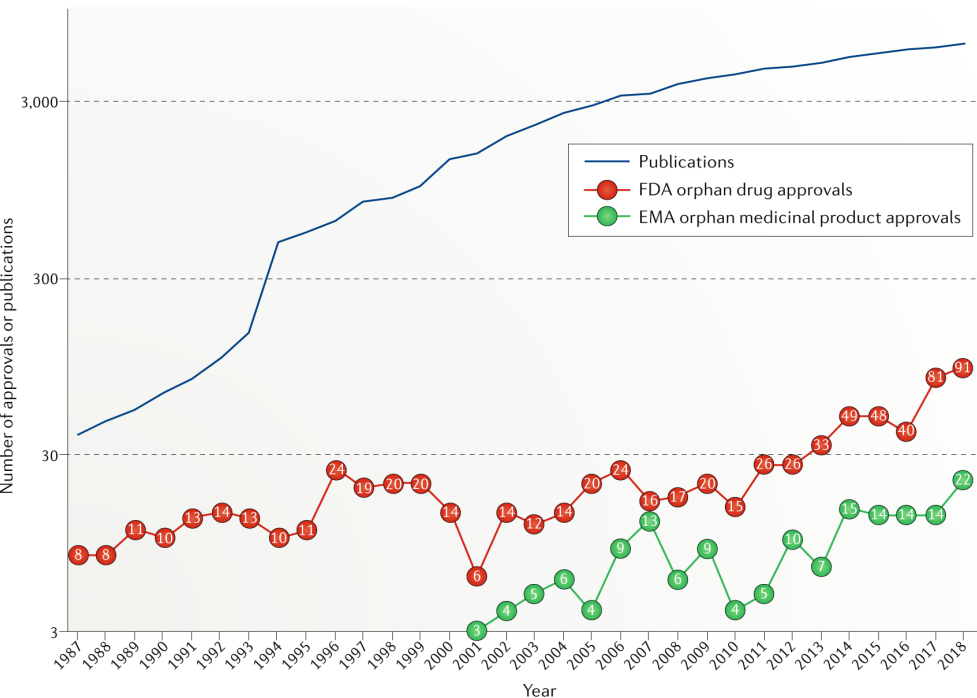
February 28 is World Rare Disease Day
Sources: 1. GlobalGenes.org 2. 1000G

 **NOVARTIS**

Cumulatively though 1:80 will have “rare disease”



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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>

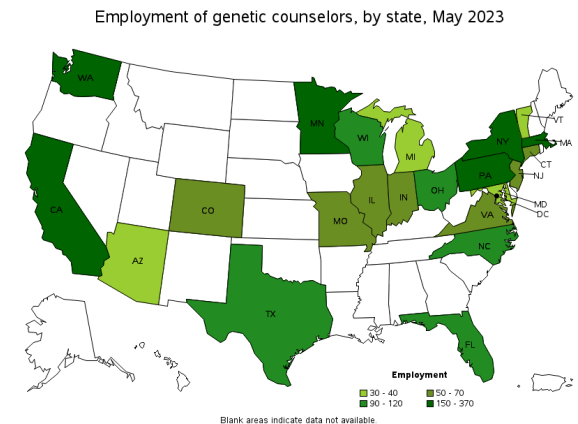
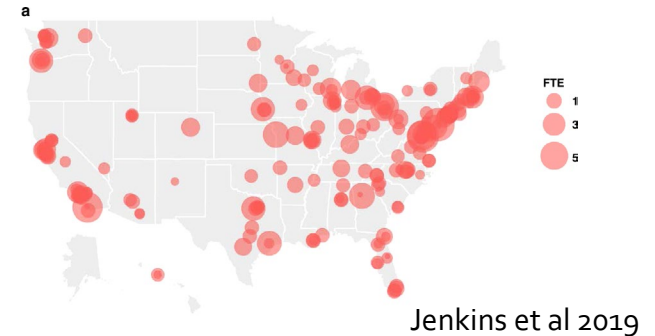
- Supportive therapies
 - Palliative
 - Unnecessary procedures
 - Ending diagnostic odyssey
 - Reoccurrence risk

- 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?

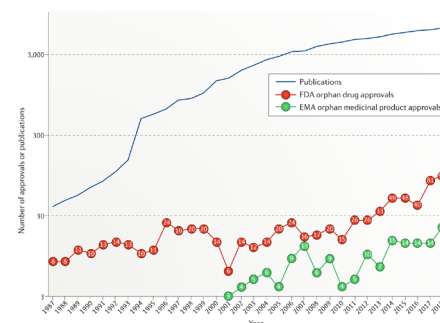
- Access! Access! Access?
 - 1 practicing clinical geneticists per 500,000 in the US [1 for 6250 with a rare disorder*]
 - * Majority are pediatric focused/trained
 - 1 practicing genetic counselor per 125,000 [1 for 1563 with a rare disorder**]
 - * * Some working in industry/ research primarily



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



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