European Reference Network
for rare or low prevalence complex diseases

Network Neuromuscular Diseases (ERN EURO-NMD)

Newborn Screening in Neuromuscular Diseases

Satellite Scientific Symposium organized by ERN EURO-NMD
March, 6th 2025

NBS for Duchenne Muscular Dystrophy

Elizabeth Vroom
World Duchenne Organization

Funded by the European Union

White Paper
2024

World Duchenne Organization

DUCHENNE AWARENESS DAY
7 sept

DUCHENNE CARE CONFERENCE

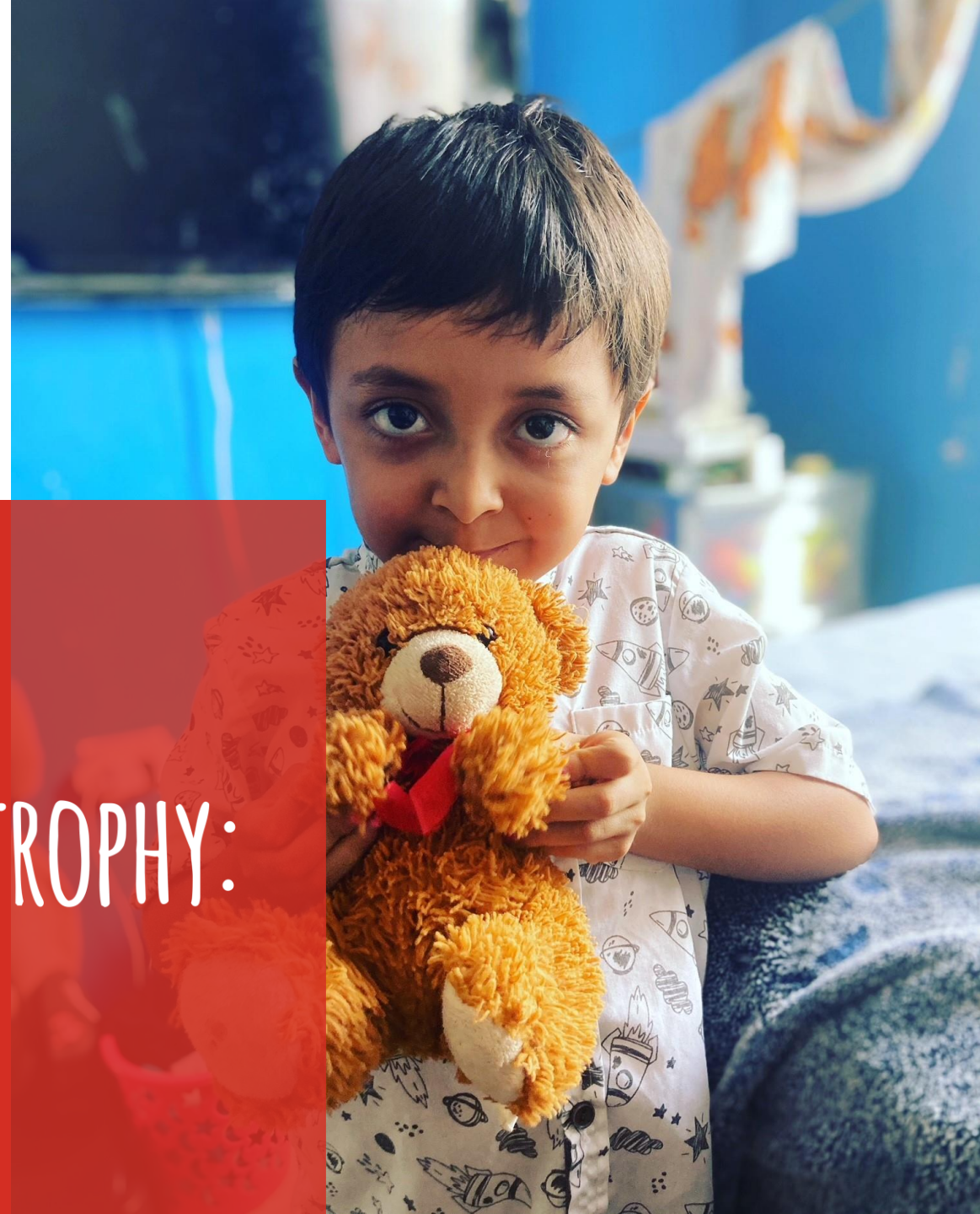
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ADC Program

Initiated by World Duchenne Organization

The Accredited Duchenne Center Program is an initiative by World Duchenne Organization.

World Duchenne Organization



Newborn Screening for Duchenne Muscular Dystrophy:

The Time to Start Is Now

For more than 25 years, a steady majority of parents have been in favour of implementing newborn screening (NBS) for DMD

From the 67% of parents surveyed at the 1997 European Duchenne Meeting in Rotterdam

Findings from subsequent studies have indicated increasing rates of support among parents ranging from 87.5% to 100%.

High rates of support are observed among parents of children with DMD who opted for NBS in pilot studies, parents whose sons were diagnosed later, and among expectant parents

(Chung et al., 2016; Parsons et al., 2002; Plass et al, 2010; Wood et al., 2014).

Reasons the time to implement NBS for DMD is now

- To avoid the diagnostic delay, which interferes with supportive parenting (and more)
- Timely and appropriate early intervention for their child
- Mitigate the dilemma in drug development
- Reproductive choices
- No such thing as a ‘care free period’

Box 1. Diagnostic delay in numbers

» Delays range from 0 to 10 years with an average between 1.1 to 2.2 years.

» Families seek help from an average of three health professionals before receiving a diagnosis.

» Nearly 1 in 3 families seek help from four or more health professionals.

"MUSCLES LOST ARE LOST FOREVER."

@FilippoBucella (Duchenne Parent Project Italy)

“It is never a good time to hear your child has Duchenne, but knowing allows to better prepare and make decisions and be a better parent”

Parent From France

"'Go faster; climb the stairs, concentrate'.....

The remorse caused by misplaced demands is rarely discussed."

Modern perspectives on NBS for DMD

The discussion of implementing NBS programs for DMD has been ongoing since the 1970s and different programs have been started and discontinued in the past.

There is a renewed interest to include DMD in NBS programs due to 3 factors

- Advancement in testing technology to minimize false-positive and false-negative cases
- Growing evidence that emerging therapies may be most effective when muscle damage is still limited (e.g., early years between 0-4 years)
- Evolving landscape of novel therapies in development
- Meanwhile
  - DMD included in the NBS program in Taiwan since 2021
  - US in the states of Ohio, New York and Minnesota.

Modern perspectives on NBS for DMD

Traditionally, public health policies on NBS have been based on 10 criteria proposed by Wilson & Jungner in 1968. At the time, the criteria were mainly developed with “chronic diseases of adults” in mind, and the authors did not intend for the criteria to serve as dogma nor remain unchanged over time.

Modern perspectives on NBS for DMD

Modern perspectives on NBS policy criteria recognize the importance of including the patients' and parents' perspective, and that the focal point of assessing benefits and risks should be the interest of the child (Cornel at al., 2014) These perspectives are expanding the original concept of a disease having to be treatable (Wilson & Jungner, 1968) to that of being actionable (EURORDIS, 2021)

The healthcare professionals' perspective

Perspective on NBS among physicians working at Certified Duchenne Centers across the USA were recently explored by survey. Results indicated that the vast majority (82%) of physicians saw benefit in NBS for DMD. (Armstrong et al. 2022)

The majority recommended multiple interventions as follows

- Early assesment of social and language development
- Testing maternal carriers and screening siblings
- Genetic counseling
- Referral to early intervention services
- Discussing clinical trials and potential participation
- Discussing exon skipping and other therapies
- Initiating approved therapies much earlier than the typical age of diagnosis

Prof. dr. Francesco Muntoni (UCL)

“In progressive muscle wasting condition [like DMD], lost muscle tissue cannot be recovered…Therapies are coming available. In the US, Japan, and Israel, there are already antisense oligonucleotides (ASOs) that can be given in infancy, and there are many ongoing trials including next generation ASOs for which much greater clinical benefit is anticipated, and a rapid approval pathway. ASO’s, but also AAV gene therapy which is likely to receive approval in 2024, can only work if there is muscle available for them to exert their actions”

Proof-of-concept for two-tiered testing

- Mendell & Loydd-Puryear, 2012-2013 CK testing followed by DMD gene testing was established in 2010
- Tresholds for interpretation are based on the timing of test in terms of days postpartum.
- Infants with an elevated CK level are referred for genetic testing to confirm diagnosis
- Several pilots ongoing

Proof-of-concept for two-tiered testing

- Reflecting the need for NBS pograms to consider local health care system infrastructure, and economic, political and culture issues, the exact nature of the screening process can vary.
- For example a 3 step approach (initial DBS, repeat DBS if borderline or elevated CK level on initial DBS and genetic test if persistently elevated CK) has been included in the NBS in Taiwan since 2021 .
- Also, a pilot study using this approach was recently completed in the province of Guangzhou, China (Jia et al., 2023)

Genetic testing process

- Best practice guidelines on genetic testing recommend a stepwise approach.
- Initial confirmatory genetic testing should focus on determining the presence of dystrophin gene deletion and duplication. These mutations represent 70% of all observed in DMD patients.
- MPLA or CGH array is preferred (Birnkrant et al., 2018)
- If single- or multiple –exon mutations are not detected then genetic sequencing (Sanger sequencing) is recommended to screen for remaining small mutations.
- If results of these genetic tests are negative, then a muscle biopsy is taken to evaluate the localization, amount and size of of dystrophin protein using Western blot and immunohistochemistry (Birnkrant et al., 2018; Duan et al., 2021)

Genetic testing process (future possibilities)

- Ongoing development indicate that the use of genetic panels (e.g., exome sequencing, whole genome sequencing, massive parallel sequencing) may become possible in the future (Duan et al., 2021; Farrar et al., 2023)
- Next generation sequencing (NGS) for DMD is a potentially cost-effective alternative to stepwise approach as NGS can identify all mutation types and can be upscaled to be used in screening procedures (Fratter et al.,2020)

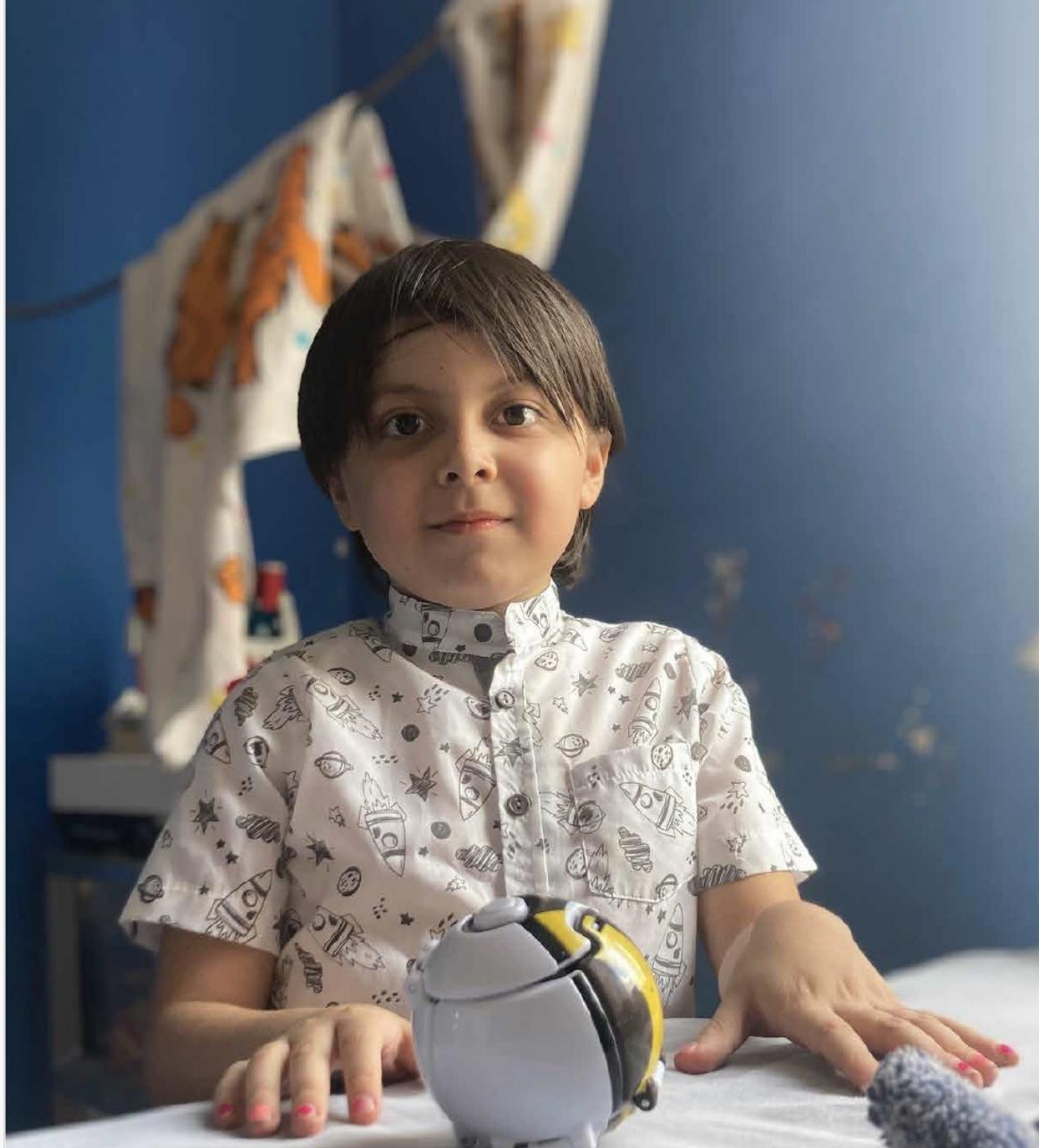
NBS is not just a test but a program

- It is critical to remember that NBS is not just about the test itself but also includes the follow-up care thereafter
- As with all NBS programs, proper governance, stakeholder involvement, and special attention for vulnerable groups (e.g. rural, indigenious, or minority communities) is essential
- Various guidance documents exist to inform the policy making and screening process (Dobrow et al., 2018; EURORDIS, 2021)

Health economic benefits of NBS for DMD

- Evidence is limited
- Canadian study indicate that costs of NBS for DMD are comparable to that for metabolic disorders
- Benefit from avoiding resource waste and lost working days for caregivers due to a protracted diagnostic process
- Financial benefits when a child's motor functions are prolonged

"WITHOUT NBS, INFANTS AND CHILDREN WITH DMD BETWEEN 0- TO 4-YEARS OF AGE **WILL CONTINUE TO MISS OUT ON THE BENEFITS** OF EARLY INTERVENTION AND **HAVE AN UNACCEPTABLE RISK** OF BEING INADVERTENTLY HARMED BY INAPPROPRIATE TREATMENTS."



Ethical issues

- Risks of not implementing NBS for DMD
- Participation in NBS for DMD, protection of parental autonomy
- Health equity

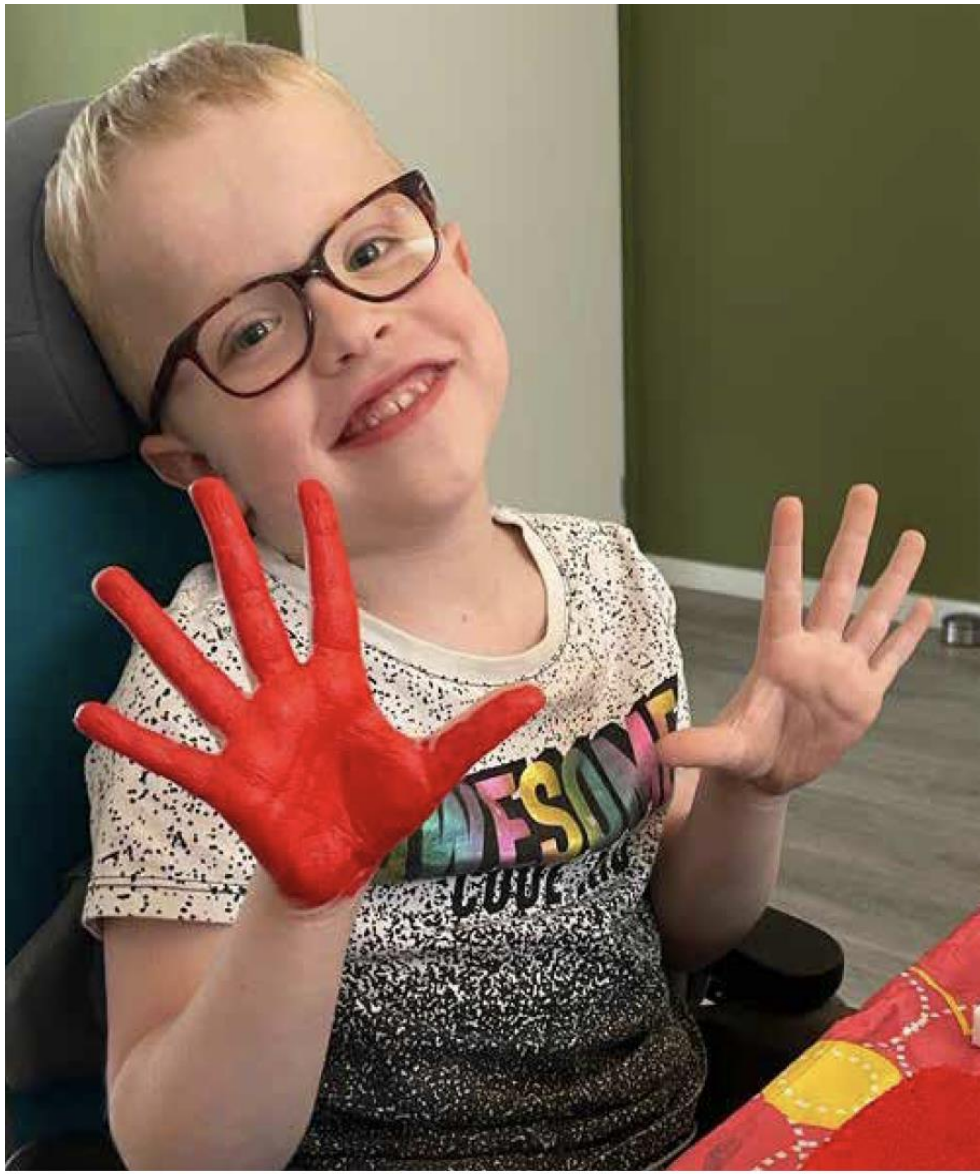
Conclusion

- Discussion ongoing since the 1970s
- Since 25 years a steady majority of parents have been in favor of NBS for DMD
- Given the combination of
  - Unacceptable risks associated with perpetuating diagnostic delay
  - Modern perspectives on NBS policy criteria that recognize the importance of patients' and parents' perspective
  - Evidence for 2 tier testing and advanced testing technology to minimize false-positive and false negative cases
  - International collaboration of stakeholders to continually develop and update practice guidelines
  - A growing number of approved therapies and emerging therapies (i.e. gene therapy)

The time to start is now

Wilson & Jungner Public Health Criteria for Screening Programs (Wilson & Jungner, 1968)

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a “once and for all” project.



worldduchenne.org
https://www.worldduchenne.org › news › apaperaday-newborn-screening-for-duchenne-muscula...

#apaperaday: Newborn Screening for Duchenne Muscular Dyst...

Today's pick is the white paper from @worldduchenne on new born screening **(NBS) for Duchenne** muscular dystrophy. The paper is available online and contains detailed descriptions of the why, how and need for **NBS for Duchenne**.

The Time to Start Is Now

NBS for DMD is now: unacceptable risks associated with perpetuating...

worldduchenne.org
https://www.worldduchenne.org › wp-content › uploads › white-paper-on-newborn-screening-for...

PDF The Time to Start Is Now - World Duchenne

NBS for DMD is now: unacceptable risks associated with perpetuating diagnostic delays; modern perspectives on **NBS** policy criteria that recognize the importance of the patients' and parents' perspective; evidence for two-tiered testing and advanced

EURORDIS - Rare Diseases Europe
https://www.eurordis.org › white-paper-newborn-screening-for-duchenne

White Paper - Newborn Screening for Duchenne - EURORDIS

The aim of this paper is to present the World **Duchenne** Organization's position on newborn screening **(NBS) for Duchenne** muscular dystrophy (DMD) based on families' experiences and scientific developments. The white paper provides a thorough analysis of the urgent need for **NBS for** DMD.

pmc.ncbi.nlm.nih.gov
https://pmc.ncbi.nlm.nih.gov › articles › PMC9589949