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Supporting orphan drug development with retrospective quantitative natural history modeling – conceptual framework, opportunities and limitations

May 2023 – Markus Ries MD PhD MHSc FCP

UK HD

COI

In the past:

Consultancy fees or research grants from Alexion, GSK, Oxyrane, and Shire

Overview

- Four seminal research questions
- Limitations / opportunities
- One practical example
- Conclusion & perspectives

Natural history studies: four seminal research questions

1) **Disease awareness:** how long does it take to make the diagnosis?
2) **Survival:** how long do patients live?
3) **Disease outcome:** can we identify any factors that are associated with mild or severe disease ?
   - genotypes,
   - particular signs/symptoms,
   - biomarker?
4) **Epidemiology:** in order to recruit subjects into clinical studies: where do patients live?

Natural history studies: patient population

TABLE 1 Retrospective quantitative natural history modeling: patient population analyzed (N = 849)

Rare disease	Number of patients (families) available for quantitative retrospective natural history modeling [N] $\sum$ = 849	Estimated prevalence/ incidence[19]	Reference
Alpha-mannosidosis	111 (82)	0.1/100000 (prevalence)	20
Farber disease	96 (81)	96 cases	21
Galactosialidosis	142 (123)	100 cases	22
Krabbe disease	248 (198)	1.0/100000 (prevalence)	23
Molybdenum cofactor deficiency	82 (67)	Unknown	24,25
Mucopolysaccharidosis type VII	53 (49)	0.1/100000 (prevalence)	26,27
Sialic acid storage disorder	116 (94)	130 cases	28

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REVIEW ARTICLE

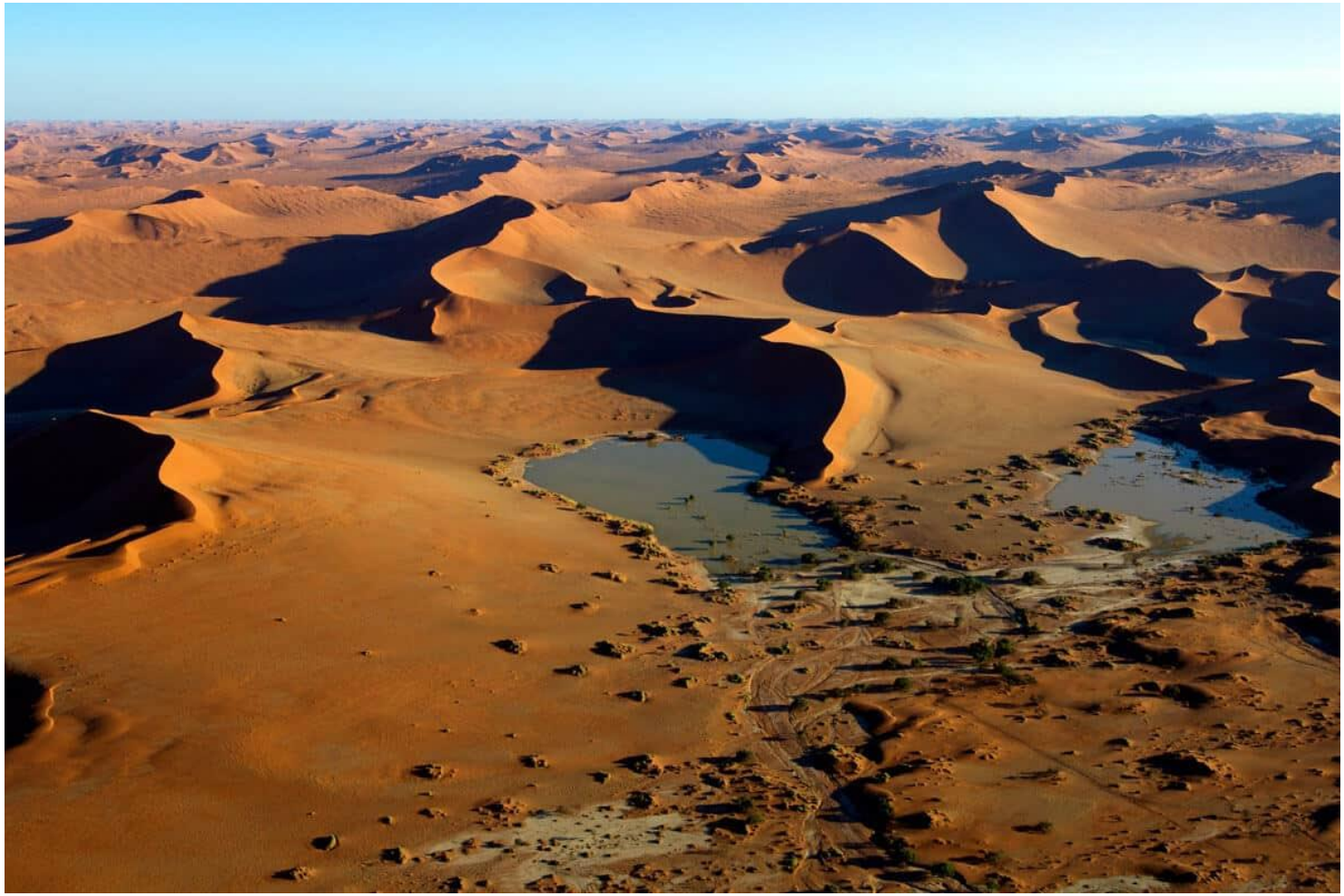
JIMD SSIEM WILEY

Quantitative retrospective natural history modeling for orphan drug development

Sven F. Garbade[1,2] | Matthias Zielonka[1,2] | Shoko Komatsuzaki[3] | Stefan Kölker[1,2] | Georg F. Hoffmann[1,2] | Katrin Hinderhofer[4] | William K. Mountford[5] | Eugen Mengel[6] | Tomáš Sláma[7] | Konstantin Mechler[8] | Markus Ries[1,2,9]

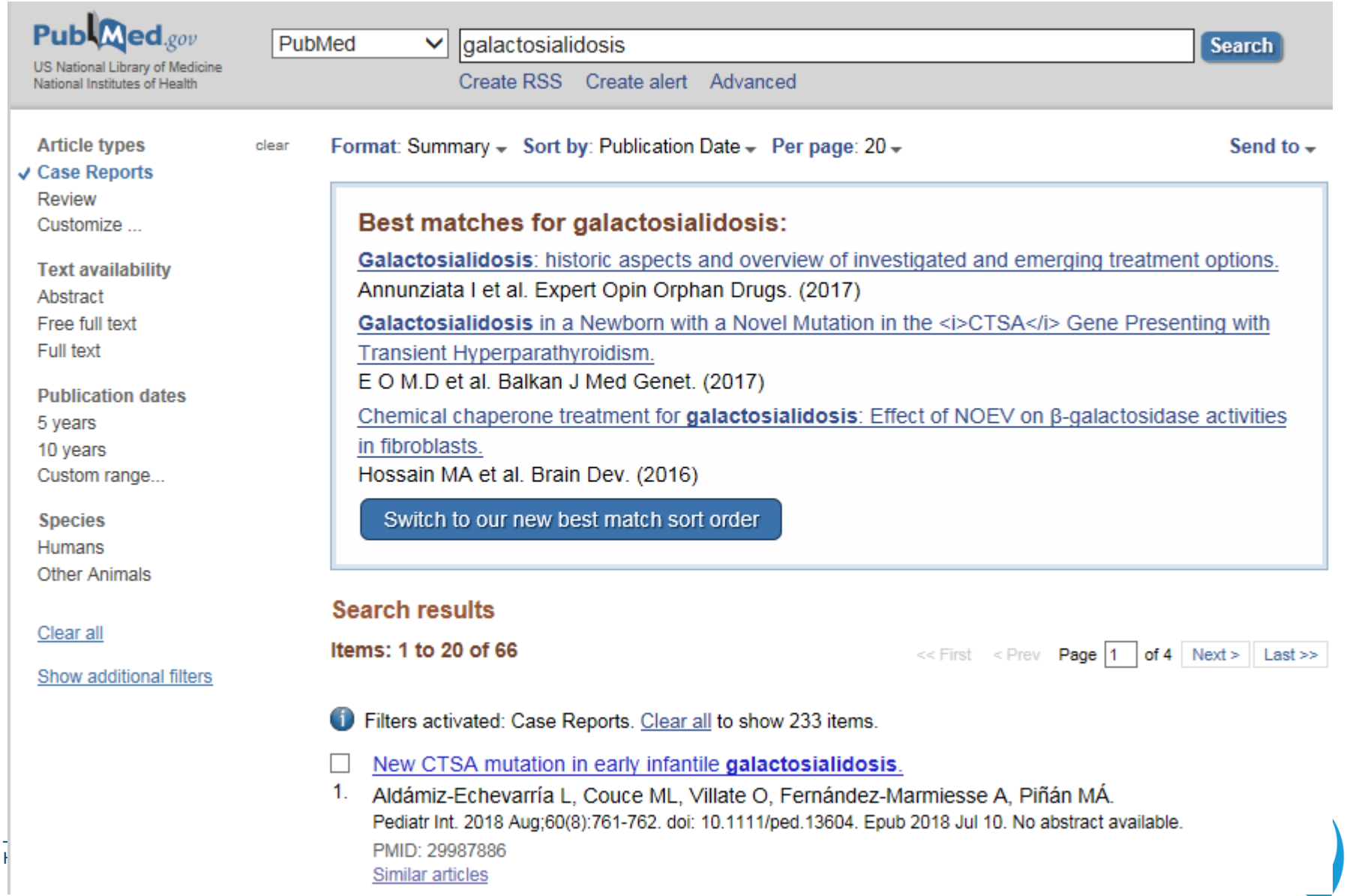
Orphanet Report Series
Rare Diseases collection
Number 1 | January 2022

Methods



https://www.madiba.de/blog/die-endlose-namib-aelteste-wueste-der-welt/

Methods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Galactosialidosis: historic aspects and overview of investigated and emerging treatment options.
Annunziata I et al. Expert Opin Orphan Drugs. (2017)
Galactosialidosis in a Newborn with a Novel Mutation in the CTSA Gene Presenting with Transient Hyperparathyroidism.
E O M.D et al. Balkan J Med Genet. (2017)
Chemical chaperone treatment for galactosialidosis: Effect of NOEV on β-galactosidase activities in fibroblasts.
Hossain MA et al. Brain Dev. (2016)
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New CTSA mutation in early infantile galactosialidosis.
1. Aldámiz-Echevarría L, Couce ML, Villate O, Fernández-Marmiesse A, Piñán MÁ.
Pediatr Int. 2018 Aug;60(8):761-762. doi: 10.1111/ped.13604. Epub 2018 Jul 10. No abstract available.
PMID: 29987886
Similar articles

Disease awareness: how long does it take to make the diagnosis?

- Age of onset and diagnostic delay (interval between age at onset of first signs or symptoms and the age at diagnosis) can provide insight into disease awareness in the medical community. In this example, 49 patients with **molybdenum cofactor deficiency** are shown. Horizontal lines indicate the median. The slope of the connecting lines represent the diagnostic delay in each patient

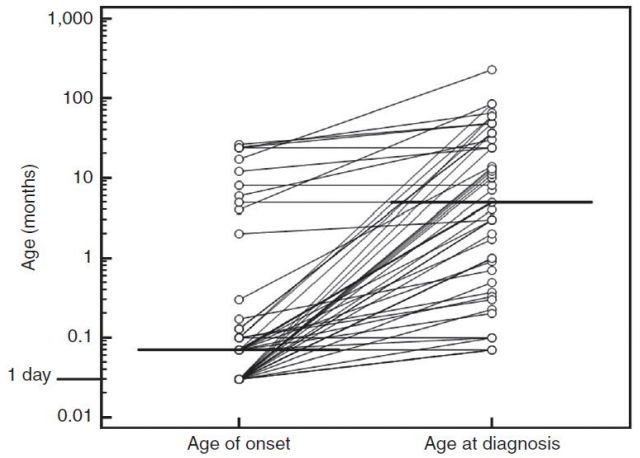
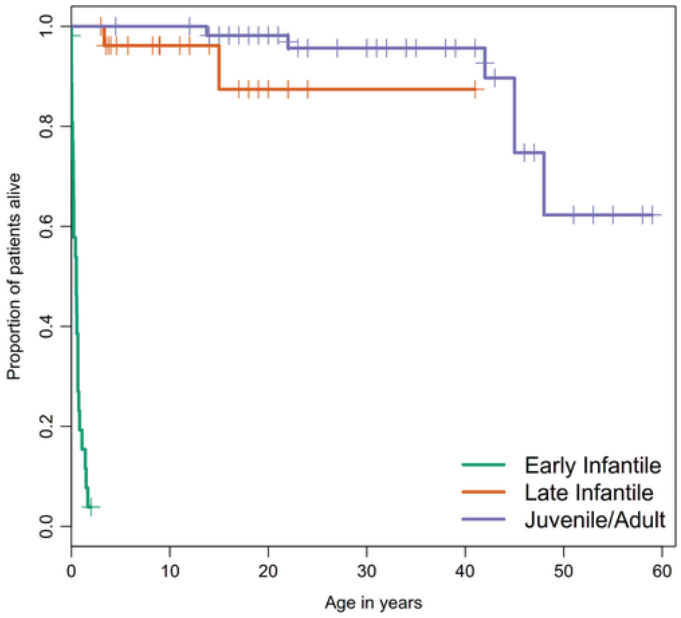


Figure 3 Age at onset (in months) of molybdenum cofactor deficiency and age at diagnosis. Data were available for *n* = 49 patients. Horizontal lines indicate the median. The slopes of the connecting lines represent the diagnostic delay between onset of the disease and making the diagnosis.

Mechler et al., Genetics in Medicine 2015

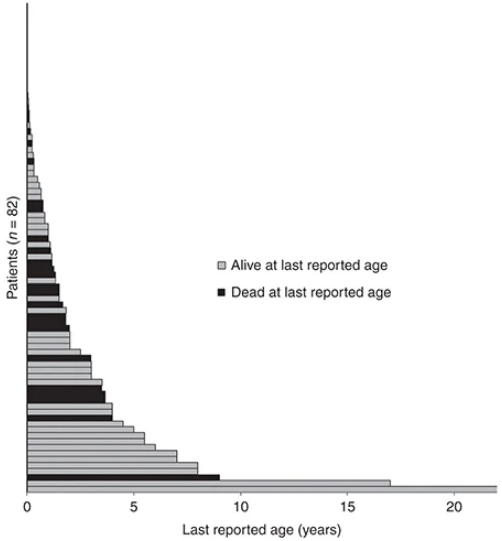
Survival: how long do patients live?

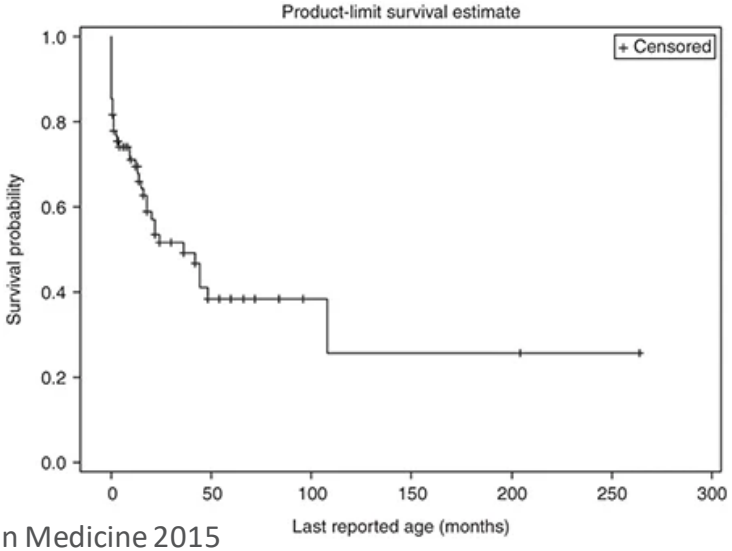
- Survival analysis is helpful for clinical counseling of afflicted families and informs planning of future therapeutic trials. The impact of clinical subtype on survival: this example shows the estimated survival distribution in **galactosialidosis** (GS) patients (N = 111) by clinical subtype. Median survival for early infantile (EI) was 6 months. EI patients N = 27, late infantile (LI) patients N = 27, juvenile/adult (J/A) patients N = 57



Sláma et al., J Inherit Metab Dis 2019

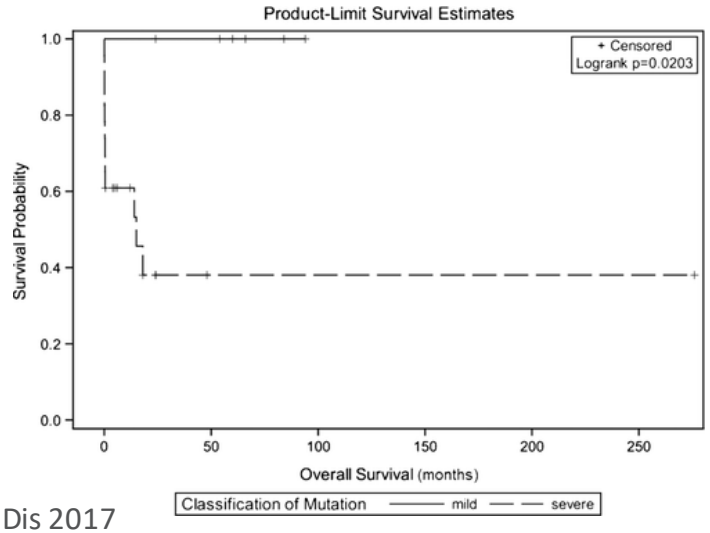
Can genotype predict mild or severe disease ?





Mechler et al., Genetics in Medicine 2015

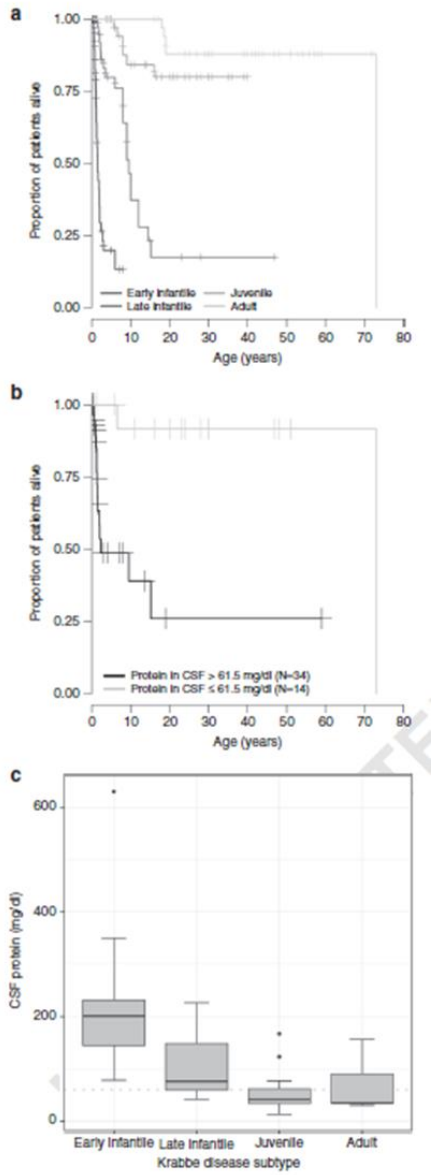
- The influence of genotype on survival in **molybdenum cofactor deficiency** (Kaplan Meier survival curves stratified by classification of genotype (mild: n = 6, severe: n = 23; p = 0.0203, Log-rank test)): patients with a genotype classified as severe showed a median survival of 15 months (mean: 10.5, SD: 1.83) and had a lower probability of survival compared to patients with a genotype classified as mild who were all alive at last reported follow-up (p = 0.0203, Log-rank test).



Hinderhofer and Mechler et al., J Inherit Metab Dis 2017

Can biomarkers predict mild or severe disease ?

- Biomarker-phenotype association, in this case in **Krabbe disease**. Elevated **CSF protein** which probably indicates a **disruption of the blood-brain barrier** in this neurogenerative condition was <u>associated with earlier onset of disease and shorter survival</u>. Again, threshold of CSF protein concentration separating the two survival groups (b) was <u>modeled by unbiased recursive partitioning.</u>



Komatsuzaki and Zielonka et al., Genetics in Medicine 2019

Can biomarkers predict mild or severe disease ?

Biomarkers of substrate storage can be associated with mild or severe disease outcome. In this example, the overall estimated survival distribution of the study population of individuals with **sialic acid storage disease** is shown in (a). Patients with a higher excretion of storage material (i.e., urinary sialic acid (b) and fibroblast sialic acid (c)) - which indicates a higher biochemical disease burden - lived significantly shorter than patients with lower urinary sialic acid excretion or lower fibroblast sialic acid storage. The threshold of sialic acid concentrations in urine (d) and fibroblasts which separates the response variable (i.e. survival) in two groups was determined by unbiased recursive partitioning.

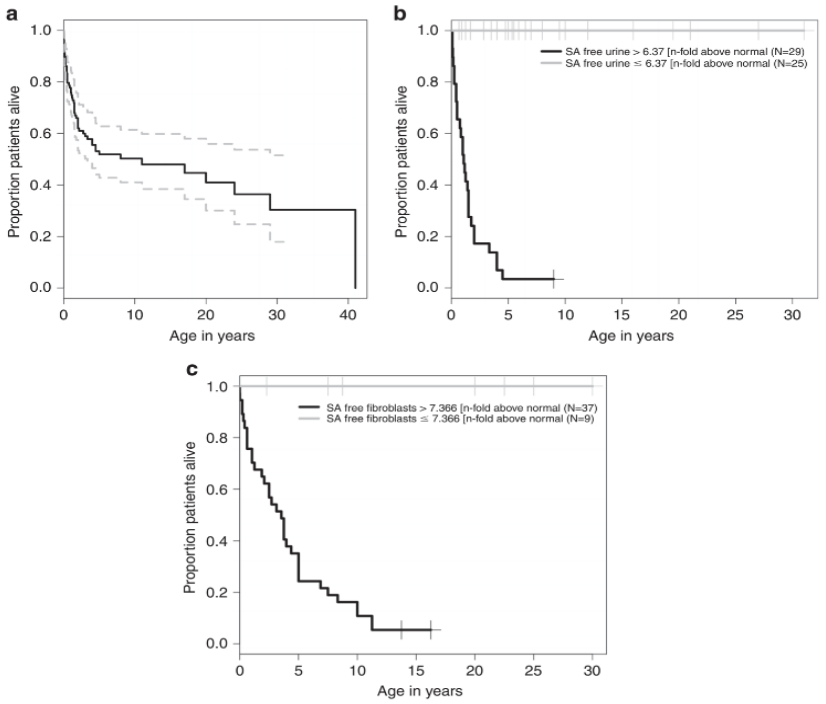
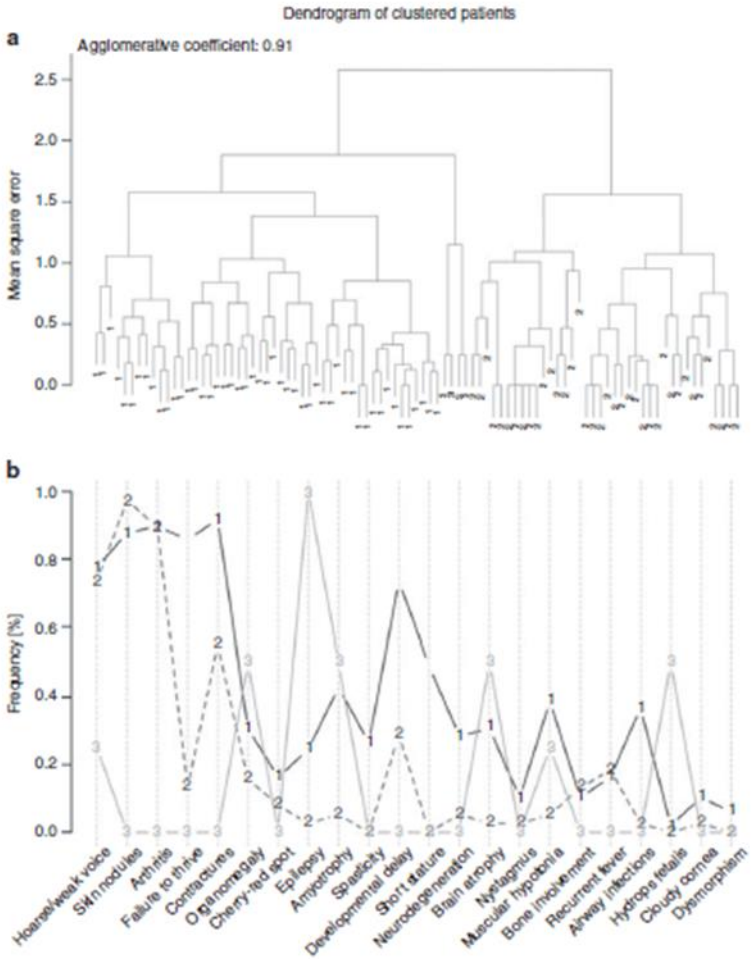


Fig. 2 Estimated survival distributions for patients with sialic acid storage disease (SASD). **a** Estimated overall survival distribution for patients with SASD ($N = 106$). Censored individuals are marked with a "+". **b** Estimated survival distribution for SASD patients with an urinary excretion of free sialic acid above 6.37-fold ($N = 29$, black line) and below or equal to 6.37-fold of normal controls ($N = 25$, gray line). Censored individuals are marked with a "+". Log-rank test, $p < 0.001$. **c** Estimated survival distribution for SASD patients with intracellular storage of free sialic acid above 7.37-fold ($N = 37$, black line) and below or equal to 7.37-fold of normal controls ($N = 9$, gray line). Intracellular free sialic acid storage was measured in fibroblasts. Censored individuals are marked with a "+". Log-rank test, $p = 0.014$

Zielonka et al, Genetics in Medicine 2019

Are there distinct disease subtypes or is there a continuous spectrum of phenotype ?

- **A cluster analysis** allows the determination whether there exist distinct disease subtypes or whether, instead, there is a continuous spectrum of phenotype.
- The dendrogram (A) shows clinical symptom clustering in **Farber disease**. Relative frequency of symptoms per group is depicted in (B). Groups 1 and 2 exhibit similar generalized disease features, with more frequent phenotypical manifestations in group 1 than in group 2. Group 3 appeared more exclusive, with epilepsy and amyotrophy**. There was no clear-cut exclusive delineation of phenotypical features across patients with Farber disease**

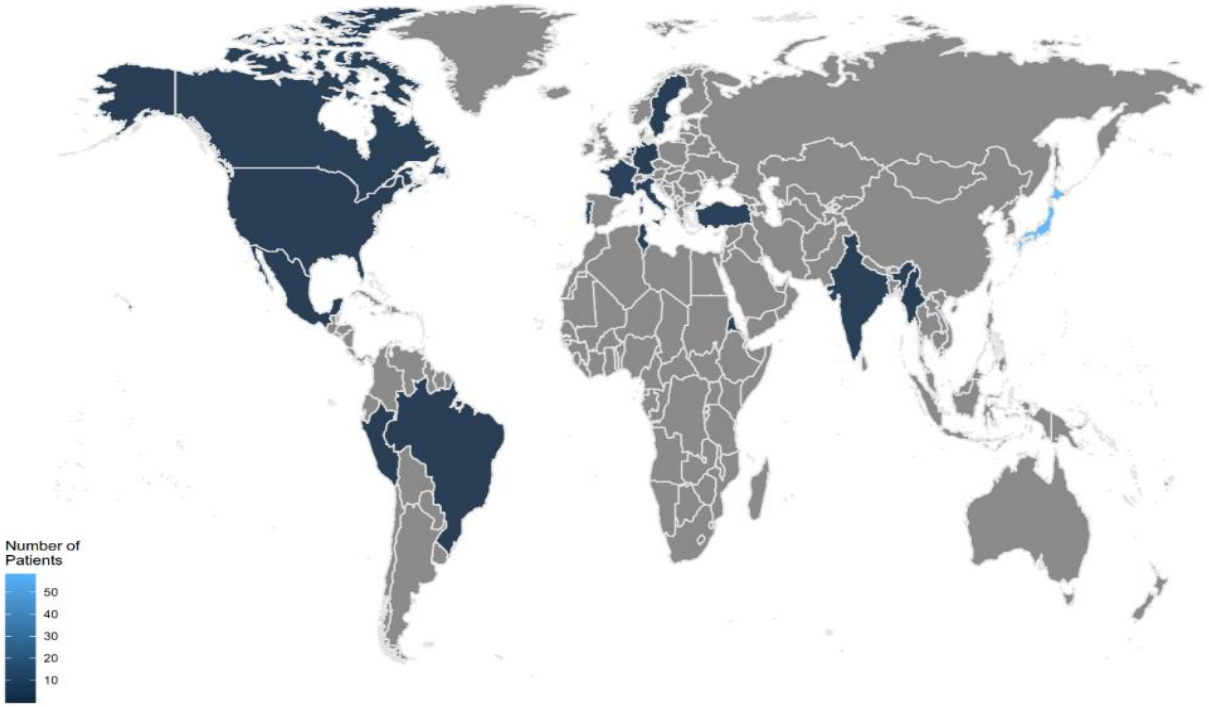


Zielonka et al., Genetics in Medicine 2019

Figure 4 Clinical feature clustering of patients with Farber disease. (a) Dendrogram: clinical symptom clustering. Each number indicates assignment to a specific group. Analysis was performed using a Ward fusion algorithm. (b) Relative frequency of symptoms per group. Groups 1 and 2 exhibit similar generalized disease features, with more frequent phenotypical manifestations in group 1 than in group 2. Group 3 appeared more exclusive, with epilepsy and amyotrophy. There was no clear-cut exclusive delineation of phenotypical features across patients.

Study recruitment: geographical distribution

- The knowledge of the **geographical distribution** patients with ophan disorders can help **recruiting subject into clinical studies.** In this example, the countries of origin of patients with **galactosialidosis** (GS) are shown. Blue scale indicates the number of identified patients with GS per country. Dark blue represents 1 to 10 patients; medium blue 20 to 40 patients; light blue represents more than 50 patients.



Sláma et al., J Inherit Metab Dis 2019

Limitations / Opportunities

- **Survival data** may be in part **historic** and may change over time which may go into both directions: improved supportive medical care would prolong life whereas a more palliative, medically less aggressive approach centered on quality of life may decrease survival time
- Method can **detect the changing publication pattern** over time.
- Epidemiological data on **geographic distribution** of patients may be of help in **identifying study centers** for future clinical research.

Limitations / Opportunities

- **Classification** of disease subtypes **may vary** across case reports in the same disease -> transparent and careful reclassification
- Case reports often **focus on a specific aspect** of the particular disease. Therefore, standardized quantitative descriptions of softer variables (e.g., quality of life, development of motor, speech or cognitive functions, seizures, joint mobility, skin nodules, etc.) are subject to ascertainment bias and missing data.
- **Published laboratory data** – which were not analyzed in a central laboratory - will have to be **pooled** in order to allow some comparative analyses which introduce statistical noise.

Limitations/opportunities: comparison of natural history study methods

TABLE 2 Comparison of advantages and limitations of methods to quantitate natural histories of ultra- orphan conditions (adapted from Reference 28)

	Time-to-availability of hard endpoints (in particular survival)	Ability to define softer clinical endpoints	Ability to define biomarkers	Logistic burden
Quantitative retrospective natural history modeling	Fast	Difficult	Difficult	Low
Prospective natural history study	Very long	Easy	Easy	Very high
Retrospective natural history study (eg, chart review)	Intermediate	Difficult	Difficult	Intermediate

Note: Seminal research questions include: (a) *Disease awareness*: how long does it take to make the diagnosis? (b) *Survival*: how long do patients live? (c) *Disease outcome*: can we identify any factors that are associated with mild or severe disease (eg, genotypes, particular signs/symptoms, biomarker)? (d) *Epidemiology*: in order to recruit subjects into clinical studies: where do patients live?

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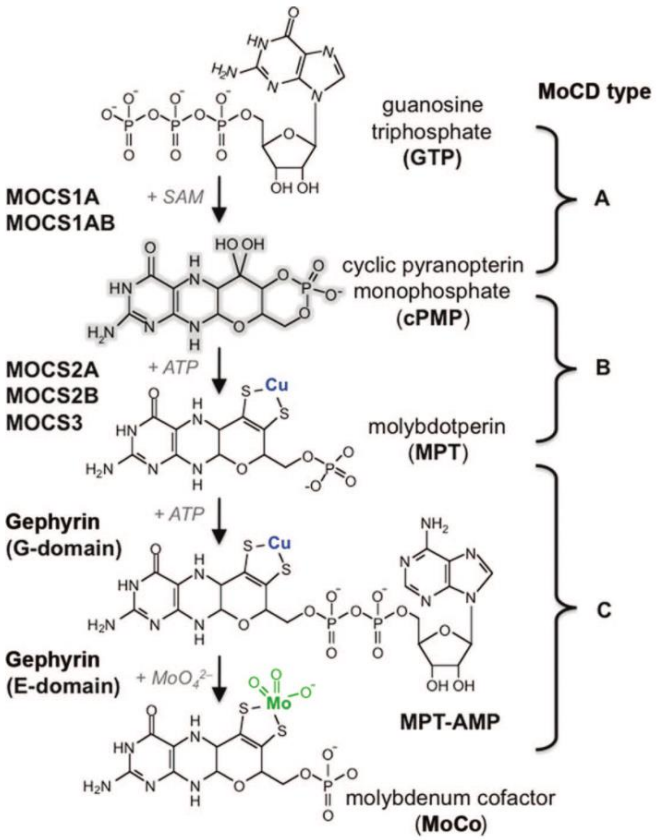

Veldman et al., Pediatrics 2010

FDA NEWS RELEASE

FDA Approves First Treatment for Molybdenum Cofactor Deficiency Type A

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For Immediate Release: February 26, 2021

Today, the U.S. Food and Drug Administration approved Nulibry (fosdenopterin) for injection to reduce the risk of death due to Molybdenum Cofactor Deficiency Type A, a rare, genetic, metabolic disorder that typically presents in the first few days of life, causing intractable seizures, brain injury and death.

"Today's action marks the first FDA approval for a therapy to treat this devastating disease," said Hylton V. Joffe, M.D., M.M.Sc, director of the Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine in the FDA's Center for Drug Evaluation and Research. "The FDA remains committed to facilitating the development and approval of safe and effective therapies for patients affected by rare diseases—an area of critical need."

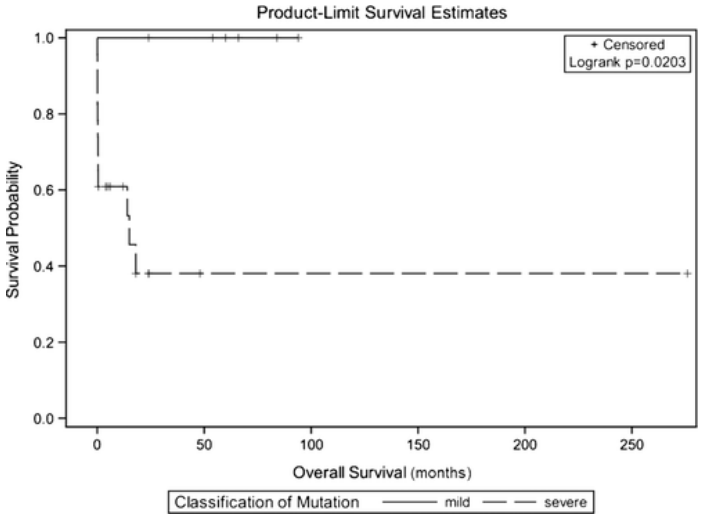
https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-molybdenum-cofactor-deficiency-type

J Inherit Metab Dis (2017) 40:801–811
DOI 10.1007/s10545-017-0077-8

ORIGINAL ARTICLE

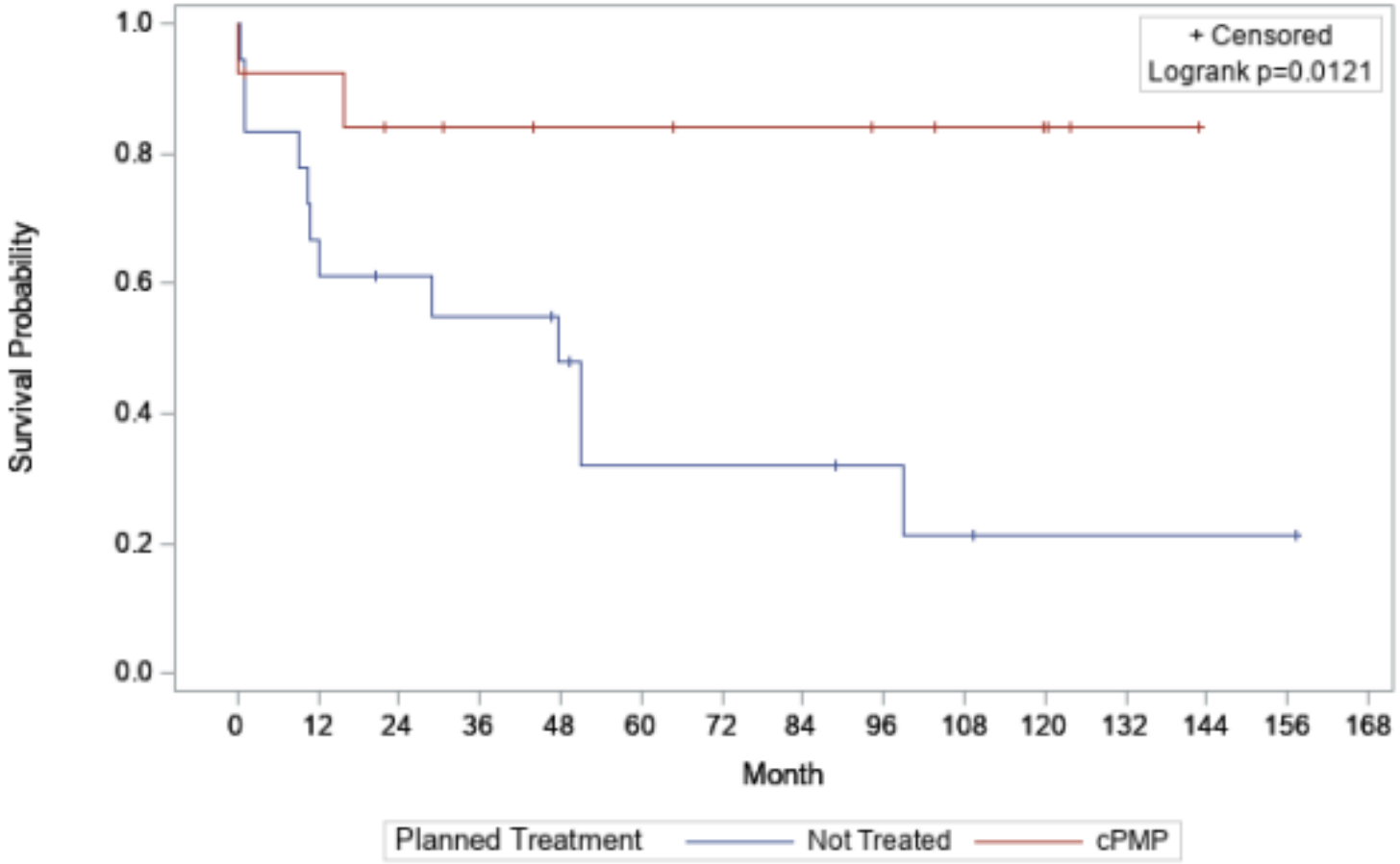
Critical appraisal of genotype assessment in molybdenum cofactor deficiency

Katrin Hinderhofer[1] · Konstantin Mechler[2] · Georg F. Hoffmann[3] · Anette Lampert[4,5] · William K. Mountford[6,7] · Markus Ries[3]



Discussion The severity of the genotype assessed by *in silico* prediction and further classification explained survival in molybdenum cofactor deficiency and may therefore be considered a confounder for the outcome of therapeutic clinical trials requiring adjustment in the clinical trial design or analysis.

Figure 5. KM Survival Curves of the Treated Versus Untreated Groups (GMAS)



Source: Reviewer's analysis based on the ADTTE.xpt dataset submitted in eCTD0030 on October 23, 2020.
Abbreviations: cPMP, cyclic pyranopterin monophosphate; GMAS, genotype-matched analysis set; KM, Kaplan–Meier

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214018Orig1s000IntegratedR.pdf

Milestones of MoCD type A drug development

6
Spiegel et al. 2022
Natural history study published

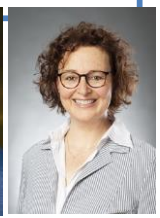
1
Schwarz et al. 2004
cPMP substitution in MoCoA mice

5
FDA approval 2021

2
Veldmann et al,. 2010
First successful human treatment (N=1)

Image made with mapchart

4
Hinderhofer and Mechler et al., 2017
Genotype stratification as clinical-regulatory strategy for drug approval



3
Schwahn et al. 2015
Uncontrolled multicenter open label study (N=16)

Conclusion

- Quantitative retrospective history modeling can provide **fast** information on **hard clinical endpoints** (i.e., survival, diagnostic delay) with a **lower logistic burden**.
- The choice of method to quantitate the natural history of a disease, e.g. within a particular drug development program, may be driven by the research question in the particular condition (e.g., organ manifestation, disease progression, nature of endpoints, and the feasibility of assessment) and may encompass **a combinatory approach** which includes quantitative natural history modeling based on published cases

Perspectives

- Expansion of the method into **epilepsy genetics**
  - Schröter J, Döring JH, Garbade SF, Hoffmann GF, Kölker S, Ries M*, Syrbe S*. **Cross-sectional quantitative analysis of the natural history of TUBA1A and TUBB2B tubulinopathies.** Genet Med. **2021** Mar;23(3):516-523.
  - A. Saffari A, Schröter J, Garbade S, Alecu JE, Ebrahimi-Fakhari D, Hoffmann GF, Kölker S, Ries M*, Syrbe S*. **Quantitative retrospective natural history modeling of WDR45-related developmental and epileptic encephalopathy.** Autophagy, **2021** Nov 24:1-13
  - Ongoing projects
    - CDKL5
    - Menke‘s disease
    - hemiconvulsion-hemiplegia-epilepsy syndrome

Literature – MoCo and lysosomal projects

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2. Mechler K, Mountford WK, Hoffmann GF, Ries M. Ultra-orphan diseases: a quantitative analysis of the natural history of **molybdenum cofactor deficiency.** Genet Med. **2015**
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