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Effectiveness of RNA interference therapies in reducing urine and plasma oxalate levels among patients with primary hyperoxaluria- A systematic review

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Abstract:

Background:Primary hyperoxaluria is a rare genetic disorder of hepatic oxalate over production. Standard of care is largely supportive with hydration, urinary alkalinization and pyridoxine. RNA interference therapies such as Lumasiran and Nedosiran have recently shown promising results. In this study we attempt to synthesize and summarize the existing body of evidence on the use of RNA interference therapies to guide clinicians in the management of patients with primary hyperoxaluria.

Methods: The systematic review was prospectively registered with PROSPERO and followed PRISMA guidelines. Pubmed, EMBASE and CENTRAL were searched from January 1974 to July 2024 for randomized controlled trials and single arm intervention studies on use of RNAi therapies in primary hyperoxaluria.

Results:We found 127 records across the databases, with 12 of them included in the final analysis. A total of 140 patients were enrolled in Lumasiran (9 trials) and Nedosiran (3 trials). Most studies demonstrated a significant reduction in the oxalate burden. Injection site reaction was the most common adverse event with a largely acceptable safety profile. Quality of studies assessed through ROB-2 and ROBINS-I showed a low risk of bias.

Conclusion:This systematic review emphasizes the effectiveness and safety of RNA interference therapies, Lumasiran and Nedosiran, in treating primary hyperoxaluria by lowering urinary and plasma oxalate levels.

Keywords: Primary hyperoxaluria, Lumasiran, Nedosiran, RNA interference therapies

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Introduction:

Primary Hyperoxaluria (PH) results from excessive endogenous production of oxalate due to an inborn error in the hepatic enzymatic degradation of its precursor, glyoxylate.[1] Up to 3 per 1000,000 persons are estimated to be affected by PH.[2] Overproduction of oxalate results in the development of complications like renal insufficiency in 20-50% of affected individuals, as it is primarily excreted by the kidneys.[3]

Three enzymatic defects are currently recognized to be the underlying cause of PH and subtyped as follows: PH Type 1 is the commonest about 70% cases requiring liver transplant ultimately. It is due to

the dysfunction of hepatic enzyme Alanine Glyoxalate Aminotransferase (mutation in AGXT gene), which is responsible for the transamination of L-alanine and Glyoxalate to the excretable form of pyruvate and glycine.[4] The type II of PH (PH-2) is due to deficiency of Glyoxalate reductase/Hyoxypyruvate reductase (mutation in GRHPR) resulting in high urinary excretion of L-glyceric acid and oxalate. The third type of PH (PH-3) occurs due to defective mitochondrial 4-hydroxy 2-oxoglutarate aldolase (mutation in HOGA gene), that results in excess oxalate production through yet unknown mechanisms.[5]

Elevated levels of oxalate in the urine results in the deposition of calcium oxalate crystals in affected individuals leading to formation of kidney stones and development of nephrocalcinosis.[6] Furthermore, the accumulation of these crystals in the renal interstitial tissue triggers an inflammatory response, contributing to the development of chronic kidney disease (CKD). [7]

Traditionally, individuals with these conditions have been managed with increased fluid intake and citrate supplementation to prevent the crystallization of oxalate in urine. [8] Vitamin B6 is a precursor of pyridoxal phosphate which act as cofactor of Alanine Glyoxalate Aminotransferase and helps in reduction of oxalate burden in PH-1.[9] However, as the glomerular filtration rate declines to less than 30 ml/min/1.73 m^2, oxalate also starts to accumulate in various body tissues causing deleterious systematic manifestations. Therefore, early initiation of renal replacement therapy is recommended along with, combined or sequential, liver and kidney transplantation if possible.[10]

Recent advances, specifically in the field of RNA interference therapy have provided promising treatment options for PH1 targeting the Glycolate oxalate pathway specifically that is not involved in the other types. [11] Lumasiran, Approved for use in USA in 2020, for instance works by suppressing the expression of HA01 gene, responsible for encoding the glycolate oxidase enzyme that catalyzes the conversion of glycolate to glyoxylate, the oxalate precursor. This action results in a reduction in oxalate levels both in the urine and plasma. [12] Similarly, Nedosiran exerts its effects by inhibiting lactate dehydrogenase (LDH), that converts glyoxylate to oxalate, leading to a decrease in the oxalate burden.[13]

Current clinical trials have demonstrated the effectiveness of RNA inference therapies in the treatment of primary hyperoxaluria. [14] To provide a comprehensive evaluation of their efficacy, we conducted a systematic review. By synthesizing the extracted evidence in a systematic manner, our aim is to assist physicians in making informed decisions regarding the potential therapeutic benefits of these drugs in their clinical practice.

Methods:

Study Selection

Our review was carried out in compliance with the Preferred Reporting Items for Systematic Review and Meta- Analysis (PRISMA) statement and prospectively registered with PROSPERO CRD42023433790. [15]

We included parallel group randomized controlled trials and single arm non-randomized trials, while excluding case-control, cohort, case series, case reports and commentaries. The target population for our study consisted of individuals with genetically confirmed primary hyperoxaluria, regardless of their age, gender or renal functions. However, individuals with systemic oxalate deposition or those who had undergone liver or kidney transplantation were not included in the study.

Trials involving RNA interference therapies such as Lumasiran and Nedosiran were included, regardless of their specific dosage, duration, or frequency. In contrast, treatments such as hyperhydration, urinary alkalinization, and pyridoxine were not considered. Trials that compared the intervention to either a placebo or no treatment were deemed eligible. The outcome was documented in the form of reduction in 24-hour urinary oxalate, oxalate to creatinine ratio and plasma oxalate level.

Data Sources and Searches

A systematic search was conducted in the Pubmed, EMBASE and Cochrane CENTRAL databases from January 1974 to July 2024. We utilized specific terms relevant to each database. Primary hyperoxaluria, Lumasiran, Nedosiran and RNA interference therapies were used as search keywords / related text words. The reference lists of the included studies were manually reviewed to identify any additional studies that met the inclusion criteria. The detail of search strategy is summarized in the supplementary 1.

The studies identified through our literature search were organized and managed in the reference manager, with duplicate articles systematically eliminated. Subsequently, two authors namely SK and IA, screened the titles and abstract of these studies to determine their potential eligibility. In case of any disagreements, resolution was achieved through consultation with other researcher in our team (SH).

The selected articles were reviewed in full by two authors, SK and IA. Data extracted from each study included the first author' s name, year of publication, mean or median age of participants, percentage of male participants, sample size, type and duration of the intervention, primary and secondary outcomes, and information on trial funding. If the study included control arm, then same variables were recoded for it.

Data synthesis and Analysis

The quality assessment of the included studies was carried out through risk of bias tool 2 (ROB-2) and ROBINS-I tool by IA and SK.

Results:

We initially identified 127 titles and abstracts through our search strategy across the databases. After careful evaluation, 23 of these studies met the criteria for full text reviews. Ultimately a total of 12 studies were deemed suitable for inclusion in the final analysis. For a detailed overview of the selection process, refer to Figure 1, which presents the PRISMA flowchart and explains the reasons for excluding specific studies.

In summary, 5 studies were excluded due to inappropriate study design, 3 were abstracts, two case reports and one was had missing outcome measures. Out of the 12 included trials, 9 studied Lumasiran and 3 evaluated Nedosiran as RNA interference therapies. Most trials were randomized except for 3 out of 9 in case of Lumasiran and 1 out of 3 in Nedosiran, which were single arm studies. A total of 140 patients with primary hyperoxaluria were enrolled in these studies (95 in Lumasiran and 45 in Nedosiran). Garrelfs et al published the initial 6-months outcome of Lumasiran, which was followed by a later extension of the study and additional results were published at 12, 24 and 36 months. Similarly, the single-arm study by Sas et al. was extended, with results reported at both 12 and 30 months. Most of the studies included in the final analysis had GFR more than 30-45 ml/min/1.73 m^2, except a single arm study on Lumasiran by Michael et al in which chronic kidney disease and hemodialysis patients were included. Basic characteristics of included studies are shown in Table 1.

Figure 1. Flow chart showing inclusion of studies

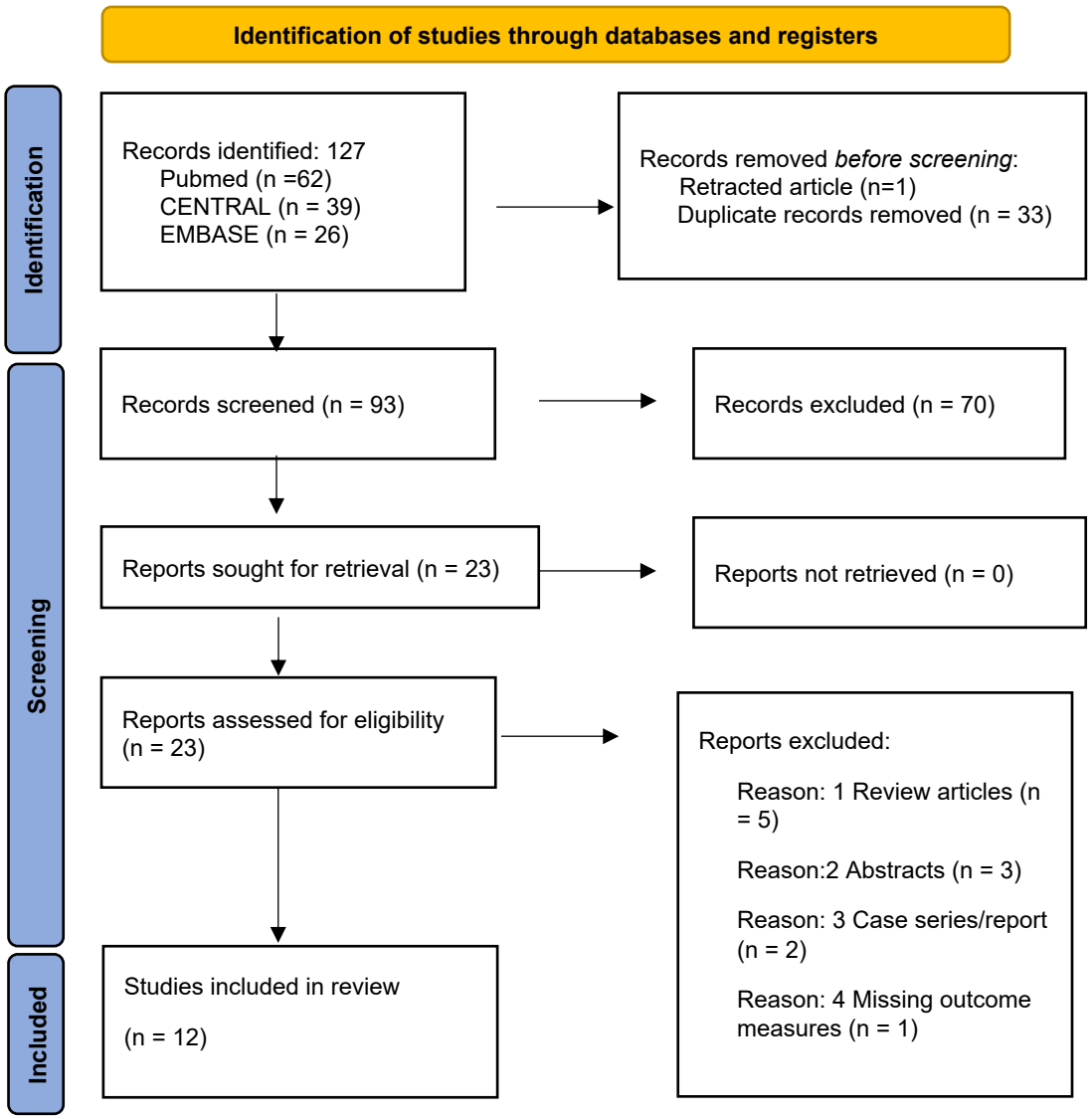

Table 1. Baseline characteristics of included studies

Study/year	Sample size/PH type		GFR ml/min/1.73m²	Male %	Mean/Median Age (years)
Frishberg et al/2021 [16]	20 (3 in placebo)/PH-1		>45	35	15 ±10
Garrelfs et al/2021 [17]	39 (13 in placebo)/PH-1		>30	67	14 (6-60)
Hulton et al /2022 [18]	39 (13 placebo crossed over to intervention)		>30	--	14 (6 – 60)
Lieske et al/2022 [19]	39 (13 placebo crossed over to intervention)		>30	--	--
Lieske et al/2023 [20]	39 (13 placebo crossed over to intervention)		>30	--	--
Sas et al/2021 [21]	18 (single arm)/PH-1		>45	44%	50.1 (3-72) months
Hayes et al/2023 [22]	18 (single arm)/PH-1		>45	44%	50.1 (3-72) months
Micheal et al/2024					
Michael et al/2023 [23]	21 (single arm)/PH-1	Cohort A CKD n=6	< 45	50%	9 (0-40)
		Cohort B On HDX n=15		60%	6 (1-59)
Hoppe et al/2022 [24]	18 (single arm) Group B/PH-1 and 2		>30	50%	23.8 (7.94)
Baum et al/2023 [25]	35 (Double blind placebo controlled)/ PH-1 and 2	Nedosiran n=23	>30	48%	23.7 (11.95)
		Placebo n=12		50%	23.6 (11.48)
Goldfarb/2023 [26]	6 (Double blind placebo controlled)/ PH-3	Nedosiran n=4	>30	50%	44.8 (13.6)
		Placebo n=2		100%	38.0 (36.8)

PH= Primary hyperoxaluria, CKD= Chronic kidney disease, GFR= Glomerular filtration rate and HDX= Hemodialysis

Studies on Lumasiran by Frishberg and Garrefels et al have shown more than 50% reduction in 24-hour urinary oxalate excretion.[16,17] The ILLUMINATE-A, ILLUMINATE-B and ILLUMINATE-C trials, which involved pediatric and CKD/hemodialysis participants respectively, reported percent changes in urinary oxalate-to-creatinine ratio of -71.7 (±3.4), -71.9 (±3.2), and -39.5 (±9.4), respectively.[18-22] The reduction in 24-hour urinary oxalate to less than 1.5 times the upper limit of normal was reported to be more than 50% in all studies except Micheal et al.[23] A statistically significant reduction in 24-hour urinary oxalate excretion was also described by Hoppe et al and Baum et al.[24,25] Reduction of 1.3 times the upper limit of normal was seen in 33.3 % and 50% participants respectively. Goldfarb et al studied the PH-3 cohort and failed to demonstrate a substantial reduction in 24-hour urinary oxalate level.[26] The analysis could not meet its primary end point of at least 30% reduction in 24-hour urinary oxalate on two separate visits. Lumasiran also led to a significant reduction in plasma oxalate levels.[16] The outcome parameters of all the included studies are shown in Table 2.

Table 2. Outcome of RNA interference therapies across the studies (n=12)

Author/year	Absolute reduction in 24-hour urinary oxalate (intervention/placebo)	Percent reduction in 24-hour urinary oxalate in (intervention/placebo)	Reduction in 24-hour / spot urinary oxalate to Creatinine ratio (intervention)/Placebo	Percent reduction in oxalate less than 1.5 times the ULN	Absolute reduction in plasma oxalate (intervention/Placebo)	Percent reduction in plasma oxalate (intervention/Placebo)
Frishberg et al/2021 Part B 85 days	–64.6 (13.6)/9.1 (NR)	NR	–62.5 (18.1)/ –8.9 (35.0)	NA	–59.5 (53.2)/ –18.7 (NR)	74 (38-94%)
Frishberg et al/2021 Part B 197 days	–64.2 (13.2)/NA	75 % (43-92%)/NA	–67.2 (13.1)/NA	100%	NR	NR
Garrelfs et al/2021 ILLUMINATE-A 6 months	–1.24 (–1.37 to –1.12)/ –0.27 (–0.44 to –0.10)	65.4 (71.3- 59.5)/ 11.8 (19.5 - 4.1)	–62.5 (–70.7 to –54.4)/ –10.8 (–21.6 to 0.0)	84%	–7.5 (–9.0 to –5.9)/ 1.3 (–1.0 to 3.5)	-39.8 (-45.8 - 33.8)/- 0.3 (-9.1 - 8.5)
Hulton et al /2022 ILLUMINATE-A 12 months	NR	(L/L) 64.1% (3.3) (P/L) 57.3%	NR	87.5% (L/L) 76.9% (P/L)	NR	35% (L/L) 48.9% (P/L)
Lieske et al/2022 ILLUMINATE-A 24 months	NR	58% (L/L) 49% (P/L)	NR	83% (L/L) 62% (P/L)	NR	56% (L/L) 61% (P/L)
Lieske et al/2023 ILLUMINATE-A 36 months	NR	63 % (L/L) 55 % (P/L)	NR	76% (L/L) 92% (P/L)	NR	36% (L/L) 37% (P/L)
Sas et al/2021 ILLUMINATE-B 6 months	---	NR	72%	50%	NR	32% (23.9 – 39.5%)
Hayes et al/2023 ILLUMINATE-B 12 months	---	NR	NR	56%	NR	47% (5%)
Michael et al/2024	NR	NR	76%	NR	NR	42%
Michael/2023 ILLUMINATE-C	NR	NR	NR	NR	NR	47%(5%)
Hoppe et al/2022 PHYOX1	Mean 55.0 (19.8)/NA Median 55 (22-100)/NA	NR	NR	NR	NR	NR
Baum et al/2023 PHYOX2	+ 3507 (788)/NA	NR	NR	NR	NR	NR
Goldfarb/2023 PHYOX4	−0.38 (0.51)/ Increase of 0.11 mmol/24 h	24.5% (22.2)/ Increase of 10.5%	NR	NR	NR	NR

I/P= intervention/placebo, L/L= Lumisiran to Lumasiran, P/L= Placebo to Lumasiran, ULN= upper limit of normal, NR= not reported

Table 3. Adverse effects of included studies (n=12)

Study/year	Injection site pain or reaction	Rhinitis/ URTI	Headache	Abdominal pain	Pyrexia	Vomiting	Drug discontinuation
Frishberg et al/2021	12%	12%/-	18%	18%	NR	NR	0
Garrelfs et al/2021	38%	8%/8%	12%	NR	NR	NR	1
Hulton et al /2022	41%	10%/10%	15%	18%	NR	NR	0
Lieske et al/2022	Mild and transient	NR	NR	NR	NR	NR	0
Lieske et al/2023	36%	NR	NR	NR	NR	NR	0
Sas et al/2021	11%	22%/17%	20%	25%	NR	NR	0
Hayes et al/2023	17%	22%/22%	NR	NR	44%	28%	0
Micheal et al/2024	17%	NR	NR	NR	NR	NR	0
Michael et al/2023	17%	NR	NR	0	17%	17%	0
	27%	NR	NR	7%	33%	7%	0
Hoppe et al/2022	39%	NR	NR	NR	NR	5.6%	0
Baum et al/2023	22%	NR	17%	13%	NR	NR	4%
Goldfarb/2023	0	NR	NR	NR	25%	NR	0

URTI= upper respiratory tract infection, NR= not reported

The most common adverse event with both drugs was injection site reaction. Details are described in Table 3.

Risk of bias in the included studies was assessed through Cochrane ROB Version-2 tool for all the randomized studies and ROBINS-I was used for non-randomized studies of interventions as shown in Figure 2 (generated through Robvis).

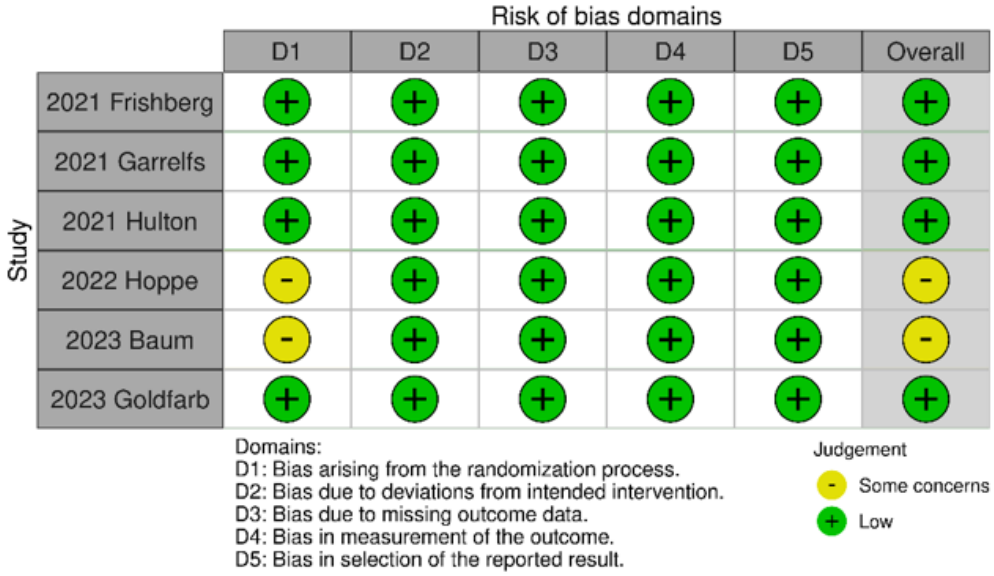

Figure 2: Risk of bias using ROB-2 tool

Discussion:

In this systematic review, we assessed the efficacy of RNAi therapies in the management of patients with PH. Both drugs (Lumasiran and Nedosiran) showed promising initial results in the reduction of plasma and urinary oxalate levels. [25,26]

Lumasiran showed a reduction of more than 50% in 24-hour urinary oxalate excretion and urinary oxalate to creatinine ratio. Significant proportion of participants across the studies were able to lower urinary oxalate to less than 1.5 times the baseline. Plasma oxalate levels followed a similar reduction pattern. The initial results of Garrelfs et al in ILLUMINATE-A trial at 6 months were consistently maintained in the extended phase at 12, 24 and 36 months.[16-20]

The hereditary nature of PH has multifold impact on the long-term survival and quality of life in young children. The ILLUMINATE-B trial at 6, 12 and 30 months displayed encouraging results in children and infants.[21,22] The reduction in spot urinary oxalate to creatinine ratio and plasma oxalate was substantial.

Lumasiran has been administered in advanced stages of chronic kidney disease with notable reduction in plasma oxalate level.[23] This has potential implication in clinical practice as patients often present in advanced stages of renal failure at diagnosis.[7]

Nedosiran, a recent addition in the management of PH 2, inhibits Lactate dehydrogenase expression and effectively reduces the oxalate burden. [24,25] Goldfarb et al found Nedosiran to be safe in PH-3 but failed to meet the primary pharmacodynamic endpoint [26]. PH-3 is relatively understudied among the other defects of primary hyperoxaluria as it has better renal functions than PH-1 and PH-2.[27] This novel approach of targeting LDH in PH-3 needs further research to improve long term outcomes.

The evidence from these trials led to approval of Lumasiran and Nedosiran by FDA for PH-1 patients in 2020 and 2023 respectively. RNAi therapies are considered safe in patients with GFR more than 30 ml/min/m2. However, a cautious approach is recommended for Lumasiran with GFR less than 30 ml/min/m2, on dialysis and under one year of age.[3] Nedosiran was approved for use in PH1 patients aged ≥ 9 years and GFR > 30ml/min/1.73 m2. However, the mechanism of action of Nedosiran indicates its potential use in all types of PH.[28]

Encouraging results from RNAi therapy in PH highlight the critical need for early diagnosis. However, there is a risk that patients might place too much confidence in these new treatments and neglect essential supportive measures, such as hyperhydration, crystallization inhibitors, and pyridoxine, that continue to play a vital role in managing PH.[29]

An imperative objective of most of these studies was to determine the safety of both drugs. Commonly reported adverse event was injection site reaction, however, the drugs had a largely acceptable safety profile. Discontinuation of therapy due to adverse effects was seen in two and one participant with Lumasiran and Nedosiran, respectively.[17,25]

The limitations to this review include clinical heterogeneity with variable age, stage of renal failure and inconsistent outcome measures. The total number of patients across studies was relatively small, especially for Nedosiran, limiting the generalizability of the findings. Due to substantial heterogeneity, pooled estimates were not generated.

Conclusion

The significant reduction in urinary and plasma oxalate levels demonstrated by the curated evidence for RNAi therapies underscores their important and emerging role in the management of individuals with PH. These therapies have the potential to reduce the risk of progressive kidney disease, thereby improving patient outcomes and quality of life. However, further focused research is needed to validate these findings across the spectrum of PH subtypes.

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