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BRIEF REPORT

PHARC (*Polyneuropathy, Hearing Loss, Ataxia, Retinitis Pigmentosa and Cataract*) – A Case Report and Clinical-Focused Literature Review

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Abstract
Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract (PHARC) is a rare condition caused by mutations in *ABHD12*. We present the first documented case of PHARC in a Brazilian patient. Describe the clinical and genetic aspects of patients diagnosed with PHARC through a literature review. A literature review was conducted in February 2024 using Pubmed/Medline database. We also report a 37-year-old Brazilian woman diagnosed with PHARC. Between 38 patients diagnosed with this condition, the majority were male (74.35%) and the median age was 35.7 years. The most common symptom reported was ataxia (79.4%). The main finding of Brain MRI was cerebellar atrophy, and demyelinating polyneuropathy was the commonest finding in electroneuromyography, both were found in 28.2% of patients. PHARC syndrome is a rare autosomal recessive condition that is increasingly reported in the literature. Refsum disease and Usher syndrome are the main differential diagnosis. A multidisciplinary approach and follow-up are crucial for accurate diagnosis and treatment.

Keywords PHARC syndrome · Hearing loss · Retinitis pigmentosa · Ataxia · Cataract · ABHD12

Introduction

*P*olyneuropathy, *H*earing loss, *A*taxia, *R*etinitis pigmentosa, and *C*ataract (PHARC syndrome: OMIM: 612,674) is a rare autosomal recessive condition caused by pathogenic biallelic mutations in *ABHD12*. The first description was in a 2009 report of a Norwegian family with three members affected by a progressive neurological disease characterized by early onset cataract, hearing loss, and neuropathy, resembling Refsum disease [1–4]. Other 19 individuals from 9 families from Norway, United Arab Emirates, United States, and Algeria, with the same condition have been reported. Until our review, around 38 cases have been identified worldwide as showed in Table 1 [1, 2, 5–7].

The *ABHD12*, located on 20p11.21, encodes the α/β-hydrolase domain-containing protein 12 [13]. Loss-of-function mutations in this gene lead to alterations in endocannabinoid metabolism, resulting in elevated levels of 2-arachidonoyl glycerol (2-AG), an endogenous agonist of CB1 and CB2 receptors, which are functionally associated with arachidonic acid. The endocannabinoid system plays a role in various biological processes, including neurotransmission, inflammation, mood regulation, appetite, pain, and addictive behavior. Additionally, *ABHD12* is expressed in various tissues, with the highest expression in microglia and macrophages, particularly in the brain and retina [13].

The classical clinical presentation of PHARC syndrome is classically asymptomatic in the first 2 years of life. Initial symptoms include night blindness and reduced visual acuity, which later progress to posterior subcapsular cataract. Ataxia and polyneuropathy usually manifest in adulthood, and sensorineural hearing loss is observed at frequencies above 1500 Hz. A literature review has documented that pathogenic variants in *ABHD12* exhibits a wide-spectrum phenotype, including variable severity and progression according to age of onset. Cataracts and hearing impairment

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Table 1 Literature review- *Y* (yes), *N* (no), *N/A* (not available), *CA* (cerebellar atrophy), *Ch* (cholesteatoma), *CNP* (cranial nerve palsy), *DMW* (distal muscle weakness), *DP* (demyelinating polyneuropathy), *II* (ischemic injuries), *IM* (involuntary moviments), *LD* (learning difficulties), *PC* (*pes cavus*), *PT* (postural tremor)

Case	Author and year	Age (y)	Sex	Polineurophaty	Hearing loss	Ataxia	Retinitis pigmentosa	Cataract	Other clinical manifestations	Brain MRI	Eletromiography
1	G Cypers MD, P Tsitsi et al. [8]	62	M	Y	Y	Y	Y	Y	PC	CA	DP
2.a	Tobias Eisenberger et al. [9]	55	F	N	Y	Y	Y	Y	IM, CNP	No abnormalities	N/A
2.b	Tobias Eisenberger et al. [9]	53	M	N	Y	Y	Y	Y	CNP	No abnormalities	N/A
3a	Hidekane Yoshimura et al. [10]	64	M	N	Y	Y	Y	N	N	CA	No abnormalities
3b	Hidekane Yoshimura et al. [10]	56	M	Y	Y	N	Y	Y	N	No abnormalities	DP
4.a	T. Li, Y. Feng, Y. Liu et al. [11]	41	M	N	Y	Y	N	Y	N	N/A	N/A
4.b	T. Li, Y. Feng, Y. Liu et al. [11]	31	M	N	Y	Y	N	Y	N	N/A	N/A
5a	M. Frasquet et al. [6]	42	M	Y	N	Y	Y	N	N	CA	DP
5b	M. Frasquet et al. [6]	41	M	Y	N	Y	Y	N	PC, DP.	CA	DP
6a- II4	Nishiguchi KM, Avila-Fernandez A, van Huet RA et al. [3]	38	F	Y	Y	N	Y	Y	N	CA	N/A
6b-II5	Nishiguchi KM, Avila-Fernandez A, van Huet RA et al. [3]	30	M	Y	Y	Y	Y	Y	N	II, Ch	N/A
6c- II6	Nishiguchi KM, Avila-Fernandez A, van Huet RA et al. [3]	30	M	N	N	Y	Y	Y	N	N/A.	N/A
6d-II7	Nishiguchi KM, Avila-Fernandez A, van Huet RA et al. [3]	30	M	N	Y	N	Y	Y	PT	II	N/A
6e-II1	Nishiguchi KM, Avila-Fernandez A, van Huet RA et al. [3]	34	M	Y	Y	Y	Y	Y	N	No abnormalities	N/A
6f- II2	Nishiguchi KM, Avila-Fernandez A, van Huet RA et al. [3]	38	F	Y	Y	Y	Y	Y	N	CA	N/A
7	Lerat J. et al. [5]	36	M	Y	Y	Y	N	N	N	N/A	DP
8a	Thimm A. et al. [12]	21	M	Y	Y	Y	N	N	N	CA.	DP
8b	Thimm A. et al. [12]	25	M	Y	Y	Y	Y	Y	N	N/A	DP
9a	Daneshi, Ahmad et al. [13]	25	M	Y	Y	Y	Y	Y	PC	CA	DP
9b	Daneshi, Ahmad et al. [13]	18	F	Y	Y	Y	Y	Y	PC	No abnormalities	DP
10a	Nguyen, Xuan-Thanh-An et al. [14]	47	M	Y	Y	Y	N/A	N/A	PC	N/A	N/A
10b	Nguyen, Xuan-Thanh-An et al. [14]	32	F	N/A	N/A	N/A	N/A	Y	N	N/A	N/A

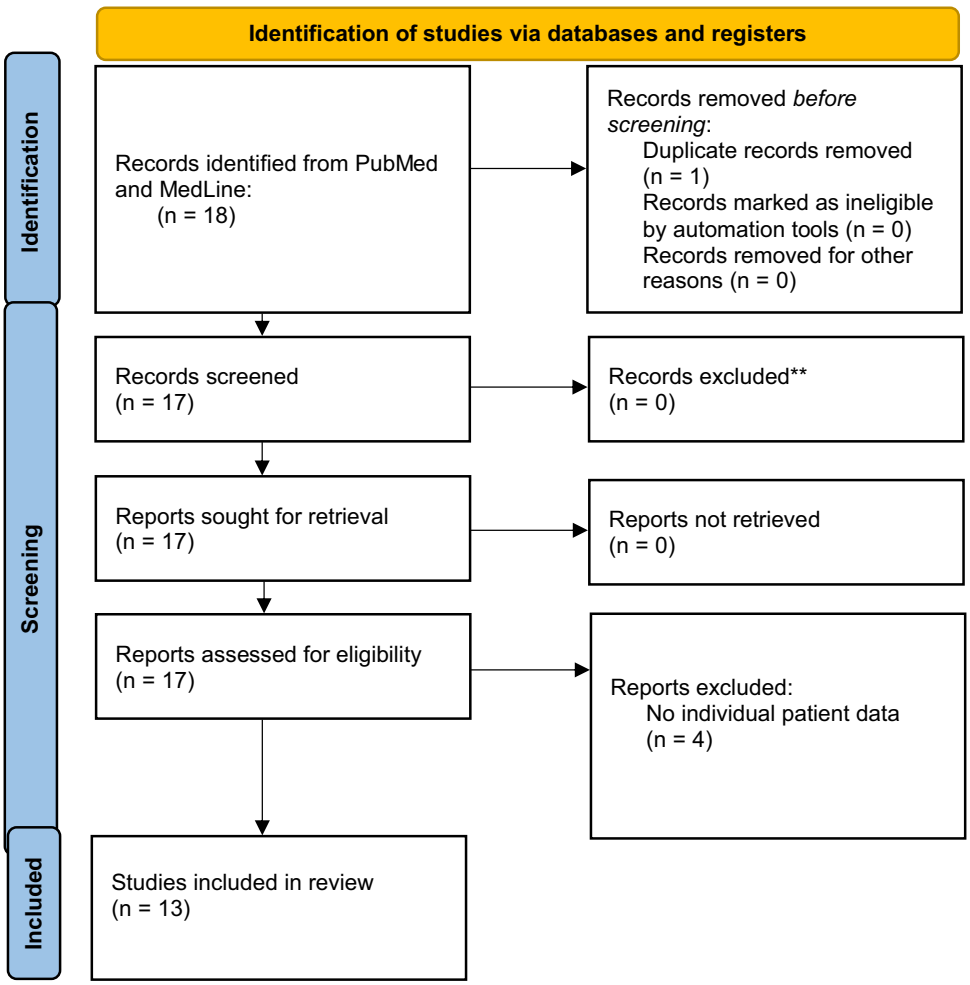
Table 1 (continued)

Case	Author and year	Age (y)	Sex	Polineurophaty	Hearing loss	Ataxia	Retinitis pigmentosa	Cataract	Other clinical manifestations	Brain MRI	Eletromiography
10c	Nguyen, Xuan-Thanh-An et al. [14]	33	M	N/A	N/A	N/A	Y	Y	N	N/A	N/A
10d	Nguyen, Xuan-Thanh-An et al. [14]	33	M	Y	Y	Y	Y	Y	DMW	N/A	N/A
10e	Nguyen, Xuan-Thanh-An et al. [14]	38	M	Y	Y	Y	Y	Y	N	N/A	N/A
10f	Nguyen, Xuan-Thanh-An et al. [14]	42	M	Y	N	N	Y	Y	n	N/A	N/A
10g	Nguyen, Xuan-Thanh-An et al. [14]	36	F	N/A	N/A	N/A	N/A	Y	N/A	N/A	N/A
10h	Nguyen, Xuan-Thanh-An et al. [14]	53	M	N	Y	Y	N	N	N/A	N/A	N/A
10i	Nguyen, Xuan-Thanh-An et al. [14]	34	M	Y	N/A	Y	Y	Y	DMW	N/A	N/A
10j	Nguyen, Xuan-Thanh-An et al. [14]	22	M	Y	Y	Y	N	N	N/A	N/A	N/A
10k	Nguyen, Xuan-Thanh-An et al. [14]	53	M	N	Y	Y	Y	Y	LD	N/A	N/A
10l	Nguyen, Xuan-Thanh-An et al. [14]	20	M	Y	Y	Y	Y	Y	N/A	N/A	N/A
10m	Nguyen, Xuan-Thanh-An et al. [14]	17	M	Y	Y	Y	N	Y	N/A	N/A	N/A
10n	Nguyen, Xuan-Thanh-An et al. [14]	46	F	Y	Y	Y	N	Y	N/A	N/A	N/A
10o	Nguyen, Xuan-Thanh-An et al. [14]	39	M	N	Y	Y	N	Y	N/A	N/A	N/A
11	Dias Bastos, Paulo Andre et al. [14]	29	F	Y	Y	Y	N	N	PT, DMW, CNP	CA	DP
12	Demir, Senol et al. [15]	25	M	Y	Y	Y	N	N	N/A	CA	DP
13	Fiskerstrand, Torunn et al. [1]	50	F	Y	Y	Y	N/A	N/A	PC	CA	N/A

are the most commonly reported symptoms in patients with pathogenic mutations in *ABHD12* [13].

Methods

Between January and February 2024, we conducted an extensive literature review in the indexed medical databases PubMed and MedLine, using the search terms "PHARC syndrome," "hearing loss," "retinitis pigmentosa," "ataxia," "cataract," and "ABHD12." This search yielded approximately eighteen articles, one of which was excluded due to duplicate record. Another four articles were excluded due no individual patient data. Among the thirteen remaining articles, we identified case reports, case series, and cohort studies (organization chart below).



Regarding the inclusion criteria of the articles, patients with a confirmed diagnosis of PHARC syndrome, verified through molecular testing, were included in the studies. This criterion ensures that only genetically confirmed cases of PHARC are considered, enhancing the reliability of findings specifically related to this condition and minimizing diagnostic variability due to symptom overlap with other neurodegenerative or hereditary sensory disorders.

In the selected studies, genetic analysis included two methods:

1) Genomic DNA was extracted from peripheral blood leukocytes of the patients. Polymerase chain reaction (PCR) was used to amplify all 13 exons and flanking intronic sequences of the ABHD12 gene. Primers were designed to flank all of the exon–intron boundaries through use of the Primer3 web-based server (http://www.bioinformatics.nl/cgi-bin/primer3plus/primer3plus.cgi/).
2) DNA was extracted from peripheral blood leukocytes of the patients and Family members. Whole Exome Sequency was performed in the probands. Exome sequencing provides > 98% coverage of all human gene including genes associated with autosomal form of deafness. Some softwares (such as FastQC version 0.11.2)

tool to filter low-quality reads. Finally, all variants were analyzed to screened objects with a frequency below 1% according to the 1000 Genomes Project and ExAC database, removed synonymous variants, and selected variants with an autosomal recessive pattern. Polyphen2_HVAR, Polyphen2_HDIV and Sorting intolerant from tolerant (SIFT) were used to analyze the possible functional pathogenic effects of the variants.

The data were organized according to clinical phenotype, age, sex, author, and relevant neuroimaging and electrophysiology findings. Following this, we calculated mean and median age values to establish an epidemiological profile of PHARC syndrome patients. Furthermore, molecular variants identified were classified and interpreted based on the 2015 guidelines from the American College of Medical Genetics and Genomics (ACMG) and ClinVar.

Additionally, we report the case of a 37-year-old Brazilian woman who presented with mild sensory symptoms, progressive hearing impairment, retinitis pigmentosa (RP), and cataracts. The diagnosis of PHARC syndrome was confirmed following clinical evaluation and whole-exome sequencing (WES). Library construction (Illumina DNA with enrichment) and capture of target regions using a kit (Twist Biosciences customized version 3) with probes for all exonic and adjacent regions. Next-generation sequencing with sequencing-by-synthesis technology (Illumina NovaSeq 6000). Alignment of DNA reads with reference to the GRCh38 version of the human genome using the BWA-MEM program. Identification of small simple variants and indels using the DeepVariant program (https://www.nature.com/articles/nbt.4235). Identification of copy number variations (CNVs) using the ExomeDepth program.

Results

A 37-year-old woman, born to consanguineous parents, with no developmental delay, started at age of 13 with severe bilateral cataracts, requiring surgical treatment, and bilateral sensorineural hearing loss. At 33-years-old, she developed progressive global cerebellar ataxia, leading to impairment of gait and dysphagia.

During our outpatient evaluation, she was 37 years-old and presented with bilateral complete hearing loss, left lower limb monoparesis (grade IV, according to Medical Research Council score) with left extensor plantar response, global cerebellar ataxia, and *pes cavus* with Achilles tendon contracture (Fig. 1A,1B,1 C). She has no cognitive impairment, or reported seizures.

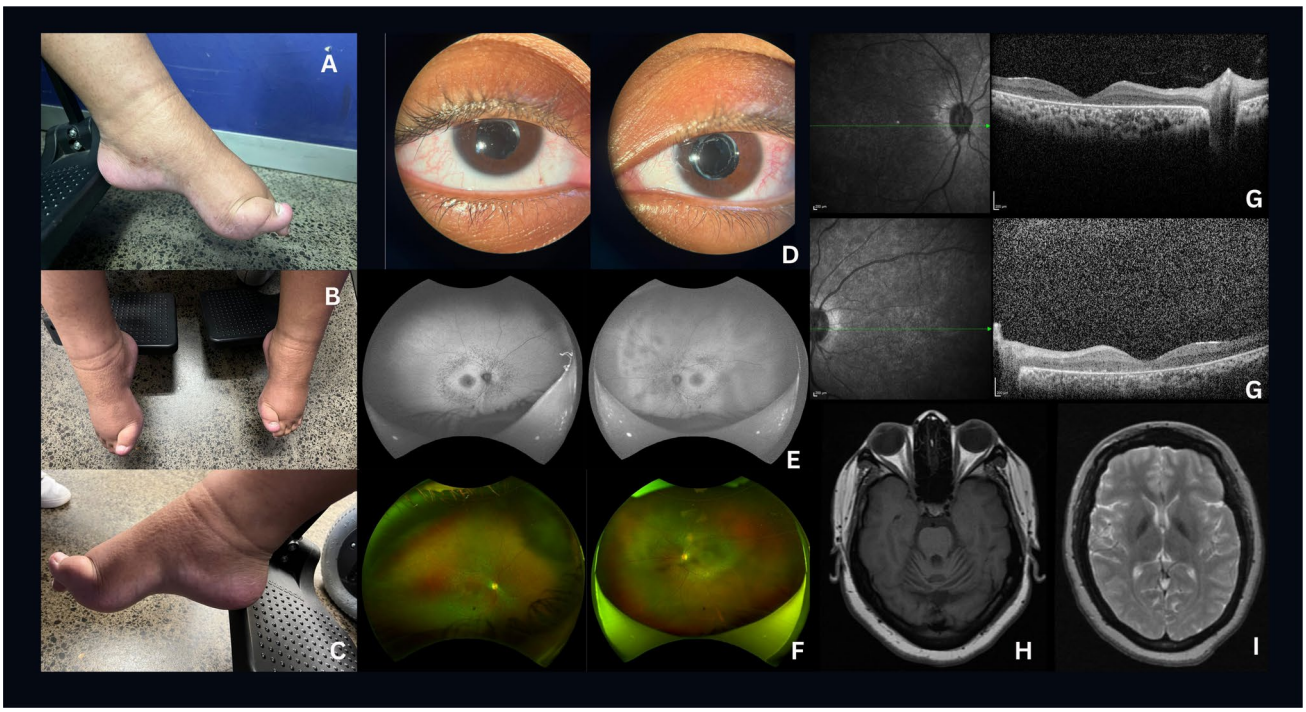


Fig. 1 **A**, **B**, **C**: *Pes cavus* with Achilles tendon contracture. **D**. Biomicroscopy showed pseudophakia in both eyes. **E** Ultra-wide field imaging: mild disk pallor, arteriolar attenuation, hypopigmented lesions in the mid-periphery, and bone spicules. **F**. Ultra-widefield fundus autofluorescence exhibited a perimacular hyper-autofluorescent ring with multiple hypofluorescent lesions in the mid-periphery. **G**. Optical Coherence Tomography (OCT) demonstrated foveal atrophy, reduced outer nuclear layer thickness, and disrupted ellipsoid zone. **H**: Global cerebellar atrophy in brain RMI. **I**: Iron accumulation in the globus pallidus in brain RMI

Her family history is notable for a 48-year-old bedridden sister with severe ataxia and childhood-onset cataracts, and a 36-year-old brother with intellectual impairment, psychiatric disorders (characterised by anxiety symptoms and psychomotor agitation) and cataracts. The symptomatic siblings undergone no genetic testing yet,

Her corrected visual acuity was 20/400 in the right eye and 20/700 in the left eye. Biomicroscopy revealed pseudophakia in both eyes (Fig. 1D). Additional evaluations on ultra-wide field imaging revealed mild disk pallor, arteriolar attenuation, hypopigmented lesions in the mid-periphery, and bone spicules. These findings establish the diagnosis of retinitis pigmentosa (Fig. 1E). Ultra-widefield fundus autofluorescence exhibited a perimacular hyper-autofluorescent ring with multiple hypofluorescent lesions in the mid-periphery (Fig. 1F). Optical Coherence Tomography (OCT) demonstrated foveal atrophy, reduced outer nuclear layer thickness, and disrupted ellipsoid zone (Fig. 1G). Brain MRI showed a global cerebellar atrophy (Figs. 1H) and iron accumulation in the globus pallidus (Fig. 1I). Electroneuromyography presented with demyelinating sensorimotor polyneuropathy in the lower limbs. Whole Exome sequencing identified a homozygous deletion of exon 1 in chromossome 20. Consent to Participate declaration has been signed.

We conducted a focused literature review of 38 patients diagnosed with PHARC Syndrome. The majority of patients were male (74.35%), and the average age at diagnosis was 35.7 years. The most common symptom reported was cerebellar ataxia (79.4%), followed by hearing loss (76.9%), cataracts (71.79%), polyneuropathy (64.1%), and retinitis pigmentosa (58.97%). Additional associated symptoms included *pes cavus* (15.38%), cranial nerve palsy (7.69%), distal muscle weakness (7.69%), postural tremor (5.12%), involuntary movements such as action tremor and dystonic tremor (2.56%), and learning difficulties (2.56%). Brain MRI findings indicated cerebellar atrophy in 28.2% of patients, while demyelinating polyneuropathy was observed in a similar percentage (28.2%). The full data is summarized in Table 1.

Furthermore, we analyzed variants and interpreted them according to the 2015 American College of Medical Genetics and Genomics (ACMG) guidelines (supplemental Table 1). The majority of mutations were homozygous (64.1%), followed by compound heterozygous (36.9%). The primary mutational mechanisms identified were *nonsense* and *frameshift* mutations.

Discussion

Our case is according with others literature reports, presenting early-onset cataracts, hearing loss and pyramidal signs. Other reported features include short stature, ptosis, and cognitive impairment with learning difficulties [16]. These latter symptoms were absent in our patient; however, intellectual deficits were noted in her brother (not tested), who also exhibited early cataracts, suggesting a potentially different phenotype.

Electroneuromyography often reveals demyelinating sensorimotor polyneuropathy in both upper and lower limbs, clinicaly presentingwith hyporeflexia and *pes cavus*, reduced vibratory and superficial sensory modalities. Neuroimaging may show cerebral and cerebellar atrophy, while fundoscopy reveals *retinitis pigmentosa*. Laboratory tests typically indicate normal levels of phytanic and pristanic acids (in our patient metabolic tests were not performed).

The differential diagnosis of this condition includes Refsum disease for its characteristic elevation of pristanic and phytanic acids. Refsum disease and PHARC syndrome is distinguished by its wide-ranging clinical heterogeneity in terms of age of onset, severity, clinical presentation, and progression. It also differs from mitochondrial diseases, Usher syndrome, and Charcot-Marie-Tooth disease (CMT) [13, 16]. Usher syndrome type IB (USH1B) typically manifests with profound sensorineural hearing loss, retinitis pigmentosa, and visual impairment, caused by homozygous or compound heterozygous mutations in the *MYO7 A* gene on chromosome 11q13. Conversely, CMT 1 A presents with cavus feet, foot deformities, distal sensory impairment showing a demyelinating pattern, and is due to duplication or mutation in the gene encoding peripheral myelin protein-22 (*PMP22*) on chromosome 17p12.

Due to the limited number of PHARC cases described in the literature, it only allows descriptive demonstrations of the cases, since this is a very rare genetic condition with a challenging diagnosis.

Given the diverse clinical presentations, a multidisciplinary approach and ongoing follow-up are crucial for accurate diagnosis and differential diagnosis. Currently, our patient is undergoing comprehensive care involving rehabilitation and medical follow-up.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12311-025-01860-9.

Author Contributions S.R.P.S.J, R.M.G.B, L.C.C and P.P.C wrote the main manuscript and reviewed the literature articles. J.C.C.U and D.Q.O prepared the figure. P.P.C and M.A.A.C classified the variants. F.M performed the ophthalmological evaluation. F.F and F.K coordinated the whole process. All authors reviewed the manuscript.

Data Availability No datasets were generated or analysed during the current study.

Declarations We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Consent Written informed consent was obtained prior to the study.

Disclosures The authors declare that there are no additional disclosures to report.

Conflict of Interest The authors declare no competing interests.

Competing Interests The authors declare no competing interests.

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