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Citation for final published version:

Wild, John M., Smith, Philip E.M. and Knupp, Carlo 2025. Machine-learning algorithms for the identification of visual field loss associated with the antiseizure medication vigabatrin-a proof of concept. British Journal of Ophthalmology 10.1136/bjo-2024-325804

Publishers page: https://doi.org/10.1136/bjo-2024-325804

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#### **Supplementary Material**

## Machine-learning algorithms for the identification of visual field loss associated with the antiseizure medication vigabatrin - a proof of concept.

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A) Adults - No Vigabatrin exposure			
FF135 (CM): 01 23	Legend		
FF135 (CS): 01 23			
C30-2T(CM): 01 23	Normal/Non-VAVFL		
C30-2T(CS): 01 23	Artefact: Non-VAVFL	(CM) - Clinical outcome, Measured field	
FF135 (AM): 01 23	VAVFL	(CS) – Clinical outcome, Symmetrised field	
FF135 (AS): 01 23	Artefact: VAVFL	(AM) - Algorithmic outcome, Measured field	
C30-2T(AM): 01 23	Artefact	(AS) - Algorithmic outcome, Symmetrised field	
C30-2T(AS): 01 23	Equivocal		
	Glaucomatous		
B) Chidren – Vigabatrin exposed			
FF135 (CM): 24 25 26 27	28 29 30 31		
FF135 (CS): 24 25 26 27	28 29 30 31		
FF135 (AM): 24 25 26 27	28 29 30 31		
FF135 (AS): 24 25 26 27	28 29 30 31		
C) Adults - Vigabatrin exposed			
FF135 (CM):	<b>3</b> B <b>4</b> D	<b>47 48 49 50 51 52</b>	53
FF135 (CS):	38 41	47 <mark>48 49 50 51 52</mark>	53
C30-2T(CM): 32 33 34 35	36 37 38 39 40 41 (	42 43 44 45 46	
C30-2T(CS): 32 33 34 35	36 <mark>37 38 39 40 41</mark>	42 43 44 45 46	
FF135 (AM):	38 41	47 48 49 50 51 52	53
FF135 (AS):	38 41	47 48 49 50 51 52	53
C30-2T(AM): 32 33 34 35	36 37 38 39 40 41	42 43 44 45 46	
C30-2T(AS): 32 33 34 35	36 37 38 39 40 41	42 43 44 45 46	
D) Adults - Vigabatrin exposed with homonymous visual field loss			
FF135 (CM): 54	60 61 62 63	64 65 66 67 68 70 71 72	
FF135 (CS): <u>54</u>	60 61 62 63	64 65 66 67 68 70 71 72	
C30-2T(CM): 54 55 56 57	58 59 60 61 62 63	64 65 66 67 68 69	
C30-2T(CS): 54 55 56 57	58 59 60 61 62 63	64 65 66 67 68 69	
FF135 (AM): 54 55	60 61 62 63	64 65 66 67 68 70 71 72	
FF135 (AS): 54 55	60 61 62 63	64 65 66 67 68 70 71 72	
C30-2T(AM): 54 55 56 57	58 59 60 61 62 63	64 65 66 67 68 69	
C30-2T(AS): 54 55 56 57	58 59 60 61 62 63	64 65 66 67 68 69	
E) Adults – Homonymous visual fi	eld loss		
C30-2T(CM): 73 74 75 76	77		
C30-2T(CS): 73 74 75 76	77		
C30-2T(AM): 73 74 75 76	77		
C30-2T(AS): 73 74 75 76	77		
F) Adults - Primarv open angle glaucoma			
C30-2T(CM): 78 79 80 81	82 83 84 85 86 87	88 89	
C30-2T(CS): 78 79 80 81	82 83 84 85 86 87	88 89	
C30-2T(AM): 78 79 80 81	82 83 84 85 86 87	88 89	
C30-2T(AS): 78 79 80 81	82 83 84 85 86 87	88 89	

**Table S1** Summary of the comparisons of the outcomes of the 'gold standard' clinically defined measured and symmetrised paired fields to those of the pattern-recognition algorithms illustrated in Figs 1 and 2 for each of the subcategories of the validation case series. Within each subcategory, the light grey shaded row contains the outcomes of the clinical evaluation and the dark grey shaded row that of the algorithm.

### S1 The EMA-approved perimetric protocol for the detection of VAVFL with the Humphrey Field Analyzer

The EMA-approved perimetric protocol with the HFA comprises the Three Zone Age Corrected Full Field 135 Screening Test (FF135) and the Central C30-2 Threshold Test (C30-2T). The FF135 contains 135 stimulus locations extending radially from the central field out to a maximum eccentricity of 90° temporally. A default Goldmann size III stimulus is presented at a luminance 8dB brighter than the corresponding age-corrected normal value. If the stimulus is 'not seen', it is re-presented at the maximum luminance (10,000asb), which is equivalent to a Goldmann V4e stimulus, and the response is documented as either 'seen' or 'not seen', as appropriate. The C30-2T determines the threshold, i.e., the minimum detectable luminance, of the default size III stimulus, at each of 76 locations, separated by 6° and offset by 3° either side of the vertical and horizontal midlines, within an eccentricity of 27° from fixation. If VAVFL is present with one type of test, the other is not mandated and its use is at the discretion of the attendant clinician.

#### S2 Symmetry Index

The degree of between-eye mirror image symmetry of each measured paired field was quantified in terms of an index consisting of two components each of which is a fraction <sup>1</sup> The numerator of the first fraction comprises the number of between-eye mirror image stimulus locations which each exhibit either relative or absolute loss for the FF135 or abnormality at p≤0.02 by Pattern Deviation probability analysis for the C30-2T. The denominator comprises the total number of stimulus locations exhibiting abnormality summed across the two eyes. The numerator of the second fraction comprises the total number of stimulus locations exhibiting abnormality summed across the two eyes. The numerator of the second fraction comprises the total number of stimulus locations exhibiting abnormality summed across the total number of stimulus locations exhibiting abnormality summed across the total number of stimulus locations exhibiting abnormality summed across the two eyes. The numerator of the second fraction comprises the total number of stimulus locations exhibiting abnormality summed across the two eyes. The index for each type of perimetry is then referenced to those obtained from the simulation of one million randomly generated pairs of abnormal fields exhibiting varying, areas and depths, and locations of loss, within- and between-eyes and provides an indication, as a function of severity of loss, as to the likelihood of obtaining symmetrical field loss due to chance. Any symmetry displayed by the measured fields becomes apparent when compared to that from the simulated fields.

The symmetry index, for the measured paired fields for each individual within the validation case series, referenced to the likelihood of symmetry occurring due to chance, is shown in Fig S1. The paired fields which were normal and those exhibiting VAVFL displayed a high level of symmetry. As would be expected, a low symmetry index was present in cases with VAVFL which exhibited considerable variability in one or both of the paired fields due to poor compliance; cases with VAVFL where the homonymous loss was more extensive than the VAVFL; cases with homonymous loss, alone, and those with glaucomatous field loss.



**Figure S1** The conversion table for the transformation utilised in the symmetrisation process (top FF135; bottom C30-2T)



**Figure S2**. The paired measured fields with the FF135 for the 4 children with VAVFL (left) and the matched measured field extracted from the case series of 123 (adult) individuals.



**Figure S3**. The two components of the symmetry index for the measured paired fields derived with the FF135 (left) and with the C30-2T (right). The abscissa represents the severity of the visual field loss. The left ordinate represents the degree of between-eye mirror image symmetry of the paired fields. The scale on the right shows the level of probability associated with a random occurrence of symmetry. The red areas each contain the data points from one million randomly generated pairs of fields with differing levels of severity and represent the likelihood of between-eye mirror image symmetry occurring due to chance at p>0.01. The black circles represent the paired measured fields of the individuals within the

validation case series. A circle positioned within the white region indicates a high level of between-eye mirror image symmetry at p<0.01. A circle in the top right corner indicates a high degree of symmetry since each of the measured fields within the pair exhibits advanced loss. A circle in the bottom left corner indicates an absence of symmetry since each of the measured fields within the pair exhibits advanced fields within the pair is normal.