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1 **Title**

2 Utilizing Advanced Technology to Facilitate Diagnosis of Rare Retinal Disorders - A Case
3 of Bietti Crystalline Dystrophy **Authors**

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9 **Running title**

10 Bietti crystalline dystrophy

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19 SIGNIFICANCE:

20 Optometrists, as primary eye care providers, encounter patients with rare ocular disease
21 such as Bietti crystalline dystrophy from time to time. Utilizing the advanced technologies,
22 which are also useful in managing common ocular conditions, to facilitate a prompt
23 diagnosis is highly recommended.

24 PURPOSE:

25 This report describes a patient with clinically diagnosed Bietti crystalline dystrophy with
26 findings on funduscopy, multimodal imaging, and visual electrophysiology.

27 CASE REPORT:

28 A 41-year-old Chinese female was referred to our clinic to test for retinitis pigmentosa,
29 who had subjectively progressing dimmed vision (especially in the left eye) for 9 months.
30 Best-corrected visual acuities were 6/6 and 6/7.6 in the right and left eye, respectively.
31 Funduscopy revealed multiple crystalline deposits on the posterior pole in both eyes. The
32 30-2 perimetry displayed bi-infero-temporal scotoma (left > right eye). Scotopic flash
33 electroretinogram (ERG) was normal, while photopic ERG was slightly attenuated. Electro-
34 oculogram showed an abnormal adaptation time course of the retinal pigmented epithelium
35 (RPE). Multifocal ERG revealed a decreased central retinal response, but para-central
36 responses were relatively better preserved. Optical coherence tomography showed multiple
37 patches of RPE atrophy, with disruption of the left ellipsoid zone. Outer retinal tubulations,
38 hyper-reflective dots on RPE-Bruch's membrane interface, and intra-retinal bright spots
39 were also identified.

40 CONCLUSIONS:

41 Rare ocular diseases like Bietti crystalline dystrophy can be encountered by optometrists.
42 This case report shows the ophthalmic findings of a rare chorio-retinal dystrophy, and
43 provides insight on how to better-utilize advanced equipment in an optometric practice to
44 facilitate prompt diagnoses.

45

46 Bietti crystalline dystrophy is a rare tapeto-retinal disease that occurs as a result of an
47 autosomal recessive genetic mutation in the CYP4V2 gene (Online Mendelian Inheritance
48 in Man identifier, 210370).¹ Its prevalence has been reported to be 3% in patients with non-
49 syndromic retinitis pigmentosa and is estimated to affect 1 in 67,000.² Bietti crystalline
50 dystrophy is more commonly found in East-Asian countries, especially China, where over
51 21,000 cases have been reported, and Japan,³ than Western countries where the incidence is
52 1 in 4,500,000,⁴ where only 5,000 and 10-12 patients have been reported in the U.S. and
53 Spain, respectively.

54 Bietti crystalline dystrophy was first described by Bietti in 1937 as the presence of
55 characteristic multiple glistening crystals on the posterior pole of the fundus, which are
56 associated with progressive retinal pigment epithelium atrophy and choroidal sclerosis.
57 Superficial limbal-corneal crystalline deposit was also reported in approximately one-third
58 of the patients with this condition.⁵ Because of the clinical presentation, the differential
59 diagnosis includes flecked retina syndrome, retinitis punctate albesens, cytinosis, drug (for
60 example tamoxifen) toxicity, talc retinopathy, and retinopathy due to Sjogren-Larsson
61 Syndrome. Patients experience decreased visual acuity, especially in their nocturnal vision,
62 and scotomas in perimetry test depending on the stage of the disease. Currently, the disease
63 is incurable and due to its progressive nature, the long-term prognosis may be blindness.

64 Optometric practices are often equipped with advanced tools to facilitate a prompt
65 diagnosis and management of common ocular diseases, including, but not limited to,
66 glaucoma, macular degeneration, and diabetic retinopathy. These tools, for instance,

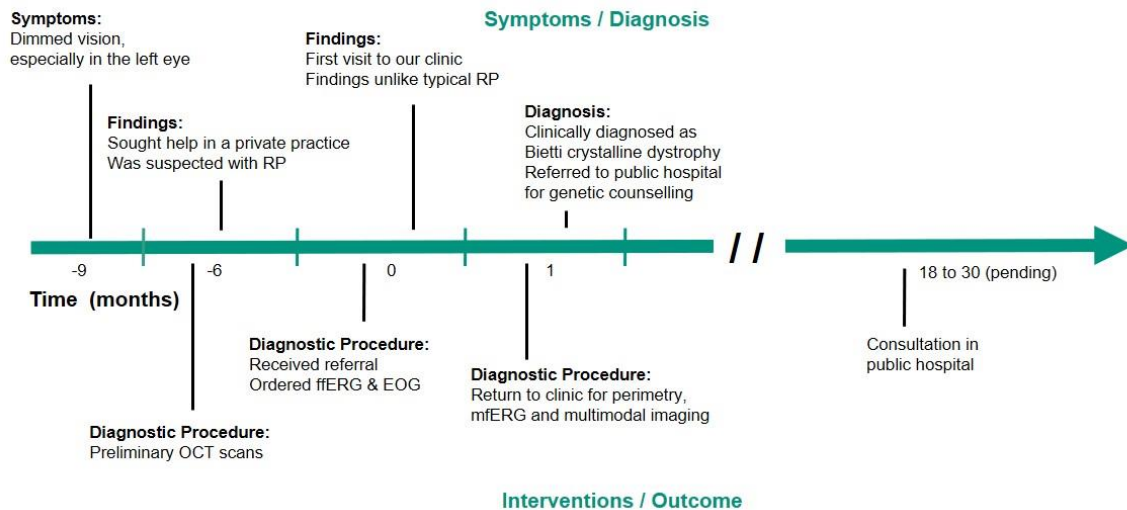
67 imaging devices and electro-diagnostics, can also be utilized to aid the diagnosis in rare
68 ocular conditions such as Bietti crystalline dystrophy.

69 **CASE REPORT**

70 No identifiable health information is included in this case report. LTY, a 41-year-old
71 Chinese female, was referred to the university optometry clinic because of suspected
72 retinitis pigmentosa. The patient reported slowly progressing vision loss in both night- and
73 daytime, especially in the left eye, which became apparent approximately 9 months ago
74 (Figure 1). She reported an unremarkable family history and ocular history, except for an
75 uneventful refractive surgery in 2003. Her pre-operative refractive error was reported to be
76 approximately -6 D of myopia and 2 D of astigmatism. She was not taking any medications
77 or suffered trauma to the eye.

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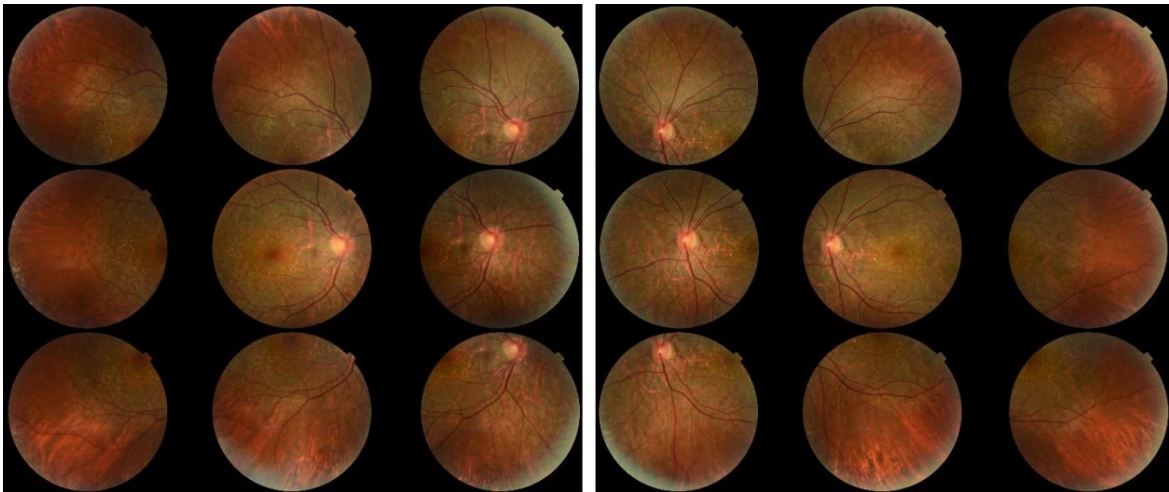
81 Figure 1. Clinical timeline of a 43-year-old Chinese female clinically diagnosed with Bietti
 82 crystalline dystrophy. Abbreviations: OCT = Optical coherence tomography, fERG = Full-
 83 field electroretinogram, EOG = Electro-oculogram, mfERG = Multifocal electroretinogram,
 84 RP = Retinitis pigmentosa

85

86 On initial examination, the best-corrected visual acuity was 6/6 and 6/7.6 in the right and
 87 left eyes, respectively, measured by crowded line Sloan letters on a computerized acuity
 88 chart. The central and para-central fundus photographs are shown in Figure 2, in which
 89 multiple tiny glistening crystals can be observed over the posterior pole in both eyes.
 90 However, her cornea did not exhibit any crystalline deposits. Full-field electroretinogram
 91 and electro-oculogram, following the International Society for Clinical Electrophysiology
 92 of Vision standards,^{6,7} were performed in the initial visit to evaluate the function of the
 93 retina in both photopic and scotopic conditions. The scotopic 0.01 and 3.0 rod responses

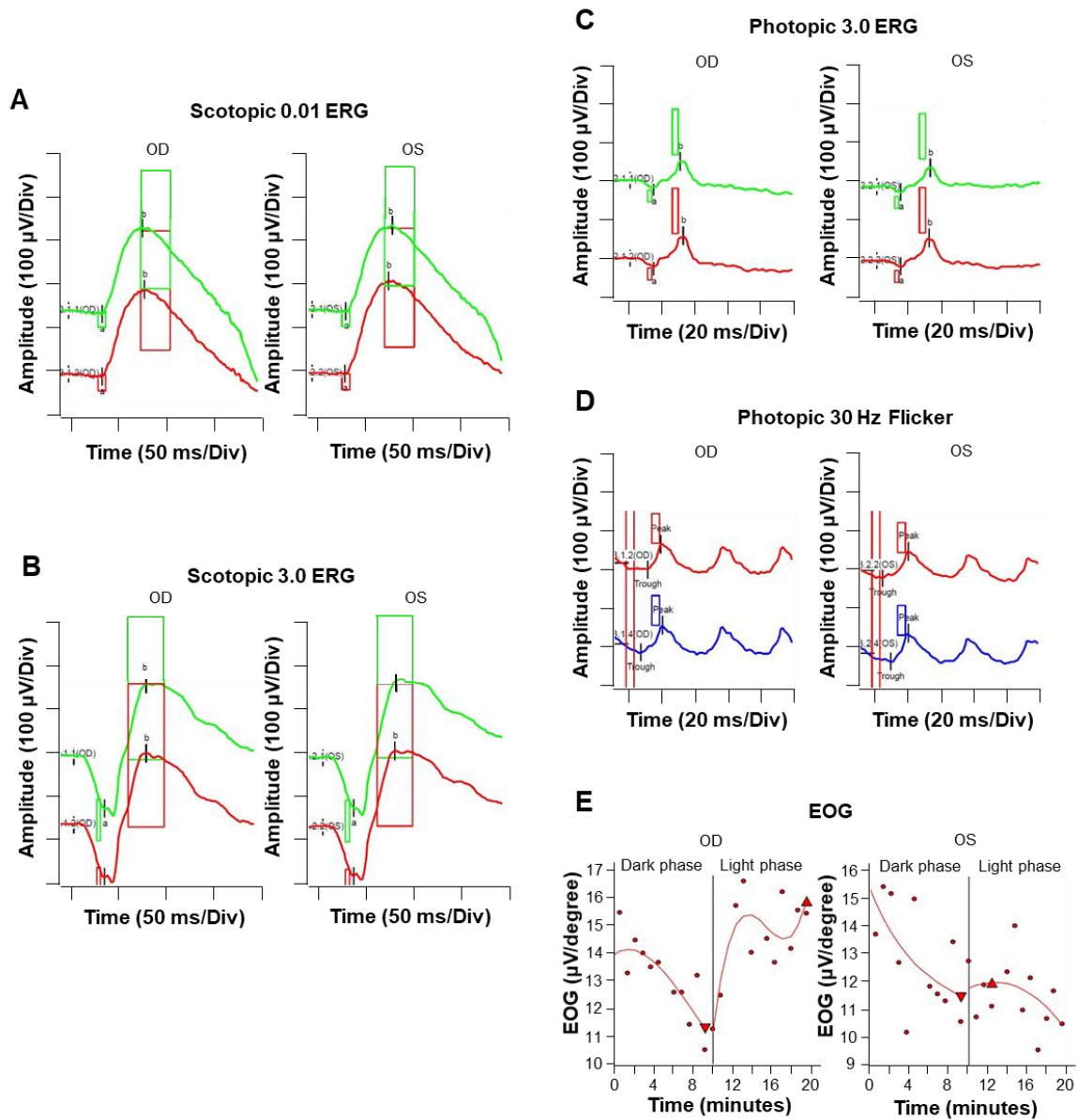
94 were normal (Figures 3A and B) while the photopic 3.0 cone response was slightly
95 attenuated (Figure 3C), which was also indicated by 30 Hz flicker responses (Figure 3D).
96 The full-field electroretinogram responses from both eyes were symmetrical. However, the
97 electro-oculogram showed an abnormal adaptation time course of the retinal pigment
98 epithelium, which was more severe in the left eye (Figure 3E).

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Figure 2. Central and para-central fundus photographs



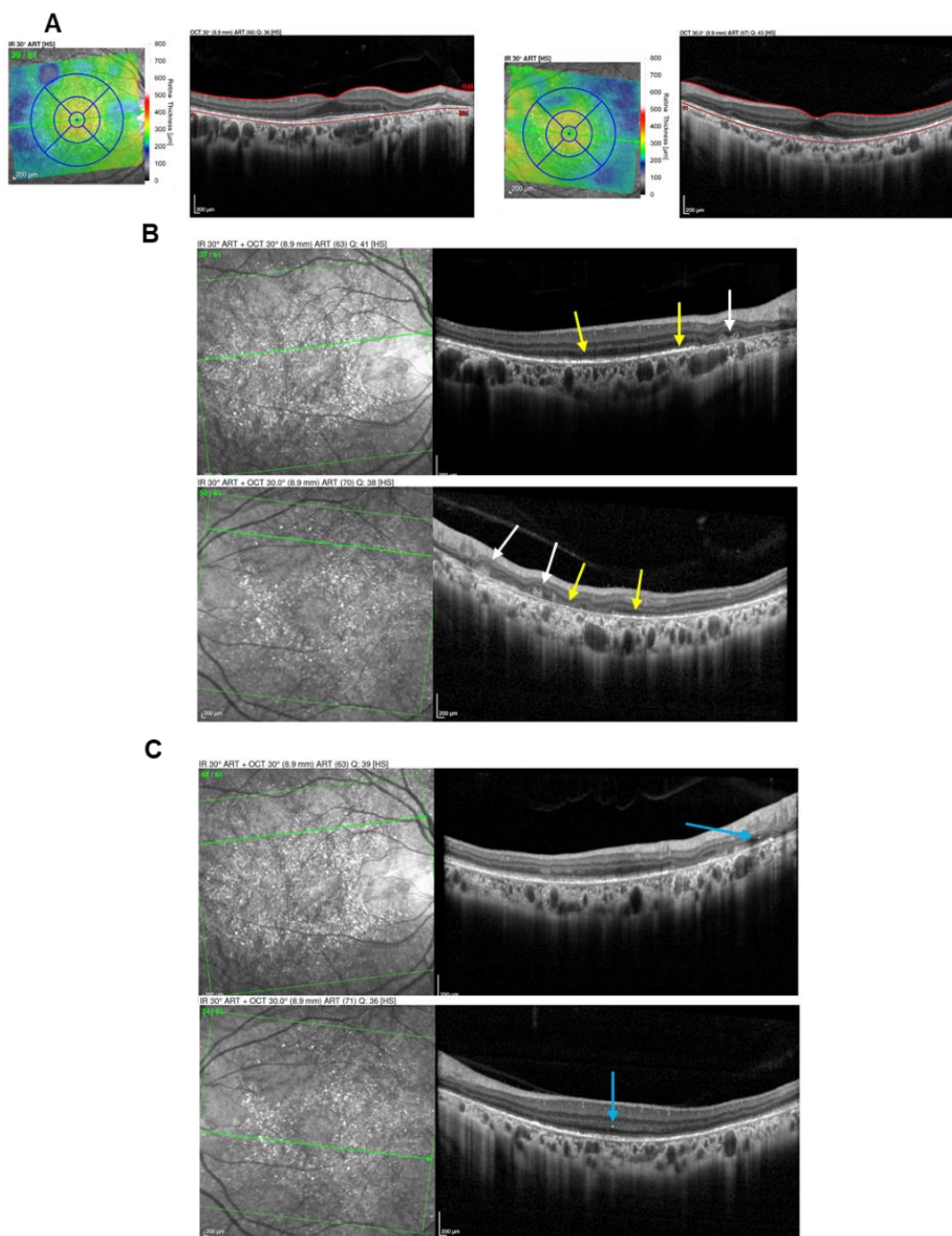
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103 Figure 3. Full-field electroretinogram (A: Scotopic 0.01 response; B: Scotopic 3.0 response;

104 C: Photopic 3.0 response; D: Photopic 30 Hz flicker responses) and E: Electro-oculogram

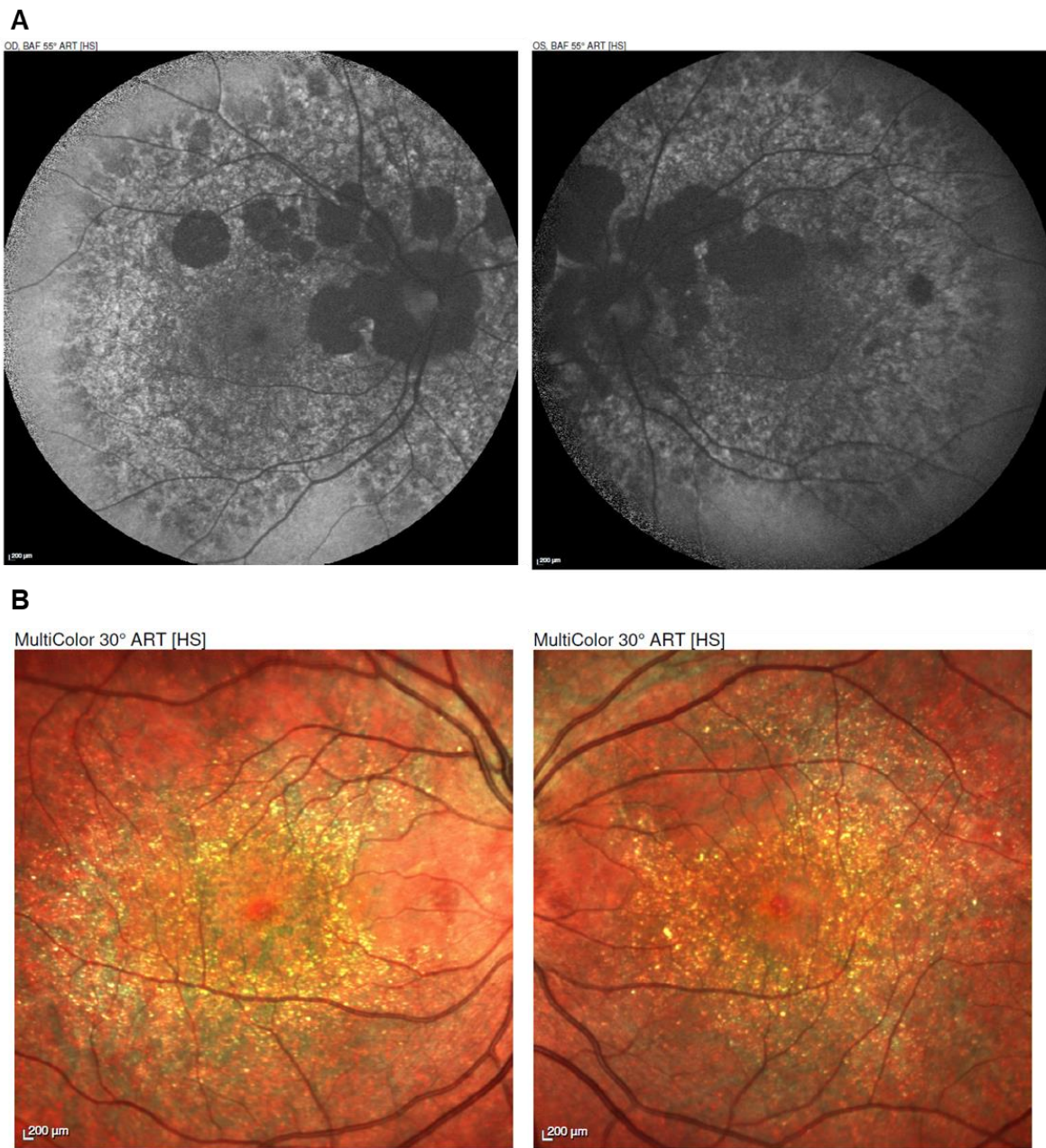
105 As the clinical and electrophysiological presentations were unlike retinitis pigmentosa,
106 patient was asked to return for perimetry, multimodal imaging, and a multifocal
107 electroretinogram. The 30-2 Swedish Interactive Thresholding Algorithm-Standard
108 perimetry recorded a mean deviation and a pattern standard deviation of -7.55 dB and 10.08
109 dB in the right eye, and -7.07 dB and 9.46 dB in the left eye. A relative scotoma on the
110 interior temporal quadrant was detected in both eyes, which was larger in the left eye.
111 Spectra-domain optical coherence tomography imaging revealed multiple patches of retinal
112 pigment epithelium atrophy (Figure 4), with disruption of the ellipsoid zone in the left eye.
113 Outer retinal tubulations were identified, which grossly corresponded to the location of the
114 perimetric scotoma (Figure 4B, white arrows). Hyper-reflective dots on retinal pigment
115 epithelium-Bruch's membrane interface were found to correspond to crystalline deposits on
116 the fundus (Figure 4B, yellow arrows). Intra-retinal bright spots were also observed (Figure
117 4C, blue arrows). Fundus auto-fluorescence imaging revealed hypo-fluorescence in areas
118 with retinal pigment epithelium atrophy and multiple hyper-fluorescence dots over the
119 posterior pole in both eyes (Figure 5A). The multicolour imaging allowed better
120 visualization of the retinal crystalline deposits than conventional funduscopy (Figure 5B).
121 No choroidal neovascularisation or blood vessel leakage was identified by optical
122 coherence tomography-angiography. The multifocal electroretinogram revealed a decreased
123 central retinal response, but a relatively better-preserved para-central retinal signal (Figure
124 6). The patient was clinically diagnosed with Bietti crystalline dystrophy and referred to a
125 retinal specialist and for genetic counselling to look for a mutation in CYP4V2 gene.
126 Familial checking was also advised. As the patient was experiencing relatively normal

127 visual acuity and acceptable visual field extent, visual rehabilitation was discussed, but not
128 arranged at this stage.

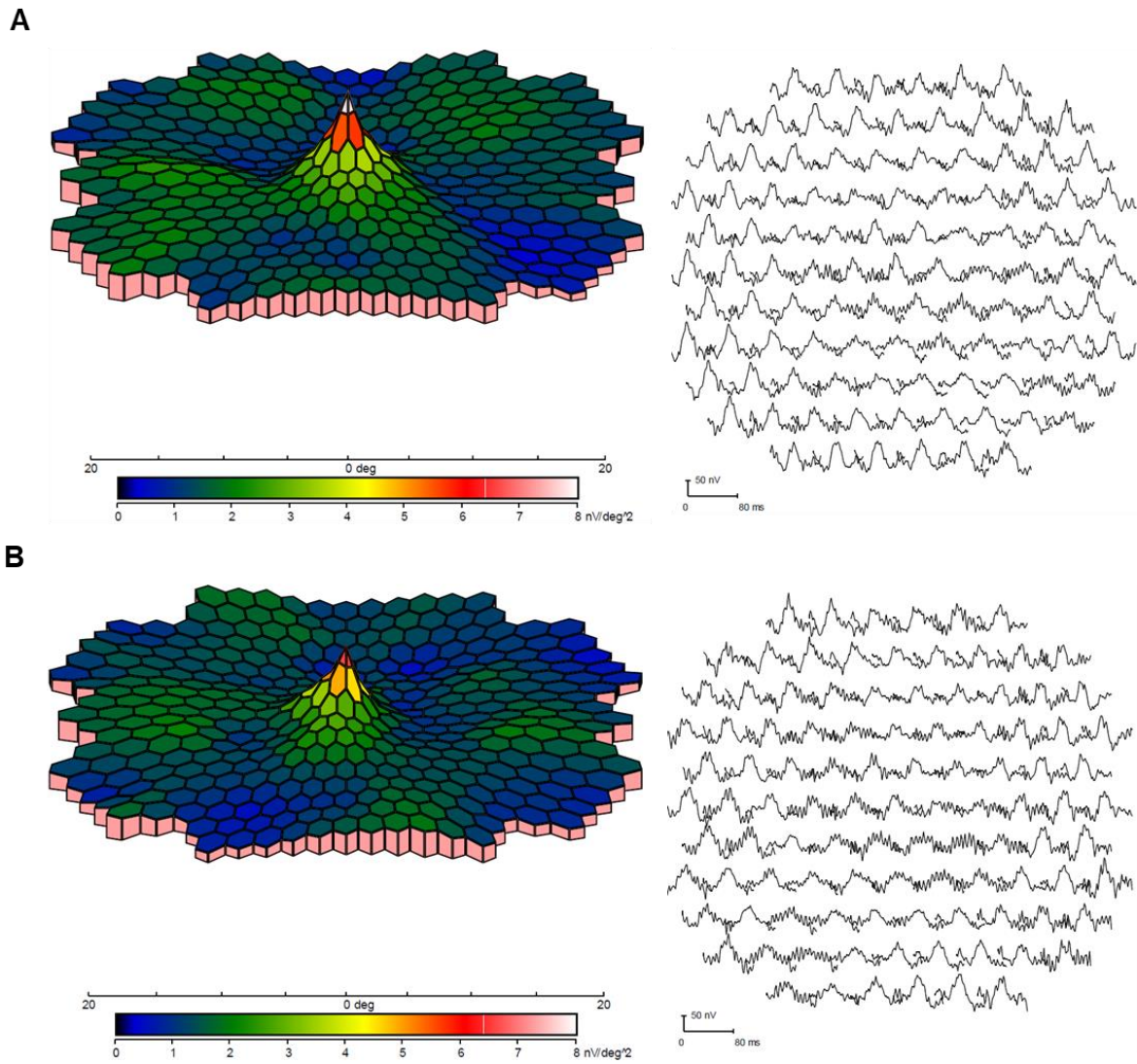


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130 Figure 4. Spectral-domain optical coherence tomography. A: Volume scan with multi-
 131 patches of retinal epithelial atrophy; B: Outer retinal tubulations (white arrows) and hyper-
 132 reflective dots correspondent to crystalline deposits (yellow arrows); C: Intra-retinal bright
 133 spots (blue arrows)



135 Figure 5. Multimodal imaging. A: Fundus auto-fluorescence; B: Multi-colour imaging



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137 Figure 6. Multifocal electroretinogram with 3-dimensional plots of response density and

138 trace arrays, with diminished central retinal response. A: Right eye; B: Left eye

139 **DISCUSSION**

140 This report presents a case of clinically diagnosed Bietti crystalline dystrophy in a 41-year-
141 old Chinese female, in which the genetic testing for CYP4V2 mutation is required to
142 further confirm the diagnosis.^{1,2}

143 The clinical findings are mostly consistent with previous reports of fundus appearance with
144 multiple glistening crystals located on the retinal pigment epithelium -Bruch's membrane
145 interface – observed using optical coherence tomography, as well as other optical
146 coherence tomography findings, including retinal pigment epithelium atrophy, outer retinal
147 tubulations, and intra-retinal bright spots.^{9,10} The absence of corneal crystals in this case
148 was also in line with the previously reported high prevalence of purely retinal involvement
149 in Asians.³ The disruption of the foveal ellipsoid zone may explain the subjectively worse
150 vision in the left eye, but it was not reflected in the generally symmetric full-field
151 electroretinogram and multifocal electroretinogram responses. Whether structural deficit
152 precedes functional deficits, or vice versa, warrants further study.

153 Although Bietti crystalline dystrophy often onsets between the second and fourth decades,²
154 the disease progression rate varies between individuals but prognosis is poor as the
155 condition may ultimately result in blindness.⁴ Classically, the disease is categorized into
156 three stages: (1) retinal pigment epithelium atrophy with fine-sized crystalline deposits near
157 the macular area; (2) retinal pigment epithelium atrophic areas enlarged and extended
158 beyond the posterior pole, while choriocapillaris atrophy is present on the posterior pole; (3)
159 extensive retinal pigment epithelium -choriocapillaris atrophy over the fundus.¹¹ Despite
160 the good visual acuity and full-field electroretinogram responses, this patient was currently

161 classified as stage 2, because the retinal pigment epithelium atrophy reached beyond the
162 posterior pole.

163 Furthermore, the incurable nature of the disease may lead to a blinding prognosis. Recent
164 research shed light on epigenetic factor modifications, as well as gene therapies to provide
165 possible therapeutic effect on retinal dystrophies including Bietti crystalline dystrophy.¹²⁻¹⁴
166 With a clinical database registry with genetic and lifestyle information, the epigenetic
167 research could be accelerated to promote patient care and health care planning.⁴

168 An early diagnosis of Bietti crystalline dystrophy may sometimes be difficult because of
169 the asymptomatic nature of the early stages.⁴ As funduscopy findings can sometimes be
170 misidentified as other less significant signs, such as scattered drusens, the use of proper
171 clinical equipment can facilitate a more accurate diagnosis.^{9, 10} In this case, the patient was
172 referred to the clinic to check for retinitis pigmentosa, for which a full-field
173 electroretinogram and electro-oculogram were ordered at the first visit, as in regular cases.
174 However, her full-field electroretinogram appeared normal, especially in scotopic condition,
175 while the electro-oculogram was compromised, which has previously been reported as an
176 atypical form of electro-retinal responses found in Bietti crystalline dystrophy.¹⁵ Hence, a
177 multifocal electroretinogram was useful to detect localized changes, as it revealed a
178 compromised central retinal function in this patient.

179 Optometrists, as primary eye care providers, are well capable of diagnosing and managing
180 common ocular diseases such as glaucoma, macular degeneration, and diabetic retinopathy,
181 which can also be aided with advanced diagnostic technologies. Occasionally, patients with
182 rare ocular diseases could be encountered. In such cases, utilizing the advance diagnostic

183 tools may enhance eye care practitioners' competency and confidence in their diagnosis and
184 management.¹⁶ The techniques applied in the current case report, optical coherence
185 tomography and electroretinography, are gaining importance in optometric practice, as they
186 are useful for diagnosis of clinical conditions including glaucoma, macular degeneration,
187 and diabetic retinopathy and for distinguishing symptomatically similar retinal and
188 neurological disorders.^{17, 18} In particular, due to the quantified nature of the outcomes,
189 longitudinal monitoring of disease progression and comparison with normative data has
190 highlighted their clinical significance. While the scope of practice of optometrists is rather
191 diversified in different countries, ranging from only refractive corrections to therapeutic
192 practice, most optometrists are eligible to use diagnostic drugs, including local anaesthetics,
193 mydriatic, and cycloplegic agents.¹⁹ In addition to slit-lamp biomicroscopy and funduscopy,
194 access to advanced diagnostic ophthalmic equipment, for example the forementioned
195 optical coherence tomography and electroretinography, has become more common,²⁰⁻²²
196 aiding eye care providers in making a prompt diagnosis to benefit patients with respect to
197 disease management and economic savings.²³ The increasing revenue generated for the
198 practitioners in the past two decades may have also provided extra incentives for improved
199 equipping of optometry practices in the private sector. According to the report, assuming
200 the revenue per scan was USD44 each for 30 minutes in 8 hours per day, a 100% utilization
201 of an optical coherence tomography device would generate USD200k every year. Even
202 with a reduced utilization rate and other operational costs, the initial cost of the instrument
203 of approximately USD60k, the return on capital would still be attractive to investors.²⁴

204 With rapid technological developments, currently “advanced” equipment gradually
205 becomes commonplace, enabling financial and spatially economic equipment,²⁵ which are
206 capable of performing the same task as their bulky counterparts,²⁶ or combining multi-
207 functions in a single piece of equipment. For instance, a handy and affordable visual
208 electrodiagnostic tool was developed recently, which eliminated the need for complicated
209 electrode setups, or even mydriasis.²⁷ The authors also speculate that the maturation of 3-
210 dimensional printing technique and the use of open-source hardware²⁸ may accelerate the
211 process of universalising the “advanced” diagnostic equipment in not only research
212 institutes, but also primary eye care providers as end users.

213 In conclusion, Bietti crystalline dystrophy is a rare chorioretinal dystrophy, which can
214 sometimes be difficult to identify and diagnose. Although the outcome for this patient may
215 not differ from being diagnosed 1.5 years later in the public hospital, a prompter diagnosis
216 can ameliorate patient anxiety, as well as improve patient loyalty. On the other hand, many
217 other rare conditions would have the prognosis deteriorated with a delayed diagnosis and
218 management. Utilizing the advanced diagnostic tools in optometric practices should be
219 considered to maximize the scope of practice, which can be beneficial to both the
220 optometrists and patients with ocular diseases.

221

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290 **FIGURE LEGENDS**

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293 field electroretinogram, EOG = Electro-oculogram, mfERG = Multifocal electroretinogram,
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297 C: Photopic 3.0 response; D: Photopic 30 Hz flicker responses) and E: Electro-oculogram

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