The cone dysfunction syndromes

Jonathan Aboshiha,1,2 Adam M Dubis,1,2 Joseph Carroll,3 Alison J Hardcastle,1,2 Michel Michaelides1,2

ABSTRACT

The cone dysfunction syndromes are a heterogeneous group of inherited, predominantly stationary retinal disorders characterised by reduced central vision and varying degrees of colour vision abnormalities, nystagmus and photophobia. This review details the following conditions: complete and incomplete achromatopsia, blue-cone monochromatism, oligocone trichromacy, bradyopsia and Bornholm eye disease. We describe the clinical, psychophysical, electrophysiological and imaging findings that are characteristic to each condition in order to aid their accurate diagnosis, as well as highlight some classically held notions about these diseases that have come to be challenged over the recent years. The latest data regarding the genetic aetiology and pathological changes observed in the cone dysfunction syndromes are discussed, and, where relevant, translational avenues of research, including completed and anticipated interventional clinical trials, for some of the diseases described herein will be presented. Finally, we briefly review the current management of these disorders.

INTRODUCTION

The cone dysfunction syndromes (CDS) are a collection of heterogeneous inherited conditions, both in terms of their clinical characteristics and molecular genetic basis. They represent an important cause of lifelong visual impairment, with inherited retinal disorders being the second most common cause of legal blindness in childhood and the leading cause among the working-age population in England and Wales.1 CDS have varying modes of genetic inheritance and have been classically described as stationary conditions in contrast to the progressive cone dystrophies.2 3

Clinically, CDS are characterised by presentation at birth/early infancy with visual loss and variable degrees of colour vision abnormalities, nystagmus and photophobia, all of which reflect the dysfunction of the foveally concentrated cone cells that constitute approximately 5% of human photoreceptors. Given that these disease characteristics have an early onset and severely impair important behaviours of daily living such as facial recognition, reading and daylight vision, the consequent debilitating impact on patients’ lives is considerable.

In this review, we describe the phenotypic and genotypic features of CDS (excluding those solely of colour vision deficiency), including complete and incomplete achromatopsia (ACHM), blue-cone monochromatism (BCM), oligocone trichromacy (OT), bradyopsia and Bornholm eye disease (BED) (table 1). Given the new era of gene therapy interventions in human retinal disease,4 we will also briefly review the management and latest progress towards developing effective treatments.

CONE DYSFUNCTION SYNDROMES

Complete achromatopsia

Complete ACHM (syn. typical ACHM or rod monochromatism) is an autosomal-recessive condition associated with a lack of cone function,5 which affects about 1 in 30 000 people.6 It is characterised by presentation at birth/early infancy with pendular nystagmus, poor visual acuity (approximately logarithm of the minimum angle of resolution (logMAR) 1.0), a lack of colour vision and marked photophobia/hemeralopia. Patients may also demonstrate paradoxical pupillary constriction when transitioned from light to dark ambient conditions; the so-called Flynn phenomenon.9 Electroretinography (ERG) typically demonstrates absent cone responses and normal rod responses,8 and psychophysical testing also reveals normal rod function but absent cone function.9 Hypermetropic refractive errors are common10 and fundus appearance is often normal, although macular changes can be observed that range from subtle retinal pigment epithelium (RPE) abnormalities to atrophy.

To date, five genes have been associated with ACHM, all encoding components of the cone-specific phototransduction cascade. Disease-causing sequence variants in these genes have been estimated to account for approximately 90% of ACHM cases.11 The first discovered, and most common, of these genes are CNGA312 and CNGB313 which encode the α-subunits and β-subunits of the cGMP-gated cation channel, respectively. CNGB3 mutations were first identified in a population of Micronesian islanders where the prevalence of complete ACHM was up to 3000 times that of other general populations; this was thought to be due to a typhoon that devastated the island in the 18th century;14 with all affected islanders able to trace their ancestry to a single typhoon survivor.13 Mutations in these two genes account for approximately 80% of all complete ACHM cases.2 15–17

The most frequently identified mutation in CNGB3 is the 1 base pair frameshift deletion c.1148delC (p Thr383Ile fs*13), which accounts for >70% of CNGB3 disease-causing alleles.16–18 There is far greater allelic heterogeneity in CNGA3 disease-causing variants (over 80 described) compared with CNGB3 (∼40). The majority of CNGB3 variants identified to date are nonsense mutations, in direct contrast to the high proportion of missense mutations observed in CNGA3, suggesting that mutations that compromise the structural and functional integrity of the CNGA3 α-subunits are less well tolerated.
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Prevalence</th>
<th>Mode of inheritance</th>
<th>Typical BCVA (logMAR)</th>
<th>Typical refractive error</th>
<th>Nystagmus</th>
<th>Fundus findings</th>
<th>Colour vision</th>
<th>Typical ERG findings</th>
<th>Functional photoreceptors</th>
<th>Associated gene(s) (cytogenetic location)</th>
<th>Successful rescue of animal model/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete achromatopsia syn. typical achromatopsia; rod monochromatism</td>
<td>1 in 30 000</td>
<td>Autosomal recessive</td>
<td>1.0</td>
<td>Often hypermetropic</td>
<td>Present</td>
<td>Usually normal</td>
<td>Absent</td>
<td>Absent cone responses; often normal rod responses</td>
<td>LW-cones: no; MW-cones: no; SW-cones: no; Rads: yes</td>
<td>CNGA3 (2q11.2); CNGB3 (8q21-q22); GNAT2 (1p13); PDE6C (10q24); PDE6H (12p13)</td>
<td>Yes</td>
</tr>
<tr>
<td>Incomplete achromatopsia syn. atypical achromatopsia</td>
<td>Uncertain</td>
<td>Autosomal recessive</td>
<td>0.6–1.0</td>
<td>Often hypermetropic</td>
<td>Present</td>
<td>Usually normal</td>
<td>Residual</td>
<td>Reduced or absent cone responses; often normal rod responses</td>
<td>LW-cones: possible; MW-cones: possible; SW-cones: possible; Rads: yes</td>
<td>CNGB3 (2q11.2); CNGB1 (8q21-q22); GNAT2 (1p13)</td>
<td>Yes</td>
</tr>
<tr>
<td>Blue-cone monochromatism syn. S-cone monochromatism; X-linked incomplete achromatopsia; X-linked atypical achromatopsia</td>
<td>1 in 100 000</td>
<td>X-linked recessive</td>
<td>0.6–1.0</td>
<td>Often myopic</td>
<td>Present</td>
<td>Usually myopic</td>
<td>Residual tritan discrimination</td>
<td>Reduced cone responses but with preserved S-cone responses; normal rod responses</td>
<td>LW-cones: no; MW-cones: no; SW-cones: yes; Rads: yes</td>
<td>Principal opsin array mutational mechanisms on Xq28: (i) LCR deletion (approx. 40% cases) (ii) Non-homologous recombination between OPN1LW/OPN1MW resulting in a single gene in the array with a subsequent inactivating point mutation (approximately 60% of cases)</td>
<td>Yes</td>
</tr>
<tr>
<td>Oligocone trichromacy</td>
<td>Uncertain</td>
<td>Autosomal recessive</td>
<td>0.2–0.6</td>
<td>Equal prevalence of myopia and hypermetropia</td>
<td>Often absent</td>
<td>Normal</td>
<td>Normal</td>
<td>Reduced or absent cone responses; normal rod responses</td>
<td>LW-cones: yes; MW-cones: yes; SW-cones: yes; Rads: yes</td>
<td>Possibly hypomorphic variants in the genes associated with achromatopsia</td>
<td>No</td>
</tr>
<tr>
<td>Bradyopsia syn. RGS9/R9AP-retinopathy</td>
<td>Rare</td>
<td>Autosomal recessive</td>
<td>0.2–0.6</td>
<td>Equal prevalence of myopia and hypermetropia</td>
<td>Often absent</td>
<td>Normal</td>
<td>Normal</td>
<td>Reduced/absent cone responses; the rod-specific ERG and the SBWF with ISI of 2 min are normal—however, the SBWF ERG with an ISCEV standard ISI of 20 s shows amplitude reduction, which is progressively less severe with increasing ISI, consistent with delayed recovery following the flash—thereby demonstrating the need for more extended testing than that mandated by ISCEV in the ERG Standard protocol</td>
<td>LW-cones: yes; MW-cones: yes; SW-cones: yes; Rads: yes</td>
<td>RGS9 (17q23-q24); R9AP (19q13.11)</td>
<td>No</td>
</tr>
<tr>
<td>Bornholm eye disease syn. X-linked cone dysfunction syndrome with dichromacy and myopia</td>
<td>Uncertain</td>
<td>X-linked recessive</td>
<td>0–0.8</td>
<td>Moderate to high myopia with astigmatism</td>
<td>Absent</td>
<td>Usually myopic</td>
<td>Deuteranopia or protanopia</td>
<td>Reduced cone responses; normal rod responses</td>
<td>LW-cones: yes, when observed with deuteranopia; no, when observed with protanopia; MW-cones: yes, when observed with protanopia; SW-cones: yes, when observed with protanopia; no, when observed with deuteranopia</td>
<td>LM interchange haplotypes (opsin array on Xq28)</td>
<td>No</td>
</tr>
</tbody>
</table>

BCVA, best-corrected visual acuity; ERG, electroretinography; ISCEV, International Society for Clinical Electrophysiology of Vision; ISI, inter-stimulus interval; LCR, locus control region; logMAR, logarithm of the minimum angle of resolution; LW, long wavelength; MW, middle wavelength; SBWF, single bright white flash; SW, short wavelength; syn., synonym(s).
Disease-causing variants have been subsequently identified in (chronological order) GNAT2,19 which encodes the α-subunit of transducin (10 variants identified), PDE6C,20 encoding the α-subunit of cGMP phosphodiesterase (19 variants identified), and PDE6H,21 which encodes the inhibitory γ-subunit of the same enzyme (two variants identified). The genes GNAT2, PDE6C, and PDE6H each comprise <2% of ACHM cases.19 21 22

In terms of functional and imaging assessment, there are no generalisable differences identified between the phenotype associated with the two most common complete ACHM genotypes (ie, CNGA3 and CNGB3), although there is a marked degree of phenotypic variation observed within the genotypes.18 21 24 Spectral-domain optical coherence tomography (SD-OCT) imaging reveals a wide spectrum of photoreceptor integrity, ranging from a continuous inner segment ellipsoid (ISe) band at the fovea to outer retinal atrophy, and these findings have been both qualitatively and quantitatively assessed.23 28 30 Adaptive optics scanning light ophthalmoscopy (AOSLO) allows direct visualisation of individual human cone and rod photoreceptors in vivo,29 32 and has identified residual cone structure in the majority of ACHM subjects imaged, although most of the cones have reduced reflectance and many ‘dark’ spaces are observed in the photoreceptor mosaic.23 31 32 More recently, split detection (non-confocal) imaging techniques have been coupled with existing AOSLO in order to visualise inner segment structure within the majority of the aforementioned ‘dark’ spaces seen on confocal AOSLO.31 These imaging results support the idea that cone structure in ACHM is disrupted, but not absent, and the degree of residual cone structure is highly variable between patients. These observations have significant implications for anticipated gene therapy clinical trial design in terms of patient selection and monitoring efficacy. Although no differences have been identified between CNGA3 and CNGB3 genotypes,23 24 there is evidence that the GNAT2 genotype may be associated with a greater degree of preservation of outer retinal architecture on SD-OCT and AOSLO assessment,32 and may retain residual cone function.34

ACHM in humans has been classically described as a non-progressive disease.2 7 16 35 36 Cross-sectional and longitudinal studies have found evidence of cone cell loss and/or progression over time,27 37–41 although this is likely to occur very slowly, to a limited degree, and is also highly variable between patients with no definite age-dependency or genotype association.53 24 41

Rod photoreceptor function in ACHM has been classically described as normal,7 42 although a number of studies have now reported abnormalities in rod-driven ERG responses13 23 37 41 44 and rod-derived dark-adaptation functions.43 46 It is not yet clear whether a lack of functional cones might affect the rod photoreceptors themselves47 or the neural pathways that subserve them.44 48 49

Several studies have demonstrated the effectiveness of using gene-based or alternative therapeutic approaches to restore cone function in multiple animal models of ACHM of various genotypes.50–54 Given these promising results in animal models of the disease, there are plans to begin human gene replacement trials in the near future. One alternative therapeutic approach has been that of a recent phase I/II clinical study55 that delivered intravitreal ciliary neurotrophic factor to achromats with biallelic CNGB3 variants; this failed to show any enhancement of cone function, although it has been suggested that the lack of assessment of residual cone number and placement during patient selection may have been a limiting factor in this study.56

Incomplete achromatopsia

A small subset of patients with ACHM have an incomplete form of ACHM associated with residual colour vision as detected by psychophysical methods57 58 and mildly better visual acuity (logMAR 0.6–1.0) than complete achromats.2 39

The first genotype to be associated with incomplete ACHM was CNGA3.3 41 It has been suggested that the CNGA3 genotype might be unique in demonstrating residual cone function, given that most known CNGB3 and GNAT2 mutations (which constitute the two other most common ACHM genotypes by prevalence) result in premature termination and therefore in truncated and presumably non-functional proteins.3 However, both GNAT2 and CNGB3 patients have now been reported who appear to show residual cone function, as demonstrated by psychophysical tests, such as the Ishihara pseudoisochromatic colour plates and anomaloscope colour-matching tests, and/or residual cone ERG responses.23 34 37 60 This finding in the latter genotype might not be entirely unexpected, given that CNGA3 subunits alone have been shown to form functional homo-oligomeric channels in vitro.61

Blue-cone monochromatism

This X-linked recessive condition is characterised by an absence of long (L)- (red) and middle (M)- (green) wavelength-sensitive cone function, the opsin for which are both encoded on the X-chromosome, while the short (S)- (blue) wavelength-sensitive opsin gene is located on chromosome 7.62 The prevalence is approximately 1 in 100 000, and affected males with BCM typically present at birth/early infancy with reduced visual acuity (logMAR 0.6–1.0), photophobia, nystagmus and are often myopic.63 Fundus examination reveals an otherwise normal myopic retina, but macular retinal pigment epithelial disturbance and atrophy have been noted in older patients.64 Vision in BCM is subserved by rod and S-cone photoreceptors alone, and consequently patients retain tritan discrimination,63 which has been reported to deteriorate with increasing illuminance.65 BCM can be clinically distinguished from ACHM by psychophysical and ERG assessment, with BCM demonstrating a profoundly reduced (but detectable) photopic ERG response and a preserved S-cone ERG,66 as well as by a corroborative family history, given the different modes of inheritance of the two conditions, and the often different refractive error. Nevertheless, the clinical distinction can be challenging in early infancy in a male patient and may not be definitively made until they are old enough to undertake detailed colour vision or ERG testing; the increased availability of genetic testing can now help to clarify the diagnosis.

The disease-causing variants in BCM fall into one of several categories, with the first two being the principal mechanisms: (i) a one-step pathway whereby the locus control region (LCR) is partially or completely deleted, thereby abolishing transcription of the opsin gene array27 (LCR is located upstream of the L-opsin gene array (OPN1LW) and M-opsin gene array (OPN1MW) genes, and controls transcription of the opsin array, resulting in only one opsin gene being expressed in any one photoreceptor28–30); (ii) a two-step mutation pathway, with the first step being non-homologous recombination between the L-opsin and M-opsin gene arrays resulting in a single-opsin gene in the array (often a hybrid gene), followed by a subsequent inactivating mutation (most commonly a missense variant) leading to a loss of functional L-cones and M-cones (the C203R missense mutation in a single L–M hybrid gene being the most frequently reported genotype28); (iii) the deletion of an entire exon in a single-opsin...
array gene,63 69 or (iv) gene conversion transferring a mutation between OPN1LW and OPN1MW.70

SD-OCT analysis of patients with BCM has shown significant, although variable, macular thinning,25 71 72 with focal ISe disruption observed in an area corresponding to the normal S-cone-free zone.71 Despite having been traditionally described as a stationary condition, Cideciyan et al62 noted a trend towards increased thinning of the foveal outer nuclear layer in older patients with BCM, and other studies have also found evidence of progression in BCM.63 87 73 There is evidence that patients with LCR deletions are more likely to have a typical non-progressive BCM phenotype.79

Confocal AOSLO imaging has demonstrated a disrupted cone mosaic with a reduced number of cones at the fovea (both reflective S-cones and non-reflective L-cones and M-cones) to that of about 25% of normal in non-LCR-related BCM, with evidence of greater loss of cone cells in LCR deletion-related BCM.71 72 In addition to the identification of residual cone structure, there is also potential for intervention in the future given the fact that gene replacement therapy in adult dichromatic monkeys lacking the L-opsin gene has been shown to produce trichromatic visual behaviour77 and has also demonstrated restoration of cone function in a rat model of BCM.76

Oligocone trichromacy

OT is characterised by severe impairment of cone function on ERG assessment coupled with normal or near-normal colour discrimination. It was first described in 1973 by Van Lint,77 who reported a boy that, despite his poor vision and reduced photopic ERG responses, had nearly normal colour vision. This was hypothesised to be due to a low number of normal functioning cones (from the Greek oligos for ‘few’), which retained their normal distribution proportions between the three cone types, hence preserving trichromatic vision. It is believed to be an autosomal-recessive condition, wherein patients present in early childhood with mild photophobia, nystagmus which may or may not be present, reduced visual acuity (logMAR 0.3–0.6), normal fundi and normal rod responses on ERG.78 79 Cone ERGs are markedly reduced, with ERG evidence in some cases of predominantly inner retinal dysfunction.78 Strikingly, however, despite these features of a CDS, colour vision is largely within normal limits, which may result in underascertainment of cases of OT. Using foveal densitometry measurements, Keunen et al80 argued that these patients possessed a reduced number of foveal cones that otherwise retained normal function. Goldmann visual fields are normal,60 79 with reports of generalised retinal sensitivity reduction with Humphrey static visual field testing.81 Although believed to be predominantly stationary,77 there is some evidence that in some patients at least there may be progression.78

The underlying molecular genetic basis remains uncertain. OT and/or a ‘marked incomplete ACHM-like’ phenotype have been reported in association with ‘hypomorph’ mutations in the ACHM genes CNGA3,81 82 CNGB3,79 78 PDE6C78 and GNA T2.80 However, some of these cases arguably have features more in keeping with incomplete ACHM per se rather than OT. In addition, only single heterozygous missense variants have been identified in other subjects, thereby rendering their significance currently unclear. Nevertheless, OT is likely to be heterogeneous both genotypically and phenotypically,7 78 79 in keeping with other CDS and inherited retinal disease as a whole. This heterogeneity has been further elucidated by Michaelides et al,8 who used adaptive optics (AO) and SD-OCT to assess the integrity of the cone photoreceptor mosaic and found that patients examined with a typical OT phenotype had a reduced number of functional cones at the fovea with no structure visible outside the central fovea, thereby confirming the original hypothesis of the underlying basis of OT; whereas patients with an OT-like phenotype had a normal cone mosaic in terms of cone density and distribution, thus suggesting that in these latter cases the cones present are dysfunctional. This study also identified that OT and bradypia (RGS9/R9AP-associated retinopathy) cannot be distinguished on the basis of clinical findings alone, with both being associated with normal colour vision.83

Extended ERG testing beyond International Society for Clinical Electrophysiology of Vision (ISCEV) standard testing is needed to identify the pathognomonic electrophysiological findings in bradypia (see the following section).34–36,87 There is evidence that these disorders can also be distinguished with high-resolution AO imaging, with patients harbouring RGS9/R9AP variants having an intact cone photoreceptor mosaic compared to patients with OT.85 86

Bradyopia

This condition was first reported in 1991 in four Dutch patients, who demonstrated an abnormally long interval of suppression in their ERG amplitude responses to the second of a pair of bright stimuli flashes. This was postulated to be due to a deficit in the normally fast regeneration of the visual pathway signalling processes.86 The term bradypia (Greek for slow vision) was devised in 2004 to describe this stationary retinal phenotype, wherein affected patients had difficulty in adapting to sudden changes in cone-mediated luminance levels and difficulty in seeing moving objects.84 However, it is now clear that these symptoms can also be seen in many other disorders of cone function including OT.85 Onset is in early childhood and is associated with delayed dark and light adaptation, mild photophobia, moderately reduced visual acuity, normal colour vision and normal fundi.85 88 89 In patients with bradypia, the rod-specific ERG, the red flash ERG under dark adaptation (both an early cone and later rod system component) and the single bright white flash (SBWF) with inter-stimulus interval (ISI) of 2 min are all normal. The SBWF ERGs with an ISCEV standard ISI of 20 s show amplitude reduction, which is progressively less severe with increasing ISI, consistent with delayed recovery following the flash, demonstrating the need for an extended ISI to obtain full recovery of the ERG following the previous flash.85 A generalised reduction or absence of cone responses is observed (pattern ERG, 30 Hz flicker and photopic ERGs).85

A similar murine ERG phenotype was subsequently identified wherein the affected mice lacked the protein RGS9. This protein significantly accelerates the hydrolysis of the α-transducin bound guanosine triphosphate to guanosine diphosphate, thus deactivating the enzyme cGMP-phosphodiesterase and causing a rise in cGMP within the photoreceptor, consequently allowing the cGMP-gated cation channels to re-open.86 A further protein, R9AP, anchors RGS9 to photoreceptor outer segment disc membranes and enhances its activity by up to 70-fold.91 Thus, RGS9 and R9AP play critical roles in enabling the rapid recovery of the phototransduction cascade after light stimulation. Recessive mutations in the genes encoding these two proteins, namely RGS9 and R9AP, have since been identified in humans.84 85 88 89 To date, 1 missense84 and 1 nonsense mutation85 have been reported in RGS9, while 5 insertions/deletions have been reported in R9AP.84 85 88

Patients with either RGS9/R9AP retinopathy or OT have very similar clinical phenotypes, characterised by stationary cone dysfunction, mild photophobia, normal colour vision and normal
fundi. However, cellular imaging may be an effective way to distinguish between these conditions: AOSLO imaging of OT reveals a sparse mosaic of cones remaining at the fovea; in direct contrast, RGS9/R9AP-retinopathy patients have a normal cone photoreceptor mosaic.81 87 This is in keeping with findings from dark-adapted flicker ERGs performed with a dim stimulus that show a normal response initially, which becomes undetectable after 10 s stimulation, in RGS9/R9AP-retinopathy patients,81 87 suggesting that cones are not only present (as demonstrated by AOSLO) but are capable of normal function and thus potentially amenable to rescue.

**Bornholm eye disease**

BED was first described in a large family that originated from the Danish island of Bornholm.92 Affected members displayed X-linked recessive infantile myopia/astigmatism and impaired visual acuity, with signs of optic nerve head hypoplasia, retinal pigmentary changes, deuteranopia and reduced cone responses on ERG.92 93 Since then, patients with protanopic BED have also been identified94 95 and the disorder can now be described as an X-linked CDS associated with myopia and dichromacy.

The condition was mapped by linkage analysis to Xq28 in the original Danish family.93 Subsequent genetic interrogation has shown that rare haplotypes (‘L/M interchange haplotypes’) at polymorphic positions in exon 3 of the opsin genes, that result from intermixing between L- and M-opsin genes, are the principal underlying genetic basis of BED.74 96 Some of these interchange haplotypes have been shown to result in aberrant splicing of the opsin genes and a variable degree of exon 3 skipping.74 97

There is SD-OCT and AOSLO evidence that patients with BED demonstrate reduced retinal thickness and a significantly disrupted cone mosaic, although to a variable degree, and the suggestion has been made that the number of cones expressing the aberrant pigment (given that there can be more than a 30-fold range in the L:M cone ratio between individuals98) may determine whether the aforementioned polymorphic opsin variants lead to the generalised cone dysfunction observed in BED.99

**MANAGEMENT OF CDS**

Although there are now promising results for therapeutic intervention in other inherited retinal conditions in humans, and successful rescue of animal models in some CDS has been demonstrated, there are at present no proven treatments. Current management includes correct diagnosis, increasingly aided by molecular genetic testing, in order to offer accurate prognosis and genetic counselling, as well as refractive correction, low visual aids and educational support. Tinted lenses can help with disabling photophobia, improving both ocular comfort and quality of vision, for example, deep red tints in ACHM to reduce rod saturation, or magenta tints in BCM that aid with disabling photophobia, improving both ocular comfort and quality of vision, for example, deep red tints in ACHM to reduce rod saturation, or magenta tints in BCM that would in addition preserve transmission of blue light.100 An accurate molecular genetic diagnosis is becoming increasingly possible and pertinent, given the likely significance this will have in directing future gene therapy. This, allied with research in other modes of intervention such as neuroprotection and pharmacological approaches, means that hopefully a new era is dawning where these hitherto untreatable conditions may be amenable to successful intervention.

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JA drafted the manuscript and provided critical revision. MM conceived and supervised the manuscript, and provided critical revision. AMD, JC and AJH provided critical revision of the manuscript.

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