Guidelines in CHARGE syndrome and the missing link: Cranial imaging

Christa M. de Geus1,2 | Rolien H. Free1,3 | Berit M. Verbiest4,5 | Deborah A. Sival1,6 | Kim D. Blake7,8 | Linda C. Meiners1,9 | Conny M. A. van Ravenswaaij-Arts1,2

1 University of Groningen, University Medical Center Groningen, Center of Expertise for CHARGE syndrome, Groningen, The Netherlands
2 University of Groningen, University Medical Center Groningen, Department of Genetics, Groningen, The Netherlands
3 University of Groningen, University Medical Center Groningen, Department of ENT, Groningen, The Netherlands
4 Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands
5 Department of Radiology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands
6 University of Groningen, Beatrix Children’s Hospital, University Medical Center Groningen, department of Pediatrics, Groningen, The Netherlands
7 IWK Health Centre, Halifax, Nova Scotia, Canada
8 Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada
9 University of Groningen, University Medical Center Groningen, Department of Radiology, Groningen, The Netherlands

"CHARGE syndrome" is a complex syndrome with high and extremely variable comorbidity. As a result, clinicians may struggle to provide accurate and comprehensive care, and this has led to the publication of several clinical surveillance guidelines and recommendations for CHARGE syndrome, based on both single case observations and cohort studies. Here we perform a structured literature review to examine all the existing advice. Our findings provide additional support for the validity of the recently published Trider checklist. We also identified a gap in literature when reviewing all guidelines and recommendations, and we propose a guideline for neuroradiological evaluation of patients with CHARGE syndrome. This is of importance, as patients with CHARGE are at risk for peri-anesthetic complications, making recurrent imaging procedures under anesthesia a particular risk in clinical practice. However, comprehensive cranial imaging is also of tremendous value for timely diagnosis, proper treatment of symptoms and for further research into CHARGE syndrome. We hope the guideline for neuroradiological evaluation will help clinicians provide efficient and comprehensive care for individuals with CHARGE syndrome.

KEYWORDS
CHARGE syndrome, CHD7, CT, guidelines, MRI

1 INTRODUCTION

CHARGE syndrome is a relatively frequently occurring genetic syndrome with an estimated incidence of 1 in 15,000. It is a very complex syndrome with a broad phenotype that can involve almost all organ and sensory systems. As a result, comorbidity is high and extremely variable. There is also a striking variability in severity, with both very mild cases and severe early lethal cases going undiagnosed. The clinical challenge of such a complex disorder is that some clinical problems may remain undiagnosed as other more severe or even life-threatening complications consume all medical attention. The diverse clinical aspects of CHARGE syndrome have been studied by several groups worldwide, resulting in extremely...
useful guidelines and recommendations. For this special issue of the American Journal of Medical Genetics (part C), we have examined these guidelines by performing a structured literature search and reviewing the existing advice, including that of hallmark papers by Blake et al. (1998) and the clinical checklist published recently by Trider (see Figure 1, (Trider, Arra-Robar, van Ravenswaaij-Arts, & Blake, 2017)).

To date, no guidelines for cranial imaging in CHARGE syndrome have been published, but we see two important reasons why there is a need for such a guideline. First, in our experience and that of others, cranial imaging in individuals with CHARGE syndrome is often performed incompletely or with insufficient resolution. As a result, some of the cranial malformations occurring in CHARGE syndrome

![CHARGE SYNDROME CHECKLIST: HEALTH SUPERVISION ACROSS THE LIFESPAN (FROM HEAD TO TOE)](image)

**FIGURE 1** The Trider checklist. Republished (with permission) from Trider C-L, Arra-Robar A, van Ravenswaaij-Arts C, Blake K. 2017. Developing a CHARGE syndrome checklist: Health supervision across the lifespan (from head to toe). American Journal of Medical Genetics Part A, 173A, 684–691. A PDF of the checklist is available for download from https://www.chargesyndrome.org/wp-content/uploads/2016/03/CHARGE-Syndrome-Checklist.pdf.
| Recommendation                                                                 | References                                                                 | Trider checklist |
|-------------------------------------------------------------------------------|---------------------------------------------------------------------------|-----------------|
| **Genetics**                                                                  |                                                                           |                 |
| CHARGE is a clinical diagnosis                                                | Bergman, Janssen, et al. (2011); Blake et al. (1998); Harris, Robert, Kallen (1997); Issenutz, Prasad, Smith, and Blake (2005); Verloes (2005) | Yes             |
| CHD7 testing can confirm uncertain diagnosis in mildly affected patients      | Bergman, Janssen, et al. (2011)                                           | Yes             |
| CHD7 testing may be performed according to flow diagram                      | Bergman, Janssen, et al. (2011)                                           | Yes             |
| A genome-wide array should be performed in patients with CHARGE syndrome but without a CHD7 mutation | Corsten-Janssen et al. (2013)                                             | Yes             |
| Clinical genetics consultation is indicated, including options for prenatal diagnosis | Bergman, Janssen, et al. (2011); Lalani, Hefner, Belmont, and Davenport (2012) | Yes             |
| Patients diagnosed with hypogonadotropic hypogonadism and anosmia should be screened for clinical features consistent with CHARGE syndrome | Jongmans et al. (2009)                                                   | Out of scope   |
| Olfactory bulb hypoplasia and semicircular canal aplasia should be considered major signs for CHARGE syndrome | Asakura et al. (2008); Sanlaville et al. (2006)                           | Out of scope   |
| If a parent has any features of CHARGE syndrome, molecular genetic testing is appropriate if a CHD7 pathogenic variant has been identified in the proband | Jongmans et al. (2008)                                                   | Out of scope   |
| CHD7 analysis should be performed in patients with a 22q11.2 deletion phenotype without TBX1 haploinsufficiency | Corsten-Janssen et al. (2013)                                             | Out of scope   |
| CHD7 analysis should be performed in patients with Kallmann syndrome who have at least two additional CHARGE features or semicircular canal anomalies | Bergman et al. (2012); Costa-Barbosa et al. (2013); Jongmans et al. (2009); Marcos et al. (2014) | Out of scope   |
| CHD7 analysis should be included in massive parallel sequencing gene panels for diagnostics in syndromic heart defects | Corsten-Janssen et al. (2014)                                             | Out of scope   |
| CHD7 analysis should not be performed routinely in patients with only atrial septal defect or conotruncal heart defects | Corsten-Janssen et al. (2014)                                             | Out of scope   |
| CHD7 analysis should not be performed in septo-optic dysplasia without features of CHARGE | Gregory et al. (2013)                                                   | Out of scope   |
| MLPA analysis is indicated if no causal CHD7 is mutation found (contrary to Bergman et al., 2008) | Wincent et al. (2008); Wincent, Schulze, and Schoumans (2009) | Out of scope   |
| MLPA analysis not indicated if no CHD7 mutation found (contrary to Wincent et al., 2009 and 2008) | Bergman et al. (2008)                                                   | Out of scope   |
| **Neurology**                                                                 |                                                                           |                 |
| MR imaging of the brain should be performed (semicircular canals, olfactory structures, pituitary and the basiocciput) | Asakura et al. (2008); Fujita et al. (2009); Gregory et al. (2013) | Yes             |
| Temporal bone CT scan should be performed (pathology of middle ear, inner ear, cranial nerves, semicircular canals, aberrant course of blood vessels or cranial nerves) | Asakura et al. (2008); Vesseur, Verbist, et al. (2016) | Yes             |
| Anticonvulsants are indicated if overt epilepsy is seen                        | Bergman, Janssen, et al. (2011)                                           | Yes             |
| EEG is indicated when seizures are observed clinically                         | Bergman, Janssen, et al. (2011)                                           | Yes             |
| Assessment of cranial nerve function (physical examination and swallowing studies) is indicated | Bergman, Janssen, et al. (2011); Blake et al. (2008); Lalani et al. (2012); (Continues)| Yes             |
| Recommendation                                                                 | References                                                                 | Trider checklist |
|-------------------------------------------------------------------------------|----------------------------------------------------------------------------|------------------|
| Eyes, ears, nose, and throat                                                  |                                                                            |                  |
| Assess patency of choanae (CT scan or nasal endoscopy), surgical correction   | Bergman, Janssen, et al. (2011); Lalani et al. (2012)                       | Yes              |
| Evaluate for cleft palate and tracheo-esophageal anomalies, surgical correction| Bergman, Janssen, et al. (2011); Issekutz et al. (2005); Stack and Wyse      | Yes              |
| In infants, brain stem auditory evoked response (BAER) is indicated to evaluate hearing as soon as the infant is medically stable | Bergman, Janssen, et al. (2011); Edwards, Kileny, and Van Riper (2002);     | Yes              |
| In older children and adults, hearing evaluation as appropriate for age and developmental status is indicated | Lalani et al. (2012)                                                      |                  |
| Hearing habilitation (e.g., hearing aids, bone-anchored hearing aid, cochlear implantation, sign language, auditory and communication training) should be started as soon as hearing loss is documented and, if possible, before the age of three | Blake and Brown (1993); Edwards et al. (2002); Thelin and Fussner (2005)    | Yes              |
| Grommet placement for chronic serous otitis                                  | Bergman, Janssen, et al. (2011); Lalani et al. (2012)                       | Yes              |
| Cochlear implantation is indicated after critical assessment                  | Arndt et al. (2010); Bauer et al. (2002); Lanson, Green, Lalwani, and      | Yes              |
| MR imaging to determine the location and course of the facial nerves is indicated before craniofacial surgery or cochlear implantation | Waltzman (2007); Song et al. (2011); Vesseur, Free, et al. (2016)           | Out of scope     |
| Presence of anosmia can predict hypogonadotropic hypogonadism, therefore smell should be tested | Bergman, Janssen, et al. (2011)                                             | Yes              |
| Advice concerning anosmia should be given                                     | Bergman, Janssen, et al. (2011)                                             | No, too detailed |
| Evaluate obstructive sleep apnea in case of sleep disturbances                | Trider and Blake (2012)                                                    | Yes              |
| At diagnosis: full ophthalmological examination including funduscopy is indicated | Bergman, Janssen, et al. (2011); Blake, Kirk, and Ur (1993); Lalani et al. | Yes              |
| Regular ophthalmologic evaluations are appropriate to follow changes in acuity, risks for retinal detachment and/or cataract and corneal abrasions (facial palsy) | (2012); Russell-Eggitt, Blake, Taylor, and Wyse (1990)                     |                  |
| Tinted spectacles for photophobia (common in coloboma) can be helpful         | Blake and Brown (1993)                                                     | Yes              |
| For eyes with visual potential, cycloplegic refraction and spectacle correction may be necessary, since substantive refractive errors of micro-ophthalmic eyes have been observed | Bergman, Janssen, et al. (2011); Blake and Brown (1993); Lalani et al.     | Yes              |
| Parents, therapists and teachers need to take visual field defects into account | Lalani et al. (2012)                                                       | No               |
| Retinal detachment, a potential complication of retinal coloboma, can cause total blindness; any change in vision should be treated as a medical emergency |                                                                 |                  |
| Artificial tears may be necessary in case of facial palsy with incomplete closure of the eye | Bergman, Janssen, et al. (2011)                                             | Yes              |
| Frequent clinical and radiologic dental evaluations should be performed, if necessary under anesthesia | Lalani et al. (2012)                                                       | Yes              |

Cardiology and respirology

(Continues)
| Recommendation                                                                 | References                                                                                      | Trider checklist |
|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|------------------|
| At diagnosis: cardiac evaluation for cardiovascular anomalies (ECG and echocardiogram) is indicated | Bergman, Janssen, et al. (2011); Lalani et al. (2012); Wyse, al-Mahdawi, Burn, and Blake (1993) | Yes              |
| Evaluate for arch vessel anomaly in case of unexplained swallowing/respiratory problems | Corsten-Janssen, van Ravenswaaij-Arts, and Kapusta (2016)                                       | Yes              |
| Extensive pre-operative assessment is indicated                                | Bergman, Janssen, et al. (2011); Blake et al. (2009); Stack and Wyse (1991)                    | Yes              |
| Longer surveillance after surgery is indicated                                 | Bergman, Janssen, et al. (2011); Blake et al. (2009); Stack and Wyse (1991)                    | Yes              |
| Surgical procedures on these patients should be combined whenever possible because of their increased risk of post-operative complications and intubation problems | Bergman et al. (2010); Bergman, Janssen, et al. (2011); Blake et al. (2009); Lalani et al. (2012) | Yes              |
| Gastroenterology and genitourinary                                            |                                                                                                 |                  |
| Genitourinary evaluation (including renal and bladder ultrasound, voiding cystourethrography screening) is indicated | Bergman, Janssen, et al. (2011); Blake et al. (1998); Lalani et al. (2012); Ragan, Casale, Rink, Cain, and Weaver (1999) | Yes              |
| Early treatment of bladder infections (especially in case of unilateral renal agenesis or vesico-urethral reflux) is recommended | Bergman, Janssen, et al. (2011)                                                                  | No, too detailed |
| Monitor cryptorchidism and perform orchidopexy if indicated                   | Bergman, Janssen, et al. (2011)                                                                  | Yes              |
| Perform swallowing studies, pH monitoring and reflux scan in case of feeding/swallowing difficulties | Bergman, Janssen, et al. (2011)                                                                  | Yes              |
| Perform gastrostomy/tracheotomy in case of severe swallowing problems         | Asher, McGill, Kaplan, Friedman, and Healy (1990); Bergman, Janssen, et al. (2011)              | Yes              |
| Where indicated, tracheotomy needs to be performed early to avoid hypoxic events | Roger et al. (1999)                                                                            | No, too detailed |
| Individualized evaluation of feeding behavior (incl. oral defensiveness) should be a part of the standard otolaryngologic and feeding team practice | Bergman et al. (2010); Dobbelsteyn, Peacocke, Blake, Crist, and Rachid (2008); Hudson, Macdonald, and Blake (2016) | Yes              |
| Endocrinology                                                                  |                                                                                                 |                  |
| Early referral for endocrinology consultation is appropriate                   | Gregory et al. (2013); Pinto et al. (2005); Wheeler, Quigley, Sadeghi-Nejad, and Weaver (2000) | Yes              |
| If growth is deviating from normal despite adequate nutrition and normalized cardiac status, evaluate for growth hormone deficiency | Asakura et al. (2008); Bergman, Janssen, et al. (2011); Blake et al. (1993); Lalani et al. (2012) | Yes              |
| Start growth hormone treatment if growth hormone deficiency is present         | Bergman, Janssen, et al. (2011); Lalani et al. (2012)                                            | Yes              |
| Routine testing of adrenal function is not indicated                           | Wong et al. (2016)                                                                              | Negative result  |
| Evaluation of hypogonadotropic hypogonadism is indicated (LH and FSH between age 2–3 months, or age 13–14 years if puberty has not occurred) | Bergman, Janssen, et al. (2011); Pinto et al. (2005); Wheeler et al. (2000)                      | Yes              |
| Consider hormone replacement therapy in hypogonadotropic hypogonadism to induce puberty and for general health reasons including prevention of osteoporosis | Bergman, Janssen, et al. (2011); Forward, Cummings, and Blake (2007); Lalani et al. (2012); Sato et al. (2015) | Yes              |
| All patients with congenital hypogonadotropic hypogonadism should be informed about the possibility of hypogonadotropic hypogonadism reversal before transition to adult healthcare | Laitinen et al. (2012)                                                                         | No, too detailed |
| DEXA scan is indicated, if osteoporosis is suspected                           | Bergman, Janssen, et al. (2011)                                                                  | Yes              |
| Thyroid function should be tested if dysfunction is suspected                  | Asakura et al. (2008); Gregory et al. (2013)                                                    | Yes              |
| Recommendation                                                                 | References                                                                                      | Trider checklist |
|-------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------|
| **Immune system**                                                             |                                                                                                 |                  |
| Perform immunological evaluation (B- and T-cell numbers and vaccination responses) in patients with recurrent infections | Bergman, Janssen, et al. (2011); Chopra, Baretto, Duddridge, and Browning (2009); Wong et al. (2015); Writzl, Cale, Pierce, Wilson, and Hennekam (2007) | Yes              |
| Consider booster vaccines in patients with low vaccine response                | Wong et al. (2015)                                                                              | Yes              |
| **Musculoskeletal**                                                           |                                                                                                 |                  |
| Periodic evaluation for scoliosis in children, especially during growth hormone treatment, is indicated | Bergman, Janssen, et al. (2011); Doyle and Blake (2005)                                       | Yes              |
| Treat severe and/or progressive scoliosis with corset or surgery              | Bergman, Janssen, et al. (2011)                                                                | Yes              |
| **Psychology and development**                                               |                                                                                                 |                  |
| Referral to deafblind education services should be made as early as possible  | Blake and Brown (1993); Lalani et al. (2012)                                                    | Yes              |
| Psychological/school evaluations should be performed by a team that includes specialists in deafblindness | Lalani et al. (2012)                                                                            | No, too detailed |
| Perform IQ tests and/or developmental evaluations regularly                    | Bergman, Janssen, et al. (2011)                                                                | Yes              |
| Extensive multidisciplinary evaluation of developmental and sensory impairments and behavioral problems is indicated | Bergman, Janssen, et al. (2011); Lalani et al. (2012)                                           | Yes              |
| Therapy for hypotonia and devices to overcome balance impairment are indicated | Bergman, Janssen, et al. (2011); Blake and Brown (1993)                                       | Yes              |
| Use formal tests to screen for autism spectrum, obsessive compulsive disorders and ADHD | Bergman, Janssen, et al. (2011)                                                              | Yes              |
| Executive dysfunction is common. Interventions targeting improved self-regulation may help to manage behavior | Hartshorne, Nicholas, Grialou, and Russ (2007)                                                  | No, too detailed |
| **General**                                                                   |                                                                                                 |                  |
| Follow-up should be by a multidisciplinary team                               | Bergman, Janssen, et al. (2011); Blake, Russell-Eggitt, Morgan, Ratcliffe, and Wyse (1990)     | Yes              |
| Autopsy should be performed in deceased patients to gain more insight into causes of death | Bergman et al. (2010)                                                                         | Out of scope     |

Recommendations were collected from the literature as described in the text and categorized according to organ system. MLPA, multiplex ligation-dependent probe amplification; TBX1, T-box 1 gene.

*Out of scope means out of the scope of the Trider checklist.
were noted first in animal models (e.g., cerebellar abnormalities (Yu et al., 2013)) or were found only after structured evaluation of images of a series of individuals (Hoch et al., 2017). Second, as individuals with CHARGE syndrome are at increased risk of post-operative airway complications, procedures under anesthesia should be combined as much as possible (Blake et al., 2009). The need to improve imaging while reducing risks therefore warrants guidelines for performing neuro-imaging in an optimal and efficient way. Altogether, we argue that standardized recommendations for neuro-imaging protocols could contribute to clinical awareness of the heterogeneous cranial abnormalities involved in CHARGE syndrome and improve care.

2 OVERVIEW OF GUIDELINES AND RECOMMENDATIONS FROM LITERATURE

A literature search using PubMed was performed on August 17, 2017 using the search string: (“CHARGE syndrome” OR “CHARGE association” OR CHD7) AND (guideline* OR consensus OR recommend* OR “best practice” OR “surveillance”). This resulted in 112 hits, of which 42 contained usable guidelines or recommendations. A further 15 articles with guidelines or recommendations were found through an examination of the references. The resulting full list with recommendations is given in Supplemental Table S1. We then categorized the guidelines and recommendations from the literature either by organ system or as “general” (see Table 1), then checked if they were included in the Trider checklist (see Figure 1 and Table 1).

Out of 73 formulated recommendations, 53 were covered by the Trider checklist or the accompanying paper. Of the other 20, only one is truly “missing” from the checklist: 12 were out of the scope of a clinical surveillance checklist, six were too detailed to be included, and one was a recommendation to not perform a test (adrenal evaluation). The missing recommendation concerns the advice to parents, therapists and teachers to take into account visual field defects. A last recommendation was actually given in the Trider paper but not included in their checklist. Trider advises screening patients with

| Recommendation | Basis for recommendation | References |
|----------------|--------------------------|------------|
| The indication for CHD7 analysis can be determined through the flow diagram provided by Bergman et al. | Validated on cohort of 280 patients | Bergman, Janssen, et al. (2011) |
| CHD7 testing can confirm uncertain diagnosis in mildly affected patients | Validated on cohorts of 280 and 28 patients | Bergman, Janssen, et al. (2011); Hale, Niederriter, Green, and Martin (2016) |
| If a parent has any features of CHARGE syndrome, molecular genetic testing is appropriate if a CHD7 pathogenic variant has been identified in the proband | Case series of five families | Jongmans et al. (2008) |
| A genome-wide array should be performed in patients with CHARGE syndrome but without a CHD7 mutation | Expert opinion | Corsten-Janssen et al. (2013) |
| There is a very low yield of MLPA analysis in patients with CHARGE syndrome but without causal CHD7 mutations | Cohort of 54 patients: 1 deletion of multiple exons; several case reports | Bergman et al. (2008); Wincent et al. (2008); Wincent et al. (2009) |
| CHD7 analysis should be performed in patients with a 22q11.2 deletion phenotype without TBX1 haploinsufficiency | 5 CHD7 mutations in 20 patients | Corsten-Janssen et al. (2013) |
| CHD7 analysis should be performed in patients with Kallmann syndrome who have at least two additional CHARGE features or semicircular canal anomalies | Yield of 6% in (2 studies combined) 96 patients with Kallmann syndrome/normosomic idiopathic hypogonadotropic hypogonadism; hearing loss enriched in probands with Kallmann syndrome and CHD7 mutation vs. without CHD7 mutation | Bergman et al. (2012); Costa-Barbosa et al. (2013); Jongmans et al. (2009) |
| CHD7 should be included in massive parallel sequencing gene panels for diagnostics in patients with syndromic heart defects | Expert opinion | Corsten-Janssen et al. (2014) |
| CHD7 analysis should not be performed routinely in patients with isolated atrial septal or conotruncal heart defects | Cohort of 46 patients, no CHD7 mutations | Corsten-Janssen et al. (2014) |
| CHD7 analysis should not be performed in patients with septo-optic dysplasia or hypopituitarism without features of CHARGE syndrome | Cohort of 100 patients, no CHD7 mutations | Gregory et al. (2013) |

MLPA, multiplex ligation-dependent probe amplification; TBX1, T-box 1 gene.
| Structure       | Abnormality                                                                 | Clinical relevance                                                                 | Imaging modality          | References                          |
|-----------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------------|---------------------------|-------------------------------------|
| Skull base      | • Basioccipital hypoplasia, small clivus, dorsally angulated clivus          | Diagnostic aid                                                                    | Sagittal T1 sagittal T2 in neonates | Fujita et al. (2009); Hoch et al. (2017) |
|                 | • Hypoplasia sella, J-shaped sella                                           |                                                                                    |                           |                                     |
| Cranial nerves  | I Hypoplasia/aplasia                                                         | Sense of smell, prediction of HH, diagnostic aid                                  | Coronal T2-TSE anterior skull base, 3D CISS, MPRAGE | Bergman, Bocca, et al. (2011) |
|                 | II Coloboma                                                                  | Vision, diagnostic aid                                                            | Transverse T2 and coronal T1 and STIR through to orbits | McMain et al. (2008) |
|                 | VII Hypoplasia/aplasia and/or aberrant course                                | Planning of CI operation                                                          | Transverse 3D CISS, temporal bone CT | Vesseur, Verbist, et al. (2016) |
|                 | VIII Hypoplasia/aplasia                                                      | Decisions around BAHA, CI or ABI operation; planning of CI operation              | Transverse 3D CISS, oblique MPRs of internal auditory canal | Vesseur, Verbist, et al. (2016) |
|                 | IX Hypoplasia/aplasia                                                        | Swallowing                                                                        | Transverse 3D CISS            | Blake et al. (2008) |
|                 | XII Hypoplasia/aplasia                                                       | Swallowing, speech                                                                | Transverse 3D CISS            | Blake et al. (2008) |
| Ear             | Cochlea                                                                     | Hearing, planning of CI operation                                                  | Temporal bone CT, 3D CISS   | Vesseur, Verbist, et al. (2016) |
| Middle ear      | • Dysplasia stapes and/or incus, absent or stenotic oval and round windows   | Aid in diagnosis conductive or mixed hearing loss, planning CI or ear surgery      | Temporal bone CT             | Vesseur, Verbist, et al. (2016) |
|                 | • Vascular anomalies os petrosum (persistent petrosquamous sinus (PSS), enlarged emissary vene, e.o.) |                                                       |                           |                                     |
|                 | • Underdevelopment middle ear cavity and underpneumatization of the mastoid |                                                       |                           |                                     |
| Semicircular canals | Aplasia/dysplasia. Typically: malformed utriculus, aplastic posterior, anterior and lateral semicircular canals | Diagnostic aid, sense of balance                                                  | Temporal bone CT, 3D CISS   | Vesseur, Verbist, et al. (2016) |
| Brain           | Cerebellum                                                                   | Unknown                                                                            | Transverse and sagittal T2-TSE, MPRAGE | Hoch et al. (2017); Yu et al. (2013) |
|                 | Vermis hypoplasia                                                            | No specific                                                                        | Transverse T2, FLAIR, T1     | Hoch et al. (2017) |
|                 | Ventricles                                                                   | Ventriculomegaly, cavum septum pellucidem                                         |                           |                                     |
|                 | Brainstem                                                                    | Hypoplasia                                                                         | Transverse T2               | Hoch et al. (2017) |
|                 | Frontal lobe                                                                 | Hypoplasia                                                                         | Transverse and coronal T2   | Gregory et al. (2013) |
|                 | Pituitary                                                                    | Ectopic posterior pituitary, anterior pituitary hypoplasia                          | Pituitary function          | Gregory et al. (2013) |
|                 | Pituitary                                                                    |                                                                                   | Sagittal and coronal T1 and T2 | Gregory et al. (2013) |

(Continues)
CHARGE for cochlear implant surgery before the age of three, however the cochlear implant box in their checklist is not shaded for the “infancy” column. Our review indicates the Trider surveillance checklist is well-supported by literature with only minor omissions. Recommendations regarding analysis for CHD7, the causative gene for CHARGE syndrome, are beyond the scope of the clinical checklist aimed at follow-up, but we have included a summary of these guidelines in Table 2.

As we discussed in the introduction, there are currently no formal guidelines for cranial imaging even though we argue that cranial imaging is an important clinical tool that needs to be handled carefully. The guidelines we present here for cranial imaging in patients with CHARGE syndrome are based on previously published neuro-radiologic recommendations (Asakura et al., 2008; Bergman, Janssen, et al., 2011; Fujita et al., 2009; Gregory et al., 2013; Pinto et al., 2005; Vesseur, Free, et al., 2016) in addition to current insights in detectable neuro-radiologic abnormalities and anatomic variants in patients with CHARGE syndrome (see Table 3).

### 3 DIAGNOSTIC VALUE OF CRANIAL IMAGING

Imaging of the semicircular canals is recommended in patients with an atypical presentation of the syndrome to decide whether CHD7 testing is warranted, or to confirm the clinical diagnosis when CHD7 testing reveals no or an unclassified variant (Bergman, Janssen, et al., 2011). This is because aplasia or hypoplasia of the semicircular canals is present in 95% of individuals with a pathogenic variant in the CHD7 gene, making it one of its most prevalent clinical features (Abadie et al., 2000; Bauer, Goldin, & Lusk, 2002; Lemmerling et al., 1998; Morimoto et al., 2006; Tellier et al., 1998; Wiener-Vacher, Amanou, Denise, Narcy, & Manach, 1999). The configuration of the labyrinth in CHARGE syndrome is typical: a malformed vestibule and aplastic or hypoplastic semicircular canals that is sometimes combined with cochlear malformation. These abnormalities can already be seen in fetal imaging (Tilea et al., 2006) and can, on their own, provide a valuable first clue toward diagnosis.

Arhinencephaly is another common feature in CHARGE syndrome (Legendre et al., 2012; Sanlaville et al., 2006) that can be observed in imaging. The olfactory nerves may be hypo- or aplastic, usually in combination with olfactory sulcus effacement. Other cranial nerves, particularly the facial and acoustic nerve, may also be hypo- or aplastic.

Hoch et al. (2017) recently published findings from MRI of the head and neck for 10 individuals with CHARGE syndrome and noted that skull base abnormalities (9/10) were often present in addition to semicircular canal abnormalities (10/10) and hypoplasia of the olfactory system (10/10). These skull base anomalies consisted of a J-shaped sella and a dorsal angulation of the clivus. These findings confirm the findings of Fujita et al. (2009) and are consistent with the preliminary results of a study in which we analyzed the clivus of 23 confirmed patients with CHARGE on MRI or CT scans. We found that the vast majority had an abnormal clivus (Figure 2) [yet unpublished
These observations thus suggest that clivus abnormalities may be used as an important additional diagnostic tool.

Lastly, orbital abnormalities such as microphthalmia and colobomata, and nasal abnormalities such as choanal atresia may also be seen on cranial MRI.

As summarized in Table 3, there are multiple features observable on cranial MRI or CT that can aid in clinical diagnosis of CHARGE syndrome. These include semicircular canal hypoplasia, hypo- or aplasia of the olfactory nerve and sulcus, other cranial nerve hypo- or aplasias, clivus abnormalities, colobomata, and choanal atresia.

### 4 | VALUE OF CRANIAL IMAGING IN TREATMENT AND MANAGEMENT

### 4.1 Hearing loss

Sixty to eighty percent of patients with CHARGE syndrome have moderate to severe hearing loss, either conductive, sensorineural, or mixed (Blake, Hartshorne, Lawand, Dailor, & Thelin, 2008). Auditory testing combined with the findings on CT and MRI are necessary for (i) diagnosing the type of hearing loss; (ii) choosing the optimal kind of rehabilitation; and (iii) planning a (possible) cochlear implantation (CI) or auditory brain stem implantation (ABI). CT and MRI provide complementary information in this situation: the bony anatomy is best studied on CT, while MRI provides additional information about the inner ear and allows visualization of the vestibulocochlear nerve.

Middle ear pathology, such as dysplastic ossicles or an absent/stenotic oval or round window, is seen on mastoid CT in over 70% of patients (Vesseur, Verbist, et al., 2016). In some of these children a bone-anchored hearing aid (BAHA, sometimes known as BCD—bone conductive device) may be a good hearing solution. A BAHA allows the perception of sound by by-passing the middle ear, provided the cochlea and auditory nerve are intact (Reinfeldt, Hakansson, Taghavi, & Eeg-Olofsson, 2015). Cochlear nerve hypoplasia or aplasia is seen relatively frequently in CHARGE (Holcomb, Rumboldt, & White, 2013), which reduces the possibilities for CI. In these cases, auditory brain stem implantation may be an option, although hearing results appear to be less successful while the surgery is more extensive than for CI (Colletti, Colletti, Mandala, & Colletti, 2014).

CT imaging also provides additional information about surgical landmarks for cochlear implantation, such as detailed information about the lateral semicircular canals, which serves as a landmark for mastoidectomy. Alternatively, an aberrant course of the facial nerve increases the risk of perioperative injury and may impede cochleostomy (Vesseur, Free, et al., 2016). Vascular abnormalities may also hamper the surgical procedure. Vesseur, Free, et al. (2016) recently published a guideline on CI implantation in CHARGE that extensively covers preoperative imaging.

### 4.2 Olfactory bulbs and puberty induction

Fetal studies found arhinencephaly in 36 of 40 (90%) fetuses with a confirmed pathogenic CHD7 variant (Legendre et al., 2012). This is seen less often postnatally, although anosmia is diagnosed in approximately 80% of individuals with CHARGE syndrome (Bergman, Bocca, et al., 2011). Bergman, Bocca, et al. (2011) showed that olfaction and spontaneous onset of puberty are correlated in CHARGE syndrome: all (11/11) patients with hypogonadotropic hypogonadism (HH) were unable to smell, whereas patients without HH had the ability to smell (4/4). This combination of symptoms is also seen in Kallmann syndrome and is explained by common factors that facilitate axon guidance for both olfactory and GnRH neurons (Yanicostas, Herbomel, Dipietromaria, & Soussi-Yanicostas, 2009). The correlation of anosmia and HH enables prediction of HH in patients with CHARGE experiencing anosmia, which is useful because after the age of 3 months endocrinological assessment of HH is impossible until the onset of puberty. Therefore, in children for whom no endocrinological evaluation was performed before the age of 3 months, anosmia can help predict whether it will be necessary to induce puberty. As the formal evaluation of sense of smell is fairly involved and only possible from a (developmental) age of 5 years, and an impaired sense of smell can have many causes, radiological evidence of olfactory nerve/bulb aplasia or hypoplasia can aid in...
predicting patients at risk for HH. However, because olfactory imaging is not a perfect predictor of sense of smell, olfactory imaging alone is insufficient to determine HH status.

4.3 Other brain abnormalities

MR imaging has revealed a variety of other brain abnormalities in CHARGE syndrome (Hoch et al., 2017). In specific cases, the presence of brain abnormalities on MRI can explain a particular clinical feature in a patient. For instance, post-asphyxia damage may explain an otherwise unexpected severe developmental delay in a child with overall mild symptoms. However, predicting clinical symptoms from MRI abnormalities is more difficult. For instance, even though cerebellar dys- or hypoplasia is fairly common in CHARGE syndrome (Yu et al., 2013), no relationship to ataxia has been reported so far (Sohn et al., 2016). Research on the clinical relevance of cerebellar anomalies is ongoing.
Since the identification of CHD7 as the causal gene for CHARGE syndrome, several animal models have been developed, with mouse models being the most-studied. This has led to the identification in mice of significant anatomical features that were not known or were only anecdotally described in individuals with CHARGE syndrome. The best example for this is the hypoplasia of the cerebellar vermis. Abnormalities of the cerebellum were sporadically mentioned in papers on CHARGE syndrome, but it was only after the identification in mice of a role for Chd7 in the isthmic organizer that a systemic study of human MRI scans revealed cerebellar abnormalities in at least half of individuals with CHARGE syndrome (Haldipur & Millen, 2013; Yu et al., 2013).

Jiang et al. (2012) described telencephalic midline abnormalities in a mouse model with a nonsense Chd7 mutation. These mice had arhinencephaly, dilated third and lateral ventricles, reduced cerebral cortex, and corpus callosum crossing failure. As described above, arhinencephaly is a well-known CHARGE feature, but it was not until recently that ventriculomegaly and corpus callosum abnormalities were described in patients with CHARGE (Hoch et al., 2017; Jiang et al., 2012).

Sperry et al. (2014) found several phenotypic features that are well-known in humans with CHARGE syndrome in Foxg1 and Wnt1 conditional knockout mice, but they also observed skull bone abnormalities such as frontal, parietal and occipital bone dysplasia and hypoplasia of the maxilla (Sperry et al., 2014). The same abnormalities were not seen in heterozygous Chd7 mice and have not been described in humans, but as described above, clivus and petrosal abnormalities are common in individuals with CHARGE syndrome.

Inner and middle ear abnormalities (os petrosum) have been studied extensively in humans and mice because of their effect on hearing. Therefore, most anatomic anomalies seen in Chd7-deficient mice had already been extensively documented in individuals with CHARGE syndrome. One lesser-known feature, however, is the otosclerosis-like fusion of the stapes footplate to the cochlear oval window as described by Ogier et al. (2014) in Looper mice. A recent study of CT images of the os petrosum of individuals with CHARGE syndrome showed that, in addition to the (known) abnormalities of the oval window, the stapes was dysplastic or not identifiable in half of the ears with a stenotic oval window (Vesseur, Verbist, et al., 2016).

It is obvious that researchers studying animal models are interested in translating their findings to humans. Performing MRI or CT scans in children with CHARGE syndrome solely for the sake of research is ethically difficult to accept, especially since most children will have to be sedated with a risk of post-sedation respiratory problems. However, when there is a clinical indication to perform imaging studies, performing imaging as complete and as detailed as possible aids both individuals with CHARGE syndrome through better and more complete diagnosis and researchers through a better and more complete picture of the features of CHARGE syndrome.

In our experience, in each individual with CHARGE, a wide variety of scans are usually performed by different medical specialists. This leads to scans that differ in completeness and sequences used. A further complication is that scans are often performed in different hospitals and parents may find it difficult to recall if and where imaging was done, illustrating that the early years of children with CHARGE syndrome are often hectic and overwhelming.

Individuals with CHARGE syndrome often undergo a great many procedures under anesthesia (Blake et al., 2009). To reduce the risk of recurrent anesthesia and minimize exposure to radiation, neuro-imaging should preferentially be completed within one efficient session. With that objective in mind, a radiology guideline, combining CT and MRI scanning and outlining the correct sequences, may enable accurate diagnostic radiologic assessment of the cranial and auditory anatomy within one session. This guideline is presented in Figure 3. In children up to 6 months of age, the unnecessary risk of anesthesia may be avoided by swaddling (CT duration 0.5–2 min, MRI duration approximately 30 min). In our opinion, avoidance of unnecessary anesthesia is more important than the small chance of movement artifacts in the MRI of a swaddled infant.

7 Conclusion

CHARGE syndrome is a complex entity with a wide range of congenital abnormalities and clinical symptoms. The multitude of issues that individuals with CHARGE syndrome face, particularly early in life, greatly increases the risk that their care will be fragmented or incomplete. Our review confirms that the Trider checklist provides a well-supported framework for clinical surveillance. Our guideline for cranial imaging provides an aid to clinicians for providing accurate and optimal care while limiting risky anesthetic procedures, and may enable more effective research into cranial abnormalities in CHARGE syndrome.

Acknowledgments
We thank Jackie Senior and Kate McIntyre for editing the manuscript.

Conflicts of interest
The authors declare no conflicts of interest.

ORCID
Christa M. de Geus http://orcid.org/0000-0002-7996-056X
Conny M. A. van Ravenswaaij-Arts http://orcid.org/0000-0002-8744-1305

References
Abadie, V., Wiener-Vacher, S., Morisseau-Durand, M. P., Poree, C., Amiel, J., Amanou, L., … Manac’h, Y. (2000). Vestibular anomalies in CHARGE
correlates with the clinical phenotype.

Jongmans, M. C. (2014). CHD7 mutations are not a major cause of atrioventricular septal and conotruncal heart defects. American Journal of Medical Genetics Part A, 164A, 3003–3009.

Corsten-Janssen, N., Saitta, S. C., Hoeftsloot, L. H., McDonald-McGinn, D. M., Driscoll, D. A., Derks, R., . . . van Ravenswaaij-Arts, C. M. (2013). More clinical overlap between 22q11.2 deletion syndrome and CHARGE syndrome than often anticipated. Molecular Syndromology, 4, 235–245.

Corsten-Janssen, N., van Ravenswaaij-Arts, C. M. A., & Kapusta, L. (2016). Congenital arch vessel anomalies in CHARGE syndrome: A frequent feature with risk for co-morbidity. IC Heart & Vascularute, 12, 21–25.

Costa-Barbosa, F. A., Balasubramanian, R., Keefe, K. W., Shaw, N. D., Al-Tassan, N., Plummer, L., . . . Crowley, W. F., Jr. (2013). Prioritizing genetic testing in patients with kallmann syndrome using clinical phenotypes. The Journal of Clinical Endocrinology and Metabolism, 98, E943–E953.

Dobbelsteyn, C., Peacock, S. D., Blake, K., Crist, W., & Rashid, M. (2008). Feeding difficulties in children with CHARGE syndrome: Prevalence, risk factors, and prognosis. Dysphagia, 23, 127–135.

Doyle, C., & Blake, K. (2005). Scoliosis in CHARGE: A prospective survey and two case reports. American Journal of Medical Genetics Part A, 133A, 340–343.

Edwards, B. M., Kileny, P. R., & Van Riper, L. A. (2002). CHARGE syndrome: A window of opportunity for audiologic intervention. Pediatrics, 110, 119–126.

Forward, K. E., Cummings, E. A., & Blake, K. D. (2007). Risk factors for poor bone health in adolescents and adults with CHARGE syndrome. American Journal of Medical Genetics Part A, 143, 839–845.

Fujita, K., Aida, N., Asakura, Y., Kurosawa, K., Niwa, T., Muroya, K., . . . Inoue, T. (2009). Abnormal basiocipitocranial development in CHARGE syndrome. AJNR American Journal of Neuroradiology, 30, 629–634.

Gregory, L. C., Gevers, E. F., Baker, J., Kasia, T., Chong, K., Josifova, D. J., . . . Dattani, M. T. (2013). Structural pituitary abnormalities associated with CHARGE syndrome. The Journal of Clinical Endocrinology and Metabolism, 98, E737–E743.

Haldipur, P., & Millen, K. J. (2013). Deficits in early neural tube identity found in CHARGE syndrome. Elife, 2, e01873.

Hale, C. L., Niederriter, A. N., Green, G. E., & Martin, D. M. (2016). Atypical phenotypes associated with pathogenic CHD7 variants and a proposal for broadening CHARGE syndrome clinical diagnostic criteria. American Journal of Medical Genetics Part A, 170A, 344–354.

Harris, J., Robert, E., & Kallen, B. (1997). Epidemiology of choanal atresia with special reference to the CHARGE association. Pediatrics, 99, 363–367.

Hartshorne, T. S., Nicholas, J., Grialou, T. L., & Russ, J. M. (2007). Executive function in charge syndrome. Child Neuropsychology, 13, 333–344.

Hoch, M. J., Patel, S. H., Jethanamet, D., Win, W., Fatterpek, G. M., Roland, J. T., & Hagiwara, M. (2017). Head and neck MRI findings in CHARGE syndrome. American Journal of Neuroradiology, https://doi.org/10.3174/ajnr.A5297 epub ahead of print.

Holcomb, M. A., Rumboldt, Z., & White, D. R. (2013). Cochlear nerve deficiency in children with CHARGE syndrome. Laryngoscope, 123, 793–796.

Hudson, A., Macdonald, M., & Blake, K. (2016). Packing and problematic feeding behaviors in CHARGE syndrome: A qualitative analysis. International Journal of Pediatric Otorhinolaryngology, 82, 107–115.

Isselkutz, K. A., Graham, J. M., Jr., Prasad, C., Smith, I. M., & Blake, K. D. (2005). An epidemiological analysis of CHARGE syndrome: Preliminary results from a canadian study. American Journal of Medical Genetics Part A, 133, 309–317.

Jiang, X., Zhou, Y., Xian, L., Chen, W., Wu, H., & Gao, X. (2012). The mutation in chd7 causes misexpression of bmp4 and developmental defects in telencephalic midline. The American Journal of Pathology, 181, 626–641.

Jongmans, M. C., Hoeftsloot, L. H., van der Donk, K. P., Admiraal, R. J., Magee, A., van de Laar, I., . . . van Ravenswaaij-Arts, C. M. (2008). Familial CHARGE syndrome and the CHD7 gene: A recurrent missense
Writzl, K., Caleb, C. M., Pierce, C. M., Wilson, L. C., & Hennekam, R. C. (2007). Immunological abnormalities in CHARGE syndrome. European Journal of Medical Genetics, 50, 338–345.

Wyse, R. K., al-Mahdawi, S., Burn, J., & Blake, K. (1993). Congenital heart disease in CHARGE association. Pediatric Cardiology, 14, 75–81.

Yanicostas, C., Herbomel, E., Dipietromaria, A., & Soussi-Yanicostas. N. (2009). Anosmin-1a is required for fasciculation and terminal targeting of olfactory sensory neuron axons in the zebrafish olfactory system. Molecular and Cellular Endocrinology, 312, 53–60.

Yu, T., Meiners, L. C., Danielsen, K., Wong, M. T., Bowler, T., Reinberg, D., ... Basson, M. A. (2013). Deregulated FGF and homeotic gene expression underlies cerebellar vermis hypoplasia in CHARGE syndrome. Elife, 2, e01305.

CHRISTA M. DE GEUS is a medical doctor in training to become a clinical geneticist. She is working toward her PhD, which focuses on neurological symptoms in CHARGE syndrome.

ROLIEN H. FREE, MD, PhD, is an otolaryngologist/otologist/pediatric otolaryngologist whose particular focus is on ear surgery and cochlear implantation. She has published extensively on this subject, including articles about radiological findings, cochlear implantation, and speech language development in CHARGE patients. She is the otolaryngologist of the CHARGE center of expertise in Groningen, The Netherlands.

BERIT M. VERBIST is a head and neck radiologist at the Leiden University Medical Center with a specific interest in otology and neurotology. Her research in that area focuses on cochlear implantation. She has published about imaging abnormalities in CHARGE syndrome and the relevance to cochlear implantation.

DEBORAH A. SIVAL, MD, PhD, is a pediatric neurologist, with a specific interest in the field of fetal and neonatal developmental neurology. She is the pediatric neurologist involved in the CHARGE center of expertise in Groningen, the Netherlands.

DR. KIM BLAKE is a Professor of Pediatrics at Dalhousie University Medical School and a General Pediatrician at the IWK Health Centre in Halifax, Canada. She is an international expert in the area of CHARGE syndrome. She runs a multi-disciplinary Atlantic Canadian CHARGE syndrome clinic at a large pediatric tertiary care center (IWK Health Centre) in Halifax.

LINDA C. MEINERS, MD, PhD, is a pediatric neuroradiologist. She has been associated with the CHARGE center of expertise in Groningen since 2009.

CONNY M. A. VAN RAENSWAAL-ARTS, MD, PhD is a consultant in Clinical Genetics and Professor in Dysmorphology at the Department of Genetics of the University Medical Center Groningen, Netherlands. Her research projects focus on neurodevelopmental syndromes, with a special interest in CHARGE syndrome and rare chromosomal disorders. She coordinates an accredited center of expertise for both these disorders and is a member of the European Reference Network ITHACA.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: de Geus CM, Free RH, Verbist BM, et al. Guidelines in CHARGE syndrome and the missing link: Cranial imaging. Am J Med Genet Part C Semin Med Genet. 2017;175C:450–464. https://doi.org/10.1002/ajmg.c.31593