

Multidisciplinary Management of Costello Syndrome: Current Perspectives

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Abstract: Costello syndrome (CS) is a rare neurodevelopmental disorder caused by germline mutations in *HRAS*. It belongs among the RASopathies, a group of syndromes characterized by alterations in components of the RAS/MAPK signaling pathway and sharing overlapping phenotypes. Its typical features include a distinctive facial appearance, growth delay, intellectual disability, ectodermal, cardiac, and musculoskeletal abnormalities, and cancer predisposition. Due to the several comorbidities having a strong impact on the quality of life, a multidisciplinary team is essential in the management of such a condition from infancy to adult age, to promptly address any detected issue and to develop appropriate personalized follow-up protocols and treatment strategies. With the present paper we aim to highlight the core and ancillary medical disciplines involved in managing the health challenges characterizing CS from pediatric to adult age, according to literature and to our large clinical experience.

Keywords: multidisciplinary team, personalized medicine, *HRAS*, Costello syndrome, RASopathies

Introduction

Originally described in 1971, Costello syndrome (CS, OMIM #218040) is a rare multisystemic disorder with a strong impact on quality of life of caregivers and affected individuals.^{1,2} In 2005, germline missense mutations in the *HRAS* gene were identified as responsible for the CS phenotype by Aoki et al, with p.Gly12Ser being the most frequently reported variant.³ The *HRAS* gene encodes a GTPase functioning as a signal hub controlling multiple signaling pathways, including the mitogen activated protein kinase (MAPK) cascade, a major pathway regulating fundamental biological functions such as cell proliferation, differentiation, and survival.^{4,5} CS is included among the RASopathies, a group of rare multisystem disorders that share the dysregulation of the RAS/MAPK pathway as the underlying pathogenetic mechanism and are characterized by an overlapping clinical phenotype.⁶ While individually rare, collectively RASopathies represent the most common family of non-chromosomal disorders affecting development and growth.⁷ Besides CS, this group of conditions includes neurofibromatosis type 1 (NF1, OMIM #162200), Noonan syndrome (NS, OMIM #163950), cardio-facio-cutaneous syndrome (CFCS, OMIM #115150), Mazzanti syndrome (also known as Noonan-like syndrome with loose anagen hair, NS/LAH, OMIM #607721), Noonan syndrome with multiple lentigines, previously known as LEOPARD syndrome (NSML, OMIM PS151100), CBL mutation-associated syndrome (CBLS, OMIM #613563), Legius syndrome (OMIM #611431), and other emerging disorders.^{6,8,9}

CS is characterized by a distinctive facial gestalt, closely resembling storage diseases, failure to thrive, ectodermal anomalies, cardiopathies, musculoskeletal problems, developmental delay (DD)/intellectual disability (ID), friendly personality, and predisposition to certain cancers.^{10–12}

In the light of the multiple and diverse comorbidities affecting individuals with CS, and given the increased life expectancy associated with a better knowledge of this condition, a multidisciplinary and personalized approach has emerged as a key aspect for more effective care of these patients.

This paper provides an overview of the workflow that we routinely apply for the multidisciplinary management of individuals affected by this rare disorder.

From Clinical Suspicion to Molecular Diagnosis: *HRAS* Variants – from 2005 to Date

In 2005, using a candidate gene analysis, Aoki et al identified four heterozygous missense mutations of *HRAS*, including p.Gly12Ser, p.Gly12Val, and p.Gly13Asp, in 12 patients with Costello syndrome, all of which had previously been reported as somatic lesions in various tumors (Figure 1).³

So far, germline *HRAS* mutations have been identified in more than 90% of patients with Costello syndrome.^{3,13–17} These mutations are generally de novo events, indicating autosomal dominant inheritance. The p.Gly12Ser substitution has been identified in approximately 80% of patients. It has been suggested that patients with p.Gly12Ala have higher risk of malignancy than those with p.Gly12Ser (Table 1).¹⁸ p.Gly12Asp, p.Gly12Glu, and p.Gly12Cys are associated with severe neonatal phenotypes with pleural/pericardial effusion, congenital lung and airway abnormalities, and cardiomegaly (Table 1).^{15,17,19–21} Recently, the p.Gly12Asp variant was described in a 31-year-old patient with special but milder manifestations.²² Only seven patients have been reported with p.Gly12Val. This amino acid change is associated with a severe lethal phenotype, including severe hypertrophic cardiomyopathy (HCM), fetal hydrops, and hepatomegaly.^{3,23–25} Excessive amounts of neuromuscular spindles have been identified in two patients carrying the p.Gly12Val substitution.^{24,26} p.Gly13Cys is associated with distinctive phenotypes, including dolichocilia (extremely long eye lashes) and loose anagen hair without multifocal atrial tachycardia.²⁷ p.Gly13Asp is associated with less coarse facial features and slow-growing sparse hair, resembling loose anagen hair.²⁸ Individuals heterozygous for the p.Gly13Cys or p.Gly13Asp changes have been reported to develop papillomata or vascular proliferation lesions, but not malignant tumors.^{28,29} A less evident phenotype has been suggested in patients with rare mutations at codon 58 (p.Thr58Ile),³⁰ 60 (p.Gly60Asp),³¹ 117 (p.Lys117Arg),³² and 146 (p.Ala146Thr/Val/Pro).^{29,33,34} The p.Thr58Ile variant was observed in a girl with no intellectual disability but with severe HCM;³⁰ the rare p.Gly60Val variant was associated to subtle dysmorphic features and early death, highlighting how individuals with less evident CS characteristics may not have a more benign development.³⁵

The c.64C>A (p.Glu22Lys) mutation has been identified in patients with fatal congenital HCM and pancreatic nodule and in patients with congenital myopathy and excessive amount of muscle spindles.^{26,36}

As anticipated, the vast majority of pathogenic variants occur as de novo events.¹⁷ Anyway, in one family, the p.Thr58Ile substitution was reported in a son–father pair, the former showing macrocephaly and HCM and the latter apparently without any evidence of cognitive and cardiac involvement.³⁷ Also a case in which p.Gly60Asp mutation was

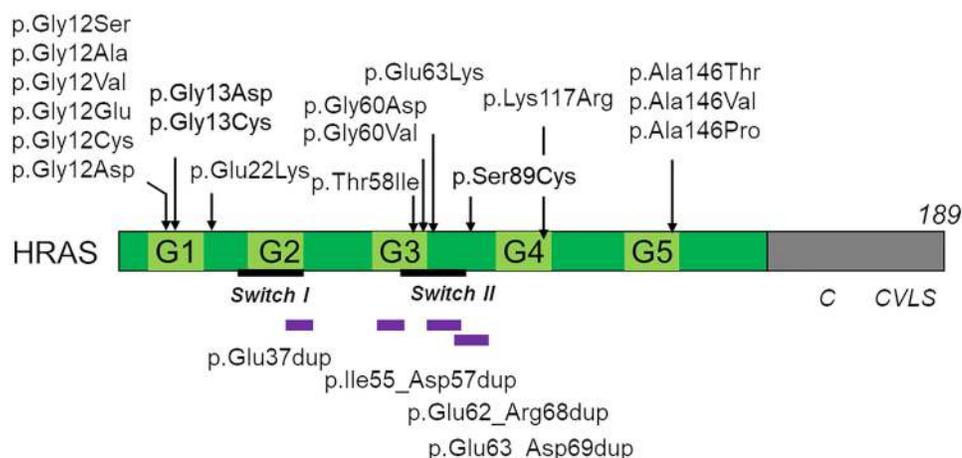


Figure 1 *HRAS* domain structure and pathogenic variants of *HRAS* identified in patients with Costello syndrome. Upper panel shows missense mutations, and lower panel shows intragenic duplications. More than 90% of pathogenic variants are clustered in codons 12 and 13. It has been shown that mutations at these codons impair the intrinsic GTPase activity, resulting in constitutive activations of downstream effectors.^{3,9,136} Reproduced from Aoki Y, Niihori T, Banjo T, et al. Gain-of-function mutations in RIT1 cause Noonan syndrome, a RAS/MAPK pathway syndrome. *Am J Hum Genet.* 2013;93(1):173–180. Copyright © 2013 The American Society of Human Genetics. Published by Elsevier Inc. All rights reserved.¹³⁷ The de novo 10-nucleotide-long deletion within the intron-D-exon (IDX) is not shown in the figure.

Table 1 Genotype-phenotype relationships in Costello syndrome with missense *HRAS* variants, duplications, and deletions

Missense Change	Clinical Description	References
p.Gly12Ser	Classic phenotype of CS; 80% of reported cases	[3,13]
p.Gly12Ala	Classic phenotype of CS; increased risk of malignancy compared to p.Gly12Ser	[18]
p.Gly12Val	Severe lethal phenotype: HCM, PVS, conduction disturbances, fetal hydrops, hepatomegaly, excessive amount of neuromuscular spindles. Most patients died before 18 months of age	[3,23–25]
p.Gly12Glu	Severe neonatal phenotype with pleural/pericardial effusion, congenital lung and airway abnormalities, HCM, PVS, cardiomegaly, patent foramen ovale, and conduction disturbances	[15,17,19–21]
p.Gly12Cys		
p.Gly12Asp		
p.Gly13Asp	Less coarse facial features, slow growing sparse hair, no malignant tumors reported to date	[3,28,29]
p.Gly13Cys	Less coarse facial features, absence of multifocal atrial tachycardia and ulnar deviation of the wrist, fewer neurological anomalies, no malignant tumors reported to date	[3,27]
p.Glu22Lys	Unusually severe fatal manifestation of HCM and hyperinsulinemic hypoglycemia or mild HCM and excess of muscle spindles	[26,36]
p.Gly60Val	Severe lethal phenotype	[35]
p.Thr58Ile	Milder/less evident phenotype	[30,37]
p.Gly60Asp		[31]
p.Lys117Arg		[32]
p.Ala146Thr		[29,33,34]
p.Ala146Val		
p.Ala146Pro		
p.Ser89Cys	Two siblings had severe fetal hydrops, but benign clinical course; the variant was inherited from the asymptomatic father	[43]
Duplications	Clinical Description	
p.Glu37dup	Mental retardation, short stature, sparse hair, mild musculoskeletal manifestations	[44]
p.Glu62_Arg68dup	Milder/attenuated phenotype	[45,47]
p.Glu63_Asp69dup		[46–48]
p.Ile55_Asp57dup		[47]
Deletions	Clinical Description	
c.481_490delGGGACCCTCT, NM_176795.4; p.Leu163ProfsTer52, NP_789765.1	Developmental delay, intellectual disability, ASD features, distinctive coarse facies, reduced growth, ectodermal anomalies	[49]

transmitted from a mother with subtle dysmorphic features to the son with a mild phenotype was reported.³¹ Patients who were suspected to have somatic mosaic mutation or germ cell mosaicism in *HRAS* were reported.^{38–41} Indeed cases of brothers affected by CS most probably due to germline mosaicism were described.⁴² The p.Ser89Cys variant was described in two siblings with a milder phenotype and their asymptomatic father.⁴³

Other than missense mutations in *HRAS*, intragenic duplications/deletions were also identified in a small proportion of patients with clinical features fitting or suggestive of CS. p.Glu37dup has been identified in two patients with mental

retardation, short stature, sparse hair, and mild musculoskeletal manifestations.⁴⁴ p.Ile55_Asp57dup, p.Glu62_Arg68dup, and p.Glu63_Asp69dup have been identified in six patients with a milder or attenuated phenotype.^{45–48} Finally, a de novo 10-nucleotide-long deletion within the intron-D-exon (IDX) exon of the gene was identified in a subject with DD/ID, autistic features, distinctive coarse facies, reduced growth, and ectodermal anomalies.⁴⁹ Of note, this deletion was demonstrated to affect *HRAS* transcript processing, promoting constitutive retention of exon IDX, which is generally skipped during *HRAS* transcript processing, resulting in a stable and mildly hyperactive GDP/GTP-bound protein constitutively targeted to the plasma membrane.⁴⁹

Early Diagnosis of Costello Syndrome: Prenatal Findings and Perinatal Features

To schedule a proper monitoring and treatment program, prompt diagnosis at birth or even prenatally has a decisive value. Anticipatory understanding of the possible complications is beneficial for a more effective management, helping physicians to apply a multidisciplinary health approach since birth and to adequately support the family. Furthermore, issues that may develop during pregnancy, such as arrhythmias, macrosomia, relative macrocephaly, and risks of preterm birth, could be more easily addressed if both the medical team and the parents are aware of them, drastically reducing labor-related complications.

Key diagnostic elements that may raise the suspicion of CS in utero are polyhydramnios (which is reported in most pregnancies), supraventricular tachycardia, increased nuchal translucency, macrosomia and macrocephaly (usually after the 20th week of gestation), and peculiar fetal posture; reduced length of long bones has also been reported.⁵⁰ Fetal arrhythmias are rare and usually responsive to therapy.^{50,51} The most common cause of polyhydramnios in association to fetal macrosomia is maternal diabetes, but once this condition is ruled out other causes of increased fetal size such as CS should be considered.⁵²

A feature that may help gynecologists in the differential diagnosis is that fetuses with CS have increased head size and body weight, but length is within the reference range. This is probably because macrosomia is mostly related to subcutaneous edema rather than a real overgrowth.²⁵

Most cases with a prenatal diagnosis reported in literature showed a severe phenotype associated to rare variants (eg, p.Gly12Val), often resulting in intrauterine or early postnatal death.^{21,25}

Typical features of newborns with CS include a characteristic facial gestalt with hypertelorism, low-set and posteriorly angulated ears, short nose with bulbous tip, full lips, and macrostomia. Hand posture is also distinctive, with clenched fists and overlapping of fingers.⁵¹ Hepatomegaly, small thorax, camptodactyly, and cryptorchidism are often associated to the neonatal lethal CS phenotype.²⁵ When all these elements are present, they should be suggestive of CS, and prompt genetic counseling should be scheduled.

Gynecologists should be aware of the main prenatal features that may raise suspicion for CS (prenatal polyhydramnios, increased nuchal translucency, fetal macrosomia, macrocephaly, and fetal arrhythmias) in order to inform neonatologists on possible medical comorbidities soon after birth and reduce the risk for the affected baby.

Core and Ancillary Medical Specialties in Pediatric Age: Combining Medical Management to Habilitative Therapies

Medical assistance in specialized hospitals is mostly recommended in infancy and childhood; during these periods, the most concerning issues to address are related to growth and neurodevelopment. Cardiorespiratory functions also need to be accurately monitored.

A relevant matter is also the evaluation of visual abilities since many patients with CS may present nystagmus and refractive errors impairing their everyday living and neurodevelopmental skills acquisition.⁵³

Looking at the different anecdotal reports about cancer in pediatric patients with CS, screening protocols should be applied in affected individuals from infancy.¹²

Considering all these issues, as soon as a diagnosis of CS is prompted, it is of utmost importance to lay the foundations to establish personalized follow-up schedules, therapeutic strategies, and habilitative protocols to ensure a good quality of life and to support families/caregivers. At the same time, a virtuous collaboration network between

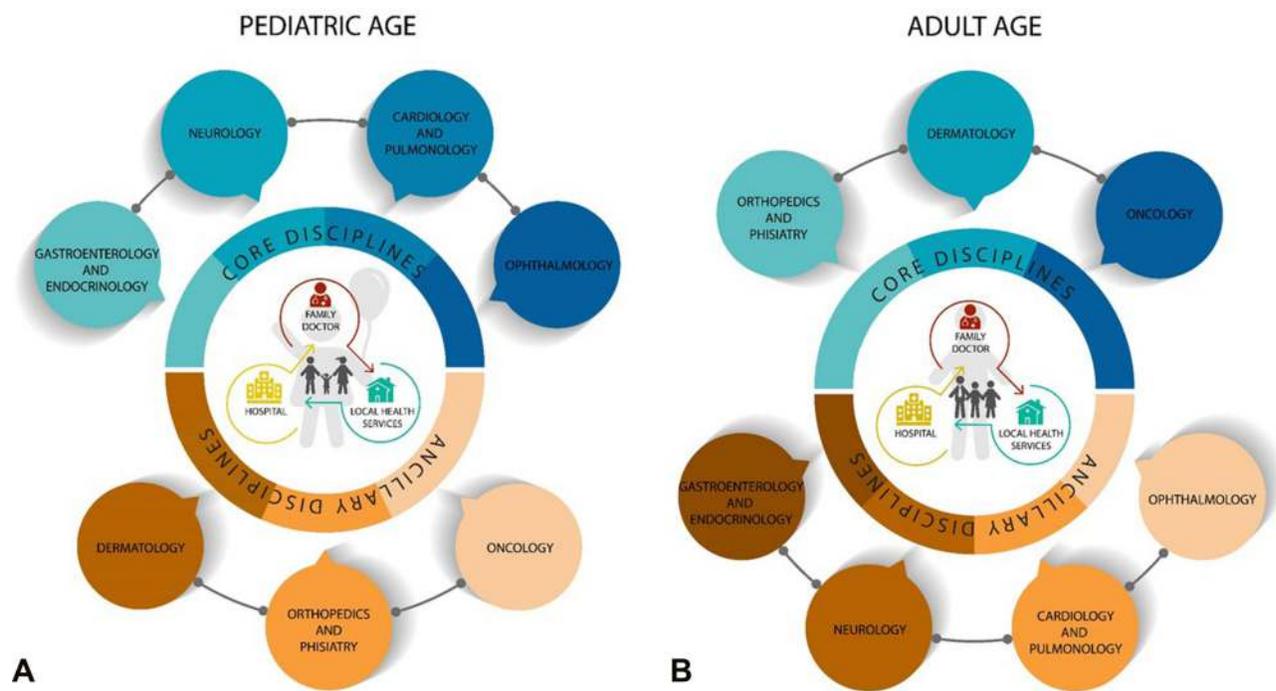


Figure 2 Core and ancillary disciplines involved in the management of pediatric and adult patients with CS. The impact of medical issues in the daily lives of patients with CS requires careful management throughout life. A comprehensive multidisciplinary assessment to be performed by physicians and therapists is needed from infancy to adulthood to promptly treat and monitor comorbidities. The latter change according to patients' age. In particular, the most concerning problem to manage in children is related to failure to thrive. The cardiorespiratory system needs to be accurately evaluated to exclude severe morphological or rhythmic cardiac anomalies. Visual and global neurological functions need to be assessed in order to plan a personalized protocol of rehabilitative therapies (A). In adults, orthopedic manifestations often require treatment; a comprehensive dermatological evaluation is important to improve skin findings, and a surveillance protocol for cancer risk needs to be followed (B).

hospital and local health services providing physical, speech, and occupational therapies needs to be established in order to achieve the best clinical outcome (Figure 2A).

Core Disciplines in Pediatric CS Population Growth and Nutrition

Soon after birth till first years of life, growth delay and severe failure to thrive are two of the most remarkable features characterizing CS, causing significant concern for parents and representing a real challenge for physicians.

Even though weight at birth is within the normal range, according to standardized growth charts for the general population, the weight-for-age is dramatically decreased below normal within the first three years.^{2,42,54} In previous reports, this first phase of development was indeed described as “marasmic”.⁵⁴ Based on these observations, normative growth charts for CS have been created.⁵⁵ Also height is significantly below the reference value for age, with a consequently normal BMI. Poor weight is probably due to a plethora of factors, among which feeding difficulties worsened by global hypotonia have a substantial role. The oro-motor dysfunction with impaired suckling and swallowing movements and oral hypersensitivity are other major contributors to such a phenotype. Severe gastroesophageal reflux disease is also common.^{42,54,56,57} Hypertrophic pyloric stenosis has also been reported with increased frequency compared to the general population.³⁴ Enteral feeding is most often required during the first three or four years of life through either nasogastric (ng-tube) tube or more commonly gastrostomy (g-tube).^{29,54,58} The use of g-tube would be preferable compared to ng-tube (when required over 3 months) to improve oral motor skills and dysphagia through personalized speech therapy. A normo-caloric diet has been demonstrated to be as effective as a hypercaloric diet in reaching the expected growth parameters with a better tolerance and fewer gastrointestinal symptoms.⁵⁴ Children affected by CS usually acquire normal feeding capacities by the age of 4 years; nevertheless growth delays with both short stature and poor weight do persist in adult age.⁵⁸ Given this complex phenotype, a close follow-up by gastroenterologists and clinical nutritionists (every 3 to 6 months) is necessary in pediatric age groups (Table 2).

Table 2 Timing of Clinical and Instrumental Follow-Up According to Literature and Our Experience

	Pediatric Age		Adult Age	References
	First Evaluation	Timing of Follow-Up Examinations*	Timing of Follow-Up Examinations*	
Gastroenterological evaluation	At birth/diagnosis	Every 3–6 months	Every 12 months	[2,29,42,54,56,57]
Clinical nutritionist evaluation	At birth/diagnosis	Every 3–6 months	According to patient's needs	[56,57]
Indirect calorimetry	12 months	Every 12 months	Every 12 months	[56,60]
Auxological/endocrinological evaluation with growth velocity monitoring	At birth/diagnosis	Every 6–12 months	N/A	[29,55,58]
Comprehensive neurological assessment	At birth/diagnosis	Every 3–6 months in individuals <5 years old; every 6–12 months in individuals ≥5 years-old	According to patient's characteristics	[70]
Evaluation of cognitive performance and adaptive behavior by using different scales according to age and level of intellectual disability	2 to 3 years	Every 12 months	According to patient's characteristics	[71,109–114]
MRI	At birth/diagnosis	According to symptomatology (if the first one is negative, to be repeated after two to three years in absence of clinical symptoms)	According to symptomatology (if the first one is negative, to be repeated after three years in absence of clinical symptoms)	[29,74,75]
Comprehensive cardiological assessment, electrocardiogram, echocardiogram	At birth/diagnosis	Every 12 months	Every 12 months	[29,76–79,82–84]
ENT evaluation	At birth/diagnosis	According to symptomatology	According to symptomatology	[85]
Polysomnography	If symptoms for sleep disturbances or apneas are present	Every 12 months (if sleep disturbances or apneas are present)	Every 12 months (if sleep disturbances or apneas are present)	[86]
Ophthalmologic evaluation with fundus oculi examination	At birth/diagnosis	Every 6 months in individuals <3 years old; every 12 months in individuals ≥3 years old	Every 12 months	[53,87,89,90]
Orthopedic evaluation	At 12 months	Every 12 months	Every 12 months	[10,29,87,91,98–101]
X-ray of spinal column	According to patient's characteristics	According to patient's characteristics	According to patient's characteristics	[10,29,87,91,98–101]
Hip X-ray	During infancy	To be repeated during adolescence	N/A	[10,91,99]

DEXA scan	From 5 years of age	Every 12–18 months	Every 12–18 months	[92,100,102]
Dosage of bone metabolism biomarkers	From 5 years of age	Every 24 months	Every 12–18 months	[92,100,102]
Complete dermatological evaluation with dermatoscopic examination	At diagnosis	Every 12 months	Every 12 months (closer follow-up schedules are suggested in case of risk factors)	[93,94,105,106]
Abdominal US	At birth/diagnosis	Every 6–12 months	Every 6–12 months	[29,95]
Routine clinical surveillance for RMS	At birth/diagnosis	Every 6–12 months	Every 6–12 months	[29,95]
Screening for bladder cancer through physical-chemical urine exam, urine cytology, and cystoscopy	From 10 years of age	Every 12 months	Every 12 months	[96]

Note: *Timing of follow-up evaluations may vary according to patient's symptomatology and characteristics.

It is known that the RAS/MAPK cascade has a role in the regulation of cellular metabolism and growth.^{56,59} It has recently been demonstrated that an increased resting energy expenditure may play a role in the poor growth pattern in CS. The use of indirect calorimetry may help clinicians provide the right amount of kilocalories per day based on personalized needs. Some factors may be at the base of the increased energy expenditure in CS such as heart defects, lung issues, infections, and endocrine dysfunction, but the intrinsic effect of *HRAS* mutation has otherwise been primarily considered.^{56,60}

GH and cortisol deficiencies were also observed in CS, sometimes associated to fasting hypoglycemia.^{61,62} The use of replacement therapy once GH deficiency is diagnosed is controversial due to comorbidities such as HCM, central nervous system (CNS) malformations, and obstructive apnea syndrome.⁶³ Routinely monitoring of growth velocity (every 6–12 months) by an experienced endocrinologist is strongly suggested in infancy, particularly in patients dropping below standard growth charts for CS.^{29,55,58}

Hypoglycemia has also been reported in the absence of pituitary gland and hypothalamus dysfunctions in humans, as well as hypercholesterolemia.⁵⁶ Similarly, metabolic changes have been reported by Oba et al in *HRAS* p.Gly12Ser knock-in mice, with growth failure and impaired fatty acid oxidation observed in mice fed with a high rich fat diet. Such findings confirm the roles that the RAS pathway and the *HRAS* gene have in metabolism regulation.^{64,65}

The risk of endocrinopathy and hypoglycemia should be assessed during prolonged fasting, as also by anesthesiologist when a surgical intervention is planned, and in some cases peri-operative glucose monitoring with steroid coverage may be considered.⁶⁶

Neurodevelopment and Central Nervous System (CNS) Morphology

Delay in neurodevelopmental milestones is almost universal in CS. A moderate to severe hypotonia is present since birth. Physical therapy (at least 2 to 3 times per week), together with the use of orthosis and postural aids, is crucial to safely feed the baby and to improve the patient's outcome. Dystonia has also been anecdotally reported contributing to abnormal postures in children with CS;^{10,67,68} a therapeutic approach with trihexyphenidyl was recently reported in a patient, showing improvement of posture and gait.⁶⁹

Cognitive impairment is always present, ranging in severity from mild to moderate or severe forms. A comprehensive neurological assessment by clinical neurological evaluation and cognitive tests needs to be performed on a regular basis. Monitoring by a child neurologist and possibly physiatrist is indicated every 3 to 6 months in small children (till 4 to 5 years) and every 6 to 12 months later on. Annual evaluation of cognitive performances and adaptive behavior profile is also recommended in pediatric age (Table 2). A high rate of individuals affected by CS show autism spectrum disorder (ASD) traits especially during early infancy, with restlessness, extreme shyness, speech delays, and aversion to touch and auditory stimuli often reported.^{70,71}

Another striking feature of CS is the relative macrocephaly, probably due to megalencephaly. Hyperplasia and increased differentiation towards astroglial cells were observed in induced pluripotent stem cells (iPSCs) carrying *HRAS* G12S, while in mouse models homozygous for *HRAS* G12V variant increased brain weight, surface area of cortex, striatum, and corpus callosum were reported.^{72,73} These models partly explain the CNS abnormalities reported in individuals with CS. It has been hypothesized that the posterior cranial fossa crowding found in patients with CS might be due either to an increased cerebellar volume in a relatively normal cranial fossa,⁷⁴ or to a hypoplastic cranial fossa, reduced cerebrospinal fluid (CSF) spaces, and an altered anatomy of the foramen magnum with relatively normal cerebellar dimensions.⁷⁵ Either way the result is a posterior fossa crowding with consequent cerebellar tonsillar herniation, often configuring as a true Chiari type I malformation. Such tonsillar herniation sometimes results in medullary compression, consequent hydrocephalus, syrinx, or hydromyelia.

CNS malformations reported are mostly asymptomatic, but feeding difficulties, respiratory distress and/or apnea, ocular palsy, arching, and headache, consistent with compression of medulla oblongata and upper cervical spine, need to be carefully monitored (Table 2).

Surgical interventions with shunt placements or ventriculostomy are the most reported neurosurgical procedures. Posterior fossa decompression is also often performed to improve severe symptoms when present.

For all the above-mentioned reasons, magnetic resonance imaging (MRI) of both brain and spine needs to be performed soon after diagnosis of CS, and personalized follow-up strategies based on major findings are mandatory. If the first MRI screening exam results are negative for CNS involvement, a subsequent MRI after two to three years, or as soon as symptoms are reported, is kindly suggested. In the presence of CNS abnormalities, follow-up schedules are personalized according to individual features (Table 2). Noteworthy, reduced prevalence of neurological abnormalities has been observed in individuals carrying the p.Gly13Cys variant (Table 1).²⁷

Cardio-Respiratory Issues

Individuals affected by CS, as with other RASopathies, require a careful cardiological evaluation at birth and/or at diagnosis. Congenital heart defects (CHD) and HCM are frequently found in CS and represent major contributors to morbidity and may be a cause of early death.^{29,66,76–79} Heart failure and cardiocirculatory collapse have also been reported as cause of death in some infants.²¹ Pulmonary valve stenosis (PVS), dysplasia, mitral valve defects, and other valve abnormalities were also described.^{15,19,20,23,51,80,81}

Electrocardiographic (ECG) anomalies such as arrhythmias (usually supraventricular tachycardia) may occur both during fetal and postnatal life; HCM is not usually present prenatally or at birth, but it subsequently develops.⁵¹ Therefore, a comprehensive cardiac evaluation with echocardiography, ECG, and cardiological evaluation needs to be routinely performed since birth, to carefully monitor HCM development and rhythmic anomalies (Table 2). HCM can be heterogeneous: either reversal, resolution, or progression has been reported. Pharmacological treatment is usually recommended as first-line therapy in cases of progression of HCM, but sometimes it is not sufficient to prevent its evolution; in such cases, surgical treatment (septal myectomy) is necessary to prevent congestive heart failure (CHF) that contributes to the worsening of clinical symptoms.^{78,79,82–84}

A subset of rarely occurring variants in *HRAS* have been associated with more severe phenotypes characterized by premature deaths often due to either cardiocirculatory or respiratory causes or multi-organ failure. Structural abnormalities, such as cardiomegaly, PVS, biventricular and septal hypertrophy, and patent foramen ovale, and conduction disturbances, such as atrial and ventricular tachyarrhythmias, have been reported in patients heterozygous for the p. Gly12Glu, p.Gly12Cys, p.Gly12Asp, and p.Gly12Val substitutions (Table 1).^{21,25}

In case of surgical intervention, preoperative ECG and echocardiogram should always be performed to screen for HCM and other complications.

Disorders concerning the respiratory system have not been frequently reported in literature, but they are commonly referred to by caregivers, especially in children. Abnormalities of both upper and lower airway tract are frequent findings, as is also a high incidence of postnatal respiratory distress, which is not necessarily associated with prematurity. As for cardiac involvement, it was shown that rare variants, such as p.Gly12Cys, p.Gly12Asp, p.Gly12Glu, and p.Gly12Val, are associated to increased morbidity and mortality linked to respiratory (and cardiac) impairment, with death within the first months of life often due to respiratory/heart failure (Table 1). In case of prenatal diagnosis of CS, especially when due to such specific variants, respiratory complications should be expected, and, after a careful evaluation, a management strategy should be planned to face a severe cardio-respiratory phenotype.

Adenoid/tonsillar hypertrophy, upper airway obstruction leading to obstructive sleep apnea (OSA), pharyngomalacia, laryngomalacia, tracheo-bronchomalacia, bronchiectasis, bronchopulmonary dysplasia, lung hypoplasia, and pulmonary vascular dysplasia are some of the reported respiratory abnormalities.^{85,86} Screening of sleep quality is often necessary, sometimes with the aid of a sleep diary, to investigate the presence of sleep disorders; if positive, ENT evaluation combined with overnight polysomnography to search for OSA is suggested (Table 2).

When planning surgery, anesthesiologists should be aware of the difficult airway management in patients with CS. The abovementioned abnormalities along with macroglossia, small jaw, airway papillomata, and scoliosis should always be assessed to choose the safest intubation.^{66,77}

Ocular Findings

Ophthalmologists are among the most visited medical specialists by CS patients in infancy since vision problems and other ocular issues are common findings.⁸⁷ Refractive errors are present in most individuals, but strabismus, nystagmus, and optic nerve anomalies were also observed. As in other RASopathies, palpebral ptosis is common.^{53,88}

Retinal dystrophy was observed in two boys with p.Gly13Cys, both having nystagmus, photophobia, and abnormal findings at electroretinogram examination (Table 2).⁸⁹

Recently, bilateral anterior capsular plaque and anterior lenticular opacities were described in a CS patient, suggesting the necessity of accurate anterior chamber examination.⁹⁰

The large number of ocular manifestations in CS underline the importance of early and periodic ophthalmological assessment. A first evaluation should be performed as soon as a diagnosis of CS is established. During infancy, an eye exam with fundus oculi every 6 months is recommended, at least till 3 years of life, to prevent a long-term vision impairment, and subsequently annually or based on major findings (Table 2). Precocious visual function rehabilitation should be performed in highly qualified centers together with physical therapy; this is crucial to improve visual impairment and overall quality of life in CS patients.

Ancillary Disciplines in Pediatric CS Population

Orthopedic Problems and Bone Impairment

The musculoskeletal system is deeply compromised in CS, with individuals carrying the common p.Gly12Ser variant having a more severe and impacting phenotype, and the less recurrent p.Gly13Cys variant associated to milder manifestations (Table 1).²⁷

Most characteristic findings in pediatric age are ulnar deviation of fingers, anterior chest wall abnormalities, tight Achilles tendons, and pes planus. Most of these manifestations do not require surgical treatment in pediatric age with the exception of tight heel-cords. In fact, the use of orthosis from walking age may both prevent the evolution towards severe tight heel-cords, and may be useful to improve the outcome of surgical treatment, when required, together with adequate physical therapy (several times per week). Therefore, proper orthopedic assessment and treatment from young age are necessary to avoid worsening of the phenotype and loss of autonomy.

Spine is commonly affected in CS with kyphosis and/or scoliosis. Spine X-ray is necessary when a clinical diagnosis of spine abnormalities is present, to monitor the evolution over time of deformities widely ranging from mild to severe (dystrophic scoliosis). Given the high prevalence of hip dysplasia reported, hip X-ray as a screening method during infancy is fundamental, also to exclude a coxa valga subluxans (Table 2).^{10,91}

Bone assessment by the age of 5 years with dual-energy X-ray absorptiometry exam (DEXA-scan) and biomarkers of bone metabolism dosage every two years may help clinicians to prevent and to timely treat a vitamin D insufficiency and bone mineral density reduction (Table 2).⁹²

Dermatologic Evaluation

As in most RASopathies, the integumentary system in CS is affected. Some ectodermal features do not have any functional implication and only contribute to the recognizable phenotype of individuals with CS, such as sparse and curly hair, deep palmar and plantar creases and pachydermatoglyphia. Papillomata, which usually develop in the nasal and perianal regions, are not present during early infancy but mostly occur in childhood. They have no malignant potential, and they are most often removed for aesthetic reasons or due to frequent itching.

Other features, such as cutis laxa, palmoplantar keratoderma, hyperkeratosis, and eczema, may appear as secondary issues, but taken together they may have a significant effect on patients'/families' quality of life. Some parents also reported an unusual body odor.^{2,93,94} Hyper-pigmented lesions and melanocytic nevi have been reported in CS, sometimes with potential malignant evolution (see below). For this reason, an annual clinical and dermatoscopic evaluation by a dermatologist is strongly suggested (Table 2).

Tumor Surveillance

As reported by Kratz et al in 2015, CS is a tumor-predisposing syndrome, with affected children having a 42.4-times increased risk to develop cancer compared to the general population of the same age.^{11,12} The most frequently reported solid tumors in childhood are neuroblastoma (NBS) and rhabdomyosarcoma (RMS), while bladder carcinoma has generally been observed during adolescence and adulthood.⁹⁵ As recommended by the consensus guidelines for CS, an abdominal ultrasound (US) every 3–6 months, or according to symptomatology, is recommended to check for internal organ tumors (Table 2).

Routine clinical surveillance with a general physical examination is the only way to detect the presence of RMS.²⁹

Since transitional cell carcinoma of the bladder has been reported from the second decade, screening protocols should start at the age of 10, with physical-chemical urine examination, urine cytology, and cystoscopy. The last-mentioned examination, even though more invasive, may allow all bladder lesions to be detected and histologically characterized (Table 2).⁹⁶

Based on available data in literature, most cases of patients with CS who developed tumors (RMS, ganglioneuroblastoma, or bladder carcinoma) carry the p.Gly12Ser or p.Gly12Ala variants. Two patients with p.Gly12Cys developed RMS (Table 1).^{15,97} No data about tumors in patients with rarer variants or with intragenic duplications have been reported to date, therefore a clear-cut genotype–phenotype correlation concerning tumor risk according to specific *HRAS* variants has not been performed yet. This bias could be related to the rarity of CS, the lack of long-term follow-up, and the paucity of variants different from the more prevalent ones.²⁸

Core and Ancillary Medical Specialties in Adult Age: Changing Medical Specialties According to Phenotype Evolution Over Time

The more accurate management of CS from young ages has led to an increased life expectancy; therefore, it has become necessary to improve assessment strategies according to the natural history of the disorder. During adult age, centers specialized in rare disorders acquire a supportive role, guiding major clinical decisions but having a minor function in everyday issues. Unfortunately, difficulties in finding effective management plans have been reported by most adult individuals affected by CS when they had to find a general practitioner or an occupational therapist,⁸⁷ underlining a significant healthcare gap in the transition process from infancy to adulthood and a more challenging management of medical problems in adult age. The multidisciplinary approach is still necessary to take care of overall comorbidities. Within them musculoskeletal and bone issues surely require a primary attention (Figure 2B).

Core Disciplines in Adult CS Population

Orthopedics Problems and Bone Impairment

Since orthopedic manifestations have a huge effect on quality of life and functional abilities, proper management of such issues is crucial in adult age.⁹⁸ Therefore, the multidisciplinary team should always include orthopedists, physical therapists, and an expert on bone metabolism (Table 2). During follow-up visits, the 6 minutes walking test (6MWT), Pediatrics Outcomes Data Collection Instrument (PODCI), and other functional tests might be useful tools to evaluate both progression and functional implications of skeletal abnormalities.^{10,98} Hip X-ray to monitor a coxa valga subluxans is suggested also during adolescence (Table 2).⁹⁹ Both clinical and radiological evaluation of spinal abnormalities is essential to monitor possible worsening in adult age due to the intrinsic role played by RAS/MAPK pathway on bone cells.^{10,87,91,99–101}

All bone deformities evolve over time in CS, resulting in more difficult surgical interventions;¹⁰ therefore, the prompt recognition and treatment of such problems leads to easier and quicker post-surgery clinical outcome. The most commonly performed surgeries are tendon releases (performed in infancy and/or adult age), hip osteotomy, and spinal fusion.⁸⁷

Another issue to take into consideration in adults concerns the reduced bone mineral density that occurs in individuals with CS, generally in association with a constitutional decrease of 25-OH vitamin D.^{92,102} Observed osteopenia/osteoporosis has also been reported in some anecdotal cases of vertebral crush fractures and bone pain.¹⁰⁰ As also suggested in individuals affected by CFCS,¹⁰³ the abovementioned findings highlight the importance of monitoring bone homeostasis in all individuals with CS with DEXA-scan and bone biomarkers of bone metabolism every 24 months

based on basal findings and personalized needs (Table 2). As it was often reported to be constitutionally low, high-dose vitamin D supplementation therapy according to patients' basal levels and needs is strongly suggested from pediatric to adult age to at least maintain stable vitamin D levels and bone density.^{92,102}

Given their peculiar phenotype, individuals with CS acquire an atypical posture, with an anteriorly flexed trunk, flexed elbows and wrists. Also small and large joint contractures are reported.¹⁰⁰ Muscles are severely impaired too, with generalized hypotrophy that may be due to alterations during myoblast differentiation.¹⁰ Such reported skeletal abnormalities, together with small and large joint contractures, are most probably involved in the chronic pain commonly reported in CS.^{98,104} This is further worsened by hypo-/hypertonia, which alters both static and dynamic posture.¹⁰⁴ Given all these issues, it is of utmost importance for orthopedics and physical therapists to share decision-making and plan together a timely monitoring of muscle-skeletal assessment in adults with CS.^{29,91}

Dermatologic Evaluation

In adults, dermatological findings may progress over time, with severe calluses, hyperpigmented and xerotic skin, and acanthosis nigricans being more frequently present. Antihistaminic oral therapy and topical treatment with moisturizing to improve patient' discomfort due to continuous itching are often necessary. Periorificial papillomata do persist in adult age, and they can be removed only surgically or with local treatment.

In all RASopathies a higher number of nevi compared to the general population was reported, and an increased risk to develop atypical lesions when the number of nevi was >30 was observed. It was also observed that mutations in downstream components of the RAS pathway, such as those resulting in hyperactivation of the BRAF, MAP2K1, and MAP2K2 kinases, may predispose to an increased number of nevi.¹⁰⁵

Since melanoma in situ and melanocytoma were anecdotally reported in CS,¹⁰⁶ a careful skin assessment through clinical and dermatoscopic examination by an expert dermatologist should be performed every 12 months in the adult population according to the patients' needs, to promptly remove atypical lesions and to provide a histopathological analysis (Table 2).

Tumor Surveillance in Adult Age

Data from literature provide evidence of reduced risk to develop RMS and NBS in adult life, whereas transitional cell carcinoma of the bladder seems to be particularly frequent both in adolescence and young adults with CS.¹⁰⁰ Bladder lesions are often asymptomatic, therefore abdominal US and urinalysis may not be sufficient to detect low-grade lesions. Cystoscopy should therefore be implemented as screening, diagnostic, and therapeutic intervention to remove any detected bladder lesion before its evolution towards malignancy (Table 2).⁹⁶

Ancillary Disciplines in Adult CS Population

Nutrition

After infancy/early childhood, feeding problems are no longer an issue. Adult individuals with CS usually do not present anymore oral motor dysfunction with swallowing difficulties, and neither aversion to food nor vomiting. Their families often report that they have an appropriate and balanced diet. Anyway, since some disturbances persist, follow-up evaluation by gastroenterologists is still recommended.

Constipation and abdominal pain, consistently to what was found in other RASopathies, are the issues that are most often reported.¹⁰⁴ Such pain may be attributed to a visceral hypersensitivity and therefore has a functional origin. Sometimes also gastroesophageal reflux disease (GERD) may persist in adult age, and therefore adequate pharmacological therapy is required.

Neuro-Psychological Issues

Besides reported anatomical and functional neurological abnormalities, consistent with the role played by the RAS pathway in neuronal function and plasticity, cognitive impairment is always present, with ID reported in the vast majority of patients with CS.^{107–109}

While in infancy a shy personality with autism disorder traits is reported, by the age of eight to ten years they are extremely sociable and happy.¹¹⁰ Some authors speculated that such improvement occurs as feeding issues resolve, as it

also occurs in patients affected by other neurodevelopmental disorders.¹¹¹ Socialization was reported as a relative strength in individuals affected by CS, while more issues were encountered in daily living skills.¹¹²

Nevertheless, consistently to what was observed in other RASopathies,¹¹³ psychiatric disorders such as depression, anxiety, and separation anxiety have been commonly reported, especially in male individuals with CS, who showed a superior number of maladaptive behaviors. To target such specific issues, after a primary neuropsychological evaluation, psychotherapy and behavioral therapy may be useful, and also medications in the most severe cases of anxiety to avoid any functional implication in everyday activities.¹¹⁴

Epileptic seizures are a rare finding in patients with CS, even though different electroencephalographic (EEG) abnormalities have been reported in literature.¹¹⁵

Cardiological Issues

Based on cardiological evaluation performed in pediatric age, a comprehensive cardiological assessment needs to be performed during the entire lifespan of affected patients. Considering the available data reporting either improvement, stabilization, or worsening of HCM during life, yearly cardiac US follow-up is strongly suggested. Moreover, based on the few case reports of sudden death in CS, and the risk to develop fatal arrhythmias, yearly ECG exam is also recommended (Table 2).

Ophthalmologic Findings

Ocular disorders reported in CS are a common cause of vision loss, with subsequent decline in the quality of life. Therefore, proper ophthalmologic evaluation with accurate fundus oculi exam should be performed every year throughout the life of individuals with CS, or with a personalized timing according to patients' needs. Visual rehabilitation therapy in specialized centers is fundamental to avoid further deterioration of visual capacity in the presence of ocular disorders (Table 2).

Discussion

In recent years, thanks to the understanding of the genetic basis of diseases, better knowledge of medical comorbidities, and implementation of personalized treatments, life expectancy for individuals affected by CS has significantly increased. Nevertheless, the pathogenetic mechanisms underlying some of the varied medical issues characterizing this disorder are still not clear, making the development of new treatments and follow-up strategies challenging. Overall, a multidisciplinary assessment is undeniably required to effectively take care of affected patients and their families, and to monitor and promptly treat comorbidities as soon as they occur. A close multisystem evaluation especially during infancy, childhood, and young ages dramatically improves the outcome of young patients. In detail, a multidisciplinary team involving pediatricians, gastroenterologists, nutritionists, endocrinologists, child neurologists, and physical therapists is required to address the failure to thrive that characterizes the first years of life of individuals with CS. The recent documentation of increased basal metabolism and resting energy expenditure surely needs to be supported by future studies on larger cohorts to confirm its negative impact on growth and metabolic profile.^{56,60}

A regular overall neurological assessment by a child neurologist and the routine rehabilitative therapies performed by physical, speech, and occupational therapists are crucial to improve quality of life, to support families, and to reach best outcomes during patients' lifespan. Changes in behavioral phenotype are frequently found in CS, with irritability during infancy and early childhood, and a more friendly and sociable attitude in adulthood, compared to all other RASopathies,¹¹³ requiring specific support by specialized doctors.

Cardiologists need to be included in the multidisciplinary team since birth to help in defining correct timing and strategies of follow-up according to the evolution over time of a cardiac phenotype characterized by HCM and arrhythmias. Pneumological evaluation is also recommended from pediatric age to exclude OSA or other pulmonary involvement mostly associated to rare variants with worse phenotypes.

Ophthalmological evaluation is recommended from birth since vision deterioration could have a negative impact on neurodevelopment, limiting social interactions and the improvement of life skills.

Orthopedists are other fundamental figures in the multidisciplinary team given the worsening musculoskeletal involvement in CS. Furthermore, the recent reports about reduction in BMD both in pediatric and adult individuals with CS, sometimes associated to an increased risk of fractures in adult age, need to be supported by further studies to understand the underlying pathogenetic mechanisms caused by *HRAS* mutation and to develop proper treatments.

A comprehensive dermatological assessment by specialized dermatologists should be routinely performed at least yearly to improve troublesome symptoms such as itching and sweating, and to monitor the progression of melanocytic nevi.

While cancer risk is now well-recognized, dedicated studies should be performed to define the prevalence and risk of tumor development more accurately as well as to properly address the issue of personalized screening protocols.

RAS GTPases function as molecular switches controlling a major intracellular signaling network that, depending on the cellular context, guides diverse biological functions, including cell fate determination, proliferation, survival, differentiation, migration, and senescence. This multifaced role is attained by the control of a number of signaling pathways mediating different cellular processes. Among these, the MAPK and PI3K/AKT/mTOR pathways are commonly dysregulated in cancer, and components of these cascades have been identified as targets for therapeutic intervention.^{116,117} Indeed the development of therapies targeting these pathways has opened a way to approach RASopathies by selective inhibition of the dysregulated cascades implicated in pathogenesis.^{118,119} First evidence of such potential beneficial effects is supported by the recent approval of MEK inhibitors (MEKi) such as selumetinib for the treatment of symptomatic inoperable plexiform neurofibromas in children affected by NF1.^{120,121} Recent evidences also support the use of trametinib for the treatment of HCM in Noonan syndrome.¹²² The use of selective MEKi, as hopefully other new targeted molecules, may be promising for early treatment or even the reversal of manifestations associated to enhanced activity of the MAPK pathway. A certain efficacy in preventing the development of RASopathy features was proven in 2015 in animal models by prenatal administration of MEKi.¹²³ Recent preclinical studies proved that inhibition of MEK could improve the myopathy associated to *HRAS* G12V variant.¹²⁴ Unfortunately, MEKi have a narrow therapeutic index, but their toxicities may be controlled by intermittent dosing. Furthermore, the combination of such molecules with RAF monomer inhibitors (which instead help ERK signaling pathway in normal cells) may be a promising therapeutic strategy to avoid adverse effects.¹²⁵

Besides the MAPK signaling cascade, overexpression of CS-causing *HRAS* mutants has been demonstrated to result in variably enhanced growth factor-dependent stimulation of the PI3K-AKT-mTOR pathway in multiple experimental in vitro systems.^{44,126} These considerations suggest that targeting of both pathways might be required for an effective managing of the evolutive complications of CS. It should be also noted that the PI3K/AKT/mTOR and MAPK cascades are interconnected with multiple points of convergence, cross-talk, and feedback loops. The presence of compensatory loops able to cross-activate one pathway following the blockade of the other has been demonstrated.^{126,127} Based on these considerations, the blockade of both pathways with a combined targeted approach should be taken into account.

Another treatment opportunity could be represented by farnesyl transferase inhibitors (FTi) such as tipifarnib, as it suppresses *HRAS* function, whereas *NRAS* and *KRAS* overcome its effects.^{69,118,125} Future studies considering other RASopathies may be promising, even if the rarity of the disease, the relatively young age of the affected population, interpatient variability, and the possible long-term evolution of such disorders may represent a challenge for clinical trial development.^{128,129}

Similarly to other rare diseases, CS represents a continuous challenge both for patients and their physicians. Starting from being diagnosed, several issues are faced by the family of a patient with CS, such as receiving optimal care and the financial burden of disease-specific treatments. Moreover, physicians struggle to obtain enough knowledge and understanding of the condition, especially in primary centers. This is the reason for which it is of great importance to collect relatively large cohorts of patients to evaluate and follow throughout their lives.¹³⁰ Primary care physicians' role is to manage patients' care together with specialized centers and facilitate communication with families and local health services. Specialized hospitals have a major role during the entire life of patients: the management of complex care needs, especially in pediatric age, the possible inclusion in research initiatives, multicenter studies, and enrollment in clinical trials for the development of new experimental therapies thereafter. It is of utmost importance for patients and

families to develop mutual trust and understanding with their primary care physician, the other specialized clinicians, and researchers taking care of their condition.¹³¹

The presence of clinical guidelines for CS makes their actual management easier;²⁹ however, many points should still be addressed to improve care and outcomes of patients affected by this syndrome. The diagnosis of a rare disease such as CS, with all its consequences, may represent a big concern for patients and their families, often becoming a cause of loneliness and isolation from society. Not only patients but also caregivers struggle, especially when adapting to a new routine and abruptly changing their everyday life and their perception of normality. In such situations, when families are spending most of their times actively looking for answers, social support may be missing, having a great impact on psychological health of caregivers. Several issues are often associated to the rarity of the disease, and to the nonexistent comparison with peers. For this reason, family support groups represent a significant resource for individuals affected by CS and their families/caregivers. They allow an easier circulation of important information and provide emotional and social support, consequently improving psychological health of caregivers. Support groups allow the patients to encounter other people with the same conditions, with whom they can share similar life experiences, thoughts, concerns, and feelings, acquiring a sense of community, allowing close interpersonal relationships outside the family environment and to develop coping mechanisms to face everyday struggles.^{131–134} Furthermore, international support communities may allow productive collaborations with clinicians and researchers, allowing a better everyday care, and also provide interesting insights and ideas for further studies and trials.¹³⁵

To conclude, CS represents a clinically complex rare condition for which good clinical management recommendations are available in literature.²⁹ However, given the advancing knowledge about comorbidities, and the only few data about adult patients and the lack of personalized target therapies, great efforts are required both by clinicians and by basic scientists to better understand the disease mechanisms leading to clinical manifestations. Future works, such as longitudinal natural history studies, are required to provide further knowledge and develop effective treatment strategies.

The comprehensive routine monitoring of patients with CS through a strong multidisciplinary network involving specialized centers, local health services, and family doctors is necessary to achieve the best patient outcomes, to improve assessment protocols on this rare disorder, and to support families during lifetime changes of care needs both based on the natural history of CS and personalized requirements. It is of utmost importance for healthcare providers, especially those who do not routinely care for individuals affected by CS, to follow existing clinical guidelines and recommendations to improve the quality of life and increase life expectancy of their patients.

Abbreviations

CS, Costello syndrome; MAPK, mitogen activated protein kinase; NF1, neurofibromatosis type 1; NS, Noonan syndrome; CFCS, cardio-facio-cutaneous syndrome; NS/LAH, Noonan syndrome with loose anagen hair; NSML, Noonan syndrome with multiple lentigines; CBLs, CBL-mutation associated syndrome; DD, developmental delay; ID, intellectual disability; HCM, hypertrophic cardiomyopathy; ng-tube, nasogastric tube; g-tube, gastrostomy tube; CNS, central nervous system; ASD, autism spectrum disorder; iPSCs, induced pluripotent stem cells; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; CHD, congenital heart defect; PVS, pulmonary valve stenosis; ECG, electrocardiography; CHF, congestive heart failure; OSA, obstructive sleep apnea; DEXA, dual-energy X-ray absorptiometry; NBS, neuroblastoma; RMS, rhabdomyosarcoma; US, ultrasound; 6MWT, six minutes walking test; PODCI, Pediatrics Outcomes Data Collection Instrument; MEKi, MEK inhibitors; FTi, farnesyl transferase inhibitors.

Author Consent

All authors meet authorship criteria. Nobody who qualified for authorship has been excluded.

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