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Healthcare recommendations for Joubert syndrome

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CONFLICT OF INTEREST

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Abstract

Joubert syndrome (JS) is a recessive neurodevelopmental disorder defined by a characteristic cerebellar and brainstem malformation recognizable on axial brain magnetic resonance imaging as the “Molar Tooth Sign”. Although defined by the neurological features, JS is associated with clinical features affecting many other organ systems, particularly progressive involvement of the retina, kidney, and liver. JS is a rare condition; therefore, many affected individuals may not have easy access to subspecialty providers familiar with JS (e.g., geneticists, neurologists, developmental pediatricians, ophthalmologists, nephrologists, hepatologists, psychiatrists, therapists, and educators). Expert recommendations can enable practitioners of all types to provide quality care to individuals with JS and know when to refer for subspecialty care. This need will only increase as precision treatments targeting specific genetic causes of JS emerge. The goal of these recommendations is to provide a resource for general practitioners, subspecialists, and families to maximize the health of individuals with JS throughout the lifespan.

Keywords

Joubert syndrome; ciliopathy; treatment; retina; kidney; liver

1 | INTRODUCTION

Joubert syndrome (JS, MIM PS213300) is a recessive neurodevelopmental disorder defined by a characteristic cerebellar and brainstem malformation recognizable on axial brain magnetic resonance imaging (MRI) as the “Molar Tooth Sign” (MTS; Joubert, Eisenring, Robb, & Andermann, 1969; Maria et al., 1997). This appearance results from a combination of abnormalities: cerebellar vermis aplasia/hypoplasia, thick and horizontally oriented superior cerebellar peduncles, and often, a deep interpeduncular fossa. Clinically, individuals with JS typically present as infants with hypotonia, abnormal eye movements, respiratory control disturbances, and as children or adults, ataxia and/or cognitive impairment (Doherty, 2009; Parisi & Glass, 1993; Romani, Micalizzi, & Valente, 2013). In addition to these core features, the majority of individuals with JS also have involvement of other body systems including the eye, kidney, liver, and skeleton (Bachmann-Gagescu et al., 2015). Therefore, rather than a purely neurological condition, JS is a multisystem disorder in which several of the additional features may be progressive, thereby substantially complicating medical management. While the diagnosis is often made initially in the setting of a neurology, genetics, or developmental pediatrics clinic, the frequent involvement of other organ systems means that monitoring for complications is required, with referral to the corresponding subspecialists when specific organ involvement is suspected. The purpose of this review is to provide management recommendations to minimize medical complications and maximize quality of life for individuals with JS. We hope to address a broad audience including

families, primary care providers and subspecialists, since JS is rare, and few providers have experience with more than a handful of affected individuals.

Given that JS is rare (prevalence estimated at 1/55,000–1/200,000; Kroes, Fransen van de Putte, Ravesloot, & Lindhout, 2007; Nuovo et al., in press; Parisi & Glass, 1993), the present recommendations represent a consensus of expert opinion, based on observed outcomes in JS and extrapolation from more common disorders. In general, these recommendations focus on the goals of monitoring and treatment without being directive as to which medical specialists or techniques are most appropriate, since the availability of subspecialists and specific medical technologies varies widely. Some of the evaluations and treatments mentioned in these recommendations are not available in all healthcare settings, so we try to provide options that will work in a variety of healthcare environments.

JS is part of the larger group of disorders called ciliopathies, based on shared genetic causes and overlapping phenotypes related to dysfunction of the primary cilium (Reiter & Leroux, 2017). Therefore, some of the present recommendations may be useful for individuals with other related ciliopathies, in particular nephronophthisis (MIM PS256100), Leber congenital amaurosis (MIM PS204000), Senior-Løken syndrome (MIM PS266900), acrocallosal syndrome (MIM 200990), oral-facial-digital syndromes (MIM PS311200), or MORM (“Mental retardation, truncal Obesity, Retinal dystrophy, and Micropenis”) syndrome (MIM 610156).

2 | METHODS

We reviewed the medical literature from the time of the initial description of JS (Joubert et al., 1969) to the present. The estimated prevalence of features is based on a cohort of >600 individuals with JS (“University of Washington (UW) cohort”; Bachmann-Gagescu, Dempsey et al., 2015), an overlapping series of 100 individuals with JS evaluated through the intramural National Institutes of Health research protocol “Clinical and Molecular Investigations Into Ciliopathies” (ClinicalTrials.gov, NCT00068224—“The NIH cohort”), and the literature. The NIH cohort appears enriched for liver involvement and coloboma compared to other cohorts; this may be due to differences in enrollment, assessment for clinical features, or other factors. No trials of monitoring strategies or treatments have been performed in individuals with JS; therefore, the recommendations below are based on professional judgment of the authors and extrapolation from paradigms for similar issues in other populations.

2.1 | Clinical diagnosis of JS: Diagnostic criteria

For the purpose of this article, the diagnosis of JS requires the presence of the MTS on axial brain MRI (or computed tomography [CT]) of optimal quality, including thin sections through the posterior fossa (Figure 1a). Despite widespread publication of the imaging features of JS, the diagnosis is initially missed in a substantial number of individuals, so review by an experienced pediatric neuroradiologist, neurologist, or other practitioner with specific knowledge of JS can be critical. In some individuals, the features of the MTS are not captured in a single image and must be reconstructed from multiple images. Superior cerebellar dysplasia on axial view (Figure 1b), thick, horizontally oriented superior

cerebellar peduncles (Figure 1c,e) and elevated roof of the fourth ventricle (Figure 1d) on sagittal views, as well as a cleft vermis on coronal view (Figure 1f) can also be helpful. Diffusion tensor imaging has been used to highlight deficient midline crossing (decussation) of the superior cerebellar peduncle tracts near the red nucleus, which appears to be present in the majority of individuals (Poretti et al., 2007; Widjaja, Blaser, & Raybaud, 2006). Multiple additional brain anomalies have been described in individuals with JS as described in the Section 2.3.1 below.

Not surprisingly, individuals with a subtle MTS or without the full combination of imaging features that result in the MTS can still have pathogenic variants in genes associated with JS (unpublished observations and (Enokizono et al., 2017; Parisi et al., 2004; Shaheen et al., 2016)). The risk of retinal, kidney, and liver involvement in individuals with partial imaging features of JS is unknown.

In the absence of an appropriate brain MRI, a provisional diagnosis of JS can be made based on classic features of hypotonia, developmental delay, ataxia, ocular motor apraxia, and respiratory rhythm disturbances (tachypnea and/or apnea), along with cerebellar vermis hypoplasia by ultrasound or CT imaging. JS is not associated with an easily recognizable facial appearance; however, some distinctive facial features, such as a prominent lower jaw, are shared by many individuals and can be supportive of the diagnosis (Braddock, Henley, & Maria, 2007; Maria, Boltshauser, Palmer, & Tran, 1999).

Prenatally, the possibility of JS can be raised by cerebellar vermis hypoplasia detected on routine ultrasound. Fetal MRI may be helpful in further delineating anomalies identified by ultrasound (Aslan et al., 2002; Doherty et al., 2005; Fluss et al., 2006; Saleem & Zaki, 2010); however, the typical MTS is often not detected prenatally (unpublished observations). In pregnant women with a prior affected child, the finding of definite vermis hypoplasia on ultrasound or MRI can be considered diagnostic. In the absence of a family history, the reliability of prenatal diagnosis by imaging is unknown; however, a combination of cerebellar vermis hypoplasia with other distinctive JS/ciliary features such as polydactyly, or enlarged, cystic, or echogenic kidneys may suggest a JS diagnosis even in the absence of a family history.

The differential diagnosis for JS includes other disorders with anomalies of the posterior fossa such as Dandy–Walker malformation, Poretti–Boltshauser syndrome (MIM 615960), and other conditions associated with ataxia and/or cerebellar vermis hypoplasia. Many children with JS are first given a diagnosis of ocular motor apraxia, or ataxic cerebral palsy before the MTS is identified. The differential diagnosis also includes genetically and phenotypically overlapping ciliopathies such as Meckel syndrome (MIM PS249000) which likely represents the severe end of a Joubert-Meckel spectrum, oral-facial-digital (MIM PS311200), acrocallosal (MIM200990), Mainzer-Saldino (MIM 266920), COACH (MIM 216360, Cerebellar vermis hypo/aplasia, Oligophrenia, Ataxia, ocular Coloboma, and Hepatic fibrosis), or hydrolethalus (MIM PS236680) syndromes. For the purpose of this review, we include all individuals with the MTS under the umbrella of JS, even if they have other clinical features consistent with other diagnostic categories. This includes diagnostic categories such as Joubert Syndrome and Related Disorders, cerebellorenal syndromes, as

well as subtypes of JS defined by features out-side the brain such as JS with renal involvement or JS with oral-facial-digital features (Brancati, Dallapiccola, & Valente, 2010; Parisi & Glass, 2003). In fact, only a minority of people with JS have isolated brain involvement. When individuals with JS have atypical clinical features (particularly in consanguineous families), the possibility of a second unrelated genetic disorder should be considered and additional genetic testing beyond known ciliopathy genes may be warranted.

2.2 | Molecular diagnosis of JS

JS can be caused by pathogenic variants in >35 genes (Table 1). Biallelic pathogenic variants (or hemizygous pathogenic *OFD1* variants) in one of the known JS-associated genes can be identified in 50–92% of individuals with JS depending on the cohort, sequencing method and criteria for causal variants (Bachmann-Gagescu, Dempsey, et al., 2015; Shaheen et al., 2016; Vilboux and others, 2017). In two overlapping cohorts, 5–6 genes (*AHI1*, *CC2D2A*, *CEP290*, *CPLANE1*, *KIAA0586*, and *TMEM67*) account for 40–70% of families (Bachmann-Gagescu, Dempsey, et al., 2015; Vilboux and others, 2017). Given this substantial genetic heterogeneity (i.e., multiple genetic causes for the same phenotype), and the fact that no single variant or gene predominates, the most time-efficient and economical means of molecular diagnosis can be achieved through next-generation sequencing (NGS) of either a panel of known JS genes, an exome (protein coding regions), or a genome (all DNA that can be sequenced). These latter methods have the advantage of requiring no specific set-up or updating as additional genes are associated with the phenotype.

For several ethnic groups, initial sequencing for common founder variants may be logical. Specifically, the *TMEM216* p.R73L variant is common in individuals of Ashkenazi origin and *TMEM237* p.R18* is common in Hutterites (Edvardson et al., 2010; Huang et al., 2011). In French Canadians, several recurring *CPLANE1*, *CC2D2A*, and *TMEM231* pathogenic variants have been identified, so genetic testing can be prioritized by ethnic background (Srour, Hamdan, et al., 2012; Srour, Schwartzentruber, et al., 2012); however, these associations are not sufficient to enable reliable prediction of the genetic cause based on the phenotypes, so sequencing of all JS-associated genes by NGS is often preferable.

The motivation underlying the identification of a molecular diagnosis, besides confirming the clinical diagnosis of JS and providing information regarding recurrence risk/family planning, lies in the known gene-phenotype correlations (Bachmann-Gagescu, Dempsey, et al., 2015; Brancati et al., 2007; Brancati et al., 2009; Doherty et al., 2010; Vilboux and others, 2017). Indeed, these correlations can be used to adjust the frequency of monitoring for progressive features such as retinal dystrophy and kidney disease, as described in Tables 3 and 4 and the Section 2.5 below. Furthermore, it may be prudent to avoid nephrotoxic medications in individuals at the highest risk for kidney involvement, without unnecessarily restricting these medications in those at low risk. In the future, the genetic diagnosis may determine eligibility for specific therapies such as gene-specific medications, antisense oligonucleotide treatments, or gene therapy (see Section 2.6 below).

2.3 | System-by-system review of potential clinical issues

2.3.1 | Neurodevelopmental—Essentially all individuals with JS experience hypotonia and motor delays during infancy and early childhood, usually evolving to ataxia as they get older. Abnormal eye movements and abnormal respiratory control are also seen in most, but may be subtle. Cognition is impaired in most, although a minority of individuals have IQs in the normal range (Bulgheroni et al., 2016; Fennell, Gitten, Dede, & Maria, 1999; Gitten, Dede, Fennell, Quisling, & Maria, 1998; Summers et al., 2017). In general, adaptive function correlates with cognitive function (Bulgheroni et al., 2016; Summers et al., 2017). However, slowed processing speed is common, so neuropsychological and school evaluations should examine both full scale intelligence quotient (FSIQ) and the generalized ability index (GAI) or similar measures to help contextualize the individual's intellectual abilities. Because the GAI relies less on speeded and motor tasks, a more accurate representation of cognitive abilities may be ascertained from this or similar scores than from a traditional measure of FSIQ. Developmental outcome studies must be interpreted with caution due to potential ascertainment biases (for more or less severely affected individuals) and difficulties measuring IQ in the presence of significant motor, communication, and visual impairments. Regardless, the range of neurodevelopmental outcome is very broad. Speech production is impacted out of proportion to language comprehension due to oral motor apraxia (Braddock, Farmer, Deidrick, Iverson, & Maria, 2006). Periodic developmental monitoring is required, as well as standard therapies (physical, occupational, and speech/language) and educational interventions to build on areas of strength and target areas of weakness. No specific types of therapy have been shown to be more or less effective in this population. Motor issues, particularly the ataxia and the ocular motor apraxia, appear to improve as children mature. Most children with JS eventually walk independently, although a subset requires wheelchairs for some or all mobility.

Multiple additional brain anomalies have been described in individuals with JS (Bachmann-Gagescu, Dempsey, et al., 2015; Poretti et al., 2017), most commonly cerebellar hemisphere enlargement, malrotation of the hippocampi, ventriculomegaly, dysgenesis of the corpus callosum, polymicrogyria, heterotopia, and occipital encephalocele. While vermis size and abnormal EEG have been associated with severity of neurodevelopmental outcome (Poretti et al., 2017; Summers et al., 2017), no imaging or clinical features can reliably predict neurodevelopmental outcome in a given individual. It is suspected that additional major brain malformations, multiorgan involvement, chronic mechanical ventilation, and sensory impairments are associated with higher risk of more severely abnormal neurodevelopmental outcomes.

Ptosis, strabismus, and abnormal eye movements including nystagmus and ocular motor apraxia are neurologically based vision issues which may be present to some degree in all individuals (Brooks et al., 2018; Khan et al., 2008; Sturm et al., 2010; Weiss et al., 2009). In particular, ocular motor apraxia (head thrusting to shift gaze) is characteristic of JS, although it can be seen in other conditions. While visual acuity is often normal and eye movements tend to improve with time, abnormal smooth pursuit and saccades likely result in some degree of functional visual impairment, particularly when objects or the individual's head are moving.

Seizures have been described in a number of individuals with JS (minimum prevalence 10%; Bachmann-Gagescu, Dempsey, et al., 2015) and must be specifically sought out during recording of the medical history. No single seizure type appears to dominate and there is no evidence to suggest that antiepileptic treatments should differ from those administered to individuals with non-JS associated epilepsy. While ventriculomegaly is noted relatively frequently on MRIs of individuals with JS, true hydrocephalus requiring treatment is rare. However, since this complication is treatable and can have adverse consequences if left untreated, regular monitoring by measurement of head circumference is recommended in young children. A small number of individuals have dystonic movements (often facial grimacing) and bite their tongues and cheeks. This is a particularly difficult problem, and no successful treatments have been published (Farmer, Deidrick, Gitten, Fennell, & Maria, 2006). Apparent temperature regulation problems have also been reported including episodic unexplained fevers (resulting in infectious disease evaluations) and heat intolerance associated with decreased function during hot weather (unpublished observations). The prevalence of these features is unknown.

A variety of behavioral and psychiatric issues have been reported in individuals with JS including tantrums, self-injury, autism, depression, anxiety, and auditory hallucinations (Bachmann-Gagescu, Dempsey, et al., 2015; Bulgheroni et al., 2016; Fennell et al., 1999; Summers et al., 2017). These issues can have an enormous impact on the quality of life for people with JS and their families. Parent-reported Child Behavior Checklist data were available for 45/76 individuals who received a neuropsychological evaluation at NIH. Scores were elevated across all scales except for the externalizing behaviors summary scale (e.g., aggression and tantrums), indicating increased rates of behavioral issues compared to the general population (Summers et al., 2017). Data on psychiatric diagnoses in JS is exceedingly scarce; however, in an Italian cohort of 54 directly-evaluated individuals, 39% were reported to have behavioral issues, and 7% were diagnosed with psychiatric conditions (two with oppositional defiant disorder and two with bipolar disorder; Bulgheroni et al., 2016). Within the NIH sample, individuals with JS took psychiatric medications at a higher rate than rates reported in typically developing children and adults; however, the rate of psychiatric medications in individuals with JS appears to be lower than rates reported in other populations with intellectual and developmental disabilities, more generally (Howie, Pastor, & Lukacs, 2014; Jonas, Gu, & Albertorio-Diaz, 2013). Furthermore, within the NIH sample, those with JS who had a greater degree of intellectual disability also appear to receive more psychiatric medications (Summers et al., 2017). Circadian rhythm abnormalities and behavioral sleep disturbances have been reported but not formally assessed (Kamdar, Nandkumar, Krishnan, Gamaldo, & Collop, 2011).

Additional research is needed to fully delineate the spectrum of neurobehavioral and psychiatric issues. Similar to neurobehavioral and psychiatric issues in other populations affected by neurodevelopmental conditions, these issues are treated with behavioral interventions appropriate for the individual (e.g., parent-child interaction therapy, applied behavioral analysis, cognitive-behavioral therapy, and other therapies), counseling, and medications when necessary. Optimizing the treatment of any medical issues is an essential component of neurobehavioral and psychiatric care, since pain and illness can exacerbate behavioral issues.

2.3.2 | Eyes and vision—In addition to the neurologically based eye issues mentioned above, visual function may be impacted by coloboma, retinal dysfunction, optic atrophy, and refractive error. Coloboma results from abnormal closure of the optic cup during development, and usually affects the retina or optic nerve, but rarely the iris in JS. Typically, colobomata involving the macula or optic nerve cause visual impairment. Retinal dysfunction in JS is likely the direct result of problems with the photoreceptor outer segment, which is a highly modified cilium. Retinal dystrophy can be apparent at birth or lead to progressive decline in vision due to degenerating photoreceptors. Retinal abnormalities can be confirmed by an ERG (ElectroRetinoGram) which would show decreased electrical responses in the retina, or OCT (Optical Coherence Tomography) which would show abnormal layering of the retina with atrophy. Although poorly detailed in the literature, the retinal dystrophy can range from congenital retinal blindness diagnosed in infancy (Leber Congenital Amaurosis) to a slowly progressive degeneration that can result in nyctalopia (night blindness) or eventual blindness after the second decade (Coene et al., 2009). Retinal involvement (defined as abnormal ERG, abnormal OCT, and/or abnormal retinal pigment with visual impairment) was present in 30% of individuals in the UW cohort, while coloboma was seen in ~17% (Bachmann-Gagescu, Dempsey, et al., 2015). In the overlapping, directly evaluated NIH cohort, 24% had retinal dystrophy, 28% had coloboma, and 9% had optic nerve atrophy (Brooks et al., 2018). Some genetic causes (e.g., *CEP290* and *AHI1* dysfunction) are more likely to be associated with more severe retinal degeneration than others (e.g., *INPP5E*, *MKS1*, and *NPHP1* dysfunction).

While ptosis is common, it rarely obstructs vision enough to require treatment. Significant refractive error (both myopia and hyperopia) have also been reported and can be treated with corrective spectacles. Patients with significant (“high”) myopia should be monitored for retinal detachment by yearly dilated retinal examination. Strabismus (ocular misalignment) is also common and may lead to amblyopia (“lazy eye”), a preventable form of vision loss if caught early enough. Surgical treatment of strabismus should be approached with caution, as the strabismus is often variable in JS (Brooks et al., 2018). Given the potential overlap with Poretti-Boltshauser syndrome (Aldinger et al., 2014; Poretti et al., 2014), high myopia should prompt a re-review of the MRI for cerebellar hemisphere dysplasia, cerebellar cysts, and patchy increased T2/FLAIR signal in the cortical white matter, characteristic of Poretti-Boltshauser syndrome.

Loss of visual function may go unrecognized in individuals with cognitive impairment, further limiting their developmental potential and interaction with the world; therefore, it is important to assess for visual impairment early and provide supportive measures to affected individuals and their families as soon as possible. Interventions should aim at improving quality of life. Ideally, a baseline assessment for the issues described above would be performed by a pediatric ophthalmologist when JS is diagnosed or suspected. Regular follow-up ophthalmological evaluations are warranted for surveillance and treatment of the issues described above.

2.3.3 | Kidney—Fibrocystic kidney disease develops in 25–30% of individuals, and frequently progresses to end-stage renal disease (ESRD; Bachmann-Gagescu, Dempsey, et al., 2015; Fleming et al., 2017). Of the 29 individuals with kidney involvement in the NIH

cohort, 31% had nephronophthisis, 35% had an overlap-phenotype of autosomal recessive polycystic kidney disease/nephronophthisis, 10% had a unilateral multicystic dysplastic kidney, and 24% had indeterminate-type cystic kidney disease (Fleming et al., 2017). Initially, individuals with nephronophthisis may display polyuria and polydipsia. Subsets of individuals can present with a kidney phenotype similar to autosomal recessive polycystic kidney disease with prenatal onset of enlarged kidneys and early onset hypertension (Fleming et al., 2017; Gunay-Aygun et al., 2009). The minimal prevalence for ESRD in the UW cohort was 5.1% (n = 30/586, 24 received a kidney transplant; Bachmann-Gagescu, Dempsey, et al., 2015), while in an overlapping cohort of individuals evaluated directly, the prevalence was 13% (n = 13/97, 11 received a kidney transplant; Fleming et al., 2017). Kidney failure appears to be the leading cause of death in JS individuals over 1 year of age, but ESRD has also been observed in infants (Dempsey et al., 2017). Anemia is a common clinical finding in those with nephronophthisis, often noted to be more severe than expected given the level of kidney dysfunction. Poor weight gain or feeding issues can also be associated with kidney dysfunction. While no specific treatments to cure or slow the progression of nephronophthisis are currently available, the goals of early diagnosis are to maintain quality of life and limit complications of chronic kidney disease (CKD) including anemia, bone mineral loss, malnutrition, and poor somatic growth. Although not systematically evaluated, the risk posed by nephrotoxic medications such as aminoglycosides may be increased, so these medications should be avoided when possible. Likewise, non-steroidal anti-inflammatory drugs should be used with caution.

Individuals should be monitored for signs and symptoms of CKD including at least yearly blood pressure measurements and laboratory testing for serum electrolytes, calcium, phosphorus, creatinine, blood urea nitrogen (BUN), and blood count with hematocrit/hemoglobin. Urine concentrating ability may provide an effective means of monitoring for CKD in JS. In one study of 93 individuals with JS, CKD was predicted in >75% with urine osmolality <600 mOsm/kg, and CKD was significantly increased in patients with an early diagnosis of isolated urinary concentrating defect (Nuovo et al., 2018). Estimated glomerular filtration rate in children (Schwartz et al., 2012) and adults (Levey et al., 2009) should be monitored by serum creatinine or creatinine and cystatin C when available, since cystatin C may be more accurate in patients with limited muscle mass.

Kidney ultrasound may be useful for identifying kidney involvement (altered size, increased echogenicity, loss of corticomedullary differentiation, or overt cysts); however, the value of periodic kidney ultrasounds for follow-up is unclear, since ultrasonographic appearance does not reflect kidney function, which guides medical management. Follow-up for kidney involvement should rely primarily on history, physical examination, and blood and urine tests. Therefore, we recommend a kidney ultrasound at diagnosis to evaluate for genitourinary malformations and establish the presence or absence of kidney involvement. It is reasonable to get a second ultrasound during adolescence, and in addition, kidneys may be evaluated periodically during the abdominal ultrasounds performed to follow spleen size (see below).

2.3.4 | Liver—Many individuals with JS have chronically elevated transaminases and GGT (Gamma-glutamyl transferase; Bachmann-Gagescu, Dempsey, et al., 2015; Strongin et

al., 2018; Vilboux and others, 2017); however, only a small subset of individuals with JS develop hepatic fibrosis severe enough to result in portal hypertension. Nonetheless, variceal bleeding can be a serious or even fatal complication. In the UW cohort, at least 13 individuals had portal hypertension indicating a minimal prevalence of 2% (four had splenomegaly, two had esophageal varices, six received a porto-systemic shunt, and three received liver transplantation). In the overlapping NIH cohort, 41% had elevated liver enzymes and 13% had probable or definite portal hypertension (Strongin et al., 2018).

The goal of monitoring is to identify and treat portal hypertension to avoid variceal bleeding. Preferred monitoring includes serial platelet measurements looking for a decreasing trend, and serial abdominal ultrasounds (every 2–3 years) looking for abnormal increase in spleen size (Gunay-Aygun et al., 2013). Chronically elevated transaminases and GGT may indicate increased risk for portal hypertension (Strongin et al., 2018). Possible gastrointestinal bleeding in individuals with JS must be evaluated urgently, with strong consideration of endoscopy to evaluate for esophageal varices. Treatment for varices is not JS-specific and can involve sclerotherapy, banding, porto-systemic shunt placement, and liver transplantation may be needed in rare cases.

Differing from cirrhosis, the liver disease in JS and other ciliopathies (congenital hepatic fibrosis) does not impair the synthetic function of the liver (Gunay-Aygun, Gahl, & Heller, 2008); therefore, individuals with JS do not appear to be at higher risk for complications from hepatotoxic medications, unless they have other risk factors such as hepatitis or liver transplantation. All children with JS should receive vaccinations against hepatitis A and B. Liver biopsy is generally not indicated in individuals with confirmed JS, since the results do not change treatment which is focused on the sequelae of portal hypertension. Liver cysts and enlarged intrahepatic bile ducts (e.g., Caroli syndrome), observed in other ciliopathies, have not been seen in JS, so the risk for cholangitis does not appear to be increased.

2.3.5 | Other gastrointestinal complications—A subset of individuals has feeding difficulties, likely due to bulbar dysfunction. Aspiration is also frequently reported. Individuals with poor weight gain or recurrent respiratory infections should be evaluated for swallow dysfunction and aspiration. Treatment can include feeding therapy from a speech or occupational therapist, and short- or long-term tube feedings may be required. In a large cohort, the minimal prevalence of tube feedings was 10% (8% G-tube and 2% nasogastric tube; Bachmann-Gagescu, Dempsey, et al., 2015). Drooling can also be a chronic issue associated with skin breakdown and social difficulties. Treatments can involve positioning, oral-motor therapy, oral medications, and injected botulinum toxin. While a few individuals have been reported with JS and Hirschsprung disease (manifested by intractable constipation), this appears to be a rare or chance association (Brancati et al., 2010; Ozyurek, Kayacik, Gungor, & Karagoz, 2008). On the other hand, constipation unrelated to Hirschsprung disease is common in JS. Management of constipation should therefore first rely on medical measures, and in case of intractable symptoms, evaluation for Hirschsprung disease and other causes should be initiated.

2.3.6 | Respiratory—Abnormal respiratory control has been clearly documented in infants and children with JS by polygraphic recordings, characterized by episodes of apnea,

tachypnea, and/or hyperpnea (Boltshauser, Herdan, Dumermuth, & Isler, 1981; Joubert et al., 1969). Abnormal respiratory patterns and sleep behaviors have also been described more recently by caregiver report (Kamdar et al., 2011), and compared to their siblings (unpublished). Although not explicitly documented in the literature, our experience indicates that the respiratory control abnormalities improve with age in most patients. Nonetheless, in some individuals, respiratory control abnormalities are severe enough to warrant chronic ventilation (Mercado, Pedraza, Mayol, Rodriguez Santana, & Tejeda, 1991). In a retrospective study of individuals with JS who had died, apnea and respiratory failure were the leading causes of death in children under 1 year of age but were also the cause of death in multiple individuals older than 1 year of age (Dempsey et al., 2017). Older children and adults with JS have an increased risk of central and obstructive sleep-disordered breathing compared to population data, especially if they are obese (Andermann, Andermann, Ptito, Fontaine, & Joubert, 1999; Wolfe, Lakadamyali, & Mutlu, 2010). Sleep-disordered breathing can also cause or worsen neurobehavioral issues (Witmans & Young, 2011), and if untreated, lead to pulmonary hypertension. No systematic data exist to guide monitoring, but at a minimum, surveillance should include yearly history and examination for sleep and breathing disturbances. Capillary blood gas and electrolytes in younger children and those with obesity can help identify hypoventilation. Sleep medicine consultation or polysomnography should be considered for symptomatic individuals. Rare individuals with JS additionally have restrictive lung disease due to co-existing skeletal dysplasia such as Jeune syndrome (Halbritter et al., 2013; Lehman et al., 2010; Shaheen et al., 2015; Tuz et al., 2014). Several male individuals with hemizygous *OFD1* variants have been reported to have recurrent respiratory infections similar to individuals with primary ciliary dyskinesia (unpublished; Budny et al., 2006; Coene et al., 2009; Hannah et al., 2019); however, additional research is required to determine whether individuals with JS are at increased risk for respiratory issues due to abnormal mucociliary clearance. Clinicians should consider evaluation for primary ciliary dyskinesia in individuals with JS and recurrent respiratory infections. Severely affected individuals are at risk for chronic respiratory failure and aspiration pneumonia.

2.3.7 | Endocrine—Various endocrinological abnormalities are increased in individuals with JS, such as central diabetes insipidus, premature puberty, hypothyroidism, growth hormone deficiency, and/or panhypopituitarism, affecting together 4% (Bachmann-Gagescu, Dempsey, et al., 2015). An additional 1–2% have Type I diabetes mellitus, hypothyroidism, polycystic ovarian syndrome, and ovarian “failure” which may or may not be increased in JS. Short stature and growth hormone deficiency have also been reported (Bachmann-Gagescu, Dempsey, et al., 2015; Stephen et al., 2017; Vilboux, Malicdan, et al., 2017); therefore, we recommend closely monitoring for symptoms of hypothyroidism, dehydration or fluid overload, poor linear growth, and precocious or delayed pubertal development. As noted above, problems with linear growth or polyuria/urinary concentrating defects may also be related to kidney involvement.

2.3.8 | Musculoskeletal—Similar to other individuals with hypotonia, those with JS have an increased risk for scoliosis which is present in at least 5% of individuals (Bachmann-Gagescu, Dempsey, et al., 2015); however, it rarely requires treatment.

Monitoring for scoliosis by physical examination should be performed every 1–2 years until growth is complete. Referral to an orthopedic surgeon is indicated if the scoliosis may progress to the point that it causes restrictive respiratory disease, difficulty with upright posture, and/or pain. Fifteen percent of individuals have polydactyly (Bachmann-Gagescu, Dempsey, et al., 2015) that can be left alone or surgically addressed, depending on the stability of the extra digits, difficulty fitting into shoes and gloves, and family preference. In a few families, skeletal dysplasia is present in addition to typical JS features, so that a mixed Joubert-Jeune syndrome phenotype is observed (Bachmann-Gagescu, Phelps, et al., 2015; Halbritter et al., 2013; Malicdan et al., 2015; Tuz et al., 2014).

2.3.9 | Cardiovascular—Rare individuals with severe complex congenital heart disease have been reported (Karp, Grosse-Wortmann, & Bowdin, 2012); however, only 1–2% of individuals have congenital heart disease, including atrial septal defect, coarctation of the aorta, bicuspid aortic valve, and aortic stenosis (Bachmann-Gagescu, Dempsey, et al., 2015). Individuals with murmurs, cyanosis, poor perfusion, and other manifestations of possible congenital heart disease should be evaluated by a pediatric cardiologist. The utility of a screening echocardiogram has not been evaluated. In the United States, screening all newborns for congenital heart disease by physical examination and pulse oximetry is recommended as part of standard newborn screening programs (Oster et al., 2016).

2.3.10 | Ear, nose, and throat—A variety of oral manifestations including tongue hamartomas, additional frenulae (under the tongue and between the cheeks and gums), and cleft lip/palate have been reported, illustrating the phenotypic overlap between JS and oral-facial-digital syndrome(s) (Poretti et al., 2012; Thauvin-Robinet et al., 2014). In a small cohort of 22 individuals with JS, conductive hearing loss was reported in six, and mild sensorineural hearing loss was reported in three, all of them older than 17 years of age (Kroes et al., 2010). In contrast, the prevalence of hearing loss in a larger cohort was 3%, which is still substantially higher than the 1–2/1,000 population prevalence in children (Bachmann-Gagescu, Dempsey, et al., 2015; Fortnum, Summerfield, Marshall, Davis, & Bamford, 2001). No systematic data indicate that individuals with JS should be screened for hearing loss differently than other individuals; however, it is important to have a low threshold for audiology evaluation, since many forms of hearing loss are treatable, and even mild hearing loss can adversely affect speech/language development.

2.3.11 | Sedation and anesthesia—Individuals with JS may require sedation for a variety of procedures, most commonly dental care. Given their known structural abnormalities of the brainstem, central respiratory control problems, airway hypotonia and swallow dysfunction, they should be considered high risk for anesthesia. In at least 20 individuals reported in the literature, apnea is a common complication, sometimes requiring airway intervention such as intubation or mask airway (Atalay, Soylu, & Tekcan, 2016; Bhaskar et al., 2013; Buntenbroich & Dullenkopf, 2013a, 2013b; Galante, Meola, Cinnella, & Dambrosio, 2009; Habre, Sims, & D'Souza, 1997; Matthews, 1989; Platis et al., 2006; Sriganesh et al., 2014; Sriganesh, Smita, & Aravind, 2010; Vodopich & Gordon, 2004). Some authors suggest avoiding sedatives known to be associated with central respiratory depression, and avoiding unnecessary conscious sedation for brief, uncomplicated

procedures such as MRI when possible; however, insufficient evidence exists to provide specific guidelines for individuals with JS. To ensure timely and appropriate management of potential complications, interventions that require sedation or anesthesia should be performed at hospitals equipped to handle any complications that may ensue.

Individuals with JS often have complex medical histories, making it imperative for them to be evaluated by an anesthesiology professional well in advance of elective sedation or anesthesia. This allows time for appropriate clinical evaluation and any required additional testing, ensuring that the anesthesiology professional and facility are as prepared as possible. Meeting with the family can also help educate the anesthesiology professional about the affected individual and about JS, since it is a rare condition and likely not well known to the provider. When anesthesia consultation is not possible prior to the procedure, it is imperative to ask for the anesthesia professional to meet the individual and the caregiver on the day of surgery. A full health history should be reviewed including medical issues, prior anesthetic exposures, and current medications (including any supplements). Allowing a caregiver to accompany an affected individual during induction of anesthesia may minimize pretreatment with sedatives. In addition, we recommend adherence to procedures for high-risk individuals and prolonged observation after sedation to evaluate for apnea.

2.4 | Genetic counseling

Genetic counseling about the mechanism of inheritance, recurrence risk, genetic testing, and reproductive options is the standard of care for individuals with JS and their families. To date, only autosomal recessive and X-linked inheritance mechanisms have been demonstrated for JS. With autosomal recessive inheritance, parents of an affected child have a 25% recurrence risk with each pregnancy, and unaffected siblings have a 67% risk of being carriers. Since the carrier frequency for any given JS gene in outbred populations is <1/500, the risk of a carrier having an affected child with an unrelated partner in outbred populations is <1/2,000. For the one X-linked gene (OFD1), the recurrence risk is also 25% (50% of sons); 50% of unaffected daughters are carriers, and all unaffected sons are noncarriers. Recurrence risk counseling in consanguineous and founder populations (e.g., Ashkenazi Jews, Hutterites, French Canadians, and others) require individualized calculations. While little is known about fertility in individuals with JS, several women have had children; therefore, teenagers and adults with JS should be counseled about recurrence risk for people with rare recessive conditions at a level appropriate to their understanding. Oligogenic inheritance, where variants in >1 gene are required to cause a disorder, has been proposed to play a role in ciliopathies (Hoefele et al., 2007; Katsanis et al., 2001), but no definitive examples have been published in JS (Abu-Safieh et al., 2012; Phelps et al., 2018); therefore, we recommend against clinical counseling for oligogenic inheritance at this time. For details about molecular confirmation of the diagnosis, see the Section 2.2 above.

Reproductive options for couples with a prior child or fetus affected by JS are best explored through formal genetic counseling. Options to reduce the risk of having a second affected child may include preimplanation genetic diagnosis for a known pathogenic variant, use of donor egg or sperm, prenatal diagnosis through chorionic villus sampling or amniocentesis, or adoption. Couples considering gamete donation should avoid donation by relatives, given

their increased risk of being carriers for the same pathogenic variant. For couples in whom the cause is unknown, egg donation may be preferred over sperm donation since the mother may be a carrier for a pathogenic *OFD1* variant. Prenatal imaging such as ultrasound and fetal MRI may be used to evaluate for features of JS during pregnancy. Imaging abnormalities may suggest a diagnosis of JS, but the absence of abnormalities is not a guarantee that the fetus is unaffected. The decision to pursue or decline alternative reproductive options is very personal, and discussion with a geneticist or genetic counselor may provide an opportunity to explore all available options. In the United States, genetic counseling providers can be identified through the National Society of Genetic Counselors (www.nsgc.org).

2.5 | Adjusted follow-up recommendations based on gene-phenotype associations

While general healthcare recommendations apply to all individuals with JS, gene-phenotype correlations can be used to adjust management based on the specific underlying genetic etiology. *CEP290* dysfunction is strongly associated with retinal dystrophy and to a lesser extent kidney disease; therefore, individuals with *CEP290*-related JS should have more frequent monitoring for retinal and kidney disease as described above. Similarly, loss of *TMEM67* function is strongly associated with coloboma and liver fibrosis (Bachmann-Gagescu, Dempsey, etal., 2015; Brancati et al., 2007, 2009; Doherty et al., 2010; Vilboux and others, 2017), so monitoring for liver fibrosis should be performed more frequently. Weaker associations also support a higher risk for retinal disease with *AHI1*, and kidney disease with *TMEM67* and *RPGRIP1L*. Conversely, individuals with loss of *TMEM67* function appear less likely to develop retinal disease; consequently, less frequent monitoring of retinal involvement may be acceptable in these individuals (Bachmann-Gagescu, Dempsey, et al., 2015).

2.6 | Precision treatments

Precision treatments are treatments specifically targeting the genetic cause or biological mechanism of a disorder. Currently, precision treatments for JS are only available as part of research studies, if at all. Although not yet used for targeting a JS gene, gene therapy has been used to improve visual function for specific types of retinal dystrophy by direct retinal injection of expression vectors in humans (Russell et al., 2017). Future trials are likely to involve the *CEP290* gene, a major cause of Leber congenital amaurosis and JS (Maeder et al., 2019; Mookherjee et al., 2018). Alternatively, antisense oligonucleotides can augment gene function by blocking aberrant splicing (Cideciyan et al., 2019; Dulla et al., 2018) or by causing exons with deleterious variants to be skipped (Ramsbottom et al., 2018). These treatments are still in early development for JS, but have been used for other disorders in humans such as spinal muscular atrophy (Finkel et al., 2017). Future medications targeting specific pathways that are disrupted in JS may be beneficial, but this work is also in its infancy (Hynes et al., 2014; Kim et al., 2018). Some promising medications developed for ciliopathy-related conditions in animal models have been ineffective or harmful in humans (Ruggenenti et al., 2016; Serra et al., 2010; Walz et al., 2010); therefore, cautious optimism is in order about the timeline for future effective treatments.

2.7 | Family support

While caring for a loved one with significant healthcare needs and/or neurodevelopmental disability is often very rewarding, it can also be emotionally and cognitively challenging. Families in need can draw support from other family members, medical providers, mental health providers, social workers, community resources, and family support organizations like the Joubert Syndrome and Related Disorders Foundation (https://jsrdf.org), the Asociación de Familias con Síndrome de Joubert y Trastornos Relacionados (https://asociacionfabert.wixsite.com/fabert), Associazione Italiana Sindrome di Joubert e Atassie Congenite (http://www.aisjac.net), and the Ciliopathy Alliance (www.ciliopathyalliance.org). In addition, "respite care" can provide primary caregiver(s) breaks from caring for others so that they can rest and care for themselves. Information about respite care resources is available from a variety of providers, and at https://www.childwelfare.gov/topics/preventing/prevention-programs/respite/ and https://archrespite.org/respitelocator for the United States.

3 | CONCLUSIONS

Given the multisystem nature of JS in the majority of individuals, ideal clinical management requires careful regular follow up for early detection and optimal management of complications. To assist families in receiving the best medical care possible, one provider should take the lead, performing the baseline and follow-up evaluations (Tables 2-4), and referring the individual for specialized care when specific organs are involved. In this manner, all the relevant information for a given individual can be centralized for coordination of care. In addition to diagnostic, carrier, and prenatal testing, a molecular diagnosis allows prognostic substratification that can guide monitoring and treatment of progressive features. Moreover, gene-specific treatments may become available in the future and will require the knowledge of the gene defect in each individual.

Ongoing research is required to identify all of the genetic causes of JS so that every individual can receive a genetic diagnosis and ultimately precision healthcare tailored to that diagnosis. Further study of phenotypic outcomes will allow more precise prognostic information, including more accurate estimates of the age of onset and long-term evolution for each of the progressive features. In addition, less-characterized phenotypic features require systematic assessment, in particular, the behavioral and psychiatric issues that often present major problems for the affected individual and their family. Finally, existing supportive treatments need to be optimized and precision treatments need to be developed and implemented.

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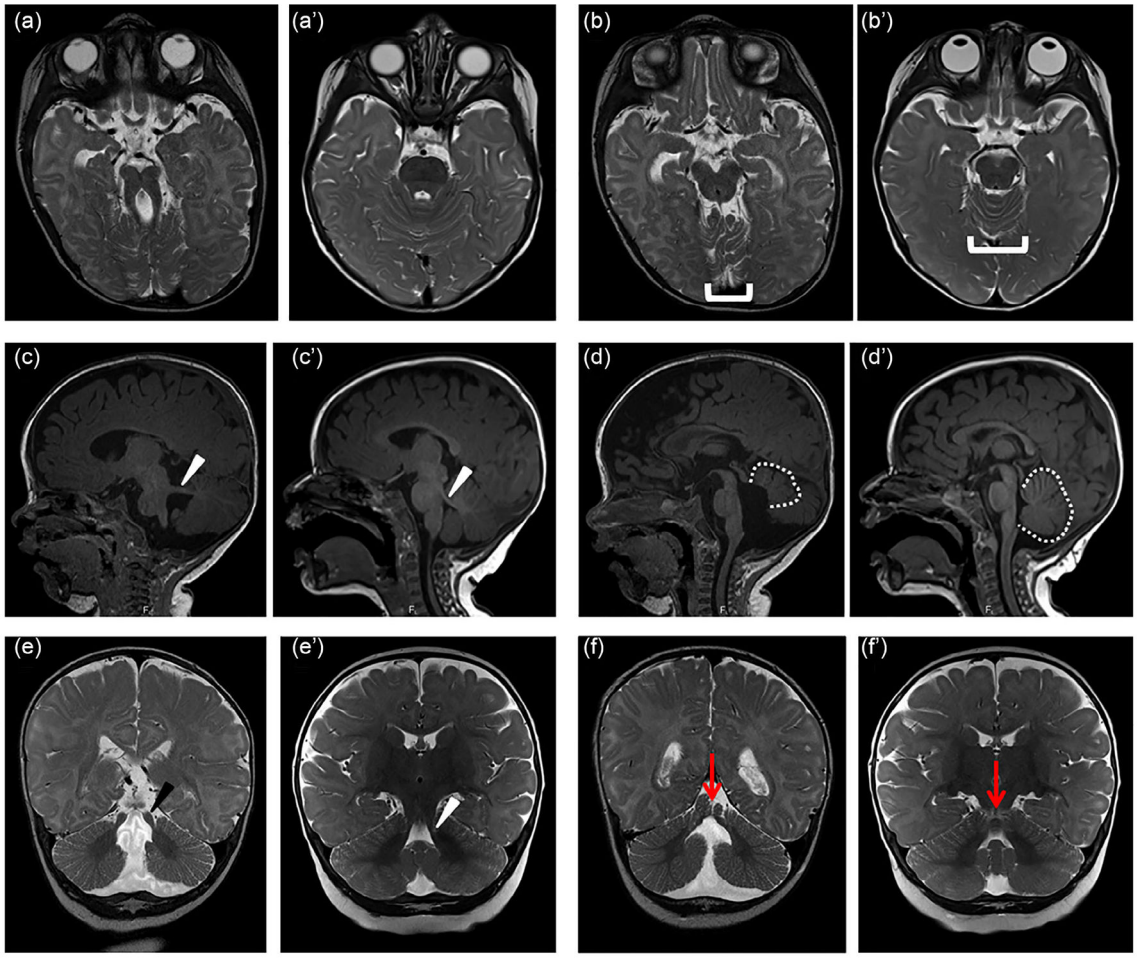

FIGURE 1.

Diagnostic features of Joubert syndrome on magnetic resonance imaging (MRI). (a) molar tooth sign (MTS) on T2-weighted axial images due to the combination of long, thick superior cerebellar peduncles (the roots of the tooth) and a deep interpeduncular fossa (the cutting surface of the tooth). This appearance is not always captured in a single plane, so it is important to evaluate the MRI as a whole rather than relying on a single image. (b) Superior cerebellar foliar dysplasia (bracket) on axial T2-weighted images, sometimes seen in the absence of the MTS in individuals carrying pathogenic variants in the JS-associated genes (note that the folia at this level are usually shaped like a U or V). (c) Horizontally oriented superior cerebellar peduncle (white arrowhead) on T1-weighted parasagittal image; (d) Vermis hypoplasia (outline), elevated roof of the fourth ventricle, and rostrally displaced fastigium on T1-weighted sagittal image; (e) Long, thick superior cerebellar peduncles (black arrowhead) T2-weighted coronal image; (f) Appearance of a cerebellar cleft (black arrow indicating fluid at the cerebellar midline) on T2-weighted coronal image. (a'-f') similar images from an unaffected individual of the same age

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TABLE 1

Genes associated with Joubert syndrome and risk of complications

Gene	Chr	%[a]	Retina[b]	Kidney[b]	Liver[b]	Other	References
AHI1	6	5–10	↑	-	-		Dixon-Salazar et al. (2004); Ferland et al. (2004)
ARL13B	3	<2	-	-	-		Cantagrel et al. (2008)
ARL3	10	Unk	-	-	-		Alkanderi et al. (2018)
ARMC9	2	<2	-	-	-		Van De Weghe et al. (2017)
B9D1	17	<2	-	-	-		Romani et al. (2014)
B9D2	19	<2	-	-	-		Bachmann-Gagescu, Dempsey, et al. (2015)
C2CD3	11	<2	-	-	-	Skeletal dysplasia	Thauvin-Robinet et al. (2014)
CC2D2A	4	5–10	-	-	-		Gorden et al. (2008)
CEP104	1	<2	-	-	-		Srour et al. (2015)
CEP120	5	Unk	-	-	-	Skeletal dysplasia	Roosing et al. (2016); Shaheen et al. (2015)
CEP290	12	5–10	↑↑	↑	-	Encephalocele	Sayer et al. (2006); Valente et al. (2006)
CEP41	7	<2	-	-	-		Lee et al. (2012)
CPLANE1	5	5–10	-	-	-	PD, OFD	Srour et al. (2012)
CSPP1	8	2–5	-	↓	-		Akizu et al. (2014); Shaheen et al. (2014); Tuz et al. (2014)
FAM149B1	10	Unk	-	-	-	PD, OFD	Shaheen et al. (2019)
HYLS1	11	<2	-	-	-		Oka et al. (2016)
IFT172	2	<2	-	-	-	Skeletal dysplasia	Halbritter et al. (2013)
INPP5E	9	2–5	-	-	-		Bielas et al. (2009)
KIAA0556	16	<2	-	-	-		Sanders et al. (2015)
KIAA0586	14	2–5	-	-	-		Bachmann-Gagescu et al. (2015); Malicdan et al. (2015); Stephen et al. (2015)
KIAA0753	17	<2	-	-	-		Chevrier et al. (2016)
KIF7	15	<2	-	-	-	ACC, PD, Skeletal dysplasia	Dafinger et al. (2011); Putoux et al. (2011)
MKS1	17	2–5	-	-	-		Romani et al. (2014)
NPHP1	2	<2	↑	↑↑	-		Parisi et al. (2004)
OFD1	X	<2	-	-	-	Encephalocele, OFD, PCD	Coene et al. (2009)
PDE6D	2	<2	-	-	-		Thomas et al. (2014)
PIBF1	13	<2	-	↑	-		Wheway et al. (2015)
RPGRIP1L	16	2–5	-	↑	-		Arts et al. (2007); Delous et al. (2007)

Gene	Chr	%[a]	Retina[b]	Kidney[b]	Liver[b]	Other	References
SUFU	10	Unk	-	-	-		De Mori et al. (2017)
TCTN1	12	<2	-	-	-		Garcia-Gonzalo et al. (2011)
TCTN2	12	<2	-	↑	-	Encephalocele, coloboma	Sang et al. (2011)
TCTN3	10	<2	-	-	-		Thomas et al. (2012)
TMEM107	17	<2	-	-	-	OFD	Lambacher et al. (2016)
TMEM138	11	<2	-	-	-		Lee et al. (2012)
TMEM216	11	2–5	-	-	-		Edvardson et al. (2010); Valente et al. (2010)
TMEM231	16	<2	-	-	-		Srour et al. (2012)
TMEM237	2	<2	-	-	-		Huang et al. (2011)
TMEM67	8	5–10	↓	↑	↑↑	Coloboma, PD	Baala et al. (2007)

Note: The following genes are not listed due to lack of sufficient evidence that they are associated with JS (only one family, insufficient clinical information, and/or lack of biallelic variants): *TTC21B* (no biallelic variants in JS, variants reported in families with other ciliopathies; Davis et al., 2011), *ZNF423* (one family with possible JS; Chaki et al., 2012), *CLUAP1* (one family with JS; Johnston et al., 2017), *EXOC8* (one family with JS; Dixon-Salazar et al., 2012), *CELSR2* (one family in each of two papers, variants not reported for one family; Shaheen et al., 2016; Vilboux et al., 2017), *POC1B* (one family; Beck et al., 2014), *CEP164* (one family with JS, variants reported in families with other ciliopathies; Chaki et al., 2012; Vilboux and others, 2017), *INTU* (insufficient imaging informaton in several patients with ciliopathy phenotypes; Bruel et al., 2017, 2018; Toriyama et al., 2016).

Abbreviations: ACC, agenesis of the corpus callosum; Chr, chromosome; OFD, oral facial digital features; PCD, primary ciliary dyskinesia; PD, polydactyly; Unk, unknown (not found in the UW cohort).

[a]Based on panel sequencing 572 families in the University of Washington cohort.

[b]↑ weak positive association, ↑↑ strong positive association, ↓ weak negative association, – no known statistical association (all studies to date are underpowered to identify small differences in risk associated with less frequent genetic causes). These features may have been reported in some individuals.

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TABLE 2

Prevalence, onset, and management of medical complications associated with Joubert syndrome

	Prevalence (%)[a]	Onset	Specialized tests/referrals to consider based on Hx/PE/routine tests	Management/treatment
Neurologic				
MTS	100	Congenital		
Encephalocele	8	Congenital	MRI, Neurosurgery consultation	Surgery if clinically indicated
Hydrocephalus	Rare	Unknown	MRI (or US or CT) if clinically indicated, Neurosurgery consultation	Shunt if clinically indicated
Dystonic episodes	Rare	Unknown	Neurology consultation	Behavioral (remove inciting factors), medication trials, tooth removal for severe biting
Seizures	>10	Unknown	EEG, Neurology consultation	Antiepileptic treatment as required
Feeding problems Dysphagia	Common	Congenital	Video fluoroscopic swallow study chest X-ray if s/s	Feeding therapy, thickened feeds, tube feeding
Cognitive and developmental delays	Common	Congenital	Standardized neurocognitive testing (private or school-based), annual school program planning[b]	Special education support Speech therapy, consider alternative communication strategies and/or augmentative communication devices Occupational therapy Physiotherapy
Ocular motor apraxia, ophthalmoplegia	~80	Congenital	Ophthalmology consultation	Supportive interventions for visual impairment
Behavior/psychiatric				
Self-injury, anxiety, stereotypies, depression, ADHD, hallucinations, sleep disturbances	Unknown	Early childhood to adulthood	Functional behavioral analysis, developmental pediatrics or psychiatry consultation, sleep medicine evaluation	Behavioral interventions, medications
Respiratory				
Abnormal respiratory control	~70	Congenital	Sleep medicine/pulmonology polysomnography	Respiratory support if indicated, home monitoring controversial, no evidence for or against caffeine
Obstructive apnea	Unknown	Neonatal to adulthood	Sleep medicine/pulmonology/ENT consultation polysomnography, echocardiogram	Supplementary oxygen, PAP, T/A, if indicated
Restrictive lung disease (w/skeletal dysplasia)	Rare	Congenital	Chest X-ray Pulmonology consultation	Respiratory support if indicated, thoracic expansion if indicated
Ophthalmology				
Strabismus	>31	Neonatal to adolescence	Cover-uncover test, Ophthalmology consultation	Spectacles, patching or pupillary dilation, surgery with caution due to underlying neurological abnormality
Ptosis	>19	Congenital	Ophthalmology consultation	Surgery if indicated
Retinal dystrophy	30	Neonatal to adulthood	Ophthalmology consultation, consider OCT, ERG, FAF if indicated	Supportive interventions for visual impairment

	Prevalence (%)[a]	Onset	Specialized tests/referrals to consider based on Hx/PE/routine tests	Management/treatment
Coloboma	17	Congenital	Ophthalmology consultation	Supportive interventions for visual impairment
Kidney				
Fibrocystic kidney disease/ nephronophthisis/cystic dysplasia	25	Neonatal to adulthood	Nephrology consultation bone density scan, kidney biopsy	Medications for support of decreasing kidney function; diagnosis and treatment of hypertension, prevention of dehydration in early disease and fluid overload in late disease; in case of ESKD: dialysis, kidney transplantation
Liver				
Congenital hepatic fibrosis	14	Congenital to adulthood	GI/hepatology consultation	Medications for management of portal hypertension ablation of varices, porto-systemic shunting if indicated, liver transplant
Musculoskeletal				
Polydactyly	15	Congenital	X-ray, orthopedics consultation	Surgery if indicated for functional or aesthetic reasons
Scoliosis	>5	Childhood-adulthood	X-ray, orthopedics consultation	Surgery if indicated for respiratory compromise or positioning (rare)
Skeletal dysplasia	Rare	Congenital	X-ray, skeletal dysplasia specialist consultation	Surgery if indicated for respiratory issues (rare)
Other				
Endocrine	4–6	Infancy to adulthood	Laboratory testing based on clinical suspicion	Hormone replacement as required
Congenital heart disease	Rare	Congenital	Echocardiogram, chest X-ray, cardiology consultation	Based on specific lesion
Hearing loss	~3	Neonatal to childhood	Audiology evaluation	Ear tubes for chronic otitis media, hearing aids, cochlear implants (rare)
Cleft palate	>3	Congenital	Craniofacial consultation	Surgery if indicated
Oral features, frenula, hamartoma	>4	Congenital	NA	Surgery if indicated (for function or comfort—rare)
Feeding difficulty, drooling	Common	Congenital	Clinical feeding evaluation, video fluoroscopic swallow study	Feeding therapy, tube feeding, medications for drooling
Genetics				
Molecular diagnosis	NA	NA	Genetics consultation, genetic testing	Prognostic, recurrence risk, and reproductive counseling, Stratification into different risk groups for specific complications, Assignment to future gene-specific treatments

Abbreviations: ADHD, attention deficit hyperactivity disorder; ENT, ear nose throat (otorhinolaryngology); ESKD, end-stage kidney disease; FAF, fundus auto-fluorescence; Hx, history; mvt, movement; PAP, positive airway pressure (continuous, bilevel, or other), PE, physical exam; s/s, signs and symptoms; T/A, tonsillectomy/adenoidectomy; US, ultrasound.

[a]Based on Bachmann-Gagescu, Dempsey et al., (2015), the prevalence of each feature likely depends on the specific population evaluated.

[b]Individualized Educational Plan (IEP) in the United States.

TABLE 3

History and physical exam checklist for managing medical provider

	At diagnosis	Routine (~yearly)	History	Physical examination
Neurologic—head				
Consequences of the MTS	X	X	Hypotonia, developmental delay, ataxia	Neurological exam
Encephalocele	X		"Bump on head?" (usually occipital)	Palpate skull
Hydrocephalus	X	X	Increasing head size (<2 yr), headaches, vomiting	OFC plot, fontanelles
Dystonic episodes	X	X	s/s	Muscle tone
Seizures	X	X	s/s	
Cognition/psychiatric/behavior	X	X	Self-injury, anxiety, stereotypies, depression, ADHD, hallucinations	Std. developmental and psychiatric assessments, focus on stereotypies, injury
Eyes				
Consequences of the MTS: ocular motor apraxia, nystagmus, ophthalmoplegia	X	X	Head shaking Tracking with head mvt	Focus on eye mvts
Strabismus	X	X	Eye deviation, head tilt	Pupillary alignment, cover-uncover test
Ptosis	X	X	Drooping eyelid, chin-up position (backward head tilt)	Drooping eyelid, chin-up position (backward head tilt)
Retinal dystrophy	X	X	Visual impairment particularly in low light, photophobia	Visual acuity
Coloboma	X		Visual impairment (only with macula or optic nerve involvement)	
Respiratory				
Consequences of the MTS: Abnormal respiratory control	X	X	Apnea, tachypnea, sleep disordered breathing	Std. Respiratory rhythm pulmonary (awake and asleep)
Obstructive apnea	X	X	Apnea, tachypnea, snoring, sleep disordered breathing	Focus on airway
Restrictive lung disease (w/ skeletal dysplasia)	X		Small chest, tachypnea, respiratory distress	Std. pulmonary
Kidney				
Fibrocystic kidney disease/nephronophthisis/ cystic dysplasia	X	X	Growth failure, anemia, polyuria, polydipsia, secondary enuresis, urinary concentration defect, osteopenia, fatigue, decreased appetite, hypertension, dehydration/fluid overload	Growth parameters, blood pressure, pallor
Liver				
Congenital hepatic fibrosis	X	X	s/s portal hypertension, splenomegaly, varices, GI bleeding	Splenomegaly, spider angiomata (chest, arms, and neck)
Musculoskeletal				
Polydactyly	X		Functional difficulty	Std. musculoskeletal
Scoliosis	X	X	Change in posture	

	At diagnosis	Routine (~yearly)	History	Physical examination
Skeletal Dysplasia	X		Short stature, small chest, short limbs, respiratory status	
Other				
Endocrine	X	X	s/s growth failure, hypothyroidism, diabetes mellitus, micropenis, abnormal puberty	Heart rate, blood pressure, growth parameters, genital exam
Congenital heart disease	X		Murmur, feeding, or exercise intolerance	Heart rate, blood pressure (arm and leg), oxygen saturation, cardiac exam, consider echocardiogram
Hearing loss	X	X	Delayed speech, decreased response to sounds	Newborn and annual hearing screening
Cleft palate	X		Nasal speech, nasal regurgitation, feeding difficulties	Std. oral
Oral features, frenula, hamartoma	X		s/s	

Abbreviations: ADHD, attention deficit hyperactivity disorder; MTS, molar tooth sign; mvt, movement; OFC, occipital-frontal circumference; s/s, signs and symptoms; std., standard.

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TABLE 4

Lab and imaging test checklist (ordered by managing medical provider, with referral to specialists as required based on findings)

	At diagnosis	Approximate interval (years)	As required based on Hx/PE/routine findings	Abnormal test results reflect involvement				
			As required based on Hx/PE/routine findings	Renal	Liver	Resp	Retinal	Other
Blood/urine tests								
Molecular genetic diagnosis	X							
CBC	X	1–2	X	anemia	Hypersplenism (↓ing plts)			
Serum electrolytes	X	1–2	X	CKD		Abnormal respiratory control, obstructive apnea, restrictive lung disease		
Capillary blood gas			X			Abnormal respiratory control, obstructive apnea restrictive lung disease		
creatinine (+cystatin C when available)	X	1–2	X	CKD				
Ca, Ph, PTH	X		X	CKD				
Urine osmolality	X	1–2	X	CKD				
Imaging tests								
Abdominal US[a]		2–3						
Kidney	X	X[b]	X	Increased echogenicity, loss of corticomedullary differentiation, microcysts, macrocysts, urological malformations				
Liver	X		X		Increased echogenicity			
Spleen (size)[a]	X		X		Increasing spleen size			

	At diagnosis	Approximate interval (years)	As required based on Hx/PE/routine findings	Abnormal test results reflect involvement				
			As required based on Hx/PE/routine findings	Renal	Liver	Resp	Retinal	Other
MRI	X		X					Dx confirmation, new neurological symptoms
Head CT/US			X					Hydrocephalus
Chest X-ray			X			Obstructive apnea/ aspiration/ pulmonary hypertension		Skeletal dysplasia
Specialized tests (requiring referral to specialist)								
Comprehensive eye exam	X	1–2	X				Retinal dystrophy, coloboma, strabismus, refractive error, amblyopia	
OCT/ERG			X				Retinal dystrophy	
Bone densitometry			X	CKD				
Upper GI endoscopy			X		Esophageal or gastric varices			
EEG			X					Seizures
Video fluoroscopic swallow study			X					Dysphagia
Standardized psychological assessment for school planning	X	3	X					

[a] Note that typically, evaluation of spleen size needs to be specifically requested as part of an abdominal ultrasound that will also include evaluation of the liver and kidneys.

[b] During adolescence.

Abbreviations: ↑ing, increasing over time; ↓ing, decreasing over time; BUN, blood urea nitrogen; Ca, calcium; CBC, complete blood count; CKD, chronic kidney disease; CT, computed tomography; ERG, ElectroRetinoGram; GGT, gamma glutamyltranspeptidase; GI, gastrointestinal; MRI, magnetic resonance imaging; OCT, optical coherence tomography; Ph, phosphorus; plts, platelets; PTH, parathyroid hormone; s/s, signs and symptoms; Std., standard; US, ultrasound.