INTRODUCTION:

The following summary of the medical expectations in Cartilage Hair Hypoplasia is neither exhaustive nor cited. It is based upon the available literature as well as personal experience in the Midwest Regional Bone Dysplasia Clinics (MRBDC). It is meant to provide a guideline for the kinds of problems that may arise in children with this disorder, and particularly to help clinicians caring for a recently diagnosed child. For specific questions or more detailed discussions, feel free to contact MRBDC at the University of Wisconsin – Madison [phone – 608 262 6228; fax – 608 263 3496; email – modaff@waisman.wisc.edu].

Cartilage Hair Hypoplasia was first described among the Old Order Amish by Victor McKusick, and so is also known as Metaphyseal Dysplasia, type McKusick. Although pan-ethnic in distribution, it is quite rare in the general population (probably around 1 in 200,000). It is far more common among the Amish (~1/1500) and Finns (~1/20,000). Although its name emphasizes its effects on cartilaginous bone and on hair development, the most serious medical problems are related to bone marrow and immune function.

Diagnosis is made both on the basis of clinical characteristics (fine and sparse hair, small stature with disproportionately short limbs, joint laxity etc.) and radiologic features, including metaphyseal abnormalities most marked at the knee and moderate to marked hand involvement with coning and metaphyseal abnormalities as well as shortening of the small bones of the hands.

MEDICAL ISSUES AND PARENTAL CONCERNS TO BE ANTIPICATED

PROBLEM: LIFE EXPECTANCY

EXPECTATIONS: Although no life tables have been generated, it is likely that life expectancy is on average diminished because of two primary concerns – overwhelming infections in infancy and
malignancy in adolescence and young adulthood. Nonetheless, clearly some individuals live into old age.

**MONITORING:** -  
**INTERVENTION:** -

**PROBLEM: GROWTH**  
**EXPECTATIONS:** Intrauterine growth retardation is usually present. There is further fall off of growth velocity in the 1st and 2nd years of life. There appears to be no substantial pubertal growth spurt. These characteristics, together, usually result in moderate to marked short stature; ultimate adult height is typically between 4’0” and 4’4”, although occasional individuals will be up to 5’0” tall. The origin of this marked variability is unknown.  
**MONITORING:** Monitor growth to insure normal or near normal growth velocity. No diagnosis-specific growth standards are available.  
**INTERVENTION:** Growth hormone has been used occasionally and seems to have some limited benefit. Limb lengthening in adolescence is a possibility and has been successfully carried out in a very few affected individuals.

**PROBLEM: DEVELOPMENT**  
**EXPECTATIONS:** No central nervous system abnormalities have been recognized. Cognitive development is normal. Variations in developmental patterns are to be expected because of short stature, joint laxity, orthopedic complications etc.  
**MONITORING:** -  
**INTERVENTION:** None

**PROBLEM: VARUS DEFORMITY**  
**EXPECTATIONS:** Leg alignment abnormalities are common. Most often this is bowing of the lower legs associated with fibular overgrowth. This is sufficiently severe to require surgery in around 15% of affected individuals. Less often, valgus deformity (knock-knees) is present.  
**MONITORING:** This requires clinical monitoring throughout childhood. Orthopedic assessment should be sought if varus is severe and, particularly, if it results in pain, decreased activity, decreased walking endurance etc.  
**INTERVENTION:** Surgery is appropriate if the varus results in instability, non-remitting pain, marked abnormality of gait etc. Surgical correction is by proximal tibial osteotomy (with either internal or external fixation).

**PROBLEM: JOINT LAXITY**  
**EXPECTATIONS:** Most joints are hypermobile. This is particularly true in the hands and wrists. The one exception is the elbows, in which limitation of movement is typical.  
**MONITORING:** Severity of laxity should be periodically assessed. In those with marked instability of the wrists or intrinsic hand joints, that may make fine motor functions fatiguing.
INTERVENTION: If excess fatigability is noted, interventions to consider include assignment modification in school, using of a stabilizing brace when doing fine motor tasks, early introduction of keyboarding to replace hand-writing etc.

PROBLEM: CERVICAL SPINE
EXPECTATIONS: Atlantoaxial instability is found in a small minority of affected individuals – certainly less than 10%.
MONITORING: Lateral flexion, neutral and extension cervical spine radiographs should be obtained at the time of first diagnosis, at school entry and then every 5 years until adulthood. Any symptoms or signs of cervical myelopathy should be sought with each medical assessment, and, if problems are suspected, then multiposition cervical magnetic resonance imaging is needed.
INTERVENTION: In those rare instances in which symptomatic instability is present, posterior cervical fusion should be done.

PROBLEM: SCOLIOSIS
EXPECTATIONS: Some scoliosis develops in around 20% of affected individuals. However, only infrequently is it sufficiently severe to require intervention.
MONITORING: Clinical evaluation for scoliosis should be done yearly to maturity. If a more than trivial curve is noted, this should be assessed radiologically
INTERVENTION: Usually no treatment is needed. Curves of more than around 25° should be evaluated by a pediatric orthopedist. Occasional individuals will require bracing; rare individuals may require surgical fusion.

PROBLEM: HAIR
EXPECTATIONS: Hair is usually both of very fine caliber (resulting in ‘silky’ character) and sparse. It is usually less pigmented than would be expected in a given family. While scalp hair character is most often recognized, body hair is also sparse. Less than 10% of affected individuals have normal hair.
MONITORING: -
INTERVENTION: In some, use of agents to thicken and condition the hair or use of a wig may be warranted.

PROBLEM: IMMUNE FUNCTION, GENERAL
EXPECTATIONS: Abnormalities of immune function are almost uniformly present – more 95% have some demonstrable abnormality by laboratory testing – but in some there are no clinical manifestations. The most common pattern is T-cell based abnormalities and resultant cellular immune dysfunction. In some there is also lymphopenia (60%) and/or neutropenia. Decreased levels of IgG and IgA are sometimes found (in about 20%). In a small number (less than 5%) severe combined immunodeficiency is present. The character and severity of immunodeficiency
may change over time. It appears that bone growth and immune function are affected by two different functions of the gene causing this disorder and so severity of bone issues is not perfectly predictive of the severity of immune dysfunction.

**MONITORING:** All affected individuals should have referral to a clinical immunologist, should be assessed at least yearly for the first 4-6 years of life and should have assessment including at least CBC and differential, T-cell subset assessment, mitogen stimulation testing and quantitative immunoglobulins. In those with normal or near-normal immune function testing, yearly reassessment after this age is probably unneeded, and repeat laboratory evaluations could be completed only every 3-4 years thereafter.

**INTERVENTION:** Aggressive treatment of infections is essential in those with immune dysfunction. Live vaccines probably should not be administered (although in those with truly normal immune screening they probably are safe), but other vaccines are safe and should be used. Some recommend routinely using intravenous immunoglobulin. Others have suggested that prophylactic antibiotic therapy should be used in those with severe neutropenia. In those with severe combined immunodeficiency (but not in general) bone marrow transplantation is indicated; it should also be considered in those with recurrent severe infections and in those with very early onset bronchiectasis (see below).

**PROBLEM: IMMUNE FUNCTION, SEVERE AND RECURRENT INFECTIONS**

**EXPECTATIONS** Around 50-60% of individuals appear to be prone to recurrent and serious infections. Particular vulnerability is present in those less than 2 y of age. In young children bacterial pneumonia is the leading cause of death, with most life-threatening events occurring in the first 12 months of life.

**MONITORING:** Those with any demonstrated immune dysfunction should be closely monitored if significant respiratory infections develop.

**INTERVENTION:** Aggressive treatment of infections is essential in those with immune dysfunction.

**PROBLEM: IMMUNE FUNCTION, VARICELLA**

**EXPECTATIONS:** Some individuals seem to have special susceptibility to varicella (chicken pox). A few persons with cartilage hair hypoplasia have had a lethal course when infected. How common such special susceptibility might be is unknown.

**MONITORING:** -

**INTERVENTION:** Affected children should not have varicella vaccination. Varicella exposure should be avoided as much as possible. If clearly exposed, varicella immune globulin should be administered. If infection occurs, it is probably appropriate to administer Acyclovir.

**PROBLEM: AUTOIMMUNE DISORDERS**

**EXPECTATIONS:** There may be an increased risk of autoimmune abnormalities of all sorts, particularly in adults. Hemolytic anemia and thyroid dysfunction are sometimes seen, for
example.
**MONITORING:** Physicians caring for adults with this disorder need to have a high level of suspicion regarding signs or symptoms suggestive of possible autoimmune disorders.
**INTERVENTION:** Management is the same as in those without Cartilage Hair Hypoplasia.

**PROBLEM: IMMUNE FUNCTION, BRONCHIECTASIS**
**EXPECTATIONS:** In those with significant impairment of immunity diffuse plasmocytic bronchiolitis and progressive bronchiectasis may develop.
**MONITORING:** In any with a history of recurrent pulmonary infections, pulmonary function testing should be done beginning at around 5-7 y of age. In those in whom chronic cough, dyspnea or other worrisome symptoms develop, high resolution CT scan of the chest allows for confirmation of bronchiectasis.
**INTERVENTION:** Aggressive treatment of pulmonary infections is essential in those with immune dysfunction. If bronchiectasis is diagnosed or suspected the help of a pediatric pulmonologist should be sought.

**PROBLEM: ANEMIA**
**EXPECTATIONS:** About 80% of those with this diagnosis have some anemia. It is typically macrocytic and thus easily distinguished from iron deficiency anemia. Clinically significant anemia occurs in around 15% and severe, potentially life threatening anemia in about 5%. When present, the severe anemia is usually permanent and results in transfusion dependence.
**MONITORING:** This should be assessed as part of the immunologic workup already summarized.
**INTERVENTION:** Those with clinically significant anemia should be referred to a pediatric hematologist. Those with severe anemia will require periodic transfusions. Bone marrow transplantation might be considered for intractable anemia, too.

**PROBLEM: MALIGNANCY**
**EXPECTATIONS:** Lifetime malignancy risk is substantial (probably at least 10-15%). Three malignancies account for most of the excess risk – non-Hodgkins lymphoma (90-fold excess risk), basal cell carcinoma (30-fold excess risk), and squamous cell carcinoma of the skin. Most malignancies that have been reported have been in individuals between 15 y and 45 y of age.
**MONITORING:** Clinical monitoring including careful skin examination beginning in early adolescence.
**INTERVENTION:** Avoidance of any unnecessary sun exposure. Management as in others who develop these malignancies.

**PROBLEM: MEGACOLON (HIRSCHSPRUNG DISEASE)**
**EXPECTATIONS:** This is an uncommon complication, arising in, at most, 5-10% of affected
individuals. It is only relevant in infancy and early childhood.
MONITORING: Clinical awareness that gastrointestinal symptoms such as chronic constipation may be more consequential in those with this disorder.
INTERVENTION: Management as in others who develop Hirschsprung disease.

**Problem: Malabsorption**

EXPECTATIONS: An unknown small minority of individuals have malabsorption resulting in chronic diarrhea, failure to thrive etc.
MONITORING: Clinical awareness.
INTERVENTION:

**Genetics and Molecular Biology**

Cartilage Hair Hypoplasia appears always to be caused by an autosomal recessive gene abnormality. This means that parents of an affected child will usually have a 25% chance that each subsequent child will be similarly affected. No one else in the family should have significantly increased risk. (About 3-5% of individuals from families with no other affected relatives have uniparental disomy of the region of chromosome 9 that houses the involved gene; in that instance recurrence risk is 0.)

Probably all affected individuals have changes in the same gene – *RMRP*. *RMRP* codes for a component of the ribosomal complex and influences both ribosomal assembly and cyclin dependent cell cycle regulation. There is some genotype-phenotype correlations, but this is not yet sufficiently precise to commend gene testing for this purpose. Mutations in the same gene can cause other, related bone dysplasias including a nonspecific metaphyseal dysplasia and anauxetic dysplasia.

Gene testing is warranted if there is diagnostic uncertainty, if the family is concerned about recurrence risk (assessment for uniparental disomy), or if prenatal diagnosis by molecular means is desired.