Guidelines for children and adults with Pitt-Hopkins syndrome

1 | INTRODUCTION

There is already quite a bit known about Pitt-Hopkins syndrome, but this information is mainly medically orientated. A group of doctors, psychologists and other caregivers who had been taking care of children and adults with PTHS realized that they did not all act in the same way when there was a problem. So together with several PTHS family support groups in the world they decided to put together all the knowledge from literature and the experience they had. The results were discussed with a large group of families during the first PTHS World conference in the Netherlands in May 2018. This has led to the first international consensus on the best course of action when there is a problem in a child or adult with PTHS.

2 | DIAGNOSTIC CRITERIA

It is important to define who has PTHS and who not, based on the clinical signs and symptoms alone. It cannot be said everyone who has a change in the TCF4 gene has PTHS as we know from many other genes that after a while it becomes clear not just one syndrome

can be caused by a change in the gene, but two and sometimes even 4 or 5 syndromes can be caused by changes in the same gene. So, we need to define for whom the guidelines are and for whom not, and, thus, define the criteria that make up PTHS.

The group of experts set up a first group of signs and symptoms that seemed important to them. We discussed these in the group and checked in a group of children and adults with PTHS whether all would fall within this definition, and that fitted well. Lastly, we checked whether children or adults with two other syndromes that can resemble PTHS (Rett syndrome and Angelman syndrome) would also fit the definition. Fortunately, that was not the case. So, the criteria worked well, and we decided these were the clinical criteria for PTHS.

We subdivided the criteria into those that are the most important ("cardinal") and those that are less important ("supportive"):

Cardinal

1. Face a. a narrow forehead
   b. the outer part of the eyebrows are thin compared to the inner part
   c. the nose (upper part-middle part-lower part) is wide
   d. the alae of the nose bulge a bit outwards
   e. the cheeks are nicely full
   f. the mouth is large, the lips full, the upper lip runs upward in the middle ("cupid bow")
   g. the rims of the ears are thick and a bit folded
   one gets **4 points** if these characteristics are present
2. Moderate to severe learning difficulties (with no or only limited speech)
   one gets **2 points** if this is present
3. Breathing abnormalities are present, either to frequent (hyperbreathing) or periods of pause in the breathing (apnoea)
   one gets **2 points** if this is present

Supportive

1. Myopia
2. Constipation
3. Unusual hands: the fingers are slender, and the creases in the palm run abnormally
4. Unstable gait

one gets **1 point** for each of these above

The definition indicates that if a child or adult has a score of 9 or higher, the clinical diagnosis of PTHS is made and DNA testing should be performed. If the score is between 6 and 8, and at least the facial characteristics are present, the diagnosis of PTHS is possible and DNA testing should be done. If the score is below 6 it is unlikely the child or adult has PTHS, and further testing is not needed (**R1**).

The score only indicates whether or not a diagnosis can be made. It does not indicate whether a child or adult is more or less markedly affected. Such a scoring system does not exist and should be developed. This can only be done if the opinion of families with a child with PTHS are used (**R2**).

Recommendations

R1 *The clinical diagnosis of PTHS is based on a combination of signs and symptoms (as indicated above). The diagnosis is confirmed by a score of 9 or higher. With a score between 6 and 8 including the facial characteristics a suspicion of PTHS remains and DNA studies should be performed.*

R2 *There is no set of criteria that indicates the severity of PTHS, and this set of criteria needs to be developed together with the families.*

3 | DNA STUDIES

Until now the only gene that can cause all the signs and symptoms of PTHS is TCF4. TCF4 stands for TransCription Factor 4. The gene is located on chromosome 18 (in medical terms: 18q21.2). The gene has many functions, for instance in the formation of the brain before birth, the formation of the various tissues that form the face, the functioning of nerves, and the way we can fight infections.

Sometimes there is not a tiny change within a gene but the whole gene is missing (in medical terms: microdeletion); that can occur with 'just' the TCF4 gene but often also genes in the

neighbourhood for TCF4 can then be missing as well. If many other genes are missing next to TCF4 someone can show unusual other signs and symptoms as well. Such children may still resemble someone with PTHS but are not labelled as having PTHS but as having '18q microdeletion syndrome'.

There are several variants detected in children or adults who do not have PTHS but still are delayed in their development. They do not have the facial characteristics and for instance also not the breathing problems. Children and adults with such changes should not be labelled as having PTHS (**R3**). A doctor should use the clinical diagnostic criteria (please see section 2) to determine whether or not a child fulfils the criteria for PTHS.

If someone with PTHS himself or herself was to have a child, there would be a 50% chance (one in two) of the baby to have PTHS as well. This is because the change in the gene is inherited in a dominant way. The group of experts had details of 273 children and adults with PTHS. In five of these families there were two children with PTHS This means there is a 2% chance that a family with a child with PTHS could have another child with PTHS (**R4**). For a healthy brother or sister of someone with PTHS the chance to have a child for themselves with PTHS is not increased compared to the chance in the general population.

Nowadays there are many ways of performing DNA tests. A test that is often done is called "next generation sequencing', usually abbreviated to NGS. With such tests one can check all genes or a selected group of genes for changes. It may occur one finds a change in TCF4 in a child in whom one had not expected such change. Then it can be very difficult to determine whether or not the change will cause any harm or not. One need to evaluate the child very carefully, and one needs to check the family whether there is someone in the family with the same or a similar syndrome. One should also check whether the change in TCF4 has been reported before and whether that was in a healthy person or someone with PTHS or with another disorder. One should furthermore check where in the gene the change is located, and what type of change it is, as that can make quite a difference. There are international criteria available for this. All together this means the doctor needs time and experience to check all the above, before it can be concluded whether or not a change in TCF4 is harmful or not (**R5**).

Recommendations

R3 *Changes in the gene TCF4 can cause PTHS but can also cause other syndromes that go along with cognitive problems. The latter group of children and adults should not be labelled as having PTHS.*

R4 *If a family has a child with PTHS in whom the diagnosis is confirmed by DNA studies, the chance that the same couple will have another child with PTHS is 2%.*

R5 *If a TCF4 variant is detected, it is not easy to determine whether it is doing any harm or not. This needs careful check-up of the child that was tested, checking whether the same or similar syndrome occurs in the family, whether the change in the gene TCF4 has occurred before, and what the type and place of the change within the gene TCF4 is.*

4 | PRENATAL STUDIES

The chance that a family that has a child with PTHS has a second child with PTHS is low. It is not zero as it does happen. The risk is estimated to be about 2%. It is very unlikely that a diagnosis of PTHS will be suspected from an ultra sound scan, as there are usually no anomalies present in a baby with PTHS that can be seen on a scan. It is only with DNA studies that a diagnosis can be made. When the change in a gene is confirmed by DNA testing in a child prenatal tests for the same change can be done in the next pregnancy. As the chance of having a second child with PTHS is not zero prenatal testing should be discussed and offered if desired. **(R6)** The studies can be performed by chorionic villi biopsies, amniocentesis or in the lab when in vitro fertilization is done. It is very reliable if the mutation in the first child with PTHS is known.

Nowadays there are opportunities to check for changes in large series of genes in the mother's blood during a pregnancy, as there is always a bit of the baby's DNA present in the mother's blood too. (in medical terms: non- invasive cell- free foetal

DNA screening.) It would be possible to check the TCF4 gene in this as well and therefore also in a family with no child with PTHS.
However, both parents' DNA would be needed for this too and doctors remain uncertain very often whether a change in a gene is a variant of normal (in medical terms: polymorphism) or really causing harm. Because of this uncertainty, the group of experts concluded that such testing, outside a family who already has a child with PTHS, is not useful. (**R7**)

Recommendation
R6 *It should be discussed with every family who has a child with PTHS, confirmed by DNA studies, that there is a small chance for another child to have PTHS as well and that there is prenatal testing available if they wish to have this.*

R7 *At present it is not recommended that prenatal testing for PTHS by DNA studies be offered to the general public in pregnancy as there are problems in interpreting the findings in a reliable way.*

5 | GASTROENTEROLOGY

Early muscle weakness (hypotonia) in infants with PTHS may lead to feeding problems. Typically, the new-born feeding is closely monitored and if needed the paediatrician will offer advice how to deal with these for each child. This is done like in any new-born with feeding problems. Generally, the problems sort themselves out as the children get older.
Feeding difficulties at a later age, such as gagging, refusing to eat, and only eating at a certain time or place, or a certain type of food, may occur, but in general those with PTHS are described as excellent eaters.

Digestion problems are common in children and adults with PTHS. Constipation occurs in the majority of children. In adults it occurs a bit less, but still frequently. Gastroesophageal reflux

disease occurs in about 40% of PTHS children and adults, and burping occurs in a third of them. Hyperbreathing can lead to swallowing air into the stomach causing lots of discomfort as the stomach swells and lots of burping. This was the case for just under half of those present at the World Congress in 2018. One child had this so badly that she had had a gastrostomy to let air escape a few times a day which fixed her problems, and we have a similar good experience in some others as well. When the swelling of the stomach is causing problems in a child or adult this should be considered.

The treatment for gastroesophageal reflux is similar to that of the general population. The first thing to try is the proton pump inhibitor. People with PTHS respond well to these if the medication is given in high enough doses (omeprazole 0.7-3.5 mg/kg/day to keep everything well (**R10).**

Many with PTHS have severe constipation all their lives. Hirschsprung Disease (when nerves are missing in parts of the intestine), is causing very severe constipation and has been associated with PTHS but it is very rare and has only been seen in one child with PTHS. It may well be this should be explained by coincidence. A study with mice that had a TCF4 deletion similar to those with a deletion in a human showed slower movement from the mouth down to the beginning of the large intestines and from end of the large intestines. There is not much data on the speed of food going through the bowel in humans.

The treatment for constipation is similar as for the general population (**R8**). (Toilet timing eg regular toilet sitting for a set period after every meal and using positive reinforcement through a reward system is also helpful. Effective control of constipation includes using constipation diaries, the Bristol stool form scale, and the section C of the Questionnaire on Paediatric Gastrointestinal Symptoms and seeing a doctor when necessary (QPGS) (**R9**).

The 47 attending the World Congress did not seem to show more food intolerance than would be expected in the general population. Other gut problems include pyloric stenosis and malrotation, but are not common. They can be treated in the same way as in children and adults without PTHS.

Recommendations

R8 *Constipation, both chronic and occasional can often occur in individuals with PTHS and should be monitored and assessed. This can be done by keeping a diary or by using a dedicated questionnaire.*

R9 *Treatment for constipation will follow the same treatment that would be given to anyone else. This might include some behavioural modification strategies.*

R10 *If the PTHS individual encounters problems with reflux, again the treatment will not differ from any other person. Sometimes anti-reflux medications will be prescribed and should be used to their maximum dosage.*

6 | RESPIRATION

Disturbed regulation of respiration is one of the main criteria of PTHS. It is most probably part of the general dysautonomia that occurs in PTHS. Dysautonomia means that all processes which are automatically steered by your nervous system are no longer regulated well. This means it might also show in characteristics such as dilated pupils with sluggish response to light, instability of temperature, decrease circulation in hands and feet, constipation, or not emptying urine completely from the bladder urinary retention.

Respiration problems can start at a variable age. We gathered data on 256 children and adults with PTHS and found that 123 (48%) had hyperbreathing which started at a mean age of 6 years, but it could start as early as 3 months or as late as 37 years. The true frequency of a disturbed respiration may well be higher, as affected individuals may have been reported at an age where they may not yet have developed the abnormal breathing. When checking this for each age group the incidence of respiration problems was 20% before 2 years of age, 23% between 3 and 5 years, 22% between 6 and 10 years, 69% between 11 and 15 years, and present in over 90% of older individuals. Rarely, hyperbreathing has started to occur in a young child and then, after months or even years, disappeared again for several years. We did not see a relation between the change in the gene and the occurrence of hyperbreathing.

The typical breathing pattern consists of rapid breathing, sometimes regular sometimes irregular, followed by a pause in breathing. It usually takes 2 to 5 minutes. It may occur several times per hour to a few times per year. The spells are not reported during sleep. Apnoea's and hyperbreathing may also occur independent of each other. Periods of hyperbreathing may be triggered by excitement, stress, or anxieties, but may also occur without clear issues that makes it arise. A period of apnoea may be followed by cyanosis (blue discoloration of lips and pale blue skin) and rarely loss of consciousness. Oxygen saturation (the amount of oxygen in the blood) may be decreased during a spell of abnormal breathing. We are not aware of any instance that the heart stopped beating provoked by a spell of apnoea (**R11**). Sometimes the epilepsy occurs first and after months or years the breathing abnormalities follow, but the reverse occurs as well, but only infrequently a spell is followed immediately by a seizure. Many affected individuals develop clubbing of fingers (broadening of the tips of the fingers) within a few years after the start of the breathing irregularities. Clubbing was present in 9 of 49 individuals with PTHS in whom the hands were evaluated during the 2018 PTHS World Conference. In some the clubbing had been noted before the hyperbreathing had started but it is more likely the hyperbreathing had gone unnoticed before. Other consequences of the abnormal breathing are excessive burping and swelling of the abdomen. Breathing spells may cause anxieties in a child or adult with PTHS and appear quite concerning, but many do not seem to be disturbed and remain comfortable. Others stop what they are doing, some sit down to prevent a fall, and in a minority loss of consciousness occurs. Infrequently, irregular breathing at night and catathrenia (an apnoea at the end of inhaling air and groaning when exhaling, both during sleep) has been reported. Parasomnias (unusual behaviour during sleep like nightmares and sleepwalking) were reported in 10 of the attendees of the 2018 PTHS World Conference. Although polysomnographies are not available for evaluation, it has been suggested that the breathing problems at night may also have a different cause and be obstructive in nature (**R12**).

There is a report from Belgium on two children with PTHS and marked spells of hyperbreathing which decreased in number and duration when using acetazolamide, and in another adult it did work too. Acetazolamide is a carbonic anhydrase inhibitor and is used in acute mountain sickness which resembles the breathing problems in PTHS to some extent. However, how it may work in PTHS is still uncertain. A major side effect may be low potassium levels which has been a reason to stop the medication in several children and adults

with PTHS. In individuals *without* PTHS, other medications such as triazolam and zolpidem have been used for central sleep apnoea, but we must assume the effect in PTHS to be low due to the different origin of the respiratory problems in PTHS. In a mouse model of another syndrome, Rett syndrome, in which breathing problems also occur, sarizotan has been shown to reduce the incidence of apnoea and hyperbreathing, and a clinical trial is now underway. If successful it may hold promise for the breathing problems in PTHS.

Recommendations

R11 *It should be explained to caregivers that spells of hyperbreathing, despite being disturbing to witnesses, are unlikely to be harmful.*

R12 *If breathing disturbances occur at night, polysomnography should be considered in individuals with PTHS to exclude obstructive sleep apnoea.*

7 | SENSES

7.1 | Vision

The structure of the eyes (lens, iris) of PTHS children is usually normal. About 10% of children may have blocked tear ducts. If it causes prolonged problems, it can be treated in the usual way.

Sight issues are common, with about 2/3rd of PTHS kids needing glasses, frequently before the age of 2 years. Short-sightedness (50%), strabismus (cross-eyed, 45%) and nystagmus (eyes rapidly moving side to side, 14%) are the most common problems. Rarely a slow reaction of wide pupils to light occurs. As sight problems are so common in PTHS, every child should be seen at a young age and regularly followed up by an ophthalmologist (**R13**).

7.2 | Hearing

Hearing loss is not very common (10%) in PTHS. Still, as it is so important for speech development, it is wise to check the hearing in all children with PTHS (**R14**). There are tests that can be carried out that do not need any type of feedback from the child (in medical terms: optoacoustic emission and auditory evoked potential), so testing can be done reliably in every child, also the ones who are not willing or able to cooperate..

7.3 | Other senses

Smell

There have not been any studies of the sense of smell in children with PTHS. Maybe some have a decreased sense of smell and others are sensitive to some smells, but this is not yet certain.

Pain

Recognising and dealing with pain is challenging in children and adults with PTHS as the majority cannot tell us this. Apparently, they can react in a different way to pain. Some parents have said that their child is more bothered by and sensitive to minor pain, such as a small scrape or cut, while they seem less bothered by something others would find far more painful such as pain after surgery. Others are showing less pain anyway. This is important to realize if the behaviour of a child has changed as for instance a fracture can go unnoticed (**R15**). It can be that the cause is a different pain sensation: the gene, TCF4, makes a protein that works in pain signalling in the Pitt-Hopkins mouse.
There are questionnaires such as the FLACC that have been developed to recognise and assess pain in children with special needs and it is advised they are used with children with PTHS if there is any doubt whether or not someone has pain (**R15**).

Recommendations

R13 *Every child with PTHS should have their eye-sight checked on diagnosis and then regularly monitored*

R14 *Hearing should be tested regularly in everyone with PTHS.*

R15 *Parents and carers should be aware of the various types of pain felt by those with PTHS; if in doubt specific questionnaires can be used to assess pain.*

8 | NEUROLOGY

It has been found that up to half of people with PTHS have epilepsy with different types of seizures that vary in severity. Someone with PTHS may have a first seizure as early as the first year of life or as late as early adulthood. Seizures can easily be misdiagnosed when there is apnoea (see glossary) as in both the lips and skin can go blue. Children with PTHS may show apnoea or hyperbreathing just before a seizure, but the abnormal breathing is not itself part of the seizure. Electroencephalographic (EEG) patterns in people with PTHS are typically abnormal, and the patterns will change over time**.** If the EEG is normal one should be careful not to miss that in fact, there is no seizure, but it is an apnoea. The EEG patterns usually are not specific to a certain type of seizure. As it is difficult to tell the difference between seizures and apnoea it is suggested that an EEG be carried out if in doubt and looked at with this in mind (**R16).** There is no need to make an EEG in everyone with PTHS. Valproic acid, levetiracetam, lamotrigine, and carbamazepine are the most commonly used seizure drugs but there are not enough data to say whether one drug is better than another **(R17)**

Other neurological (glossary) problems are not very common in people with PTHS. Seven of the 47 people with PTHS who attended the 2018 PTHS World Conference were shown to have a tremor (shake) that did not get worse over time. The common wide standing position and movement may be linked to problems with a person's nervous system, but there has not been enough study on it. There is a noticeable difference in muscle tone in people with PTHS: three-quarter will have truncal (torso) hypotonia, and less than 10% has a high muscle tone (hypertonia). One-third has this high muscle tone in arms and legs. It has been suggested the difference in muscle tone is due to the autonomic nervous system being disrupted (see section 6).

Sleep problems are seen in a small number of those with PTHS with many parents saying that their child sleeps extremely well. Some parents mention that their child does not sleep through the night or have night terrors. Melatonin had been used by 10 of the 51 attendees of the World Conference in 2018: in two it had worked well, in six it had no effect and in the

remaining two the result was uncertain. Sleep has not been looked at in full detail yet and further studies are needed.
Different brain scans (MRI) have been done and smaller changes in the formation of the brain have been seen in some but in most the scans just show normal results. Almost invariably the results are not important in how a child with PTHS should be looked after. So, it is suggested that an MRI is only needed when there are neurological signs and symptoms, such as repeated seizures but not in all children with PTHS. An MRI is also not needed just because a child has microcephaly (small head) (glossary) (**R18)**

Recommendations
R16 *EEG studies should only be carried out when there are clear seizures or when one remains in doubt if someone with PTHS shows seizures or apnoea's.*

R17 *Clinical seizures can be treated just the same as in the general population; there is no evidence that one specific drug works better than others.*

R18 *MRIs need only be carried out if there are neurological signs and symptoms that this would be useful. Microcephaly (small head) on its own does not mean a child should have an MRI.*

9 | ORTHOPEDICS

Musculoskeletal problems occur frequently in both children and adults with PTHS.
The hands are quite small and slender, and the fingers are often tapering. But this does not appear to cause major problems. The thumbs can be bowed less than usual in half of the children and rarely even not at all. Usually no therapy is needed. Also rarely someone with PTHS cannot move all fingers in the normal way; then physical therapy in the first year of life might make this better.

Major problems occur frequently in the feet: these are almost always slender and flat and can be turned outwards. Also, a pes cavus (high arch) occurs. Overlapping toes are not uncommon.

Minor limb anomalies do not require therapy, but the shape and function of the feet and ankles often require special footwear, inserts, or orthotics (**R19**). In selected cases, surgical procedures may be beneficial, for example, flat foot reconstruction.

Scoliosis (curving of the spine to one side) has been reported in 18% of children with PTHS (**RH20**). It can arise during puberty but also at younger ages. There is no study available on the results in larger groups on the management of scoliosis. Our joint experience indicates that the way a doctor deals with the scoliosis should be as for the general population (**R21**). Someone with a scoliosis can best be followed regularly, as that is the best way to show if treatment is needed or not.

Very infrequently other orthopaedic problems occur such as kyphosis (forward bending of the upper part of the spine), pectus excavatum (chest bone running inward), and decreased mobility in a knee. Each can be treated as in anyone with this problem without PTHS.

Recommendations

R19 *Flat feet and valgus positioning often require special footwear, inserts, or orthotics. Surgical correction may be necessary if walking remains impaired.*

R20 *Individuals with PTHS should have their spine checked regularly from an early age.*

R21 *The way doctors need to deal with a scoliosis in individuals with PTHS can be the same as in the general population.*

10 | PAEDIATRIC MEDICAL FOLLOW-UP

In the first year of life most children with PTHS have a low muscle tone and a delayed development. Motor skills are delayed: about one-third walk unaided between 3 to 5

years of age, and three-quarter between 6 to 10 years of age. They walk typically with a wide-based, unsteady (in medical terms: ataxic) gait. Some may walk only with help, and still others never learn to walk on their own. Of those who are unable to walk alone, some achieve independent mobility by using a wheelchair. Speech is frequently markedly delayed, with many remaining non-verbal. Up to 55% of individuals speak single words before 10 years of age, and only a minority (less than 10%) use whole sentences. Of the 47 individuals present during the 2018 PTHS World Conference 39 used 0 to 5 words, two 10 to 20 words, and six were able to use short sentences. Few children develop dressing or toileting skills. One in five children will be toilet trained for urine between 11 and 15 years of age.

Growth in length and weight is usually normal at birth; less than 10% is small at birth. After birth height drops below the lowest lines in one-third of the children, and head circumference will be just below the lowest line of the curve in half of the kids. No major teeth anomalies have been reported, and teething and the loss of milk teeth occur at a normal age. Increased spacing of teeth is common. It is prudent to have children with PTHS evaluated regularly (usually once per 6 months) by a dentist as children with developmental disabilities are more likely to have unmet dental needs (**R22**).

Burping (28%), reflux (38%), and constipation (80%) are common in children. During feeding they may gag, choke, and not chew properly. Some refuse food, or have very strict rituals during feeding. , In general however, many are described as excellent eaters. Drooling is seen in 80%, usually more prominent in young children, and teeth grinding occurs in one-third. Repeated infections of the airways (otitis media, tonsillitis, bronchitis) and kidney and bladder have been reported in one-third, occurring mainly in childhood. An abnormality in the way the children and adults deal with infections (in medical terms: immunological disturbances) are reported only a few times and include low levels of several proteins needed to fight infections (in medical terms: low IgA, IgM, and IgG levels). Of 49 affected individuals at the 2018 PTHS World Conference immunological testing was performed in seven, and abnormalities in immune-globulin levels were found in three. Vaccinations should be given according to national schemes (**R23**). There are still many things not explained in infections in PTHS, and it seems wise to perform detailed immunological studies in everyone with repeated infections.

Abnormalities of heart, lungs, kidneys, liver and intestines are quite infrequent, and ultrasounds of the heart and kidneys are only indicated in case of suggestive symptoms (**R24**). One-third of boys has non descended testicles, and infrequently small or fused (glued together) labia majora, and a small womb occur in girls. As far as we know now puberty develops at a normal age and pace.
The paediatrician, preferably one with experience in PTHS, should play a central role in the clinical care for children with PTHS. He or she should regularly check for health problems (surveillance), coordinate multidisciplinary care, and oversee the social support system surrounding the child (**R25**).

Recommendations
R22 *Individuals with PTHS should undergo regular check-ups for their teeth*.

R23 *Vaccinations should be given to every child with PTHS according to national guidelines*.

R24 *Ultrasounds of heart and kidneys should be done only in children showing signs or symptoms that would fit an abnormality of the heart or kidneys are present*.
R25 *Every child with PTHS needs regular follow-up, preferably by a paediatrician familiar with PTHS*.

11 | ADULT MEDICAL FOLLOW-UP

About one-fifth of adults is just below the expected height. There are no reports of related endocrine issues such as shortage of growth hormone or abnormal functioning of the thyroid gland. Some become somewhat overweight as time goes on, but excessive weight gain is not often a problem in most with PTHS. Mild microcephaly is seen in a quarter of adults. Adult facial characteristics do not change much from those in in infancy.

Feeding problems are not common in adults with PTHS. Problems with drinking and swallowing solids is seen in about 10%. Constipation is very common and occurs in three-quarter of adults (see Section 5). Gastroesophageal reflux is present in one-third and usually responds well to anti-reflux medication.

Flat feet (pes planus) and turned out feet (pes valgus) are seen in half of the adults. These should be checked for as orthopaedic shoes or other orthotic devices, physiotherapy, or other specific treatments may be needed (**R26)**. When an adult with PTHS has limited mobility, physiotherapy is required to prevent the mobility to become permanently affected (contractures). Other, usually less important problems can be overriding toes, scoliosis, and limited thumb mobility.

Although frequent infections are not common, urinary tract infections can be missed or manifest as unusual behaviour changes (**R27**).

Adults with PTHS have widely spaced teeth. Many grind their teeth and drooling is seen often. A protruding jaw (prognathism) may develop and can cause problems with chewing. Advice from a speech therapist may be helpful (**R28**). If there are unexplained behavioural changes, the teeth should be checked as they could be a cause of pain.

In about a third of those with PTHS genital differences are seen such as undescended testes (cryptorchidism), a small penis, and unusual labia. Adult males should be checked for cryptorchidism, as this may have been missed when they were younger. If present, management is as in the general population (**R29**).

It is hard to give an accurate idea of the life span in PTHS as only few older people have been diagnosed, and most are still young adults. It is thought that they will have a typical life span. Three adults are known who have developed a form of cancer: two with Hodgkin lymphoma, and one with medulloblastoma; there is also a child with a rhabdomyosarcoma. It is uncertain whether there is a relation between these tumours and PTHS as this can well be explained by coincidence. Data on cardiovascular functioning, osteoporosis, and dementia in adults with PTHS are not available.

Recommendations

R26 *Special shoes or AFOs (ankle foot orthoses) should be looked at to improve the stability and mobility of those with PTHS.*

R27 *When there is a change of behaviour in someone with PTHS it could be caused by pain and there should be careful physical exams for constipation, infections and dental problems*.

R28 *Issues such as drooling, and chewing can be helped with the advice of a speech therapist*

R29 *Every male with PTHS should be checked to see that both testes have come down into the scrotum. If they haven't, the treatment should be the same as in the general population*.

12 | CARE PLANNING

12.1 | Medical care

It is important that everyone with PTHS has lifelong care from a team of medical professionals, each with a different specialty. This holistic approach to healthcare helps to avoid problems and in doing so improves their quality of life (**R30**).

Regular follow-up by a paediatrician, neurologist, psychologist/psychiatrist, and speech therapist will have great benefit. Assessments of development are needed to make sure every child and adult gets the medical services they need. They should be rechecked from time to time by a physician who is coordinating their care, or by a clinical geneticist who knows most up to date medical information about PTHS. Information booklets designed to give guidance on syndrome-specific issues (intellectual and physical disabilities) and family support groups are helpful.

Several factors have been identified that could influence the prognosis for the person with PTHS. These include age at diagnosis, degree of intellectual disability, presence of seizures, capacity of verbal and non-verbal communications, and access to multidisciplinary medical and social care.

12.2 | Transition

Transition of care is an important aspect of the care of adolescents and young adults, due to the rapid changes involved in their physical growth, sexuality, environment, and development of independence depending on their skills. Transition should be a purposeful and planned change, and the involvement of parents is an essential part of this process. Individuals with PTHS themselves should also be involved, as much as possible, depending on their ability to participate.

No data are available specifically for transition of individuals with PTHS. However, general principles apply, using as starting point the needs of the individual with PTHS, and based on standard healthcare for adults with intellectual disability. Early identification of the health care needs of the adult individual, and careful communication and coordination between paediatric and adult care providers are essential (**R31**).

12.3 | Sexuality and reproduction

Underdevelopment of external and internal reproductive organs occurs regularly in those with PTHS, such as a small penis and undescended testes in males and labial fusions, and, rarely, absent vagina and absence of uterus and ovaries in females. No data are available on fertility in either males or females. Sexual education should be provided according to suit the level of emotional and cognitive functioning. The recommendations for the general population regarding contraceptive options should be followed, if possible adapted for persons with intellectual disability which is available in several countries (**R32**). The use of contraceptives to suppress menstruation in females that experience difficulties in dealing with their periods should be considered. Screening for cervical and breast cancer as well as prostate cancer should be performed according to national standards.

Recommendations

R30 *Individuals with PTHS and their families require lifelong care, preferably provided by a multidisciplinary healthcare team.*

R31 *Preparations for transition of care should start early, even already in puberty. Transition should include early and careful handing over of all information that is available on the child with PTHS, so both medical information and information on behaviour.*

R32 *Information on sex and contraception should be offered to every adult with PTHS. If it is available the special standards for this for individuals with intellectual disability should be used. If unavailable, the information for the general population can be used.*

13 | COGNITION AND BEHAVIOUR

13.1 | Cognition

TCF4 is necessary for the development of the nervous system and it plays an important role in cognition (learning) and behaviour. Children and adults with PTHS often have problems with filtering the stimuli coming from outside their body and within. If parents and caregivers manage to make the environment quieter ('filtering') the children and adults will more easily get the really relevant information, are no longer overloaded with information, and often have less behavioural problems as well.

Identifying suitable assessment tools for the PTHS population is difficult. Still, all with PTHS in publications show moderate to severe intellectual disability. In most reported people with PTHS their developmental ages range from 9 to 36 months (mean 14 to 16 months). A mild cognitive delay has been reported in some, but they had unusual changes in the gene but when assessed more carefully it is clear they do not have PTHS.

People with PTHS have mild to severe motor learning problems like with rolling, sitting and walking, and often make repeated movements such as hand clapping and flapping, repeated hand to mouth movements, head shaking, head banging, body rocking, washing, finger crossing, and rubbing toes together. Motor milestones and self-care skills like feeding themselves are delayed (see Section 10). Very few learn to dress themselves or use the toilet on their own. It has been seen that many can help with dressing, like unzipping their coats.

Skills can continue to develop as they get older. In very few older people this ability was lost. Once someone is diagnosed with PTHS, they should have developmental assessments to work out the services and educational solutions they need to help with their development (see also section 10) (**R33**).

13.2 | Language and communication

Children and adults with PTHS usually have problems with recalling words and language development. Most do not learn to speak. Just over a half will say single words before the age of 10, but many will have no speech at all their whole life (**R34**). Everyone with PTHS should be assessed for the best communication options to them (**R35**). Speech therapy including access to augmentative and alternative communication (AAC) should be considered. Other areas to consider for input are special education services focussing on the development of life skills and help aimed at changing behaviour such as self-harming and anxiety (**R36**). Physiotherapy and occupational therapy are recommended for the development of motor coordination, with the goal that a child can carry out an intended movement like picking up a toy. When a child is being assessed for communication and language abilities all aspects including motor abilities should be taken into account.

13.3 | Behaviour

Most children with PTHS are described as friendly and show lovable behaviours, but many will also pull hair, have temper tantrums, throwing their arms and legs out, and banging on or throwing or kicking objects. Half are described as having a smiley appearance. Self-harming such as pinching, pressing, and hitting themselves is seen, as well as problems connecting with others. Other behaviours are anxiety, distress, repetitive actions, and autism spectrum disorder (ASD). Problems in filtering and processing sensory input like bright lights increase the risk of under- or overstimulation and can lead to inappropriate behaviours eg head shaking. However, there is evidence that some children's mood is improved by music as they enjoy it. Children and adults with PTHS need a sensory processing assessment to help work out what to avoid or to introduce to prevent under- and/or overstimulation (**R37**).

13.4 | Anxiety and agitation

More than one-third of people with PTHS have anxious, agitated and/or aggressive behaviours. This may be due to frustration in not being able to communicate (**R38**). Unrecognized pain or other sensory or body issues may cause these behaviours. Aggression and shouting are often associated with changes in routine. The start of puberty can increase these behaviours.

13.5 | Repetitive behaviours/stereotypies

Most with PTHS studied show repeated movements eg flapping, twisting body movements or flicking hands or fingers. This can be seen in the way they hold objects like toys eg turning over in the hand and being fascinated by certain objects. These repeated behaviours may become stronger when they are anxious or when they are not able to get away from situations like a room with loud music.

13.6 | Autism spectrum disorder

It is common for children with PTHS to have a lack or reduced social and communication interaction skills along with repeated behaviour patterns, such as hand clapping and flapping, head banging, body rocking, or finger movements. They are also likely to have less adaptive skills Often the lack of skills cannot be explained by the degree of their intellectual disability. Therefore, careful observation of behaviour including autism-specific assessments are warranted. If ASD is present as a separate diagnosis, next to PTHS, this is helpful in caring for someone with PTHS, for instance by preventing overstimulating and/or under-stimulating (**R39**).

13.7 | Pharmacotherapy (use of medications)

Persistent problematic behaviour like self-harming can be very distressing and therefore needs to be treated. It should first be considered if there are some physical, mental, and environmental issues that are leading to the problematic behaviour This should be by careful assessments and solutions should be looked for by changes in the environment such as softer lighting, and behavioural therapy. If these solutions are not enough, medication should be considered. There is not much scientific proof that psychotropic medication is effective in children with PTHS, and there have been no controlled studies. Still, in a survey on medication during the PTHS World Conference 28 families gave their experience on different types of medication and their effects and side effects. Melatonin and/or gabapentin was used for sleep problems, methylphenidate and clonidine were used for irritability, agitation and hyperactivity, and lorazepam had been used for agitation. Antipsychotic agents, pipamperon and promethazine, were used to help with challenging behaviour. These antipsychotics should be carefully monitored, evidence for effectiveness is limited and long-term use may result in significant harmful effects such as weight gain, high blood pressure and diabetes. Overall, parents reported satisfaction with medications prescribed and noted few significant side effects, but no single medication was found to be extraordinarily effective. In general prescriptions should start at low doses and gradually give more or less medication, in a slow way, to obtain the best effectiveness. One should monitor health before starting and while giving medications, and consider from time to time if stopping of continuing medication is useful. One should ask for the opinions of the caregivers on the effects of medications (**R40**).

Recommendations

R33 *Everyone with PTHS should be assessed for levels of cognition, social-emotional development, and communication.*

R34 *Most individuals with PTHS cannot speak. Every effort should be made to explore other methods of communication including augmented communication techniques.*

R35 *Additional developmental and educational support should be provided to maximise cognitive and educational potential, taking into account how well the children and adults can communicate.*

R36 *Special education strategies should focus on learning skills to enhance daily life skills and to modify anxious and/or self-injurious behaviours.*

R37 *Assessing the sensory processing profile in children and adults with PTHS helps care, especially in preventing under- and/or overstimulation.*

R38 *The first signs of anxiety, agitation or aggression may be difficult to recognize in someone with PTHS as they may have difficulties in communication. Detailed face-to-face assessments and observations in the environment of the individual are needed.*

R39 *A separate diagnosis of ASD, next to PTHS, should be considered in everyone with PTHS. If such diagnosis is made, interventions specific for ASD will be helpful.*

R40 *No specific medication is known to be generally effective in problematic behaviour of children or adults with PTHS, and prescribing practices as in the general population should be followed.*

14 | CONCLUSION

The current recommendations aim to improve the judgement of signs and symptoms in anyone with PTHS, to better serve the caregivers and families in caring for the child or adult with PTHS.
The diagnostic pathways (judgement process) has been done in such a way that a judgement can be made universally, so with or without the access to modern technology, and recommendations are meant to be cost effective and avoid any unnecessary measures.
We realise that local circumstances such as medicolegal environments (medicine related legal systems) may cause changes to the recommendations. Together with the various national PTHS support groups we aim to go on and review the guidelines from time to time, to better the recommendations.

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Some important literature references on PTHS

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Major research issues in PTHS recognized at the PTHS World Conference

- What is the natural history of Pitt-Hopkins syndrome in adults and older individuals?
- Breathing anomalies: what are the long-term consequences of breathing anomalies, both physically and cognitively? What is the prevalence of obstructive sleep apnoea? Can breathing anomalies be decreased if needed?
- Seizures: are seizures primary or consequences of breathing anomalies?
- Other symptoms caused by autonomic nervous system dysregulation: what is the exact pathogenesis? If needed, can consequences (especially drooling and constipation) be influenced?
- Immune system: what are the consequences of PTHS variants causing Pitt-Hopkins syndrome for immunological functioning, including reactions to vaccination?
- Motor functioning: what is the pathogenesis of the foot position anomalies? Can physical therapy, drugs or surgical procedures effectively influence these anomalies?
- Communication: what are the communication abilities? Are there biomarkers that predict these abilities? Which approach best increases communicative abilities?
- Behaviour: what are the specific characteristics of autism or autism spectrum disorder in individuals with Pitt-Hopkins syndrome? In which way do factors such as autonomic dysregulations, food or other environmental factors influence behaviour?

Is it possible to address behavioural difficulties effectively through psychotherapy, contextual adjustments and/or drugs if needed?

- Genotype – phenotype correlations
- Molecular characteristics: can a functional study be developed that indicates with sufficient certainty causality of a Pitt-Hopkins phenotype? Can the mRNA derived from the wild type allele be stabilized in vitro? Does this lead to increase protein formation and if so, does this influence the consequences of haplotype insufficiency for TCF4 in animal models?