Diagnosis and management of Cornelia de Lange Syndrome: first international consensus statement (Adapted for easy access and wider distribution).

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The text of this document and figures 1, 2, 3, 4 and 5, tables 1 and 2, and box 1 are adapted from the original article.

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Note: *References to published papers will be indicated by (number), e.g. (1) or (2). The full reference for the paper can be found next to the corresponding number in the reference section at the end of the document.*

What is Cornelia de Lange Syndrome?

Cornelia de Lange Syndrome (CdLS) is a rare developmental disorder that is present from birth. The syndrome was named after the Dutch children's doctor Cornelia de Lange, who first described the disorder in 1933 (1). It is estimated that between 1 in 10,000 and 1 in 30,000 people in the population have CdLS (2).

CdLS can affect many parts of the body and individuals with CdLS may display physical, cognitive and behavioural characteristics (1). Cognitive characteristics are brain-based processes like memory and thinking. Behavioural characteristics refer to certain behaviours that individuals with CdLS are more likely to have. These characteristics can vary widely among affected individuals and range from small differences compared to other people to very noticeable differences.

Classic (or typical) CdLS can be easily recognised from birth by an experienced children's doctor (paediatrician) or clinical geneticist (a doctor who diagnoses and supports families with genetic disorders). This is because individuals with CdLS often have distinctive facial features, growth patterns, and limb differences (see Figure 1 on the next page). These characteristics form the classic CdLS phenotype, which the physical, cognitive and behavioural characteristics associated with the syndrome.

It is important to note that if a person has a diagnosis of CdLS it does not mean they will display all the characteristics associated with the syndrome. There may be different degrees of difference in the face and limbs for example. It is also very important to remember that everyone with CdLS is an individual and will also have characteristics passed down from their family.

CdLS is a genetic disorder. This means that it is caused by a change in genetic material; this change is called a mutation. The genetic causes of CdLS are complicated and research to fully understand all the genetic causes is still ongoing. CdLS is usually caused by a change in one of seven genes (individual genetic instructions in DNA that make us who we are). The seven genes associated with CdLS are named: NIPBL, SMC1A, SMC3, RAD21, BRD4, HDAC8 and ANKRD11. A change in one of these genes affects the 'cohesin complex'. This means that the cohesin protein complex does not function as it should in the cells of the body, causing altered human development. See the section *'What causes Cornelia de Lange Syndrome'* on page 7 for more information.

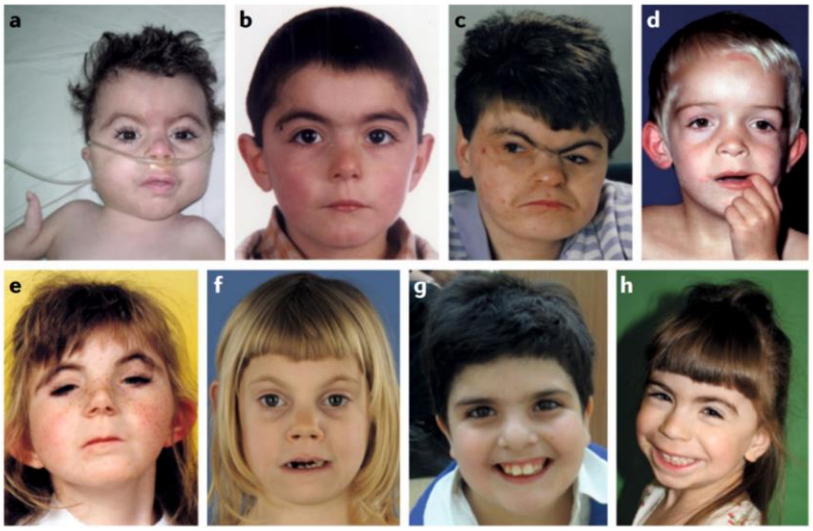


Fig. 1 | Facial phenotype of individuals with Cornelia de Lange Syndrome. *a | Classic Cornelia de Lange Syndrome (CdLS) phenotype resulting from an NIPBL variant. b | Non-classic CdLS phenotype in an individual with an NIPBL variant. c | Adult with NIPBL variant and classic phenotype. d | Non-classic phenotype in individual with an SMC1A variant. e | Classic phenotype in an individual with an SMC3 variant. f | Non-classic phenotype in an individual with a RAD21 variant. g | Non-classic phenotype in an individual with an HDAC8 variant. h | Non-classic phenotype in an individual with an ANKRD11 variant.*

Over the last 10 years, genetic tests have been developed for the diagnosis of individuals with developmental disorders. These genetic tests are performed by molecular geneticists and can identify changes in any of the seven genes that are associated with CdLS. Genetic tests have shown that there is an overlap in the causal genes and characteristics of individuals with CdLS and other developmental disorders.

For example, some changes in the SMC1A gene have been identified in individuals with characteristics that resemble Rett syndrome (another neurodevelopmental disorder associated with intellectual disability) and few characteristics that resemble CdLS. This is despite SMC1A being confirmed as a causal gene for CdLS (3). Another example is that some individuals have changes in genes (such as ANKRD11 and NAA10) that are associated with developmental disorders other than CdLS but they show characteristics associated with the CdLS phenotype (4,5).

As a result, the overall CdLS phenotype has been characterised as a spectrum, implying a range of clinical findings and characteristics (see Figure 2, page 4). The CdLS spectrum includes the classic (typical) CdLS phenotype, alongside other syndromes with similar but non-classic (atypical) characteristics of CdLS, which are caused by changes in genes associated with CdLS.

Note: Syndromes caused by changes in genes associated with CdLS, but without many CdLS characteristics are not included in the spectrum.

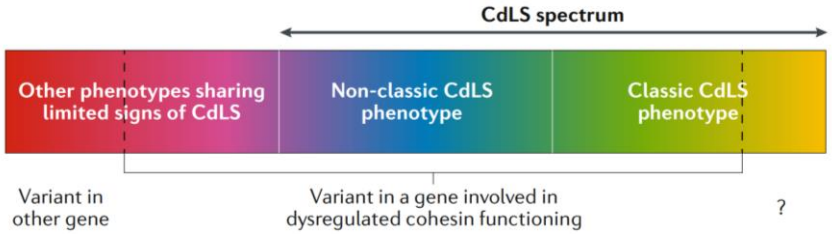


Fig. 2 | The phenotypes classified as Cornelia de Lange Syndrome (CdLS) can be defined as a spectrum. *All seven identified genes that are associated with CdLS affect the cohesin complex (explained further on page 7). The CdLS spectrum includes individuals with the classic CdLS phenotype in whom the affected gene has or has not been identified (if a genetic test is unable to identify a CdLS diagnosis, this can be determined through assessment of clinical features). The spectrum also includes individuals with a non-classic CdLS phenotype who have a gene variant affecting the cohesin complex. There are also individuals who carry a gene variant involved in cohesin functioning (see page 7) but present little or no resemblance to the classic CdLS phenotype. These individuals do not fall within the CdLS spectrum. Note that both classic and non-classic CdLS may affect individuals mildly or severely. The question mark in the figure indicates that there may be genes causing CdLS spectrum that do not have a cohesin function; such genes are unknown at present, but they may exist and must not be excluded.*

Grouping individuals affected into the CdLS spectrum helps knowledge exchange and contact between affected individuals and their families. This means individuals and families can support each other; and leads to increased attention from researchers. However, identification of differences between individuals within the CdLS spectrum is also important to tailor care to each individual.

The International CdLS Consensus Group

Due to the great variability of the CdLS spectrum, as well as in the care and management of individuals, a group of international experts have formed the "International CdLS Consensus Group" to make a series of recommendations. Experts in this group are part of the Scientific Advisory Council of the World Federation of CdLS Support Groups. These recommendations are outlined and explained throughout this document and the full list of recommendations is also available at the end.

What are the Physical Characteristics of Cornelia de Lange Syndrome?

There are a combination of signs and symptoms that define the CdLS spectrum phenotype. Experts from the International CdLS Consensus Group (see Table 1 on page 5 for voting process) have classified these into cardinal features (considered to be most common in CdLS) and suggestive features (which are less specific to CdLS) (**Recommendation 1 = R1**). When assessing characteristics, cardinal features are assigned 2 points each if present, and suggestive features are given 1 point each if present (**R2;** See Box 1, page 5).

Table 1 | Details of the Delphi consensus voting process *(structured communication process between a panel of experts used to gain consensus on the CdLS recommendations).*

Level of evidence	Definition	Votes (%)
+++	Evidence or general agreement indicate full agreement with the recommendation	≥70
++	Evidence or general agreement favour the recommendation	50–69
+	Evidence or general agreement are weak for the recommendation	26–49
–	Insufficient evidence or general agreement for the recommendation	<26

37 international experts voted on the recommendations digitally. For all recommendations, over 90% of experts were in full agreement with the recommendations. Patient group representatives did not vote.

Box 1 | Clinical features of Cornelia de Lange Syndrome

Cardinal features (considered to be the most common; 2 points each if present)

Meeting of the medial eyebrows in the midline and/or thick eyebrows
Short nose, concave nasal ridge (nasal ridge curving posteriorly to an imaginary line that connects the nasal root and tip) and/or nose with an upturned tip
Long and/or smooth philtrum (vertical indentation in the middle area of the upper lip)
Thin upper lip and/or downturned corners of mouth
Presence of fewer than the normal number of fingers and/or absence of fingers or toes from birth
Congenital diaphragmatic hernia (abnormal opening in the diaphragm present from birth)

Suggestive features (less specific to CdLS; 1 point each if present)

Global developmental delay and/or intellectual disability/learning disability
Prenatal growth retardation (restricted growth prior to birth)
Postnatal growth retardation (restricted growth after birth)
Microcephaly (decreased size of head, can occur prior to or after birth)
Small hands and/or feet
Short fifth finger
Abnormally increased hair growth

Clinical score
11 points and above, of which at least 3 are cardinal: classic CdLS
9 or 10 points, of which at least 2 are cardinal: non-classic CdLS
4-8 points, of which at least 1 is cardinal: individual should be genetically tested for CdLS
Less than 4 points: insufficient to indicate genetic testing for CdLS should conducted

It is important to remember that an individual with CdLS may not have all of these characteristics. An individual with CdLS may have many of these characteristics or only a few.

CdLS Spectrum Clinical Criteria (scoring)

The International CdLS Consensus Group has agreed on criteria for the CdLS spectrum which is based on the cardinal and suggestive features (as shown in Box 1, page 5). These criteria are based on points.

- A score of 11 or more indicates **classic CdLS** if at least 3 cardinal features are present.
  If a score of 11 or more is reached the diagnosis of CdLS is confirmed, regardless of whether there is a change in one of the 7 known genes for CdLS.

- A score of 9 or 10 indicates **non-classic CdLS,** if at least 2 cardinal features are present.

- A score of 4 or more is sufficient to warrant genetic testing for CdLS if there is at least 1 cardinal feature present.

- A score of 4 or less is insufficient to warrant genetic testing.

The following figure shows some of the cardinal features of CdLS:

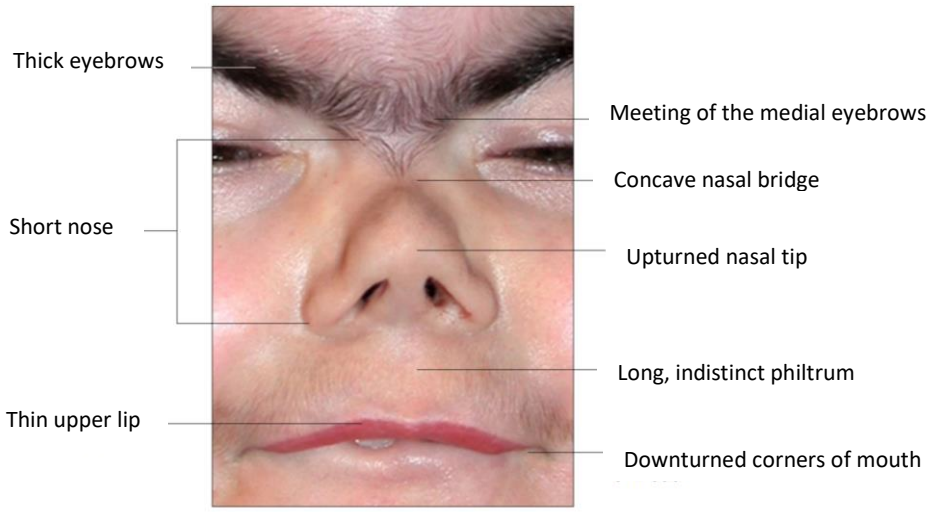


Fig. 3 | **Cardinal facial features of Cornelia de Lange syndrome.** *Facial features that are the most characteristic for Cornelia de Lange Syndrome (CdLS) include the meeting of the medial eyebrows in the midline, thick eyebrows, a short nose, concave nasal ridge and upturned nasal tip, a long and smooth philtrum, a thin upper lip and downturned corners of the mouth. Non-facial features (not shown) that are considered to be cardinal features of CdLS include the absence of one or more fingers, the absence of all fingers and/or toes and hernias in the diaphragm.*

Severity Scores

Severity scoring procedures have been described to indicate the severity of CdLS (2, 10-12). It should be noted that **none of these procedures consider the severity of CdLS as experienced by families.** Scoring procedures also do not estimate the severity of all organ systems that may be affected in CdLS.

The International CdLS Consensus Group suggests current severity scoring schemes should be used cautiously. The group acknowledges the need for the development of a severity score that represents severity as experienced by families (R3).

Summary section

Physical characteristic recommendations:

R1: The CdLS spectrum encompasses a range of phenotypes consisting of classic (or typical) CdLS and non-classic CdLS, which are characterised by a combination of features (see Box 1, page 5).

R2: The International CdLS Consensus Group propose consensus criteria based on the presence of a combination of signs and features (see Box 1, page 5). A diagnosis of classic CdLS can be confirmed if a score of 11 is reached, irrespective of the presence of a variant in a gene known to result in CdLS.

R3: Presently available severity scoring schemes should be used cautiously as these do not adequately reflect the severity as experienced by the individuals with CdLS and their families.

What causes Cornelia de Lange Syndrome

The genetic causes of CdLS are complex and research to fully understand all the genetic causes is still ongoing. The genetic make-up of a child cannot be changed after conception.

The CdLS spectrum has been associated with a change (mutation) in genetic material. Usually, CdLS is caused by a change in one of seven genes. Genes are individual genetic instructions in DNA that make us who we are. The seven genes associated with CdLS are: *NIPBL, SMC1A, SMC3, RAD21, BRD4, HDAC8 and ANKRD11* (**R4**). A change in one of these genes affects what is known as the cohesin protein complex (13-18).

The cohesin complex has many functions. One of these includes regulating the process of a fertilised egg dividing many times during the development of a baby. This process requires all of the DNA (genetic material present) to produce a second copy of itself before it divides. Changes to the genetic code can occur when the DNA is copied. The cohesin complex also regulates the expression, structure and organisation of a person's genetic code (19-22).

If a change in genetic code affects one of the seven genes associated with the CdLS spectrum, the cohesin complex does not function properly. This can cause altered human development and is believed to be the underlying cause of CdLS and syndromes in the CdLS spectrum.

The known causes of CdLS are therefore called cohesinopathies. This is because changes in genes associated with CdLS affect the cohesin complex. However, not all cohesinopathies result in CdLS.

The cohesin complex has multiple parts. It is thought that there is a core centre which includes a ring which can open to hold the copies of DNA together until they divide, as well as associated proteins which help regulate the core centre. Genes always code for a single protein; in this case each gene related to CdLS codes for a different part of the cohesin protein complex.

Mutations that occur in genes can have small or large effects. There can be single small mutations (missense mutations) that change only a single part of the gene; these tend to produce proteins that might be able to do some of the work but not all, or that do the work slightly differently. Larger or more severe mutations (loss of function mutations) usually lead to more severe effects, such as resulting in no protein being produced at all. Deletions within a single gene, larger than mutations, can result in effects similar to a loss of function mutations or may have more severe effects. Specific gene variants (mutations or deletions in genes) have been identified in up to 84% of individuals with CdLS.

The seven known genes that are implicated in CdLS differ in the clinical features presented (See Table 2 on the following page).

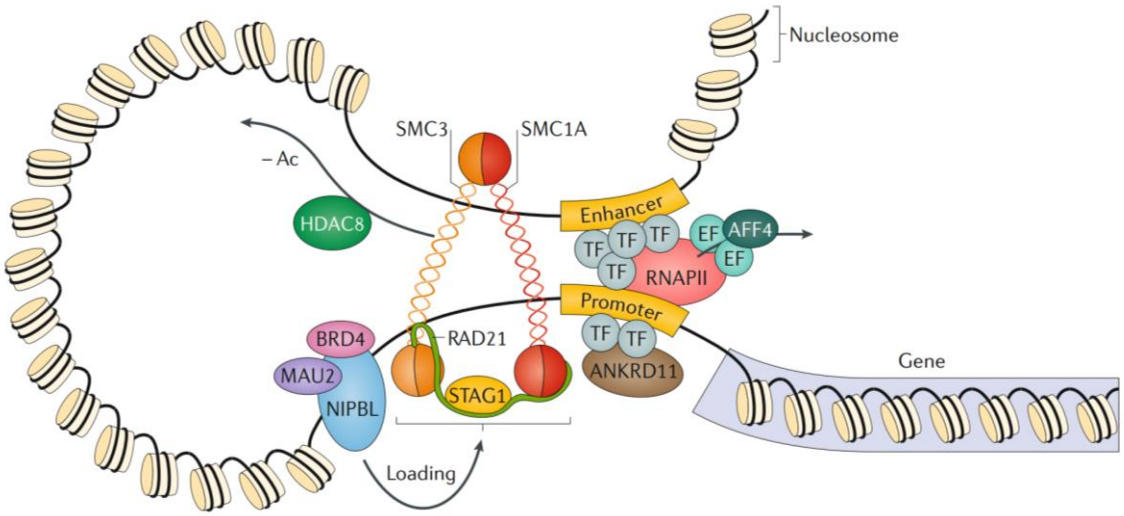


Fig. 4 | **Cornelia de Lange Syndrome (CdLS) is a cohesinopathy (changes in genes associated with CdLS affect the cohesin complex).** *CdLS is caused by genetic variants that affect regulators of the cohesin complex. The structural components form a ring and cohesin subunits (such as STAG 1) attach to the ring and form part of the core complex.*

Table 2 | **Comparison of the main clinical findings in individuals with different genetic variants of Cornelia de Lange Syndrome.**

NR =Not reported
++++ = more than 90% of individuals
+++ = 70-89% of individuals
++ = 50-69% of individuals
+ = 20-49% of individuals
- = less than 20% of individuals

	The different genes linked to Cornelia de Lange Syndrome						
	NIPBL	**SMC1A**	**SMC3**	**BRD4**	**HDAC8**	**RAD21**	**ANKRD11**
Growth							
Prenatal growth retardation	+++	++	+	++	++	++	-
Short stature	+++	++	++	+	+	++	++
Microcephaly *(decreased head size)*	++++	++	++	++	+	++	+
Head and facial features							
Wide skull shape	++	+	+++	+	+++	++	+
Low frontal hairline	+++	+++	+++	++	+	+	+
Arched, thick eyebrows	+++	+++	++++	+++	+++	+++	+
Meeting of the eyebrows in the midline	++++	+++	+++	+++	++++	+++	+
Long eyelashes	++++	+++	+++	+	+	+++	+
Flattened nasal bridge	+++	+	+	+	+	+	A*
Nose tip upturned	+++	++	++	++	+++	+++	+
Wide tip of nose	++	++	+++	+	+	-	++
Long, smooth philtrum *(vertical indentation in the middle area of the upper lip)*	+++	++	++	++	++	++	++
Thin upper lip	++++	+++	+++	++	+	+++	++
Downturned corners of the mouth	++++	+++	++	+	++	+++	-
Highly arched palate	++	+	+	+	+	++	+
Widely spaced teeth	+++	+	+	-	++	-	B*
Small, underdeveloped jaw	+++	+	+	++	++	+	-
Low-set and malformed ears	++	+	+	-	+	+	-
Body							
Absence of few or all fingers	+	-	-	-	-	-	-
Small hands	+++	+++	+++	++	++++	+++	++
Thumbs attached close to wrists	++	+	+++	+++	+++	+	-
Bent or shorter fifth finger	+++	+	++	+	++	+++	++
Small feet	++++	++	+++	NR	+++	+++	+
Abnormally increased hair growth	+++	+++	++++	-	+	++	++

	NIPBL	SMC1A	SMC3	BRD4	HDAC8	RAD21	ANKRD11
Heart problems	+	+	+	+	+	+	-
Abnormal vertebrae *(bones forming the backbone)*	-	-	+	-	-	++	+++
Cognition and behaviour							
Intellectual disability/learning disability *(any degree)*	++++	++++	++++	++++	++++	+	++++
Autism spectrum disorder	+	+	+	-	+	+	+
Self-injurious behaviour	+++	+	NR	+	+	-	++
Stereotypic movements *(repetitive, simple movement that can be suppressed*)	++	++	NR	NR	-	-	-

A = Prominent nasal bridge rather than flattened nasal bridge, B* = Teeth are not widely spaced but are larger than normal*

NIPBL

The *NIPBL* gene codes for a protein which is part of the regulatory centre of cohesin and, along with another gene (*MAU2*) helps the ring to be loaded onto the duplicated DNA. Changes (mutations) in *NIPBL* can be found in approximately 70% of individuals with CdLS. Classic CdLS is usually caused by changes in *NIPBL* (13,14). The missense mutations (single small mutations) cause milder phenotypes than the loss of function mutations, as described on page 8. Deletions may occur in *NIPBL* in about 3% of those with CdLS. Also, there are quite a few people with classic CdLS who have been found to have mosaicism for mutations in *NIPBL*, which means that not all of the cells tested show the mutation (e.g. the mutation is unable to be found in a blood sample, but can be detected on a cheek swab which takes cells from the inside of the cheek (see below).

While individuals with the classic CdLS phenotype are likely to have changes in *NIPBL*, individuals with changes in the other causative CdLS genes can also fulfil the criteria for classic CdLS.

SMC1A

SMC1A is responsible for producing and maintaining the core component of the cohesin complex ring. Changes in *SMC1A* have been found in approximately 5% of individuals with CdLS (3).

Many individuals with changes in *SMC1A* usually display a non-classic phenotype (3,15,16,24,29) and have fuller eyebrows, less shortening of the nasal bridge and a rounder face compared to individuals with changes in *NIPBL.*

40% of individuals with changes in *SMC1A* display a phenotype that resembles Rett Syndrome (another neurodevelopmental disorder associated with intellectual disability) more than CdLS (3,30,31).

The gene *SMC1A* is on the X chromosome. There are two copies of the X chromosome in all of the cells of females and only one in all of the cells of males. For the majority of genes, one of the X chromosomes in females is inactivated (turned off) to have the same balance as in males. However, some genes are not

inactivated and that is the case for *SMC1A* (32). This means that males are typically more severely affected than females, as females have two copies of the gene, with one likely to not have a mutation (3,15). There has been a report of mosaicism for a variant in this gene in one person only (16).

SMC3

SMC3 is responsible for producing the other major part of the ring of the core cohesin complex. Changes in *SMC3* were initially reported in a single individual with non-classic CdLS (16) and changes to this gene are an uncommon cause (1%) of non-classic CdLS (33).

Changes in *SMC3* have however, been found in individuals with intellectual disability, short stature (height) and congenital abnormalities (birth defects) who do not fulfil the criteria for non-classic CdLS (24,33). Changes in *SMC3* are typically linked to missense mutations (single small mutations; see page 8) (33).

RAD21

RAD21 also forms part of the core cohesin complex (34). Changes in *RAD21* have been found in a small percentage (1-2%) of causes for CdLS. Individuals with changes in *RAD21* are reported to have a non-classic CdLS phenotype (17,24,35). Both loss of function and missense mutations have been reported, as well as deletions within the *RAD21* gene (36). It is difficult to look at the relationship between this specific gene mutation and clinical characteristics due to the low number of individuals reported to have a mutation in the *RAD21* gene.

BRD4

BRD4 codes for a protein that associates with *NIPBL* and likely attaches to the protein once the cohesin ring has bound the DNA (37). The number of reported individuals with variants involving *BRD4* is small, but a deletion that includes *BRD4* has an atypical phenotype for CdLS.

HDAC8

Changes to the gene *HDAC8* were first reported in individuals with classic and non-classic CdLS (18). *HDAC8* is also on the X chromosome but it can be inactivated. It is important to note that changes on *HDAC8* may also result in characteristics that do not resemble CdLS (39). Currently, variants in *HDAC8* have been found in about 5% of individuals with CdLS (24,38-42).

There is a wide variation in the phenotype shown by individuals with a mutation in *HDAC8*. Typically, individuals with a mutation in *HDAC8* have a non-classic CdLS phenotype, but some individuals do fulfil the criteria for classic CdLS. In addition to the features of CdLS, individuals with a change in *HDAC8* may show some other distinctive features.

These include: A large anterior fontanel (the soft spot on an infant's head before the skull bones meet at approximately 2 years of age), widely spaced eyes or a happy personality.

Because *HDAC8* is randomly inactivated when there is more than one X chromosome (41), both males and females can be affected when there is a mutation in this gene. Some of these females can be completely healthy, and in those cases, most have non-random inactivation of the *HDAC8* with the mutation (41,42).

ANKRD11

Changes in the gene *ANKRD11* have been reported in several individuals with a non-classic CdLS phenotype (24, 43), and others have been noted in several clinical observations. Individuals with changes in *ANKRD11* show features that overlap with the facial characteristics and suggestive features of CdLS (see Box 1, page 5).

Other genes

Changes in several other genes associated with a phenotype of the CdLS spectrum have also been found. Individuals with changes to these genes show a small number of clinical features seen in CdLS.

- Changes in the gene *EP300* have been found in individuals with some features suggestive of CdLS (44).
- Changes in the gene *AFF4* have been found in several individuals with CHOPS syndrome. "CHOPS" stands for cognitive impairment (e.g. problems with memory, communication and thinking), coarse facial features, heart defects, obesity, pulmonary involvement, short stature and skeletal dysplasia (disorder that affects bones/joints and hinders growth). CHOPS syndrome includes features which overlap with CdLS (45).
- Changes in the gene *NAA10* have been found in some individuals with some resemblance to CdLS that is limited to the region around the eyes (5).
- Changes in the gene *TAF6* have been found in two families with children who showed features that overlap with CdLS (4).

Mosaicism

Mosaicism, means there are different groups of cells with different genetic make-up in a person. This means that some cells in the person will have the mutation and others will not. Mosaicism has been found to occur frequently in CdLS (23). Approximately 15-20% of individuals with classic features of CdLS have mosaic changes in *NIPBL;* and although it is rare, individuals with CdLS can also have mosaic changes in *SMC3*, *RAD21* or *SMC1A*. These mosaic changes cannot be found using genetic testing that examines an individual's DNA from their white blood cells (23,24,46).

In some circumstances, if an individual is found to be mosaic for a mutation, it is thought that there could be a variation in the severity of the clinical findings. However, there is no evidence that this occurs in CdLS. It is suggested that there may be a selection against these gene changes occurring in blood cells (41, 23,

46), meaning they may not be identified using blood tests. Genetic testing can evaluate DNA for mosaicism by examining fibroblasts (connective tissue cells), buccal cells (cheek cells) or bladder epithelial cells (cells in urine) instead (**R5**) (23,24).

Family Recurrence Risk

Genetic counselling should be offered to all families with a family member with CdLS. Genetic counselling is when prospective parents are given advice about the risks of having a child with a genetic disorder. The International CdLS Consensus Group advises that the recurrence risk of CdLS in a future child differs depending on which gene is involved.

The genes (*NIPBL, SMC3, RAD21, BRD4* and *ANKRD11*) that are not on the X chromosome are autosomal (dominant) genes, meaning that if a mutation is fully present, the clinical effects will occur. Most of the time the mutation will be new in the family when a child is born with CdLS. Families have been reported to have more than one child with CdLS, with parents unaffected (47, 48). This is due to a small population of some of a parent's eggs or sperm cells carrying the mutation (this is called germline mosaicism). For this reason, the recurrence risk for future children is never said to be zero. There also could be a very mildly affected parent, with a mutation in one of these genes, who would have a 50% (1 in 2) chance of passing on that mutation in each subsequent pregnancy. The authors' joint experience based on 560 families having a child with a variant in *NIPBL* is that the recurrence risk due to germline mosaicism is 0.89% (slightly less than 1 in 100).

For the genes (*SMC1A* and *HDAC8*) on the X chromosome (X-linked), most of the time the mutation is new in the family. If the mother is unaffected but carries the mutation, the recurrence would be 50% (1 in 2) with each subsequent pregnancy. Sometimes genetic counselling is difficult, because affected siblings can be variably affected clinically (3, 35, 41, 42). This is also true for families with *RAD21* mutations.

If no molecular testing has been done, the total overall recurrence risk for CdLS has been calculated in the past to be 1.5% (1½ in 100) (49) (**R6**).

Summary section

Causes of Cornelia de Lange Syndrome recommendations:

R4: Classic CdLS is usually caused by variants in *NIPBL;* however, variants in one of six other genes – *SMC1A, SMC3, RAD21, BRD4, HDAC8 or ANKRD11* – should also be considered, as they may lead to a similar phenotype.

R5: Mosaicism should be considered in individuals with CdLS in whom a variant in a gene known to cause CdLS cannot be detected in blood cells, in which case other tissues such as fibroblasts (skin), buccal (cheek) cells or bladder epithelial cells from urine should be studied.

R6: Genetic counselling should be offered to all families with a family member with CdLS. Families should be counselled that the recurrence risk of CdLS differs depending on the gene involved. In the non-X-linked forms, the recurrence risk is 0.89% due to germline mosaicism. Autosomal dominant

inheritance of CdLS does occur, meaning if one copy of the mutation is present, the individual will show clinical effects. In clinically diagnosed individuals with CdLS, the recurrence risk is 1.5%.

How is Cornelia de Lange Syndrome Diagnosed?

Can CdLS be diagnosed prenatally (before birth)?

There are several indicators that can lead to diagnosis of CdLS prenatally (before birth). Indicators may include parents with an earlier child with CdLS, or a new pregnancy in a family with a known genetic change in a gene associated with CdLS.

Another indicator may be no family history but features suggestive of CdLS on an ultrasound scan of an unborn baby.

Prenatal features suggestive of CdLS may include:

- ***Intrauterine growth restriction (IUGR)***
  IUGR is a condition in which a baby's growth slows or stops during pregnancy. It is the most common suggestive feature of CdLS in a developing baby and typically begins in the second trimester (months 4 to 6) of pregnancy (50).
- ***Prenatal limb differences***
  E.g. Small hands and feet and/or missing portions or shortening of limbs.
- ***Abnormal facial profile***
  E.g. An undersized jaw (micrognathia) or protruding upper jaw (prominent maxilla) (51).
- ***Increased nuchal thickness***
  A collection of fluid under the skin at the back of a baby's neck.
- ***Diaphragmatic hernia***
  A hole in the diaphragm, the muscles under the lungs that is responsible for breathing. The hole allows organs from the abdomen to move into the chest.
- ***Cardiac malformation***
  Heart defects (50).

If an ultrasound scan reveals features suggestive of a genetic disorder, a midwife or doctor will discuss the possible benefits and risks of prenatal genetic testing with the baby's parents. The midwife or doctor will help parents to make a decision about the investigations that are available (**R7**).

If parents have a previous child with CdLS or there is a family member with a known change in a gene associated with CdLS, a midwife or doctor will discuss the possible benefits and risks of prenatal genetic testing.

Prenatal genetic testing can be carried out using DNA from samples of cells from the placenta (the organ linking the mother's blood supply with the developing baby) or amniotic fluid (the fluid that surrounds the developing baby in the womb). Genetic testing can identify changes in any of the seven genes that are associated with CdLS (**R8**).

The tests can help parents make choices about further tests, care or treatment during the pregnancy or after the baby is born. It is important to remember that any prenatal test offered is optional. It is up to the family to decide whether any tests that are offered would be helpful or wanted.

The newest prenatal screening test, non-invasive cell-free foetal DNA (also called non-invasive prenatal screening or NIPS) can screen for various genetic changes in the developing baby in the mother's blood. This might detect changes in genes that could cause CdLS. In families with a previous child with CdLS and a known mutation, this test may be a useful way to examine the specific gene that may be affected. However, in families without a previous child with CdLS, the result would be difficult or impossible to determine with accuracy, and would likely need extensive interpretation. Mosaicism also cannot be assessed using this testing method. This means this type of testing may not be useful for CdLS.

Genetic Testing for the CdLS Spectrum (post birth)

Genetic tests have been developed to identify changes in any of the genes associated with the CdLS spectrum. A referral to a clinical geneticist can be made if parents feel that it would be useful to discuss the possibility of testing for the child with a CdLS spectrum syndrome. Genetic testing is not always appropriate or necessary (particularly if a doctor is very certain about the clinical diagnosis), but would be the only way to approach prenatal testing for future pregnancies.

Panel Sequencing

The most effective genetic test to identify a change in a gene known to cause CdLS is panel sequencing. Panel sequencing analyses multiple genes at once. When testing for CdLS spectrum the panel should include at least the seven known CdLS genes (see Figure 5 on page 16). Most laboratories for genetic testing will include additional genes that can cause a phenotype resembling CdLS, such as *CREBBP* and *EP300.*

Sanger Sequencing

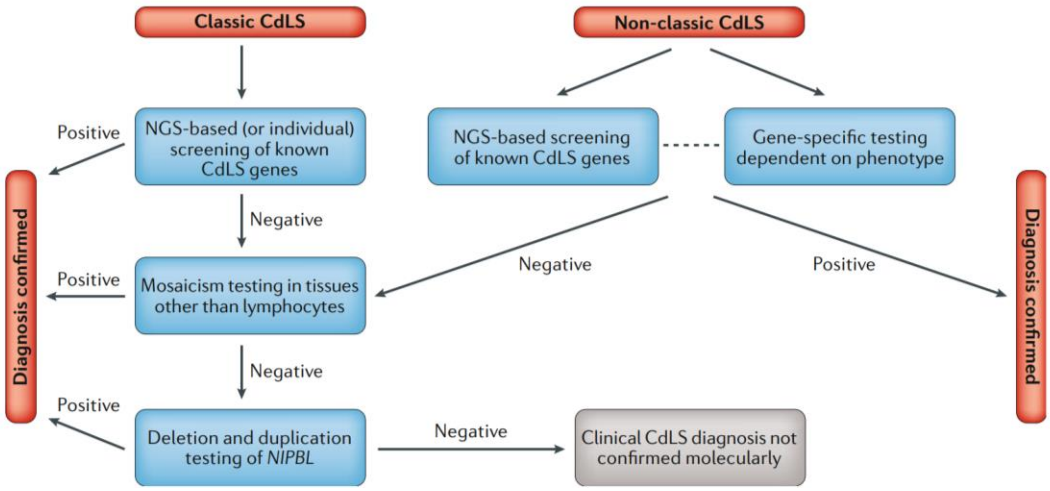
Although panel sequencing is the most effective genetic test, it may not be available in some parts of the world. Clinical geneticists may use other genetic tests, such as Sanger sequencing. Sanger sequencing uses a computer to look for gene mutations in a person's DNA. If an individual has a classic CdLS phenotype, Sanger sequencing of the *NIPBL* gene is the preferred initial test. If an individual has a non-classic CdLS phenotype, other genes associated with the CdLS spectrum can be sequenced (**R9**).

Testing for Mosaicism

When a change in a gene associated with CdLS cannot be found using panel or Sanger sequencing, genetic testing can evaluate an individual's DNA for mosaicism. Mosaicism is where there are different populations of cells which have a different genetic make-up in a single person. *See the Mosaicism section on page 12.*

Multiplex Ligation-dependent Probe Amplification

If genetic testing is not able to find mosaicism in an individual's DNA, a test called multiplex ligation-dependent probe amplification (MLPA) can be considered. MLPA looks for deletions or duplications in the *NIPBL* gene.



NGS = next generation sequencing/modern genetic testing approaches.

Fig. 5 | Diagnostic pathways for Cornelia de Lange (CdLS) Syndrome. *In individuals with the classic phenotype, the first-line approach should be modern genetic testing approaches by either examining multiple genes at once, examining all of the genes that code for proteins in an individual or by examining the complete DNA of an individual. This should include all of the currently known CdLS genes (NIPBL, SMC1A, SMC3, RAD21, BRD4, HDAC8 and ANKRD11). If these approaches are not available, genetic testing should begin by examining NIPBL (classic CdLS phenotype). In individuals with the non-classic CdLS phenotype, the phenotype itself may allow experienced clinicians to determine which gene should be sequenced first; if this cannot be determined, modern genetic testing approaches can be performed. In the case of negative results, NIPBL and the other CdLS genes should be tested for mosaicism using tissues other than blood (as not all of the cells tested may show the mutation), for example, cells in connective tissues, cheek/mouth swabs or cells from urine. There are other tests that can be carried out to investigate the NIPBL gene (i.e. whether it has been deleted or duplicated), these are called multiplex ligation-dependent probe amplification or chromosome microarray. These tests can be used before other genetic testing approaches, or may be used following these approaches to investigate gene variants further.*

Summary section

Diagnosis recommendations:

R7: If a prenatal ultrasound scan (sonography) detects features consistent with CdLS, possibilities for prenatal genetic testing should be discussed with the parents.

R8: If a causative gene change has been detected in an earlier child or pregnancy, reliable prenatal diagnostic testing should be discussed with the family. Targeted variant testing can be performed using DNA derived from the placenta or amniotic fluid.

R9: If available, first-line genetic testing should be performed using panel sequencing to screen all genes known to cause CdLS spectrum (*NIPBL, SMC1A, SMC3, RAD21, BRD4, HDAC8* and *ANKRD11*). Medico-legal, technical, and insurance-related national practices may require other tests, such as Sanger sequencing of individual genes.

What medical care may a child with CdLS need?

Paediatric Medical Care

CdLS is usually recognised from birth by an experienced children's doctor (paediatrician or clinical geneticist). Paediatricians or clinical geneticists play a key part in the clinical care of a child with CdLS. Once an infant or child has been diagnosed with CdLS, they will need to be assessed for common structural abnormalities of the body associated with the syndrome. These may require management or surveillance.

Individuals with CdLS may have heart and/or kidney malformations (birth defects) (49). Every infant and young child diagnosed with CdLS should have a heart and kidney assessment by an echocardiogram (heart scan) and kidney ultrasound respectively. If malformations are found, the child may need to be referred to a specialist to help with management. If the diagnosis is made in adolescence, these tests may not be necessary if related symptoms have not been reported (**R10**).

Rarely, some children with CdLS may show neurological symptoms such as seizures. Seizures are caused by an abnormal discharge of electrical activity in the brain. A test of electrical activity in the brain (electroencephalogram, or EEG) can assess for seizures. Routine brain imaging (e.g. CT or MRI scans) is usually not recommended unless indicated to be of clinical use.

Treatment and surveillance of malformations in children with CdLS are the same as for typically developing children. However, the procedure of intubation (inserting a tube through the mouth into the airway during medical procedures) has been difficult in many children with CdLS. Children may also have an adverse allergic reaction to some anaesthetic medications (such as Midazolam or Versed), though complications from most anaesthetic medications are rare (52, 53).

Growth in Childhood

Birth weights in CdLS are significantly lower than the average birth weight and children with CdLS are almost always short in stature. Young children tend to have a below average weight when compared to others their age, although obesity can occur in later life. A small head size is also often common in

individuals with CdLS. Growth charts are available that are specific to individuals with CdLS (54). CdLS-specific growth charts should be used to monitor the growth of every child with CdLS (**R11**).

Growth in CdLS is influenced by the specific gene implicated in the development of CdLS (10,24). Individuals with CdLS caused by a change in *SMC1A* tend to show more growth than individuals with CdLS caused by a change in *NIPBL* (3). If growth is lower than expected in CdLS, there may also be gastrointestinal (stomach/intestines) problems, thyroid gland dysfunction (leading to dysfunction in bodily functions such as metabolism, growth and development) or growth hormone disturbances.

The release of growth hormone (important for growth, body structure and metabolism) is normal in most children with CdLS (55). However, a case study with one child with CdLS (*NIPBL* mutation) with low growth hormone levels experienced a growth increase after being administered growth hormone injections (56). The benefits of increased growth from growth hormone supplementation should be weighed against the burden of daily injections and the lack of positive impact of an increased adult height on quality of life for most individuals with CdLS.

Feeding and Dental Difficulties

From infancy to adulthood, feeding difficulties are very common in individuals with CdLS. Preferably, individuals with CdLS should be fed orally (by mouth). However, feeding difficulties may sometimes result in feeding times becoming unsafe, stressful and taking many hours out of the day. In these circumstances, doctors may temporarily supplement an individual's feeding with a gastrostomy tube (57). A gastrostomy tube delivers food straight into an individual's stomach. It is important that dieticians (experts on diet and nutrition) are involved (**R12, R13**).

Feeding difficulties can be caused by several physical issues such as a cleft palate, micrognathia (undersized jaw) or dental issues (57). Cleft palate is where there is a gap or split in the roof of the mouth. It is present from birth and occurs in 20% of individuals with CdLS. After being diagnosed with CdLS, all individuals should have the roof of their mouth closely examined to assess for cleft palate. If an individual has a cleft palate, they should be referred for specialist assessment (**R14**).

Dental problems in CdLS may include:

- Delayed secondary tooth eruption
- Small or absent teeth
- Malposition (abnormal positioning of teeth)
- Malocclusion (misalignment between the lower and upper teeth when the jaw closes)
- Overcrowding of teeth
- Tooth decay or cavities
- Periodontal disease (infection affecting the gums of the mouth)
- Bruxism (teeth grinding)

Dental problems may worsen due to poor oral hygiene, especially in individuals with CdLS who have marked intellectual disability. Sometimes, individuals with CdLS may not brush their teeth regularly or thoroughly enough. This may lead to early onset dental decay and periodontal (gum or mouth) disease

(59). It is important to ensure regular dental assessment and cleaning to prevent early dental decay. A healthy diet can also help to keep teeth in good condition (60, 61; **R15**).

Motor Development

Motor development refers to the development of a child's bones and muscles the child's ability to move around and manipulate the environment. Motor development can be divided into gross motor development (involving the larger muscles) and fine motor development (involving the small muscles of the body).

Motor development in CdLS is almost always delayed and developmental milestones should be monitored closely (**R16**). There is some evidence to suggest children with CdLS caused by a *SMC1A* gene mutation may reach milestones (e.g. sitting, walking and first words) at a younger age than children with CdLS caused by changes in the *NIPBL* gene (3). By five years of age, most children with CdLS caused by a change in *NIPBL* are able to sit, walk independently and start to speak.

Vaccinations should be given to every child with CdLS according to national guidelines (**R17**). It is common for individuals with CdLS to have recurrent respiratory infections which can affect the sinuses, throat, airways or lungs. Respiratory infections in CdLS are thought to be influenced by differences in anatomy (how the airways have formed), hypotonia (low muscle tone and strength) and poorer co-ordination of swallowing and coughing.

Some individuals with CdLS may have an immunodeficiency. This is where the body's immune system has a lower ability to fight infection. If the child with CdLS has unusually frequent or severe infections, the GP or paediatrician can make a referral to assess for an immunodeficiency (62).

Thrombocytopenia (low platelet count) can also occur in CdLS. Platelets are blood cells which help the blood to clot to stop bleeding (e.g. when a person falls and grazes their knee). Specific testing is not needed for thrombocytopenia in CdLS and individuals tend to not show symptoms (63, 64).

Pain and Behaviour

Pain in CdLS can be caused by dental problems, bladder and upper respiratory tract (including ears and sinuses) infections, gastro-oesophageal reflux disease (GORD) and/or hip abnormalities. GORD is a condition in which a weakness in the muscles above the stomach allows stomach acid to move upwards into the oesophagus (see page 24). Due to limited communicative abilities, individuals with CdLS may be unable to report pain and it may be difficult to identify the cause (65). Pain in CdLS can lead to substantial behavioural difficulties.

Scales have been developed to help identify pain in individuals who have difficulties communicating. If it is suspected that a person with CdLS is in pain, the Face, Legs, Activity, Cry, Consolability (FLACC) scale is a useful tool that can assist in identifying pain (66). The FLACC scale can help to identify different sources and symptoms of pain in a person with CdLS (**R18**).

Puberty

Most individuals with CdLS will go through puberty, though puberty is usually mildly delayed. The average age of puberty onset in CdLS is 15 years of age in boys and 13 years of age in girls (2). A small number of females with CdLS will never menstruate. For those who do menstruate, the menstrual cycle will often be irregular. Most girls with CdLS will develop breast tissue.

Some females with CdLS may have a bicornuate (heart-shaped) womb. There are no extra difficulties with conception or in early pregnancy for women with a bicornuate womb, however, there is a slightly higher risk of miscarriage and premature birth.

Boys with CdLS may have undescended testicles, a small penis and/or hypospadias (where the opening through which urine passes is not at the tip of the penis) (2). Only a small number of boys with CdLS have hypospadias. Undescended testicles are very common in males with CdLS. There are risks associated with not having corrective surgery, including a heightened risk of developing testicular cancer, hernias, and twisting of the testicle. Usually there is no lowering of voice at puberty for boys with CdLS (2).

Teenagers with CdLS can become overweight or develop obesity. This is often related to the consumption of high calorie food in combination with limited physical activity (2). Regular evaluation of weight is important.

Paediatric Follow-Up

Preferably, all individuals with CdLS should be followed up by a paediatrician or clinical geneticist experienced in CdLS. Follow-up varies between countries but is frequent in infancy and early childhood, and make occur annually to once every 3–5 years in adolescence and adulthood. In case of problems, the schedule should be adapted to include more frequent follow-up visits (**R19**).

Medical Care in Adulthood

Most people with CdLS reach adulthood because of improved care, especially in the first year of life. Several individuals with CdLS have lived to 50+ years of age (23, 67). Many medical disciplines tend to be involved in the medical care of adults with CdLS. As many disciplines are involved, it is important that there is co-ordination in care.

Can individuals with CdLS have children?

A small number of women with CdLS have given birth. Often, mothers have only been diagnosed after their child has been diagnosed with CdLS (3,36,41,68). Few men with CdLS have fathered a child, though there is little data about fertility in males with CdLS (69, 70). Sexual education should be offered to individuals with CdLS and education should be appropriate to the level of understanding. Contraceptive options are the same as for the general population (**R20**).

For some women with CdLS it may be preferable to control or prevent menstruation. There are several contraceptives that can do this. Hysterectomies are not recommended as a primary method of contraception in CdLS. A hysterectomy is a surgical procedure to remove the womb and means the woman can no longer become pregnant. However, a woman with CdLS may have a hysterectomy to treat unusually heavy periods which do not respond to treatment (**R21**).

Premenstrual syndrome (physical and emotional symptoms occurring before a period) and menstrual period pain occur in women with CdLS and can be associated with behavioural changes. Treatment options are the same as in the general population. It is not known if women with CdLS undergo menopause.

Weight Management in Adulthood

Some adults with CdLS are overweight and may be obese (49,59). Close attention should be paid to ensuring a healthy, low calorie diet and physical activity is encouraged (**R22**).

A very small number of adults with CdLS develop type 2 diabetes (2). Type 2 diabetes is a common condition that causes high sugar (glucose) levels in the blood, resulting in excessive thirst and tiredness. Individuals who are overweight have a higher risk of developing type 2 diabetes.

How are the Organs Affected in Adults with CdLS?

Organ involvement in adults with CdLS is similar to that seen in children with CdLS. Heart defects are common in CdLS and around 1 in 4 children with CdLS are born with a heart condition. These are usually detected in infancy or childhood. Typically, heart defects do not cause unexpected complications in adulthood. A small number of individuals with CdLS may have hypertension (high blood pressure) or heart failure (where the heart is unable to pump blood around the body properly) (2,73). A very small number of individuals with CdLS have been reported to have a heart attack or stroke (73).

It has been identified that a number of individuals with CdLS have structural differences in their kidneys. Even so, kidney failure has only been reported in 1% of individuals with CdLS (73). The kidneys are responsible for filtering waste products from the blood, alongside regulating blood pressure, electrolyte balance and red blood cell production. When there are structural differences in the kidneys, they may not be able to function properly. Kidney function should be monitored regularly in children and adults with CdLS who have structural kidney malformations (**R23**).

Prostate enlargement has been found in 10% of men with CdLS by the age of 41 years. The prostate is a small gland located between the penis and the bladder. Enlargement of the prostate can cause difficulty with urination. Prostate enlargement is common in men aged over 50 in the general population (75). Prostate enlargement in men with CdLS should be assessed earlier and treated according to national guidelines for the general population (**R24**).

Risk of Cancer in CdLS

There is no increased risk of cancer at a young age in CdLS in comparison to the general population. It is unclear whether there is an increased risk of cancer for middle-aged and older individuals with CdLS. Cancer of the oesophagus has been reported in three individuals with CdLS who had Barrett's oesophagus. This can be caused by Gastro-oesophageal reflux disease (GORD) which is common in CdLS. GORD is a condition in which a weakness in the muscles above the stomach allows stomach acid to travel into the oesophagus (see page 24). Over many years, stomach acid can cause changes in cells lining the oesophagus. This is called Barrett's oesophagus. These abnormal cells are at increased risk of becoming cancerous.

Women with CdLS should be offered cervical and breast cancer screening according to national guidelines for the general population (77,78) (**R25, R26**).

Causes of Death in CdLS

The most common causes of death in infants with CdLS are congenital diaphragmatic hernia (hole in the diaphragm) and respiratory (breathing) problems. In children with CdLS, the most common causes of death are heart defects and respiratory and gastrointestinal (stomach/intestines) problems (73).

Causes of death in adults with CdLS relate to gastrointestinal, pulmonary (lung) and cardiac (heart) systems, as well as infections or anaesthesia (medically induced loss of sensation) (2,67,73,79).

Several countries use emergency medical cards which report the main clinical data of the patient. The use of these emergency cards should be considered for every person with CdLS (**R27**) (see the supplementary section at the end of the document for a template). Emergency cards can report the most frequent and potentially life-threatening medical complications of CdLS.

Summary section

Medical care recommendations:

R10: Every infant and young child with CdLS should be assessed for cardiac (heart) and renal (kidney) malformations subsequent to diagnosis.

R11: The growth of every child with CdLS should be monitored by using CdLS-specific growth charts.

R12: In every CdLS individual with prolonged and marked feeding difficulties, the multidisciplinary assessment (from healthcare workers across many disciplines) should consider (temporary) placement of a gastrostomy (surgical opening through the abdomen into the stomach) as a supplement to oral feeding.

R13: In individuals with CdLS who have recurrent respiratory infections, reflux and/or aspiration (breathing foreign objects into airways) should be ruled out.

R14: The palate should be closely examined at diagnosis. In case of symptoms of a (submucous) cleft palate, referral for specialist assessment is indicated.

R15: Dental assessment and cleaning should take place regularly; a more thorough dental examination or treatment under anaesthesia may be necessary.

R16: Developmental milestones should be closely monitored.

R17: Vaccinations should be given to every child with CdLS according to national guidelines.

R18: As pain can easily remain unrecognised in a child with CdLS, all care providers should be aware of the different manifestations and the possible sources of pain. Specific tools to assess pain are recommended.

R19: Regular follow-up of every child with CdLS is needed, preferably by a paediatrician or clinical geneticist experienced in treating individuals with CdLS; schedules depend on local practices and possibilities.

R20: Sexual education appropriate to the level of understanding should be offered, and contraception management should follow local standard for the general population.

R21: Hysterectomy is indicated if abnormally heavy bleeding at menstruation is present and does not respond to medical treatment.

R22: Specific attention to diet and stimulation of activities are recommended as obesity can occur.

R23: Renal (kidney) function should be regularly monitored in children and adults with CdLS who have structural renal malformations.

R24: Prostate enlargement in men with CdLS should be treated according to national guidelines for the general population.

R25: Women with CdLS should be offered breast cancer screening according to national guidelines for the general population.

R26: Routine gynaecologic care including cervical screening should be performed in women with CdLS, according to national guidelines for the general population.

R27: The use of emergency cards should be considered for every person with CdLS.

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What health difficulties might a child with CdLS face?

Research shows that children and adults with CdLS tend to suffer from more health problems compared to other individuals with intellectual disability. The health difficulties that occur most frequently include eye problems, stomach/intestinal issues, genital problems and limb abnormalities.

Gastrointestinal Problems

Gastrointestinal problems are one of the most common health problems in CdLS. Difficulties with the upper gastrointestinal tract, including the oesophagus, stomach and upper small intestine are common. Many gastrointestinal problems in CdLS are present from birth and often constrict or block areas of the digestive system. Frequent gastrointestinal problems include:

- ***Duodenal Atresia*.** Duodenal Atresia is the blockage of the duodenum bowel which prevents food and fluid passing from the stomach to the intestines.
- ***Annular Pancreas.*** A ring of pancreatic tissue constricts the duodenum bowel which adjoins to the stomach. This can block or impair the flow of food to the intestines (80).
- ***Imperforate Anus.*** This is where the opening to the anus, where stools leave the body, is missing or blocked (81).
- ***Meckel Diverticulum.*** This is a slight bulge in the small intestine. It is often present at birth and is left over from the umbilical cord (59).
- ***Congenital Diaphragmatic Hernia*.** This is where there is a hole in the diaphragm (muscles under the lungs that are responsible for breathing) allowing organs from the abdomen to move into the chest (82, 83).
- ***Pyloric Stenosis.*** Pyloric Stenosis is where the opening from the stomach to the first part of the small intestine is smaller than usual. It occurs in up to 7% of patients with CdLS (2, 35).
- ***Inguinal Hernia*.** An Inguinal hernia occurs when part of the bowel pokes through the groin due to a weakening in the groin muscles. Inguinal hernias are common in childhood in CdLS (2).

Every individual suspected or proven to have CdLS should be carefully evaluated for signs and symptoms of any of these gastrointestinal problems that are likely to be present from birth (**R28**).

Intestinal malrotation

A small number of individuals with CdLS have been reported to have intestinal malrotation (10, 2). This is an abnormality that can happen early in pregnancy when a baby's intestines do not form into a coil in the abdomen. Malrotation means that the intestines (or bowels) are twisted, which can cause a blockage. Intestinal malrotation may recur during infancy, childhood or puberty (84, 85). Usually, the first sign of intestinal malrotation is volvulus. Volvulus is a complication of malrotation that occurs when the intestines twist in such a way that the blood supply to part of the bowel is cut off.

Due to a lack of awareness by physicians, atypical symptoms and difficulty in effective communication in individuals with CdLS, intestinal malrotation may go undiagnosed. Intestinal malrotation should be considered in any individual with CdLS who experiences intense abdominal pain, regardless of the individual's age (**R29**). Evaluation for the presence of intestinal malrotation should be discussed and decided together with the family, balancing the potential gain in health and burden for the individual with CdLS (**R30**).

Constipation

Constipation is common in CdLS and occurs in almost half of all individuals with the syndrome (2, 73, 3, 59). Treatment for constipation in CdLS is the same as for the general population (**R31**). Diarrhoea, gassiness and lactose intolerance are also fairly common in CdLS (2).

Gastro-oesophageal reflux

The most common and severe gastrointestinal problem in CdLS is reflux, otherwise known as gastro-oesophageal reflux disease (GORD) (88, 89). GORD is a condition in which a weakness in the muscles above the stomach allows stomach acid to travel into the oesophagus.

GORD tends to persist or worsen with time. GORD is more common in individuals with CdLS caused by changes to the NIPBL gene (3, 91). GORD is also common in other individuals with CdLS who display the classic CdLS phenotype (92).

Symptoms of reflux can be highly variable and can include feeding problems, poor appetite, vomiting, belching, heartburn, failure to thrive, agitation, restlessness or poor sleep. Sometimes GORD may be related to a change in behaviour, such as increased self-injurious or aggressive behaviour (3, 90), abnormal positioning of the body, or irritability (**R32**).

Reflux can sometimes be 'hidden' if a person does not vomit or belch. Hidden or 'Silent Reflux' could be occurring if refluxing stomach acids rise into the oesophagus without heartburn or other symptoms. This can be dangerous because this material contains gastric acid, and enzymes that may cause harm to the lining of the oesophagus, leading to scarring and narrowing of the food-pipe (2, 93, 59). This may only present as difficulty swallowing, choking or vomiting and aspiration. 'Silent Reflux' may be more common in CdLS. It may be helpful to be aware of the behavioural signs or indicators of pain and discomfort (see the 'Pain and Behaviour' section on page 19) when obvious signs of reflux are not apparent.

Other signs of reflux include back arching, teeth grinding, lying over objects, constant fidgeting and movement, increased salivation, bad breath, hesitation when eating food and attempting to put objects or hands down the back of the throat. These behaviours do not mean that reflux is definitely occurring, and further investigation is required by a GP or paediatrician. It is important that these signs are monitored regularly.

First-line treatments for GORD include changing nutrition and proton pump inhibitors (PPI). PPIs are a group of drugs which reduce the amount of acid made in the stomach. Individuals with CdLS appear to respond well to maximum dosages of PPIs (57,96) (**R33**). If individuals still experience reflux symptoms after changing nutrition or taking PPIs, doctors may consider looking inside the body to see what is happening using an endoscope (**R34**). Although there are surgical interventions for GORD, they are typically limited to individuals with CdLS who have not responded to changes in nutrition or medical treatments (**R33**).

Over many years refluxing stomach acids rising into the oesophagus can damage the cells lining the oesophagus. This is called Barrett's Oesophagus. Damaged cells in the oesophagus are at increased risk of becoming cancerous as mentioned on page 21 (95). Several individuals with CdLS with long-term GORD have developed cancer in the oesophagus as young adults (92, 94). It is important that all people with CdLS are regularly monitored for reflux and long-term follow-up is also recommended. This is because GORD is often chronic, which is a major risk factor for developing Barrett's Oesophagus (95). The most reliable way to monitor reflux and Barrett's Oesophagus is by repeated endoscopes, which puts substantial burden on the individual with CdLS and their family, particularly because anaesthesia is needed for the procedure.

Parents should be pro-active in seeking help from local doctors or GPs in relation to reflux. A paediatrician or gastroenterologist (a specialist in gastrointestinal problems) should discuss the pros and cons of monitoring Barrett's Oesophagus with the family and, if possible, the individual with CdLS. Families and doctors should decide together what treatment or care is the best for the individual (**R35**).

Problems with the Senses

The eyes and the visual system

Facial features of CdLS are similar in both adults and children. Some individuals with CdLS may have facial features that make them seem older than their actual age. Eyebrows meeting in the middle, thick eyebrows and long eyelashes are very common in individuals with CdLS. They are considered hallmark features of the syndrome.

Ptosis (inability to fully open the eyes) is also common and can occur in one or both eyes (26, 97, 98). If an individual's vision is significantly affected by ptosis, surgical correction can be considered, particularly if the individual is lifting their chin in attempt to see more clearly and it is affecting the individual's ability to move around. Surgical correction should also be considered if ptosis has caused a lazy eye or vision to become blurry (**R36**).

Blepharitis is also common in CdLS. It is a condition where the eyelids become infected and swollen. Symptoms can include excessive watering of the eye, recurrent conjunctivitis, crusty eyelashes, small lumps on the eyelid and itchy red eyelids. These symptoms can be bothersome, particularly for young children (97, 99). Blepharitis in CdLS can be treated in the same way as in the general population. Treatment includes eye lid hygiene using baby shampoo or eyelid scrubs (**R37**). If symptoms of blepharitis do not improve with lid hygiene, one or both tear ducts may be blocked or obstructed (41). Blocked tear ducts can be treated using a surgical probing and irrigation procedure. Surgical probing and irrigation unblock the tear ducts and should be considered if other treatment for blepharitis is not successful (97, 98).

Individuals with CdLS often experience visual impairment (3,41,98). Usually, individuals with CdLS are short-sighted (myopia). This means that distant objects appear to be blurry whilst close objects can be seen normally. Far-sightedness is less common in CdLS (98). Short-sightedness and far-sightedness are not eye diseases or eye health problems, they are simply a problem relating to how the eye focuses light. Individuals with CdLS may also have astigmatism, in which the outer layer of the eye is curved, causing blurred vision.

Vision should be assessed regularly in all individuals with CdLS, especially in infancy and childhood (**R38**). Correction of short-sightedness, far-sightedness or astigmatism should be performed as early as possible to prevent lazy eye. Children may have difficulty tolerating glasses or contact lenses, especially as self-injurious behaviour in CdLS may include hitting, pressing or poking the eyes. Surgical procedures, such as laser eye therapy, can help to improve visual function (100).

Some individuals with CdLS have been reported to have abnormal optic nerves (98). Another finding is a ring of pigment found around the optic nerve, seen on an eye exam in over 80% of children with CdLS,

although this does not cause any harm. There is risk for retinal detachment in CdLS, either due to very severe near-sightedness or self-injurious behaviour relating to poking the eye.

A small number of individuals with CdLS may have nystagmus (rapid, involuntary eye movements) or strabismus (where one eye looks directly at the object they are viewing, while the other eye is misaligned) (97,98). In the case of strabismus in CdLS, strategies for the general population should be followed.

Ears and hearing

Typically, individuals with CdLS have ears that are set lower, are hairy and are atypically formed. Some individuals may have small and narrow ear canals (ear canal stenosis) (101). Ear canal stenosis is associated with external ear and middle ear abnormalities, such as:

- Atypically formed small bones in the ear
- Impaired function of the cochlea (portion of the ear that receives sound vibrations and sends them to the brain to interpret)
- Impaired function of the vestibules (which are important for a person's sense of balance)
- An inflamed middle ear (102, 103)

Scans of the ear indicate that increased ear abnormalities are associated with a higher degree of hearing loss in CdLS (103). Hearing loss is very common in CdLS and occurs in 85-90% of individuals (101,104,105). Usually hearing loss in CdLS affects both ears. It is typically present from infancy and can range from mild to severe (101). Loss of hearing in CdLS can be caused by abnormalities in the inner ear (sensorineural hearing loss) and outer ear (conductive hearing loss) (105). Persistent middle ear infections (otitis media) often results in conductive hearing loss (101,104,106).

Ear infections and infection of the sinuses (sinusitis) are common problems in adults with CdLS (107). Regular eye (ophthalmologic) and ear, nose and throat (otolaryngologic) assessments are recommended (**R40**).

As hearing loss is common in CdLS, all individuals should have their hearing assessed at an early age and hearing assessments should continue long-term (**R39**). Individuals with CdLS often find it difficult to have their ears inspected and sometimes sedation may be needed. Initial auditory assessment should test a person's ability to hear sounds (standard audiometric testing) and how well the inner ear is working (otoacoustic emissions testing) (108). Occasionally, individuals with CdLS may experience severe hearing loss caused by an inner ear abnormality. These individuals should be assessed for auditory neuropathy, a hearing disorder in which the inner ears successfully detect sound but has trouble sending sound from the ears to the brain. Tests are available to assess whether the brain is receiving the correct information from the inner ear (auditory brainstem response audiometry) (106, 108). It is important that hearing loss is identified quickly in individuals with CdLS to maximise communication skills (101). Hearing has been found to improve over time in 50% of adults with CdLS (106).

Treatment options for hearing loss vary according to the type and severity of the loss. Middle ear infections and sinusitis should be treated according to the national guidelines for the general population (**R41**). Treatment for infections usually involve relieving pressure or draining fluid from the middle ear. Sometimes treatment options may include mastoidectomy, a procedure which removes infected cells

from the ear (102). Hearing loss may also be treated by using hearing aids, however, hearing aids are often poorly tolerated by individuals with CdLS (109). Other treatment options for hearing loss include a cochlear implant or surgical correction of small bones in the ear that have formed atypically. A cochlear implant is a device that replaces the function of the damaged inner ear by providing sound signals to the brain. Cochlear implantation has resulted in variable levels of hearing gain (110, 111).

Nose and throat

In individuals with CdLS, the nose is often characterised by a low, inward curving nasal bridge and easily visible nostrils. Recurrent sinus infections are common in CdLS and are thought to be caused by an atypically structured nose and impaired immune system (55). Some individuals with CdLS have been reported to have soft, painless growths on the lining of their nasal passages or sinuses (nasal polyps) (2).

Treatment of sinus infections in CdLS is the same as for the general population (112, 113). If an individual with CdLS has an immune deficiency (where the body has a lower ability to fight infection) more aggressive treatment may be required. This could include immunoglobulins (antibodies that fight infection) and antibiotic treatment (62).

Intubation (inserting a tube through the mouth into the airway during medical procedures) can be difficult in individuals with CdLS. This is because individuals usually have a small mouth, small chin, short neck, stiff jaw joints and cleft palate (52,114). Therefore, anaesthesiologists should be made aware of the potential difficulty with intubation in individuals with CdLS before surgery (**R42**).

The musculoskeletal system

Children and adults with CdLS usually receive rehabilitation services across their lifespan. Adaptive equipment can help enhance individuals motor functions and mobility, increasing their quality of life. Equipment may include orthotics (e.g. splints and braces), tripods (walking stick), and wheelchairs. Safety equipment (for example, helmets, door alarms and seat belt harnesses) limits the risk of injuries and should be considered for every individual with CdLS.

Musculoskeletal problems are common in CdLS. Major limb defects appear to be more frequent in individuals with CdLS caused by a change in the NIPBL gene than in individuals with other changes that cause CdLS (3,11,25,26,115).

Upper limb abnormalities:

Major limb defects are almost always found in the upper limbs. Often, the right side is the more affected side (115,116). Major limb abnormalities may include:

- An absent forearm
- Atypical connection of the bones in the forearm (radioulnar synostosis)
- Missing radius or ulna (bones in the forearm)
- Underdevelopment of the radius bone or radial dislocation (117)
- Fewer than five fingers or toes on a hand or foot (oligodactyly)

- More than five fingers or toes on a hand or foot (Polydactyly)
- Small hands

Minor limb abnormalities such as proximally based thumbs (thumbs attached close to wrists) or curvature of the little finger (clinodactyly) are common in CdLS (3,115-118). Research has indicated an association between major limb abnormalities, organ abnormalities and more marked intellectual disability. It is likely that the association can be explained by a change to the *NIPBL* gene in individuals with CdLS with major limb abnormalities (3,25,115,118).

Physical function is usually remarkably good in individuals with CdLS who have major limb abnormalities. Therefore, physical therapy (physiotherapy) or surgical procedures are usually not required (**R43**). Prosthetic devices may be used to aid physical function, however, individuals with CdLS may find difficulty tolerating them. Specific devices, such as devices enabling independent eating, are available and usually tolerated (**R44**). When considering the treatment of musculoskeletal (muscle and skeleton) problems in CdLS, parents and doctors should consider the individuals prognosis regarding development and mobility (**R45**). Minor limb abnormalities usually do not require therapeutic interventions.

Lower limb abnormalities:

Major lower limb abnormalities are rare in CdLS (46,119). Approximately half of people with CdLS have minor differences in the length of their legs. Leg length differences should be assessed at regular medical check-ups (**R46**). A small number of individuals with CdLS have a hip disorder due to reduced blood flow to the thigh bone. Hip dislocations may also occur in later life, especially in individuals who are wheelchair bound or bed-ridden (118). Lower limb abnormalities should be managed in the same way as for the general population. Preventative measures are important and can include physical therapy or orthoses (e.g. a brace or splint to support the limbs). Sometimes Botox injections or surgery can be beneficial (120).

Individuals with CdLS frequently experience minor lower limb abnormalities. Individuals may have small feet, toes that are joined together, short fourth toes or inward curving big toes (hallux valgus) (3,10,59). Hallux valgus is often referred to as a 'bunion'. Bunions are common in adults with CdLS and may cause walking difficulties, though often surgical repair is not required (59,118).

Tight hamstrings and Achilles tendons are fairly common in CdLS. Contractures (permanent shortening of a muscle or joint) can also occur in a small number of individuals (59,115). Contractures in CdLS usually occur in the knees, elbow and/or hip, which can interfere with movement e.g. sitting, standing and walking (118,122).

Scoliosis:

Scoliosis is a sideways curvature of the spine. It develops in approximately 30% of individuals with CdLS by 10 years of age (118) and is common in adults with decreased mobility (59). Scoliosis in CdLS should be assessed at regular medical check-ups (**R46**). Management of scoliosis in CdLS is the same as for the general population and scoliosis surgery appears to be effective. Decisions regarding surgery in CdLS should take the prognosis for development and mobility into account. Spine malformations are very rare in CdLS and usually there are no symptoms (121).

Neurology

Seizures are common in the CdLS spectrum (2,3, 31,123). A seizure is caused by an abnormal discharge of electrical activity in the brain. The most common type of seizure in CdLS is partial epilepsy. Partial epilepsy is where a seizure occurs in just one area of the brain. It usually develops before 2 years of age in individuals with CdLS (124,123). Individuals typically respond well to standard epilepsy therapy, such as sodium valproate medication (124) (**R47**). Very rarely, anoxic epileptic seizures can also occur in CdLS, which is the result of insufficient blood flow to the brain (125).

The autonomic nervous system is responsible for controlling bodily functions without a person needing to think about them, for example, breathing, heartbeat and digestion. Most individuals with CdLS have mild abnormalities in their autonomic nervous system and approximately 25% of individuals with CdLS will have marked abnormalities (2). Dystonia (uncontrolled muscle movements) and catatonia (apparent unresponsiveness and inability to move) are rare in CdLS (126,127).

There is some evidence that individuals with CdLS have sensory deficits and temperature insensibility. This means that the part of the nervous system associated with pain and sensation might not be sending the right signals to the brain. For example, in an individual with temperature insensibility, the nervous system may not send signals to the brain to indicate that boiling water is too hot for the skin. Such sensory deficits could be linked to self-injurious behaviour in CdLS (3).

Some individuals with CdLS may have structural changes in the brain. Brain abnormalities are especially likely in individuals with CdLS caused by a change to the NIPBL gene (128,129). Structural brain abnormalities can affect the cerebellum (the area of the brain controlling movement and coordination), the brainstem (which helps to control breathing, blood pressure and temperature), and how parts of the brain are linked together (130). Brain abnormalities are not associated with behaviour in CdLS (131). Spinal cord abnormalities are rare in CdLS (129, 132). MRI (a scan) of the brain should only be done if there are neurologic abnormalities seen in the individual with CdLS (**R48**). Tethered spinal cord has been reported in CdLS and an MRI of the spinal cord could detect this if this was suspected.

Sleep

Sleep-related difficulties are very common in CdLS and can begin as early as infancy (135). Difficulties can include insomnia (difficulty falling and/or staying asleep), apnoea (breathing temporarily stops during sleep), daytime drowsiness and frequent daytime napping (90,133-136).

Approximately 60% of individuals with CdLS are affected by insomnia and some affected individuals are reported to go for several days without sleep (135). Snoring is also fairly common in CdLS and can lead to daytime drowsiness (134,136). Sleep-related difficulties in individuals with CdLS can have serious consequences. Behavioural sleep interventions and melatonin can be helpful in treating sleep problems in CdLS (**R49**). Sleep-related difficulties are less common in adults with CdLS. Research suggests that sleep difficulties spontaneously improve over time.

Summary section

Health recommendations:

R28: Every new born suspected or proven to have CdLS should be carefully evaluated for signs and symptoms consistent with gastrointestinal malformations.

R29: Presentation of any abdominal symptoms in an individual with CdLS, irrespective of age, should prompt consideration of intestinal malrotation.

R30: Evaluation for the presence of intestinal malrotation needs to be discussed and decided together with the family, balancing the potential gain in health and burden for the individual with CdLS.

R31: Constipation is present in almost half of all individuals with CdLS and should be treated as in the general population.

R32: Consider always gastro-oesophageal reflux disease (GORD) in any individual with CdLS owing to its frequency and wide variability in presentation, which includes challenging behaviour.

R33: Modification of nutrition and proton pump inhibitors (PPI) are the first-line treatments of GORD. Anti-reflux medications need to be used to their maximum dosage. Surgical interventions for GORD should be limited to those individuals with CdLS in whom nutritional and medical treatments have been unsuccessful or airway safety is at risk.

R34: If GORD symptoms persist, endoscopy should be strongly considered whilst an individual with CdLS is still in paediatric care.

R35: Surveillance for Barrett's Oesophagus needs to be discussed with and decided together with the family, balancing the potential gain in health and burden for the individual with CdLS.

R36: Surgical correction of ptosis should be considered if vision is significantly affected or if the individual is lifting their chin in attempt to see more clearly and it is affecting the individual's ability to move around.

R37: Blepharitis in individuals with CdLS should be treated conservatively with lid hygiene. Nasolacrimal duct obstruction (blocked tear ducts) should be suspected if symptoms are not improved with lid hygiene.

R38: Vision should be regularly evaluated in all individuals with CdLS, especially in infancy and childhood. Problems with vision should be corrected early to prevent amblyopia (lazy eye), although children may have difficulty tolerating glasses or contact lenses.

R39: Hearing should be assessed in individuals with CdLS at an early age and should be followed up over time. Those with severe sensorineural hearing loss should be assessed for auditory neuropathy.

R40: Regular eye (ophthalmologic) and ear, nose and throat (otolaryngologic) evaluations are recommended in adults with CdLS.

R41: Otitis media (middle ear infections) with fluid build up and sinusitis in individuals with CdLS should be considered and treated according to the national guidelines for the general population.

R42: The anaesthesiologist should be aware of the potential difficulty with intubation in individuals with CdLS.

R43: As function is often remarkably good in major limb anomalies, caution is recommended regarding surgical procedures in individuals with CdLS.

R44: Prosthetic devices targeting a single function should be considered depending on the needs and tolerance in individuals with CdLS.

R45: Prognosis regarding development and mobility should be taken into account when considering treatment of musculoskeletal problems in individuals with CdLS.

R46: Scoliosis and leg length differences need specific attention in adults with CdLS at regular medical check-ups.

R47: Seizures in individuals with CdLS should be treated using the general management schemes.

R48: An MRI of the brain should be considered only if the individual with CdLS shows neurological signs other than microcephaly (smaller than normal head).

R49: Sleep problems in individuals with CdLS can have serious consequences, and behavioural sleep management should be considered.

What are the Cognitive and Behavioural Characteristics of Cornelia de Lange Syndrome?

Cognitive and behavioural characteristics in CdLS can vary widely among affected individuals and range from relatively mild to severe. Cognitive characteristics refer to brain-based processes which are involved in skills such as thinking, learning, remembering, paying attention and reading. 'Executive function' is a term that is used to describe a group of brain-based cognitive processes that control and regulate our behaviour. Individuals with CdLS are more likely to engage in certain behaviours than people without the syndrome, these behaviours can be described as behavioural characteristics or a 'behavioural phenotype'.

Intellectual Disability

Intellectual disability is a term that is used when a person has difficulties with cognitive (intellectual) functioning and adaptive behaviour (everyday practical and social skills). It can also be referred to as developmental disability or learning disability. Intellectual disability can be described as mild, moderate, severe or profound. This indicates the degree of disability and is based on the impact the intellectual disability has on the individual's day to day functioning.

Most individuals with CdLS have moderate to severe intellectual disability and a small number have mild intellectual disability. Research has suggested that individuals with CdLS caused by an *NIPBL* mutation usually function at a lower level than individuals with CdLS caused by a mutation in another known CdLS gene, *SMC1A* (3). The type of *NIPBL* mutation does not seem to be associated with the level of intellectual disability (11,26,137), although missense mutations (single small mutations, explained on page 8) have

been noted to produce less severe effects, however individuals with an *NIPBL* mutation can also have mild intellectual disability (138).

Executive Function

Executive function is a term that refers to brain-based processes that control and regulate our behaviour. Individuals with CdLS may have specific difficulties in executive functions. Usually, these difficulties affect individuals' mental flexibility (ability to shift thoughts or attention) and visual short-term memory (139). However, some executive functions, such as inhibition (stopping a behavioural or verbal response) may be relative strengths in CdLS (140).

Executive functioning abilities in CdLS are suggested to be associated with aspects of the CdLS behavioural phenotype. For example, executive functioning difficulties in CdLS may be associated with frequent repetitive behaviour and social anxiety (139,140).

Individuals with CdLS can benefit from having their environment structured according to their cognitive strengths and weaknesses. Environment enrichment strategies can be used to facilitate cognitive and learning abilities in CdLS.

Sensory Processing

Sensory processing is a term that describes how the brain takes in and manages input from all the senses. In sensory processing, the brain deals with information from the five traditional senses (touch, taste, smell, sound and sight) and two other senses which contribute to a person's balance (movement and awareness of where their body parts are in space).

Difficulties in sensory processing can lead to hyposensitivity and hypersensitivity (141,142,143). Hyposensitivity occurs when an individual is under-sensitive to stimuli and has trouble processing information from the senses. Hypersensitivity occurs when an individual is over-sensitive to stimuli, for example, common sounds could be painful or overwhelming. Individuals with hypersensitivity usually have low sensory thresholds. This means that the sensory system is activated by very little sensory input.

Individuals with CdLS usually experience difficulties in sensory processing (145), regardless of their level of intellectual disability (146). In addition to hypo- and hypersensitivity, there can be confusion or fixation on sensory stimuli. For example, gastrointestinal problems and other organ issues can lead to anxiety, mood disorders and self-injury. Individuals with CdLS who also have an autism spectrum disorder (ASD) may have low sensory thresholds (141) and defensive responses towards sensory stimuli (147). Hyper- and hyposensitivity and other sensory processing difficulties should be assessed, and support strategies should be implemented in individuals with CdLS throughout their lifespan (**R50**). Interventions should address individual's sensory needs in order to enhance development and participation in daily living (146).

Adaptive behaviour in CdLS

Adaptive behaviours are age-appropriate behaviours that people need to function well in daily life and live independently. Adaptive behaviours include life skills such as dressing, grooming, food handling, safety, making friends, communication, cleaning, managing money and ability to work.

Individuals with CdLS demonstrate difficulties in adaptive behaviour across the lifespan. This means that many children and adults with CdLS will need help with daily tasks, such as washing and dressing. Many individuals with CdLS do not develop verbal communication skills. Expressive communication skills (ability to express oneself) are usually significantly more impaired than receptive language skills (ability to understand communication). Individuals with CdLS often use a number of non-verbal strategies to communicate, for example, social approach and pushing a person's hand away.

Adaptive behaviour difficulties are usually more marked in individuals with CdLS caused by a NIPBL mutation (148,149). Difficulties in adaptive behaviour in CdLS are comparable to difficulties seen in Angelman syndrome and Rubinstein-Taybi syndrome, though deficits in adaptive skills are usually more marked in CdLS compared to other genetic conditions (151-153,150). Adaptive behaviour skills in CdLS can change over time and changes tend to vary depending on the specific skill. For instance, individuals tend to show increases in specific self-help skills with age (for example, washing and feeding) and decreases in other skills (for example, ability to call for help or to move independently) (10,154, 109). However, reports of changes in adaptive behaviour skills vary, and more research is needed (109,155).

To enhance independence in CdLS, it is important to increase adaptive skills throughout the lifespan. Cognitive strengths and weaknesses should be assessed in order to design personalised educational and interventional programmes that should include specific goals for the individual. Additional developmental and educational support should be provided to individuals with CdLS to reach their maximum cognitive and educational potential, taking into account their specific cognitive impairments (**R51-R53**).

Self-injurious and aggressive behaviours

Self-injurious behaviour refers to non-accidental behaviours that have the potential to cause damage, such as reddening of the skin, bruising, bleeding, hair loss, etc. Self-injurious behaviour is common in individuals with CdLS and includes behaviours such as self-hitting, head banging or self-biting (156), although it is not an inevitable consequence of the syndrome. Some behaviours shown in CdLS can be identical to self-injurious behaviour but do not cause any bodily damage. These behaviours may develop into self-injurious behaviour over time (157).

There are several risk markers for self-injurious behaviours in CdLS. Individuals with more severely impaired cognitive abilities, communication skills and adaptive behaviours are more likely to display self-injurious behaviour. Risk markers may also include CdLS caused by an *NIPBL* gene mutation, and increased levels of impulsivity, repetitive behaviours and characteristics associated with autism spectrum disorder (156).

Approximately half of individuals with CdLS display clinically significant self-injurious behaviour (158). Usually this is directed towards the individual's hands (159). Self-injurious behaviour can result in physical

injury, the severity of which is dependent on the amount of damage and functional loss (156). Sometimes it may be necessary to use restraints to prevent permanent damage (107).

Self-injurious behaviour in CdLS may be a sign of or response to pain and has been associated with common medical conditions in CdLS, such as gastrointestinal problems, ear infections, constipation, dental disease or hip problems. It is important that the cause of self-injurious behaviour in individuals with CdLS be identified. This often requires medical assessment to specifically look for the sources of pain, as well as behavioural assessment and consideration of the individual's environment. Treatment or intervention strategies can then be matched to the function of self-injurious behaviour. Treatment should include both medical and behavioural strategies (**R54, R55**).

Repetitive behaviour

Repetitive behaviour is a term that includes a wide range of behaviours such as stereotyped behaviours (e.g. rocking, spinning, hand flapping), compulsive behaviours (e.g. lining up objects), insistence on sameness (e.g. adhering to a routine), restricted interests (e.g. attachment to a particular object) and repetitive speech (e.g. asking the same questions over and over again). Some of these behaviours are seen in certain stages of development in typically developing infants but may reappear with age in some disorders, including in CdLS. Repetitive behaviour in CdLS may be associated with anxiety, sensory problems or social demands (161-163). More frequent repetitive behaviours are usually seen in individuals with more marked intellectual disability or with ASD (161,163). Stereotyped behaviour and compulsive-like behaviours are common in CdLS (162), and also may include ritualistic behaviours such as lining up or tidying objects. Repetitive behaviour in CdLS does not seem to be associated with the genetic cause of the syndrome (10) and research into repetitive behaviour in CdLS has not indicated any clear changes in repetitive behaviour over time (161,163).

It is often not appropriate to intervene with repetitive behaviour unless the behaviour is causing a problem for the individual. If interventions are needed, they should consider the function of the repetitive behaviour and the reasons why the individual is engaging in the behaviour (e.g. due to anxiety). Interventions should consider these factors as well as environmental factors, such as predictability in daily structure.

Specific medications, such as selective serotonin reuptake inhibitors (SSRIs) (e.g. Prozac), have been increasingly used in CdLS, especially for obsessive-compulsive disorders and mood disorders, although these have not proven successful in reducing repetitive behaviour in individuals with autism. These medications can result in the worsening of behaviours or activation of other behaviours. Another group of medications, second generation anti-psychotics, can also be used in CdLS, especially in managing body rigidity and need for sameness, which can escalate into disruptive behaviours.

Social functioning and Autism Spectrum Disorders (ASD)

ASD, social anxiety and mood disorders are common mental health difficulties in individuals with CdLS (109,137,152,154,165–169). These mental health difficulties do not seem to be linked with the specific gene or genetic mutation that has caused CdLS (10,137,148,149,169). Because most individuals with CdLS

are unable to reliably report their own discomfort, behaviour or feelings, it can be difficult to assess difficulties that they may be experiencing. Often, difficulties are detected from observation of an individual's behaviour or reports of their behaviour from parents or carers. Behaviours suggesting difficulties could include eye-gaze avoidance, pushing away and screaming (80,170,171). These behaviours are often associated with the social setting and can sometimes be associated with parental stress (109,137).

Approximately just under half of all individuals with CdLS display symptoms of ASD (159). The three core characteristics of ASD include:

- Poor or unusual social interaction skills
- Delayed development or difficulties in verbal and non-verbal communication (e.g. gestures, pointing, showing, etc)
- The presence of repetitive behaviour

ASD has been associated with poorer adaptive behaviour skills in individuals with CdLS caused by an *NIPBL* mutation (10). ASD should be considered when individuals with CdLS display social, communication and behavioural impairments beyond what would be expected for their cognitive ability.

Symptoms of ASD in CdLS are not always associated with an individual's degree of intellectual disability (150,172,173). Research has shown that when compared to individuals with ASD, individuals with CdLS show a lot of similarities but also small differences in specific areas of communication and social interaction (173). These small differences especially concern social anxiety (worry), extreme shyness and selective mutism (not speaking in social situations where there is an expectation for speaking, e.g. at school), which are all more common in CdLS (2,65,109,150,152). Differences in communication and social interaction between CdLS and ASD become clearer with age and with increased social demand. Social motivation, social communication and enjoyment are similar in both CdLS and ASD (175).

A clinical diagnosis of ASD should be considered in all individuals with CdLS throughout life, taking into account atypical presentations (**R56**). Assessment for ASD in CdLS may use standardised ASD diagnostic tools. It is also important that detailed observations are carried out to accurately assess ASD and social functioning, and to understand the level and characteristics of communicative, adaptive and language abilities in an individual with CdLS (**R57**). ASD-specific interventions should be considered in all individuals with CdLS, however, it is important that interventions to aid social functioning are sensitive to CdLS-specific aspects of communication and social interaction (65,66,174) (**R58**).

Anxiety

Anxiety is common in individuals with CdLS. Anxiety in CdLS usually presents as social anxiety (excessive worry about daily life events with no obvious reason for worry), separation anxiety (excessive fear about separation from home or a parent/carer) or selective mutism (not speaking in social situations where there is an expectation for speaking, e.g. at school) (168,148).

Anxiety in CdLS can lead to increased repetitive behaviour, mood-related symptoms or disruptive, aggressive and self-injurious behaviours (109). It is important that any intervention targeting problematic

repetitive behaviour in an individual with CdLS be sensitive to anxiety, sensory problems and social demands. Interventions should also consider environmental factors (**R59**).

Social interactions can also provoke anxiety in individuals with CdLS and lead to behavioural responses that can be observed, such as fidgeting, avoiding eye gaze and active avoidance (152,175). Individuals with CdLS often have an increased preference for sameness, meaning many individuals have difficulty adjusting to changes in their routine. This can make transitional periods more challenging and provoke anxiety (148,162,174). During transitional periods, plans can be put in place to help individuals adjust to changes and reduce levels of anxiety (**R61**).

Assessing anxiety in CdLS can be difficult, particularly in individuals who display challenging behaviour such as self-injury, aggression, shouting and screaming (137). Often, anxiety and mood disorders can be identified by observing behavioural changes in individuals with CdLS (**R60**). Treatment of anxiety and mood disorders may include psychosocial interventions (therapy to improve health and well-being) and/or medication (**R62**).

Communication and language

Communication abilities vary widely in CdLS. Typically, individuals with CdLS experience major difficulties in communication and many individuals do not develop verbal communication. Speech difficulties in CdLS often occur due to abnormal muscle tone. However, visual impairment, hearing loss and mouth structure or jawbone abnormalities (e.g. cleft palate, page 18) can also lead to speech and communication difficulties. Difficulties in communication and understanding communication can also arise from cognitive impairment (problems with memory, thinking and communication)(176,178).

Currently there is little research on the relationship between intellectual functioning, behaviour and communication skills in CdLS (169). Individuals with CdLS tend to communicate with a low-pitched cry when young, and then speak with a low monotone (expressionless) voice (140,179). Selective mutism (not speaking in social situations where there is an expectation for speaking e.g. at school) is often seen in CdLS. Selective mutism in CdLS may occur as a part of ASD or as an expression of anxiety (148,152). Expressive language difficulties are common in CdLS (170,176,177). Individuals with CdLS usually experience more marked difficulties in expressive language than receptive language (ability to understand communication). Receptive language difficulties in CdLS usually specifically relate to sentence grammar (138).

Individuals with CdLS will often develop methods of non-verbal communication. Non-verbal communication skills can include approaching, touching, showing, pointing, giving or gesturing. These methods of non-verbal communication are usually subtle and can be easily missed (178). The teaching of sign language such as Makaton may prove helpful.

It is important to remember that difficulties in language and communication do not occur in all individuals with CdLS. Some individuals will develop good speech and language skills.

Social anxiety and difficulties in social interaction can impact negatively on an individual's language skills and engagement in non-verbal communication (138,174). Communication difficulties in CdLS are also associated with, and often occur alongside, challenging behaviours such as self-injury or aggression (3).

Assessment of communication skills in CdLS should consider whether an individual experiences vision and hearing problems, speech impairments, intellectual disability, difficulties in social interaction and social anxiety (**R63**).

Effective verbal and non-verbal communication skills can greatly improve quality of life for individuals with CdLS. Developmentally appropriate communication interventions can be used to help develop effective communication skills from 18 months of life (138,181,182). Communication interventions may include speech therapy or alternative and augmentative communication (AAC) (**R64**). AAC may include use of gestures, icons, pictures and written language. Assessment of an individual's level of communication and limitations will help to decide which communication intervention will be most effective (180).

Parents are typically experts in understanding the communication signals of their child. The experience parents acquire over the years is invaluable and extremely helpful to behavioural specialists and speech therapists. Detecting and identifying small communicative signals, awareness of one's own reactions and understanding their meaning facilitates adjustment of communication and responses. Responsive milieu teaching (arranging objects in a child's environment to create a setting that encourages communicative behaviour) and video observations can be very helpful in detecting and identifying subtle communication signals, their meanings and appropriate responses, especially for individuals with marked cognitive impairments (183,184).

Summary section

Cognitive and behavioural recommendations:

R50: Hyper- and hyposensitivity and other sensory processing difficulties should be assessed, and support strategies should be implemented in individuals with CdLS throughout their lifespan.

R51: Increasing adaptive skills to enhance independence should remain a focus throughout the lifespan and should include personalised specific goals and teaching strategies.

R52: Additional developmental and educational support should be provided to individuals with CdLS to reach their maximum cognitive and educational potential, taking into account their specific cognitive impairments.

R53: Cognitive strengths and weaknesses of individuals with CdLS should be assessed in order to design educational and interventional strategies.

R54: To identify the cause of self-injurious behaviour in individuals with CdLS, medical assessment, specifically looking for sources of pain, should be followed by behavioural assessment of self-restraint then functional analysis.

R55: Treatment of self-injurious behaviour should include both medical and behavioural strategies.

R56: A clinical diagnosis of autism spectrum disorder (ASD) should be considered in all individuals with CdLS throughout life, taking into account atypical presentations.

R57: In addition to standardised ASD diagnostic tools, fine-grained observations should be carried out to accurately define the profile of social functioning in an individual with CdLS.

R58: ASD-specific interventions should be considered in all individuals with CdLS in combination with approaches that consider the broader social functioning profile of the syndrome.

R59: Interventions targeting problematic repetitive behaviour in individuals with CdLS should be sensitive to anxiety, sensory problems and social demands. These interventions should also consider environmental factors.

R60: Atypical presentation of anxiety and mood disorder should be considered when behaviour changes occur.

R61: As anxiety is common in individuals with CdLS during periods of environmental change/transitions, a planned program should be implemented.

R62: Treatment of anxiety and mood disorders in individuals with CdLS should be considered using psychosocial interventions (therapies) and pharmacotherapy (medication).

R63: When assessing communication, vision and hearing problems, speech impairments, intellectual disability, difficulties in social interaction and social anxiety should be considered. Video observations can be very useful.

R64: Developmentally appropriate communication strategies (such as speech therapy, augmented communication input) should be implemented within the first 18 months of life.

Do Cognitive and Behavioural Characteristics Change with Age in CdLS?

Research has suggested that behavioural, emotional and cognitive characteristics in CdLS can change with age (2,137,139,148,172). Findings from one study suggest an association between age and a higher number of behavioural difficulties in individuals with CdLS (137). In this study, older age was specifically associated with lower levels of interest and pleasure, and greater insistence on sameness (148). This suggests older individuals with CdLS display more difficulties.

Research has also suggested that individuals with CdLS can experience increasing difficulties in the frequency and severity of many behavioural characteristics with age. These changes are reported to affect verbal working memory, ASD symptoms, anxiety, low mood, self-injurious behaviour and impulsivity (2,90,109,139,154,166,172,174). Aggression, hyperactivity and sleep difficulties in CdLS may not become more frequent or severe with age.

Challenging behaviour may begin during adolescence and early adulthood (109,167,172). Individuals with CdLS benefit from support during these transitional periods, which can help to reduce mental health issues and challenging behaviour (**R65**). Support should include using a person-centred approach, gradually introducing changes and considering the individual's social environment.

Summary section

Changes with age recommendations:

R65: Individuals with CdLS should receive extra support during adolescence and early adulthood, using a person-centred approach to reduce mental health issues and challenging behaviour.

Care Planning in CdLS

Medical care

Individuals with CdLS require lifelong medical, multidisciplinary and social care. Access to clinical assessments, counselling and follow-up by a multidisciplinary team is likely to improve health care and increase quality of life. Barriers to accessing care have been recognised, and include health or behavioural complications, geographical isolation and financial considerations (185-187). Individuals with CdLS are now likely to live into adulthood and old age. This brings about the risk of individuals developing common chronic diseases alongside CdLS-related medical problems. Individuals with CdLS are more likely to experience delayed treatment, to be hospitalised and to have more complications and longer admissions than individuals without CdLS. Often, this is due to a lack of knowledge regarding CdLS by healthcare providers, difficulties in obtaining medical history and, possibly, stigmatisation. Healthcare providers and social services should access information about CdLS. Syndrome sensitive, personalised care plans should be offered to every individual with CdLS and their caregivers. Individuals should also receive regular health checks, with planning of admissions and discharges made in advance. Procedure specific information booklets using simple language and photos can be very beneficial for individuals and their families and are recommended (188,189) (**R66, R67**).

Transition

In CdLS, the transition from paediatric (child) to adult medical care can bring about substantial challenges and require parental involvement (190). Transitions are usually associated with changes in daytime environment, leaving home and social changes. An individual's care changes from family-focused to individual-focused. Transition of care should be initiated at an early phase, with proper transfer of medical history and knowledge about the personal characteristics of the individual with CdLS. Transitions that are initiated too late can result in a gap in communication and co-ordination between paediatric and adult services. Care can be improved by current and future health care providers jointly assessing individuals with CdLS in order to smooth the transition (109,191,192) (**R68**).

Decision making

The involvement of individuals with CdLS and their care providers in health-care decisions is essential. Intellectual disability and executive functioning impairments in individuals with CdLS can reduce an individual's ability to make decisions. In these instances, care providers and health-care professionals have to decide what is best and document an individual's values, preferences and quality of life (193).

Knowledge about CdLS is essential to manage expectations, and health-care providers and social services need to be aware of the needs and problems that may be expected. Family support groups and social media have proved to be extremely helpful for awareness of the needs and problems that individuals with CdLS can face (194,195). Guardianship rules vary among countries, and it is essential for guardianship to be determined and assigned before adulthood.

Summary section

Care planning recommendations:

R66: Individuals with CdLS and their families need life-long care provided by healthcare providers and social services, who should educate themselves about CdLS.

R67: Syndrome-specific and personalised care plans through shared decision-making should be offered to every individual with CdLS and their caregivers.

R68: Transition of care should be initiated at an early phase, with proper transfer of medical history and knowledge about the personal characteristics of the individual with CdLS. It is recommended that current and future health care providers jointly evaluate individuals with CdLS in order to smooth the transition.

Full List of Recommendations

Physical characteristics

R1: The CdLS spectrum encompasses a range of phenotypes consisting of classic (or typical) CdLS and non-classic CdLS, which are characterised by a combination of features. *(Page 4)*

R2: The International CdLS Consensus Group propose consensus criteria based on the presence of a combination of signs and features. A diagnosis of classic CdLS can be confirmed if a score of 11 is reached, irrespective of the presence of a variant in a gene known to result in CdLS. *(Page 4)*

R3: Presently available severity scoring schemes should be used cautiously as these do not adequately reflect the severity as experienced by the individuals with CdLS and their families. *(Page 7)*

Causes of Cornelia de Lange syndrome

R4: Classic CdLS is usually caused by variants in *NIPBL;* however, variants in one of six other genes - *SMC1A, SMC3, RAD21, BRD4, HDAC8 or ANKRD11* – should also be considered, as they may lead to a similar phenotype. *(Page 7)*

R5: Mosaicism should be considered in individuals with CdLS in whom a variant in a gene known to cause CdLS cannot be detected in blood cells, in which case other tissues such as fibroblasts (skin), buccal (cheek) cells or bladder epithelial cells from urine should be studied. *(Page 12)*

R6: Genetic counselling should be offered to all families with a family member with CdLS. Families should be counselled that the recurrence risk of CdLS differs depending on the gene involved. In the non-X-linked forms, the recurrence risk is 0.89% due to germline mosaicism. Autosomal dominant inheritance of CdLS does occur, meaning if one copy of the mutation is present, the individual will show clinical effects. In clinically diagnosed individuals with CdLS, the recurrence risk is 1.5%. *(Page 13)*

Diagnosis

R7: If a prenatal ultrasound scan (sonography) detects features consistent with CdLS, possibilities for prenatal genetic testing should be discussed with the parents. *(Page 14)*

R8: If a causative gene change has been detected in an earlier child or pregnancy, reliable prenatal diagnostic testing should be discussed with the family. Targeted variant testing can be performed using DNA derived from the placenta or amniotic fluid. *(Page 14)*

R9: If available, first-line genetic testing should be performed using panel sequencing to screen all genes known to cause CdLS spectrum (*NIPBL, SMC1A, SMC3, RAD21, BRD4, HDAC8* and *ANKRD11*). Medico-legal, technical, and insurance-related national practices may require other tests, such as Sanger sequencing of individual genes. *(Page 15)*

Medical care

R10: Every infant and young child with CdLS should be assessed for cardiac (heart) and renal (kidney) malformations subsequent to diagnosis*. (Page 17)*

R11: The growth of every child with CdLS should be monitored by using CdLS-specific growth charts. *(Page 17)*

R12: In every CdLS individual with prolonged and marked feeding difficulties, the multidisciplinary assessment (from healthcare workers across many disciplines) should consider (temporary) placement of a gastrostomy (surgical opening through the abdomen into the stomach) as a supplement to oral feeding. *(Page 18)*

R13: In individuals with CdLS who have recurrent respiratory infections, reflux and/or aspiration (breathing foreign objects into airways) should be ruled out. *(Page 18)*

R14: The palate should be closely examined at diagnosis. In case of symptoms of a (submucous) cleft palate, referral for specialist assessment is indicated. *(Page 18)*

R15: Dental assessment and cleaning should take place regularly; a more thorough dental examination or treatment under anaesthesia may be necessary. *(Page 18)*

R16: Developmental milestones should be closely monitored. *(Page 19)*

R17: Vaccinations should be given to every child with CdLS according to national guidelines. *(Page 19)*

R18: As pain can easily remain unrecognised in a child with CdLS, all care providers should be aware of the different manifestations and the possible sources of pain. Specific tools to assess pain are recommended. *(Page 19)*

R19: Regular follow-up of every child with CdLS is needed, preferably by a paediatrician or clinical geneticist experienced in treating individuals with CdLS; schedules depend on local practices and possibilities. *(Page 20)*

R20: Sexual education appropriate to the level of understanding should be offered, and contraception management should follow local standard for the general population. *(Page 20)*

R21: Hysterectomy is indicated if abnormally heavy bleeding at menstruation is present and does not respond to medical treatment. *(Page 20)*

R22: Specific attention to diet and stimulation of activities are recommended as obesity can occur. *(Page 21)*

R23: Renal (kidney) function should be regularly monitored in children and adults with CdLS who have structural renal malformations. *(Page 21)*

R24: Prostate enlargement in men with CdLS should be treated according to national guidelines for the general population. *(Page 21)*

R25: Women with CdLS should be offered breast cancer screening according to national guidelines for the general population. *(Page 21)*

R26: Routine gynaecologic care including cervical screening should be performed in women with CdLS, according to national guidelines for the general population. *(Page 21)*

R27: The use of emergency cards should be considered for every person with CdLS. *(Page 22)*

Health

R28: Every new born suspected or proven to have CdLS should be carefully evaluated for signs and symptoms consistent with gastrointestinal malformations. *(Page 24)*

R29: Presentation of any abdominal symptoms in an individual with CdLS, irrespective of age, should prompt consideration of intestinal malrotation. *(Page 24)*

R30: Evaluation for the presence of intestinal malrotation needs to be discussed and decided together with the family, balancing the potential gain in health and burden for the individual with CdLS. *(Page 24)*

R31: Constipation is present in almost half of all individuals with CdLS and should be treated as in the general population. *(Page 24)*

R32: Consider always gastro-oesophageal reflux disease (GORD) in any individual with CdLS owing to its frequency and wide variability in presentation, which includes challenging behaviour. *(Page 25)*

R33: Modification of nutrition and proton pump inhibitors (PPI) are the first-line treatments of GORD. Anti-reflux medications need to be used to their maximum dosage. Surgical interventions for GORD should be limited to those individuals with CdLS in whom nutritional and medical treatments have been unsuccessful or airway safety is at risk. *(Page 25)*

R34: If GORD symptoms persist, endoscopy should be strongly considered whilst an individual with CdLS is still in paediatric care. *(Page 25)*

R35: Surveillance for Barrett oesophagus needs to be discussed with and decided together with the family, balancing the potential gain in health and burden for the individual with CdLS. *(Page 25)*

R36: Surgical correction of ptosis should be considered if vision is significantly affected or if the individual is lifting their chin in attempt to see more clearly and it is affecting the individual's ability to move around. *(Page 26)*

R37: Blepharitis in individuals with CdLS should be treated conservatively with lid hygiene. Nasolacrimal duct obstruction (blocked tear ducts) should be suspected if symptoms are not improved with lid hygiene. *(Page 26)*

R38: Vision should be regularly evaluated in all individuals with CdLS, especially in infancy and childhood. Problems with vision should be corrected early to prevent amblyopia (lazy eye), although children may have difficulty tolerating glasses or contact lenses. *(Page 26)*

R39: Hearing should be assessed in individuals with CdLS at an early age and should be followed up over time. Those with severe sensorineural hearing loss should be assessed for auditory neuropathy. *(Page 27)*

R40: Regular eye (ophthalmologic) and ear, nose and throat (otolaryngologic) evaluations are recommended in adults with CdLS. (*Page 27)*

R41: Otitis media (middle ear infections) with fluid build-up and sinusitis in individuals with CdLS should be considered and treated according to the national guidelines for the general population. *(Page 27)*

R42: The anaesthesiologist should be aware of the potential difficulty with intubation in individuals with CdLS. *(Page 28)*

R43: As function is often remarkably good in major limb anomalies, caution is recommended regarding surgical procedures in individuals with CdLS. *(Page 28)*

R44: Prosthetic devices targeting a single function should be considered depending on the needs and tolerance in individuals with CdLS. *(Page 28)*

R45: Prognosis regarding development and mobility should be taken into account when considering treatment of musculoskeletal problems in individuals with CdLS. *(Page 29)*

R46: Scoliosis and leg length differences need specific attention in adults with CdLS at regular medical check-ups. *(Page 29)*

R47: Seizures in individuals with CdLS should be treated using the general management schemes. *(Page 29)*

R48: An MRI of the brain should be considered only if the individual with CdLS shows neurological signs other than microcephaly (smaller than normal head). *(Page 30)*

R49: Sleep problems in individuals with CdLS can have serious consequences, and behavioural sleep management should be considered. *(Page 30)*

Cognitive and behavioural

R50: Hyper- and hyposensitivity and other sensory processing difficulties should be assessed, and support strategies should be implemented in individuals with CdLS throughout their lifespan. *(Page 33)*

R51: Increasing adaptive skills to enhance independence should remain a focus throughout the lifespan and should include personalised specific goals and teaching strategies. *(Page 34)*

R52: Additional developmental and educational support should be provided to individuals with CdLS to reach their maximum cognitive and educational potential, taking into account their specific cognitive impairments. *(Page 34)*

R53: Cognitive strengths and weaknesses of individuals with CdLS should be assessed in order to design educational and interventional strategies. *(Page 34)*

R54: To identify the cause of self-injurious behaviour in individuals with CdLS, medical assessment, specifically looking for sources of pain, should be followed by behavioural assessment of self-restraint then functional analysis. *(Page 34)*

R55: Treatment of self-injurious behaviour should include both medical and behavioural strategies. *(Page 34)*

R56: A clinical diagnosis of autism spectrum disorder (ASD) should be considered in all individuals with CdLS throughout life, taking into account atypical presentations. *(Page 36)*

R57: In addition to standardised ASD diagnostic tools, fine-grained observations should be carried out to accurately define the profile of social functioning in an individual with CdLS. *(Page 36)*

R58: ASD-specific interventions should be considered in all individuals with CdLS in combination with approaches that consider the broader social functioning profile of the syndrome. *(Page 36)*

R59: Interventions targeting problematic repetitive behaviour in individuals with CdLS should be sensitive to anxiety, sensory problems and social demands. These interventions should also consider environmental factors. *(Page 36)*

R60: Atypical presentation of anxiety and mood disorder should be considered when behaviour changes occur. *(Page 36)*

R61: As anxiety is common in individuals with CdLS during periods of environmental change/transitions, a planned program should be implemented. *(Page 36)*

R62: Treatment of anxiety and mood disorders in individuals with CdLS should be considered using psychosocial interventions (therapies) and pharmacotherapy (medication). *(Page 36)*

R63: When assessing communication, vision and hearing problems, speech impairments, intellectual disability, difficulties in social interaction and social anxiety should be considered. Video observations can be very useful. *(Page 37)*

R64: Developmentally appropriate communication strategies (such as speech therapy, augmented communication input) should be implemented within the first 18 months of life. *(Page 37)*

Changes with age

R65: Individuals with CdLS should receive extra support during adolescence and early adulthood, using a person-centred approach to reduce mental health issues and challenging behaviour. *(Page 39)*

Care planning

R66: Individuals with CdLS and their families need life-long care provided by healthcare providers and social services, who should educate themselves about CdLS. *(Page 40)*

R67: Syndrome-specific and personalised care plans through shared decision-making should be offered to every individual with CdLS and their caregivers. *(Page 40)*

R68: Transition of care should be initiated at an early phase, with proper transfer of medical history and knowledge about the personal characteristics of the individual with CdLS. It is recommended that current and future health care providers jointly evaluate individuals with CdLS in order to smooth the transition. *(Page 40)*

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Supplementary Box 1. Cornelia de Lange syndrome emergency card

Health Care Professionals Information about Cornelia de Lange Syndrome (CdLS)

Main medical problems in CdLS

- Short stature (specific growth charts available)
- Microcephaly
- Long term feeding difficulties
- Developmental delay/Intellectual disability
- Speech problems
- Behavioural problems, especially self-injurious behaviour
- Severe recurrent gastro-oesophageal reflux
- Constipation
- Small hands, missing fingers to absent fingers
- Hearing loss
- Ptosis, recurrent blepharitis, myopia
- Cryptorchidism
- Cutis marmorata, hirsutism

Acute life-threatening complications in CdLS

- Bowel obstruction, volvulus
- Aspiration pneumonia (gastro-oesophageal reflux/swallowing difficulties)
- Seizures
- Cardiac problems
- Bladder infections
- Retinal detachment
- Small airways (anaesthesia risk)

Less frequent medical problems in CdLS

- Heart malformations (ventricular septal defect, pulmonary stenosis)
- Diaphragmatic hernia
- Seizures
- Intestinal malrotation, duodenal atresia, annular pancreas
- Perthes disease, hip dislocations
- Scoliosis
- Barrett esophagus
- Renal malformations
- Immunological problems
- Dental crowding, caries
- Nystagmus, strabismus
- Cleft palate

Further information on CdLS can be obtained from World Federation of CdLS Support Groups

www.cdlsworld.org

Using your CdLS Emergency Care Card
The CdLS Emergency Care Card enables the multi-disciplinary team necessary for best management of CdLS to be aware of the actions of other specialists. As well as filling out personal and medical details, carers should record details every time the patient sees a specialist. By listing the contact details and the date of visit, other specialists can get in touch. By listing medications, your doctors can be confident that there are no conflicting treatments being recommended. Listed specialists may include: geneticist, gastroenterologist, cardiologist, neurologist, dentist, optician, psychologist, occupational therapist, anaesthetist, paediatrician, social worker, surgeon and speech therapist. Carers should make sure they indicate the speciality of the professional.
When the card has been filled-up, extra copies can be downloaded from www.cdlsworld.org

Fold 1

CdLS Emergency Care Card

Patient Details

Name

DoB Gender

Address

Phone

Family Doctor Details

Name

Practice/Clinic Name

Address

Phone

Email

Fold 3

Last Updated (/ /)

Emergency Contacts

Name

Relation to Patient

Address (if different)

Phone

Email

Name

Relation to Patient

Address (if different)

Phone

Email

Fold 2

Cornelia de Lange Syndrome

The Patient this card refers to has

General information

Cornelia de Lange Syndrome (CdLS) is characterised by intellectual disability, typical facial features, upper limb anomalies, growth disturbances, and a large variety of other signs and symptoms. It can be caused by pathogenic variants in one of six genes, the most common one being NIPBL.

Cornelia de Lange Syndrome

Emergency Care Card

Typical Vital Parameters of Patient

Oxygen saturation (%) ....

Heart rate (bpm) ....

Blood pressure (mmHg) ....

Temperature regulation ....

Height (cm) .... Date (..../..../......)

Weight (kg) .... Date (..../..../......)

☐ NG tube ☐ G-tube type and size ....

☐ Tracheostomy ☐ Mechanical ventilation

☐ Vascular access device ....

Allergies

....

....

Major Malformations

☐ Cleft palate

☐ Genital anomalies: Type ....

☐ Intestinal malrotation:

☐ Surgery; Date (..../..../......)

☐ Cardiac anomaly: Type ....

Last evaluation (..../..../......)

☐ Surgery; Date (..../..../......)

☐ Upper limb malformation

Psychomotor/Cognitive Development

☐ Normal ☐ Borderline ☐ Disabled

Degree of delay: ☐ Mild ☐ Moderate

☐ Severe ☐ Profound

Verbal communication

☐ Absent ☐ Strongly limited

☐ Limited ☐ Near normal

Behavioural problems

☐ Anxiety ☐ Aggression ☐ Self-injurious

☐ Hyperactivity ☐ Autism spectrum disorder

Likes: ....

Dislikes: ....

....

Medical Complications

☐ Gastroesophageal reflux: ....

☐ Surgery; Date (..../..../......)

☐ Feeding problems

☐ Constipation: ☐ Occasional

☐ Often/Frequent

☐ Food intolerance: ☐ Lactose

☐ Gluten ☐ Other ....

☐ Special diet ....

☐ Seizures: ☐ Frequent ☐ Rare

Type ....

☐ Medication: ....

☐ Hearing loss: ☐ Sensorineural

☐ Conductive ☐ Mild ☐ Moderate

☐ Severe ☐ Hearing aids

☐ Visual impairment: Type ....

☐ Glasses

☐ Ptosis: ☐ Surgery; Date (..../..../......)

☐ Small airways

☐ Pneumonia (recurrent); Dates ....

....

☐ Ear Infections (frequent)

☐ Sinus infections

☐ Renal problems: Type ....

☐ Hip problems: Type ....

☐ Dental anomalies: ☐ Cavities

☐ Crowding ☐ Allows inspection

☐ Other medical problems:

Type ....

Medications

Medication	Dosage	Frequency	Reason

Specialists Treating your CdLS Person

Name	Clinic/Hospital	Phone	Email
Speciality	Date of Visit	Treatment	
Name	Clinic/Hospital	Phone	Email
Speciality	Date of Visit	Treatment	
Name	Clinic/Hospital	Phone	Email
Speciality	Date of Visit	Treatment	
Name	Clinic/Hospital	Phone	Email
Speciality	Date of Visit	Treatment	
Name	Clinic/Hospital	Phone	Email
Speciality	Date of Visit	Treatment	
Name	Clinic/Hospital	Phone	Email
Speciality	Date of Visit	Treatment	
Name	Clinic/Hospital	Phone	Email
Speciality	Date of Visit	Treatment	
Name	Clinic/Hospital	Phone	Email
Speciality	Date of Visit	Treatment	
Name	Clinic/Hospital	Phone	Email
Speciality	Date of Visit	Treatment	
Name	Clinic/Hospital	Phone	Email
Speciality	Date of Visit	Treatment	
Name	Clinic/Hospital	Phone	Email
Speciality	Date of Visit	Treatment	
Name	Clinic/Hospital	Phone	Email
Speciality	Date of Visit	Treatment	
Name	Clinic/Hospital	Phone	Email
Speciality	Date of Visit	Treatment	

Table 3. *Studies reporting level of intellectual disability in individuals with Cornelia de Lange syndrome.**

Study	Participant characteristics				Assessment	Individuals scoring within categories of intellectual disability n (%)					
	N	Age in years Mean (SD) range	% Male	Molecular confirmation		Profound	Severe	Moderate	Mild	Borderline	Normal
Ajmone et al. (2014)	17[1]	8.2 2.5-13.4	47.1	Yes	LIPS-R, GS	2 (12%)	0 (0%)	4 (23%)	1 (6%)	2 (12%)	3 (17%)
Basile et al. (2007)	56[2]	10.6 *(8.5)* 1-31	51.8	No	LIPS-R, WS, SBIS; GS	12 (21%)	15 (27%)	15 (27%)	5 (9%)	7 (12%)	2 (4%)
Beck (1987)	36	Median: 16	N/A	No	Unknown	14 (39%)	5 (14%)	7 (19%)	6 (17%)	2 (6%)	2 (6%)
Berney, Ireland & Burns (1999)	49	10.2 *(7.8)*	42.9	No	Unknown	(43%)	(20%)	(18%)	(8%)	(10%)	---
Kline et al. (2007)	49	17.8 11–50	71.4	53% received molecular testing	Medical records	---	(51%)	(24%)	(16%)	(6%)	(4%)
Olioso et al. (2009)	45	22.4	51.1	No	Unknown	---	24 (53%)	17 (38%)	4 (9%)	---	---
Sarimski (1997)	27	7.1 (4.9) 1–16	44.4	No	Estimated from parental report	---	19 (70%)	8 (30%)	---	---	---
						Mean (*SD*); range					
Fraser et al., (1978)	6[3]	14-22	100.0	No	SBIS; LIPS	IQ = <30–54)					
Kline et al. (1993)	14	3.2 – 19.0	N/A	No	SBIS; MSCA; WISC-R; WPPSI-R	IQ = 53; 30–85					
Lorusso et al. (2007)	6	14.8 *(13.1)*	16.7	No	WPPSI, WISC-R, WAIS-R	IQ = 63.8 (*17.7*) 47–95					

*Inclusion criteria for studies varied and may explain in part differences in scoring results
[1] 5 participants were unable to be assessed for reasons not given.
[2] 8 participants were unable to be formally assessed due to level of disability.
[3] 3 participants were unable to be assessed for reasons not given

Moeschler & Graham (1993)	3	0.8-13	100.0	No	Unknown; SBIS; WISC	IQ = 63–66					
	4	5.25 4–5	75.0	No	WPPSI	VIQ = 52.8; 45–58. PIQ = 61.3; 51–66					
Parisi, Di Filippo & Roccella (2015)	39(SMC1A)	Median13 0-46	27.5	Yes	physician report	1/20 (5%)	5/20 (25%)	8/20 (40%)	4/20 (20%)	---	2/20 (10%)
Huisman (2017)	67(NIPBL)	Median 14 0-46	50.7	Yes	physician report	11/58 (19%)	27/58 (47%)	16/58 (28%)	4/58 (7%)	---	0/58 (0%)

VIQ = Verbal IQ**; PIQ =** Performance IQ; **GS** = Griffiths' Scale; **LIPS-R** = Leiter International Performance Scales-Revised; **MSCA** = McCarthy Scales of Children's Abilities; **SBIS** = The Standford-Binet Intelligence Scale; **WS =** Welchsler Scales); **WAIS-R** = Wechsler Adult Intelligence Scale-Revised; **WISC-R** = Wechsler Intelligence Scale for Children – Revised; **WPPSI** = Wechsler Preschool Performance Scale of Intelligence; **WPPSI-R** = Wechsler Preschool Performance Scale of Intelligence - Revised.

Table 4. *Studies reporting level of developmental delay in individuals with Cornelia de Lange syndrome.**

Study	Participant characteristics				Assessment	Individuals scoring within categories of developmental delay n (%)					
	N	Age in years Mean (SD) range	% Male	Molecular confirmation		Profound	Severe	Moderate	Mild	Borderline	Normal
Bhuiyan et al. (2006)	36	N/A	N/A	Yes	VABS	19 (53%)	6 (16.5%)	6 (16.5%)	4 (11%)	1 (3%)	---
Marchisio et al. (2008)	50	Median: 6.5 1-18	46.0	No	Categorised based on language and cognition	---	20 (40%)	24 (48%)	6 (12%)	---	---
Moss et al. (2008)	34	12.4 *(3.8)* 5-18.96	47.2	No	VABS	9 (26%)	16 (47%)	6 (18%)	3 (9%)	0 (0%)	---
Nakanishi et al. (2013)	66	14.7 4 – 44	47.0	No	VABS	9 (14%)	3 (4%)	9 (14%)	35 (53%)	10 (15%)	---
Oliver et al. (2009)	54	13.9 *(9.0)*	46	No	VABS	27 (50%)	13 (24%)	8 (15%)	6 (11%)	---	---
Richards et al. (2009)	12	11.0 *(5.2)* 5.0-18.0	33.3	No	VABS	---	4 (33%)	5 (42%)	3 (25%)	---	---
Selicorni et al. (2007)	62	12.0 0.5-48.0	61.3	Yes	Unknown	16 (26%)	0 (0%)	36 (58%)	5 (8%)	---	---
Wulffaert et al. (2009)	37	18.1 *(13.0)* 1.4 – 46.2	56.8	Yes	VABS	19 (51%)	6 (16%)	6 (16%)	5 (14%)	1 (3%)	---
Yan et al. (2006)	28	10.9 3–27	53.6	Yes	Based on criteria from Gillis et al. (2004)	---	15 (54%)	9 (32%)	4 (14%)	---	---
						Mean (*SD*); range					
Basile et al. (2007)	56	10.6 *(8.5)* 1-31	51.8	No	VABS	AE (years) = 3.5 (*2.9*) 1.5–11					
Crawford et al. (2015)	15	18.4 *(9.8)* 6.7-33.4	53.3	No	VABS	SS = 60 (*25)*; 21–121					
Kline et al. (1993)	36	3.2 – 19.0	N/A	No	VABS	SS = 48; 20–87					

Moss et al. (2005)	8	9.8 4.3-14.3	62.5	No	VABS	AE (months) = 25; 6–47
Oliver et al. (2006)	16	7.6 1.7-16.1	56.3	No	VABS	AE (months) = 11.6 *(4.9)*; 4–23
Srivastava et al. (2014)	41	11.4 *(3.8)* 5–18	43.9	No	VABS	SS = 38.3 (*23.1*)

AE = Age Equivalence**; SS** = Standard Score; **VABS**= Vineland Adaptive Behavior Scales ; *Inclusion criteria for studies varied and may explain in part differences in scoring results