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1 **Management of growth failure and other endocrine aspects in patients with Noonan syndrome**
2 **across Europe: A sub-analysis of a European clinical practice survey**

3

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10

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21

1 **Abstract (347 / 350 words)**

2

3 *Aim:* To date, there is a lack of international guidelines regarding the management of the endocrine
4 features of individuals with Noonan syndrome (NS). The aim was to develop a clinical practice survey
5 to gather information on current treatment and management of these patients across Europe.

6

7 *Materials and Methods:* A group of 10 experts from three clinical specialities involved in the
8 management of NS patients (clinical geneticists, paediatric endocrinologists, and paediatric
9 cardiologists) developed a 60-question clinical practice survey. The questionnaire was implemented in
10 Survey Monkey and sent to physicians from these three specialities via European/national societies.
11 Contingency tables and the Chi-Squared test for independence were used to examine differences
12 between specialities and countries.

13

14 *Results:* In total, responses of 364 specialists (paediatric endocrinologists, 40%; geneticists, 30%;
15 paediatric cardiologists, 30%) from 20 European countries were analysed. While endocrinologists
16 mostly referred to national growth charts for the general population, geneticists mostly referred to NS-
17 specific growth charts. Approximately half of the endocrinologists perform growth hormone (GH)
18 stimulation tests in short patients with low IGF1 levels. Two thirds of endocrinologists begin GH
19 treatment for short patients in early childhood (4–6.9 years), and over half of them selected a threshold
20 of -2 standard deviation score (SDS) according to national growth charts. The main concerns about
21 GH treatment appear to be presence of hypertrophic cardiomyopathy (HCM) (59%), increased risk of
22 malignancy (46%), and limited efficacy (31%). When asked if they consider HCM as a
23 contraindication for GH treatment, one third of respondents skipped this question, and among those
24 who replied, two thirds selected ‘cannot answer’, suggesting a high level of uncertainty. A total of 21
25 adverse cardiac responses to GH treatment were reported. Although most respondents had not
26 encountered any malignancy during GH treatment, six malignancies were reported. Finally, about half
27 of the endocrinologists expected a typical final height gain of 1–1.5 SDS with GH treatment.

28

1 *Conclusion:* This survey describes for the first time the current clinical practice of endocrine aspects of
2 NS across Europe and helps us to identify gaps in the management but also in the knowledge of this
3 genetic disorder.

4

5 **Keywords**

6 Noonan syndrome | RAS/MAPK signalling pathway | Clinical practice survey | Europe | Endocrine |

7 Growth hormone

8

1 **Introduction**

2

3 Noonan syndrome (NS) is a developmental disorder with a roughly estimated incidence of 1 in 2000–
4 2500 live births. This syndrome is caused by germline mutations in genes encoding components or
5 regulators of the RAS/mitogen-activated protein kinase (MAPK) signalling pathway (Roberts et al.,
6 2013; Tajan, M. et al., 2018; Tartaglia et al., 2011). The phenotype varies in severity and can involve
7 multiple organ systems, including distinctive facial appearance, cardiac defects, short stature, skeletal
8 abnormalities, variable cognitive deficits, and predisposition to certain cancers (Tajan, M. et al., 2018).

9

10 Short stature affects 50–70% of patients with NS and is one of the main features leading to a
11 diagnosis. Although one quarter of neonates with NS are born small for their gestational age, prenatal
12 growth is usually considered to be only mildly affected with decreased growth velocity and short
13 stature becoming obvious by two years of age (Cessans et al., 2016; Ranke et al., 1988). During
14 childhood, mean height usually follows the lower limit of the normal population, after which it usually
15 declines further because of delayed puberty and a reduced pubertal growth spurt (Ranke et al., 1988).
16 Bone age is usually delayed by about two years throughout childhood, which leads to prolonged catch-
17 up growth at the end of the second decade of life (Ranke et al., 1988; Sharland et al., 1992). In most
18 studies, spontaneous adult height standard deviation score (SDS) is around -2 in females and -2 to -2.5
19 in males (Cessans et al., 2016; Malaquias et al., 2012; Ranke et al., 1988). However, because of
20 prolonged catch-up growth, reported adult height should be interpreted with caution (Giacomozzi et
21 al., 2015). In recent years, it has been demonstrated that growth patterns in NS significantly vary
22 according to the causative gene (Cessans et al., 2016; Malaquias et al., 2012). Abnormal growth
23 hormone (GH) secretion pattern, partial GH insensitivity, as well as defective chondrocyte
24 differentiation during endochondral bone growth have been suggested to underlie growth retardation,
25 as all of these levels of growth regulation may be affected by aberrant RAS/MAPK signalling (De
26 Rocca Serra-Nedelec et al., 2012; Tajan, Mylène et al., 2018). Recombinant human GH received
27 approval by the US Food and Drug Administration in 2007 to treat short stature in patients with NS.

1 More recently, this treatment has also been approved by the European Medicines Agency (EMA).
2 With regards to other endocrine features besides delayed puberty, fertility does not seem to be affected
3 in females with NS; however, gonadal dysfunction with deficient spermatogenesis has been described
4 in males (Ankarberg-Lindgren et al., 2011; Moniez et al., 2018). Finally, thyroid dysfunction (Quaio et
5 al., 2012) as well as decrease in bone mass (Baldassarre et al., 2017; Choudhry et al., 2012;
6 Delagrangé et al., 2021; Noordam et al., 2002; Stevenson et al., 2011) have also been reported.

7

8 To date, there is a lack of international guidelines regarding the screening and the management of the
9 different endocrine aspects of individuals with NS. To describe the current clinical practice across
10 Europe and to identify the gaps and the differences in the management of patients with NS, a clinical
11 practice survey was developed by the European Medical Education Initiative on NS.

12

1 **Methods**

2

3 *Study design*

4 A group of 10 experts from three clinical specialities closely involved in the management of patients
5 with NS (clinical geneticists, paediatric endocrinologists and paediatric cardiologists) developed a 60-
6 question clinical practice survey on the diagnosis and clinical management of patients with NS.
7 Physicians from these three specialities were invited to participate in this survey, which was
8 implemented using the Survey Monkey platform. Support was provided by several European and
9 National societies for the distribution of the survey. More details regarding the development and
10 distribution of the survey have been published separately (Garcia-Minaur et al., 2021). While the
11 survey contained a number of questions that were applicable to each of the clinical specialties
12 surveyed, there were also speciality-specific subsections designed to collect information on specific
13 aspects of treatment and management. While these sections could be skipped if desired, all survey
14 respondents could potentially view and answer all questions in the survey. Some questions were
15 included within two separate sections of the survey designed to be completed by either paediatric
16 cardiologists or paediatric endocrinologists. As some clinical geneticists answered either one or both
17 of these questions within the cardiology and/or endocrinology subsections, their responses were
18 merged in this analysis. The present article describes the results from questions dealing with the
19 management of endocrine aspects of patients with NS. The responses of paediatric endocrinologists
20 were mainly reported, analysed according to their country of origin, and compared with those of
21 clinical geneticists and paediatric cardiologists where appropriate.

22

23 *Statistical analysis*

24 For each question presented in this study, the number of physicians who answered the question was
25 defined along with the percentage of the total number of respondents within that category (*i.e.*, for
26 each speciality). As a second step, only the responses of physicians who gave an answer were
27 considered for the statistical analysis. Differences between specialities and countries were assessed
28 using contingency tables and the Chi-Squared (χ^2) test for independence. The Friedman's test was used

1 for related samples. Given the variable distribution of respondents across countries, responses from
2 endocrinologists and geneticists were only compared between the most represented countries (defined
3 as countries with > 10 respondents [paediatric endocrinologists: France, Italy, Germany, Spain, Czech
4 Republic, UK; clinical geneticists: France, Spain, Italy, UK]). All tests were two-tailed and $p < 0.05$
5 was considered significant throughout the study. Statistical analyses were performed using SAS
6 software, version 9.4 (SAS Institute Inc., Cary, NC, USA) or IBM SPSS statistic for Windows, version
7 25.0 (Armonk, NY: IBM Corp, Armonk, NY, USA).

1 **Results**

2

3 *Description of survey respondents*

4 In total, there were 462 respondents from 25 countries. Of these, 98 were removed from this analysis
5 (81 respondents skipped the survey early, 6 were from outside the 28 European countries selected for
6 analysis, and 11 were from other specialities). This resulted in a core analysis set of 364 respondents
7 from 20 European countries (including 18 European Union member states, the United Kingdom and
8 Switzerland). Respondents were evenly distributed across paediatric endocrinology (n = 146, 40%),
9 clinical genetics (n = 108, 30%) and paediatric cardiology (n = 110, 30%). With regards to their
10 country of origin, most respondents were from France (21%), Spain (18%), Germany (16%), Italy
11 (15%), United Kingdom (8%) and the Czech Republic (6%). Similarly to clinical geneticists and
12 paediatric cardiologists, most of the paediatric endocrinologists (69%) were based in university
13 hospitals alone or in combination with other affiliations (general hospital: 19%; private or independent
14 clinic: 7%; specialist centre: 6%). Seventy-four percent of paediatric endocrinologists follow ≤ 10
15 patients in an average year, and 92% follow ≤ 20 patients, which is significantly lower than clinical
16 geneticists (51% follow ≤ 10 patients and 70% follow ≤ 20 patients) ($p < 0.0001$).

17

18 *Diagnosis of NS*

19 When paediatric endocrinologists were asked about the characteristics that frequently lead to a clinical
20 diagnosis of NS, most indicated that short stature and/or delayed puberty were the leading cause (87%
21 answered with ‘frequently [26–50% of cases] or ‘most [$>50\%$]’). Concerning the age at referral, most
22 children with NS were referred to endocrinologists during childhood (4–12 years; 63% answered with
23 ‘frequently [26–50%] or ‘most [$>50\%$]’). Most paediatric endocrinologists (73%) indicated that a
24 clinically evident diagnosis of NS did not mean they were less likely to conduct or order genetic
25 testing (21% said they would less likely perform genetic testing with a clinically evident NS diagnosis,
26 and 6% selected ‘cannot answer’). There were significant differences between specialities, with
27 paediatric endocrinologists being less likely to order genetic testing when compared with clinical
28 geneticists ($p = 0.004$).

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Screening and investigation of short stature and indication for GH treatment

Physicians were surveyed on the growth charts that they use for the follow-up of patients with NS. In this analysis, only the responses of clinical geneticists (who refer children with NS and short stature to paediatric endocrinologists) and paediatric endocrinologists (who evaluate children with NS and short stature) were considered. National growth charts and NS-specific growth charts were generally used more often compared with non-specific growth charts (*i.e.*, Centers for Disease Control and Prevention [CDC] and World Health Organization [WHO] growth charts). However, there were differences between both specialities. Paediatric endocrinologists mostly referred to national growth charts for the general population ($p < 0.0001$), whereas geneticists mostly referred to NS-specific growth charts ($p = 0.005$) (**Fig. 1A**). Although the differences between the top six countries were not significant for paediatric endocrinologists, NS-specific growth charts were more likely to be used by clinical geneticists from the United Kingdom, and less frequently by geneticists from France ($p < 0.0001$).

Regarding hormonal investigation of patients with NS and short stature, the attitude of paediatric endocrinologists was highly variable (and sometimes diverging). Physicians were asked if they usually perform a GH stimulation test in patients with NS and short stature. Among the 63% of paediatric endocrinologists who did not skip the question, half of them (52%) answered that they only performed GH stimulation tests in patients with low insulin-like growth factor 1 (IGF1) levels. Furthermore, 10% answered that they never performed GH stimulation tests, and 36% answered that they always performed a test regardless of IGF1 levels. There were differences between countries with paediatric endocrinologists from Italy more frequently performing GH stimulation test regardless of IGF1 levels ('always' answer) compared with physicians from the Czech Republic and Germany ($p = 0.002$). In contrast, a higher frequency of paediatric endocrinologists from the Czech Republic do not perform any GH stimulation tests ('never' answer) when compared with the other countries ($p = 0.01$) (**Fig. 1B**).

1 Interestingly, whatever the differences in the baseline investigation of short stature, more than half of
2 the paediatric endocrinologists (57%) reported that GH deficiency (GHD) is found occasionally
3 (defined as a frequency between 6–25% of cases) in patients with NS. There were no significant
4 differences between countries ($p = 0.65$) (**Fig. 1C**).

5
6 Two thirds of paediatric endocrinologists (66%) start GH treatment for patients with NS and short
7 stature in early childhood (4–6.9 years) (**Fig. 2A**). For one quarter of these physicians (23%), an
8 earlier age would be optimal (1–3.9 years). There were no significant differences across countries ($p =$
9 0.309).

10
11 Regarding the height threshold below which GH treatment should be considered in short children with
12 NS, among the 63% of paediatric endocrinologists who did not skip the question, over half of them
13 (55%) proposed a threshold of -2 SDS and 22% a threshold of -3 SDS according to growth charts for
14 the general population (**Fig. 2B**). Moreover, 7 out of 16 respondents who answered with ‘other
15 criteria’ proposed a height threshold of -2.5 SDS. A lower threshold (-3 SDS) tended to be preferred
16 by the paediatric endocrinologists from Germany ($p = 0.057$). Geneticists mostly considered a
17 threshold of -3 SDS according to growth charts for the general population, which was lower compared
18 to paediatric endocrinologists ($p = 0.040$ using the Chi^2 test and $p = 0.051$ using the Fisher’s bilateral
19 exact test).

20

21 *Concerns about GH treatment*

22 In this survey, it was possible to analyse the main concerns about GH treatment in short children with
23 NS across the three specialities. It is important to note that many responders skipped this question
24 (21% of geneticists, 30% of paediatric endocrinologists, and 24% of paediatric cardiologists), and of
25 those who replied, many could not answer the question (22% of geneticists, 2% of paediatric
26 endocrinologists, and 31% of paediatric cardiologists). Among the 224 remaining respondents (62% of
27 the total number of respondents), the main concerns about GH treatment appear to be the presence of

1 hypertrophic cardiomyopathy (HCM) (59%), the increased risk of malignancy (46%), and the limited
2 efficacy (31%), with important differences across the three specialities (**Fig. 3A**).

3

4 *Hypertrophic cardiomyopathy*

5 When physicians were asked about their concerns regarding GH treatment (**Fig. 3A**), geneticists
6 appeared to be less concerned about HCM when compared with paediatric endocrinologists and
7 cardiologists ($p = 0.041$). Physicians were also asked if they consider HCM a contraindication to the
8 use of GH therapy (**Fig. 4**). It is important to note that many responders skipped this question (74% of
9 geneticists, 37% of paediatric endocrinologists, and 35% of paediatric cardiologists), and of those who
10 replied, many selected 'cannot answer' (32% of geneticists, 9% of paediatric endocrinologists and
11 24% of paediatric cardiologists). About one third of respondents from the three specialities (29%)
12 considered that GH treatment is not a contraindication with frequent ultrasound monitoring, and 8%
13 considered HCM not a contraindication at all. Conversely, 19% of respondents considered that GH
14 treatment is a clear contraindication if HCM is present, and 26% considered it a contraindication
15 'sometimes'. There were no significant differences between the specialities ($p = 0.528$). When asked
16 whether they arrange regular monitoring for patients on GH, most respondents (80%) selected 'yes'.

17

18 Physicians were also asked if they have encountered an adverse cardiac response to GH therapy (**Fig.**
19 **3B**). It is important to note that one third of paediatric endocrinologists and paediatric cardiologists
20 skipped this question, and of those who replied, two thirds replied that they could not answer the
21 question. A total of 21 adverse cardiac responses to GH treatment were reported by less than 10% of
22 respondents (10% of paediatric endocrinologists and 7% of paediatric cardiologists).

23

24 *Risk of malignancies*

25 When physicians were asked about their concerns regarding GH treatment (**Fig. 3A**), paediatric
26 cardiologists were less concerned about the increased risk of malignancy compared with paediatric
27 endocrinologists ($p < 0.0001$), the geneticists being in an intermediate situation.

28

1 Respondents were asked if they had encountered any malignancy in a child with NS receiving GH
2 treatment (**Fig. 3C**). Among the 92 paediatric endocrinologists who responded to the question, 69
3 (75%) answered they had not encountered any malignancy, 3 (3%) had encountered a malignancy, and
4 20 (22%) selected ‘cannot answer’. When the 3 paediatric endocrinologists were asked to specify the
5 type of malignancy, two provided an answer (one stated “leukaemia and cerebral dysembryoplastic
6 neuroepithelial tumour [DNET]” and the second stated “DNET cancer”). While this question was
7 contained in the endocrinology subsection of the survey, 16 geneticists (15%) also answered the
8 question. Geneticists also reported three other malignancies, including one juvenile myelomonocytic
9 leukaemia (JMML), one brain tumour and one DNET. Overall, six malignancies were reported by
10 paediatric endocrinologists and geneticists from different institutions: four brain tumours including
11 three DNET, and two cases of leukaemia.

12

13 *Limited efficacy*

14 When physicians were asked about their concerns regarding GH treatment (**Fig. 3A**), 33% of
15 geneticists and 35% endocrinologists were concerned about limited efficacy. This finding is in
16 accordance with the expected final height gain in patients treated with GH (**Fig. 5**). Indeed, among the
17 63% of paediatric endocrinologists who did not skip the question, about half (45%) expect a final
18 height gain between 1 to 1.5 SDS, and one-third (31%) below 1 SDS; this answer was homogenously
19 distributed across countries (no statistically significant differences; $p = 0.439$).

20

21 *Other endocrine aspects of NS*

22 Regarding puberty, which is usually delayed in NS, the need for pharmacological induction was
23 occasional or very seldom as reported by most physicians (**Fig. 6A**). There were no differences
24 between patient genders.

25

26 Regarding the assessment of fertility in males with NS, it is important to note that 37% of paediatric
27 endocrinologists skipped this question, and of those who replied, many could not answer the question
28 (11%). Most (47%) paediatric endocrinologists perform investigations assessing fertility in males who

1 have experienced cryptorchidism, and one third (28%) in males who have experienced pubertal delay
2 **(Fig. 6B)**. Only 15% of physicians perform investigations assessing fertility in all male patients,
3 regardless of the clinical history.
4
5 Thyroid dysfunction was not reported frequently (93% and 99% of respondents answered with ‘never
6 and very seldom’ or ‘occasionally’ for hypothyroidism and hyperthyroidism, respectively) **(Fig. 6C)**.
7
8 Finally, one third (29%) of paediatric endocrinologists do not routinely evaluate bone health (*i.e.*,
9 mineral homeostasis and vitamin D, osteodensitometry) in patients with NS, 58% assess mineral
10 homeostasis and vitamin D, and 24% osteodensitometry **(Fig. 6D)**.

1 **Discussion**

2

3 This survey reports a general picture of the current clinical practice for patients with NS across Europe
4 and helps us to identify gaps and differences in their management. The present article describes the
5 results from the survey dealing with the management of endocrine aspects of patients with NS.

6

7 *Growth charts*

8 With regards to the growth charts used for the follow-up of patients with NS, there were differences
9 between paediatric endocrinologists, who mostly referred to national growth charts for the general
10 population, and clinical geneticists, who mostly referred to NS-specific growth charts. Although NS-
11 specific growth charts may have significance to describe the natural history of the disease, their
12 usefulness to monitor growth is questionable. Indeed, these NS-specific growth charts were
13 established more than 30 years ago in small cohorts of patients (about one hundred patients) without a
14 molecular diagnosis of NS (Ranke et al., 1988). In recent years, it has been demonstrated that growth
15 patterns in NS are distinct according to the causative gene. Thus, the frequency of short stature
16 (defined as height SDS below -2) varies according to the genotype (*e.g.*, 35% of short stature in *SOS1*
17 patients, 73% in *PTPN11*, 84% in *KRAS*, and 85% in *RAF1*) (supplemental data (Cessans et al.,
18 2016)). As reported by Malaquias *et al.*, patients with mutations in *RAF1* and *SHOC2* genes were
19 shorter than other genotypes, whereas patients with *SOS1* and *BRAF* mutations had more preserved
20 postnatal growth (Malaquias et al., 2012). In the study by Cessans *et al.*, growth retardation was
21 significantly less severe and less frequent at two years of age in patients with *SOS1* mutations
22 compared with patients with *PTPN11* mutations (Cessans et al., 2016). To date, there is no gene-
23 specific growth chart in NS. Finally, the essential issue during follow-up of NS patients is to compare
24 their growth with normally growing children. Consequently, national growth charts for the general
25 population are probably more appropriate to monitor growth in these patients.

26

27 *Hormonal investigation*

1 Regarding investigations performed in NS patients with short stature, the attitude of paediatric
2 endocrinologists was highly variable (and sometimes diverging) across countries. Indeed, although
3 half of the physicians performed GH stimulation tests in patients with low IGF1 levels, some of them
4 never performed these tests, whereas others always performed these tests regardless of IGF1 levels. In
5 view of the mechanisms underlying short stature in patients with NS, the usefulness of GH stimulation
6 tests is disputable. Indeed, while there have been reports on GHD (Cotterill et al., 1996; Romano et al.,
7 1996) or neurosecretory dysfunction (Ahmed et al., 1991; Noordam et al., 2001b; Tanaka et al., 1992),
8 patients with NS (notably those with *PTPN11* mutations) usually display normal or slightly increased
9 GH levels associated with low serum IGF1 levels, suggesting GH insensitivity (Binder et al., 2005;
10 Limal et al., 2006). GH insensitivity, as well as abnormal chondrocyte differentiation, both involving
11 hyperactivation of the RAS/MAPK signalling pathway, were confirmed *in vivo* in transgenic mice
12 expressing a NS-associated *Ptpn11* allele (De Rocca Serra-Nedelec et al., 2012; Tajan, Mylène et al.,
13 2018). Interestingly, whatever the differences in the baseline investigation of short stature reported in
14 this survey, more than half of the paediatric endocrinologists reported that GHD is found occasionally
15 in patients with NS. In fact, before GH was approved for NS *per se*, this treatment could only be used
16 for NS patients with growth retardation associated with GHD, or for children born small for
17 gestational age. As a result, GH testing has probably been used more frequently in order to find an
18 indication for GH treatment. With the GH now being approved for NS in Europe, GH testing is
19 expected to decrease significantly.

20

21 *Height threshold and optimal age to start GH treatment*

22 There were differences in the height threshold below which GH treatment should be considered in NS
23 children with short stature, with clinical geneticists considering a lower threshold compared with
24 paediatric endocrinologists. The prolonged catch-up growth at the end of the second decade that has
25 been well documented in NS (Ranke et al., 1988; Sharland et al., 1992) may be a reason for some
26 specialists to apply a lower threshold at the start of treatment. This prolonged growth and late catch-up
27 growth should lead to cautious interpretation of reported GH treatment efficacy on adult height,

1 because in non-controlled studies, this effect leads to an overestimation of the GH effect size
2 (Giacomozzi et al., 2015).

3

4 Two thirds of paediatric endocrinologists proposed to start GH treatment for NS patients with short
5 stature in early childhood (4–6.9 years). For one quarter of these physicians, the optimal age would be
6 earlier (1–3.9 years); it is likely that this answer includes the age group 3–4 years, which was not
7 individually specified in the survey. The determination of optimal age to start GH treatment is a
8 challenging issue and should take into account the nutritional status and potentially the motor
9 development of these children. Indeed, feeding difficulties (such as a weak sucking, prolonged feeding
10 time or recurrent vomiting) are reported in three quarters of infants with NS and can contribute to
11 failure to thrive (Sharland et al., 1992; Shaw et al., 2007). Although these feeding problems usually
12 resolve in the first months/years of life, about one quarter of these infants require tube feeding for two
13 weeks or longer. In NS patients with the most severe failure to thrive in infancy, there is probably a
14 nutritional contribution to short stature. In other syndromes associated with failure to thrive such as
15 Silver-Russel syndrome, international guidelines have stressed that the main therapeutic goals for the
16 first two years of life should be nutritional support and recovery of any calorie-related length or height
17 deficit, which should be addressed before initiation of GH therapy (Wakeling et al., 2017). On the
18 other hand, early GH administration may have a potential beneficial effect on muscular hypotonia and
19 motor development as it has been reported in patients with Prader-Willi syndrome (Reus et al., 2014).
20 Further prospective trials in infants with NS are needed to address and clarify this issue.

21

22 *Concerns about GH treatment*

23 The main concerns about GH treatment appear to be the presence of HCM, the increased risk of
24 malignancy, and limited efficacy, with important differences according to the three specialities. A
25 significant proportion (12–17%) of respondents had no concerns.

26

27

28 *Hypertrophic cardiomyopathy*

1 Patients with NS are predisposed to cardiac diseases, notably pulmonary valve stenosis and HCM,
2 occurring in 50–60% and 20% of patients with NS, respectively, with variable prevalence depending
3 on the gene involved and the specific type of mutation (Calcagni et al., 2017; Prendiville et al., 2014).
4 Given the known stimulating effect of the GH/IGF1 axis on cardiac mass (Twickler et al., 2004),
5 concerns have been raised about a possible increased risk of alteration in cardiac function in patients
6 with NS treated with GH, particularly the development or deterioration of HCM. In this survey, there
7 are significant discrepancies between respondents regarding the meaning of HCM as a
8 contraindication for GH. These discrepancies may be attributed in part to the lack of a clear definition
9 of the term HCM in the survey, which may imply a very broad clinical spectrum ranging from mild
10 myocardial hypertrophy without any functional impairment to severe progressive HCM. It is also
11 important to note that one third of respondents skipped this question, and of those who replied, two
12 thirds replied that they could not answer the question, which suggests a high level of uncertainty; it is
13 notable, therefore, that adverse cardiac events were reported in this survey from a small number of
14 respondents. This uncertainty is likely due to a lack of robust data in the published literature regarding
15 this particular question. Two short-term studies specifically addressing the effect of GH on cardiac
16 function in NS did not find any effects (Cotterill et al., 1996; Noordam et al., 2001a). Similarly, two
17 long-term prospective trials of GH therapy in NS did not find any cause for concern, but children with
18 known HCM were excluded from these trials (Noordam et al., 2008; Osio et al., 2005). In contrast,
19 Horikawa *et al* included altogether eight patients with HCM in a long-term study of two different
20 dose-regimes and did not report any ultrasound data on the effect of GH in these patients. In this study,
21 altogether nine adverse cardiac responses were reported, four of those arrhythmias (three in high-dose
22 group and one in low-dose group), all in patients with pre-existing but not specified cardiac disease
23 (Horikawa et al., 2020). Several post-marketing observational studies including a large number of
24 patients with NS treated with GH provide interesting data because a significant proportion of these
25 patients had cardiac defects at baseline; however, the precise description of the type and the severity of
26 cardiac defect is often lacking in these studies. Of the 429 patients with NS included in the Kabi
27 International Growth Study (KIGS) database, seven cardiac adverse events were reported during the
28 course of GH therapy, including cyanotic periods (one patient), cardiac arrhythmias (three patients),

1 angina pectoris (one patient), left ventricular hypertrophy (one patient), and cardiomyopathy requiring
2 heart transplantation (one patient) (Otten and Noordam, 2007); the pre-existing cardiac situation was
3 not described in this article. Of the 370 patients with NS included in the National Cooperative Growth
4 Study, 46% had cardiac disorders (Romano et al., 2009). During the course of GH therapy, three
5 cardiac adverse events were reported (increased biventricular hypertrophy, HCM, and supravalvular
6 aortic stenosis), but all of them were considered to be comorbidities of NS. Finally, of the 412 patients
7 included in two complementary non-interventional studies (NordiNet IOS and ANSWER), 41 patients
8 had cardiovascular comorbidities, including congenital pulmonary stenosis (19 patients), HCM (3
9 patients), and unspecified congenital malformation of the heart (3 patients) (Rohrer et al., 2020). No
10 other cases of HCM or other cardiopathies were reported during GH therapy.

11

12 These safety data are reassuring in patients with NS without known HCM, as long as cardiac status is
13 monitored while on GH therapy. However, current knowledge is insufficient to conclude about the
14 safety of GH treatment in patients with NS and pre-existing HCM (even mild).

15

16 Increased risk of malignancy

17 In this survey, most respondents answered they had not encountered any malignancy during GH
18 treatment. However, it is important to note that many respondents skipped this question, and of those
19 who replied, most replied that they could not answer the question. Overall, six malignancies were
20 reported in this survey: four brain tumours including three DNET, and two leukaemias. Patients with
21 NS are predisposed to have a higher risk than the general population for leukaemia (e.g., juvenile
22 myelomonocytic leukaemia) and solid tumours, including neuroblastoma and central nervous system
23 tumours such as DNET. The cumulative risk of developing cancer was 3.5-fold higher among
24 individuals with a *PTNP11* mutation (Jongmans et al., 2011) and 8.1-fold higher among individuals
25 with molecularly confirmed NS than in the general population (Kratz et al., 2015). This raises
26 concerns about the use of GH treatment in patients with NS. A literature review performed by
27 McWilliams *et al* identified nine reports of DNET and 13 non-DNET brain tumours in individuals
28 with NS (McWilliams et al., 2016) in this series, tumour growth while receiving GH occurred in two

1 patients. Bangalore Krishna *et al* described two other NS patients who developed brain tumours while
2 being on GH treatment (Bangalore Krishna et al., 2017) Molecular diagnosis of NS is usually lacking
3 in previous case reports and it may be hypothesized that specific mutations may convey higher tumour
4 risks. Jacquinet *et al* reported a 22-year-old patient with NS related to a *LZTR1* mutation who
5 developed a ganglioblastoma; this patient had been transiently treated with GH between ages 15 and
6 17 (Jacquinet et al., 2019). Finally, in the post marketing observational studies published by Rohrer *et*
7 *al*, four events were reported in three patients (3/412; 0.7%) including brain neoplasm (reported as a
8 serious adverse event [SAE] unlikely to be related to GH treatment) in one patient, glioneuronal
9 tumour (reported as an SAE unlikely to be related to GH treatment) in one patient, and one event each
10 of brain neoplasm and metastases to the spine both reported as a serious adverse reaction (possibly
11 related to GH treatment) in one patient (Rohrer et al., 2020). Given the estimated risk of 1–2% for
12 paediatric malignancies in patients with NS (Kratz et al., 2015), it is currently unclear whether
13 reported cases of malignancy occurring during GH treatment do significantly exceed this baseline risk.
14 Long-term studies taking into account patient stratification based on the mutated gene and type of
15 mutation are needed to assess differences in incidence and the relationship with GH therapy.

16

17 Limited efficacy

18 One third of physicians were concerned about the limited efficacy of GH treatment. This finding is in
19 accordance with the expected final height gain in patients treated with GH. Indeed, about half of
20 paediatric endocrinologists expect a final height gain between 1 to 1.5 SDS, and one-third below 1
21 SDS in patients with NS treated with GH. Although short-term trials on GH treatment in children with
22 NS and short stature have reported an enhancement of growth velocity and mean height standard
23 deviation (Ahmed et al., 1991; Cotterill et al., 1996; De Schepper et al., 1997; Lee et al., 2012;
24 MacFarlane et al., 2001), the benefit on adult height is still uncertain. To date, nine studies have
25 reported data on adult height or near adult height (NAH) outcomes in patients with NS treated with
26 GH (Kirk et al., 2001; Malaquias et al., 2019; Noordam et al., 2008; Osio et al., 2005; Raaijmakers et
27 al., 2008; Ranke et al., 2019; Rohrer et al., 2020; Romano et al., 2009; Tamburrino et al., 2015).
28 However, these trials are difficult to compare because of differing protocols (variations in age at start

1 of treatment, doses and duration of treatment) and outcome criteria (different definitions of NAH).
2 None of these studies were randomised controlled trials and all were significantly biased (Giacomozzi
3 et al., 2015). In these studies, the height gain SDS on final height ranged from 0.6 to 1.7 (about 5 to 10
4 cm respectively), which is comparable to those reported in other non-GHD indications of GH
5 treatment such as Turner syndrome and SHOX deficiency. All these studies reported a high individual
6 variability of response to GH treatment. Similarly to genotype-phenotype correlations reported for
7 spontaneous growth, different genotypes may explain part of this variability. However, in most of the
8 studies, the diagnosis of NS was made clinically without molecular confirmation, which does not
9 allow for investigation of genotype-phenotype correlations. Although a lower growth response was
10 initially suggested in patients with a *PTPN11* mutation (Limal et al., 2006), this result was not
11 confirmed in long-term studies with a similar height gain compared to other genotypes (Noordam et
12 al., 2008). In a study by Tamburrino *et al*, patients harbouring a *SHOC2* mutation showed a better
13 response to GH treatment than patients with *PTPN11* mutations (Tamburrino et al., 2015). Earlier
14 initiation of GH treatment and longer pre-pubertal duration of therapy were associated with improved
15 efficacy of GH therapy (Osio et al., 2005; Ranke et al., 2019; Romano et al., 2009). Finally, a recent 4-
16 year randomized, double-blind, multi-centre trial investigating the effect of two doses of GH (66
17 versus 33 µg/kg/day) in pre-pubertal children with NS demonstrated a significant improvement in
18 height gain with the higher dose (Horikawa et al., 2020).

19

20 Long-term data on the effect of GH treatment on height outcomes and on the factors modulating this
21 effect are needed in a large cohort of patients with NS. Notably, further prospective studies are needed
22 to investigate possible genotype-phenotype correlations in terms of efficacy and safety (including
23 HCM and risk of malignancy) of GH therapy. In order to answer this key question, a genetic diagnosis
24 should be available in all NS patients. As a result, paediatric endocrinologists must be aware of the
25 importance of genetic testing. Regarding this issue, it should be stressed that 15% of physicians (21%
26 of paediatric endocrinologists) responding to this survey were less likely to perform genetic testing in
27 patients with a clinically evident diagnosis of NS. One explanation for this could be that access to
28 genetic testing services and associated costs could be problematic for physicians in some countries.

1 However, results from the survey published in the companion manuscript by Garcia-Minaur et al.
2 (Garcia-Minaur et al., 2021) indicated that reimbursement was not a limiting factor for geneticists
3 completing the survey. There is a need for the creation of coordinated European registries to collect
4 data on the evolution of these patients, the medical complications that may arise during their lives and
5 the response and possible side effects of growth hormone treatment.

6

7 Although classically mentioned in NS, some features, such as the need of pharmacological induction
8 for delayed puberty and the higher risk of thyroid dysfunction, were occasionally reported by the
9 paediatric endocrinologists, which is in accordance with the published data. Thus, in a large cohort of
10 patients with NS reported by the Shaw et al study, delayed puberty was induced by sex steroids
11 hormones in only 6% of patients (Shaw et al., 2007). Similarly, in a cohort of 42 patients with NS and
12 other RASopathies, Quaio *et al* reported a frequency of 7% of overt hypothyroidism requiring
13 hormone replacement, which was only slightly higher than those observed in the general population
14 (Quaio et al., 2012).

15

16 Regarding the assessment of fertility and bone health in patients with NS, only half of the physicians
17 were able to answer this question, suggesting a high level of uncertainty. Sertoli cell-specific primary
18 testicular insufficiency and infertility have been reported in patients with NS (Ankarberg-Lindgren et
19 al., 2011; Moniez et al., 2018); However, the exact frequency of infertility in adult males is unknown.
20 Similarly, although several studies have reported decreased bone mass in patients with NS patients and
21 other RASopathies (Baldassarre et al., 2017; Choudhry et al., 2012; Delagrangé et al., 2021; Noordam
22 et al., 2002; Stevenson et al., 2011), the long-term risk of bone fragility in adults and the elderly is
23 unknown. More generally, although the features of NS are well described during childhood, little is
24 known about the progression of the disease in adulthood. Prospective long-term follow-up studies are
25 required to further investigate fertility, bone health and also metabolic status in NS adults and to
26 clarify the long-term follow-up of these patients.

27

28

1 **Conclusion**

2 This survey describes the current clinical practice of endocrine aspects of NS across Europe and helps
3 us to identify the gaps in the management and also in the knowledge of this genetic disorder. This
4 underlines the importance to establish international guidelines regarding the screening and the
5 management of the different endocrine aspects of individuals with NS. Moreover, further data are
6 needed to investigate some unresolved issues, such as possible genotype-phenotype correlations in
7 terms of efficacy and safety of GH treatment in patients with NS (including height outcomes, HCM,
8 and risk of malignancy).

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1 TE, MZ, IÖS, CMW, EBW, AV, SGM, MT, GS and JL contributed to development of the survey
2 questions, analysis of the results, and drafting of the manuscript. EOC performed statistical analysis.
3 All authors have read and approved the final version of the manuscript for submission.

4

5 **Data Availability Statement**

6 All of the data supporting the results presented in this paper are available on request.

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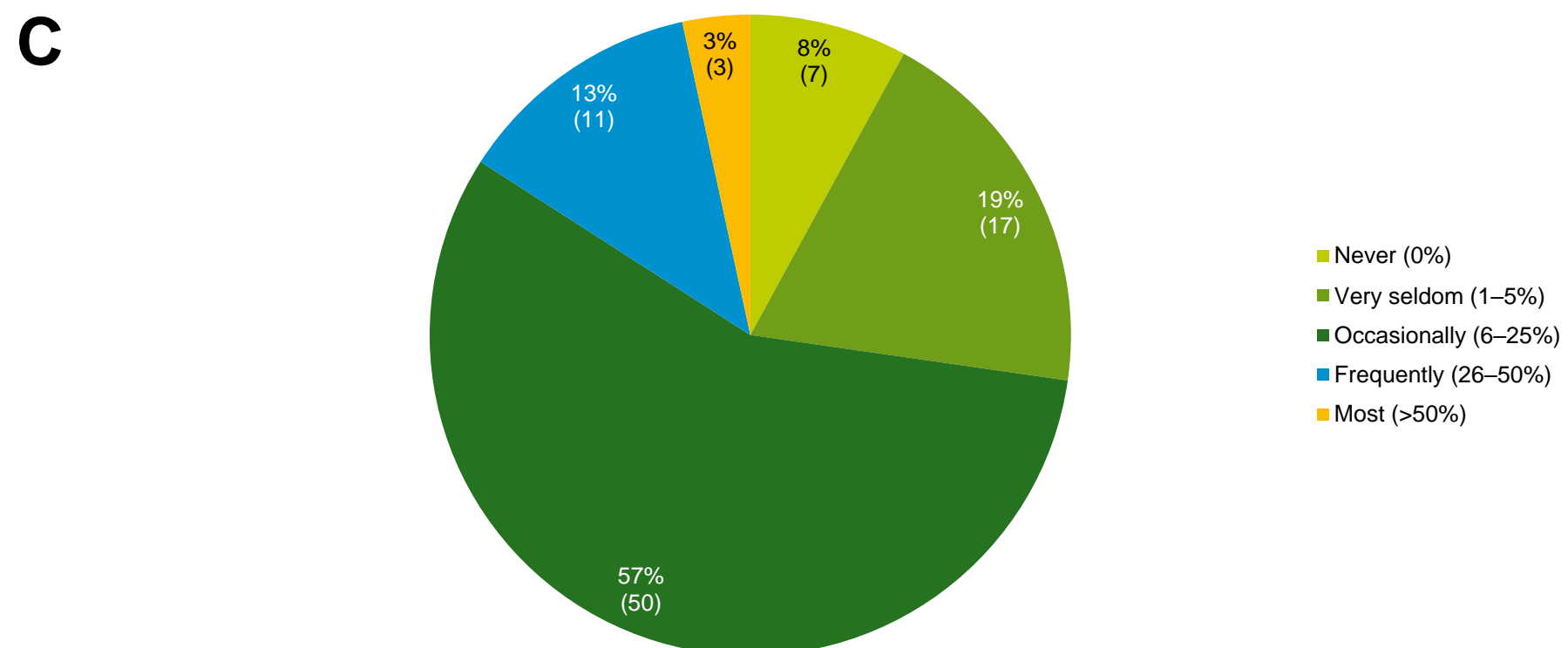
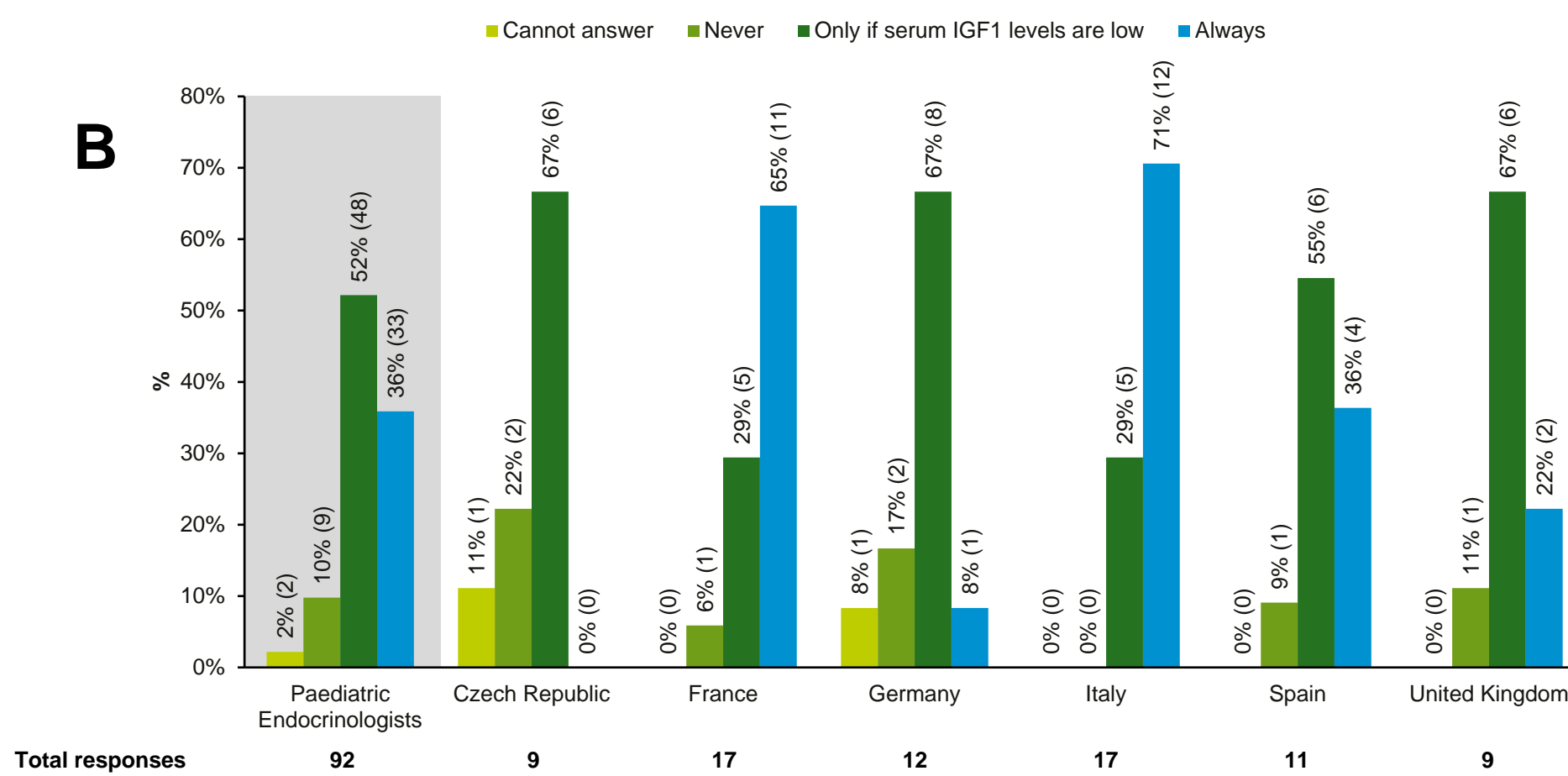
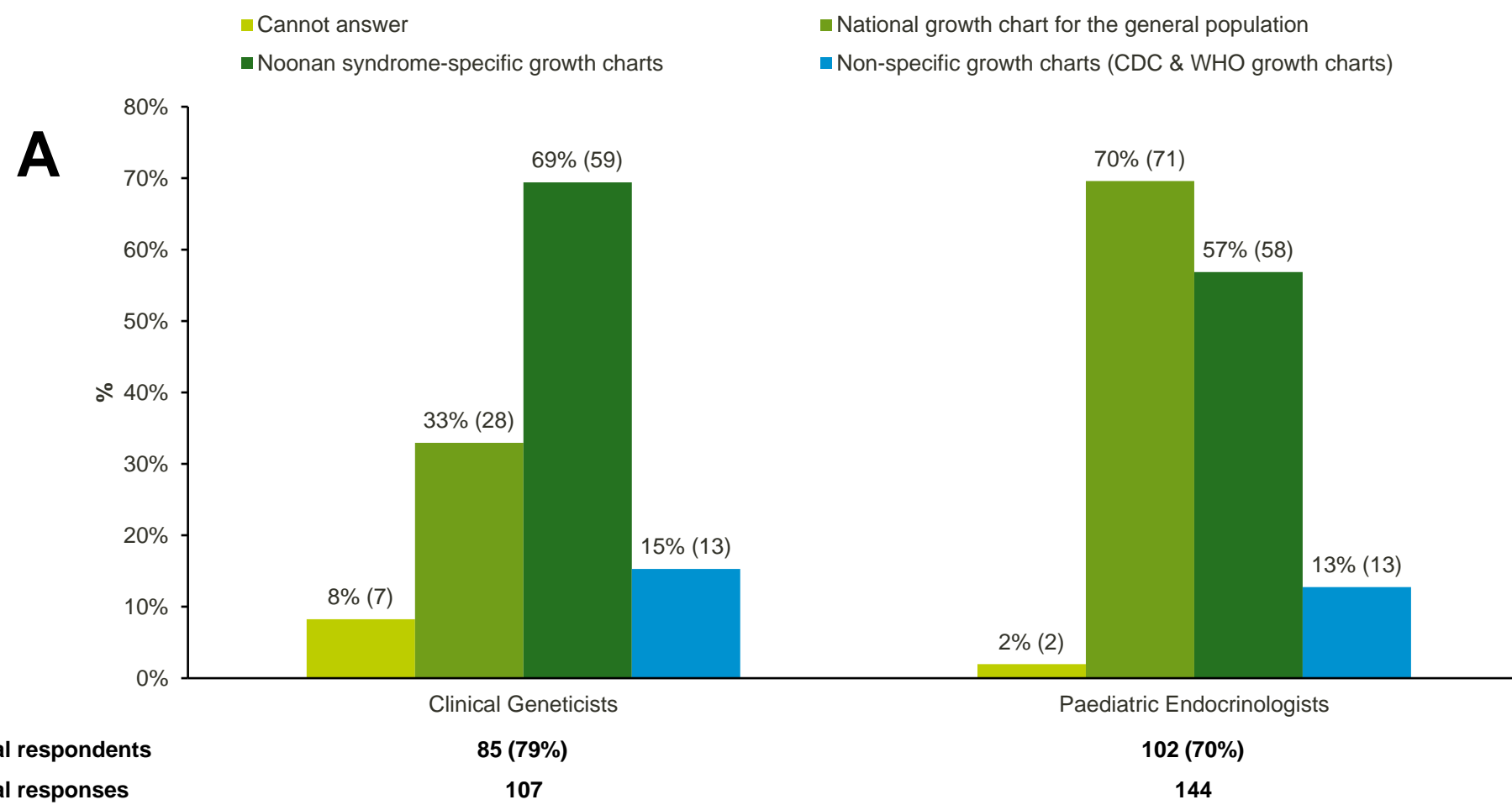
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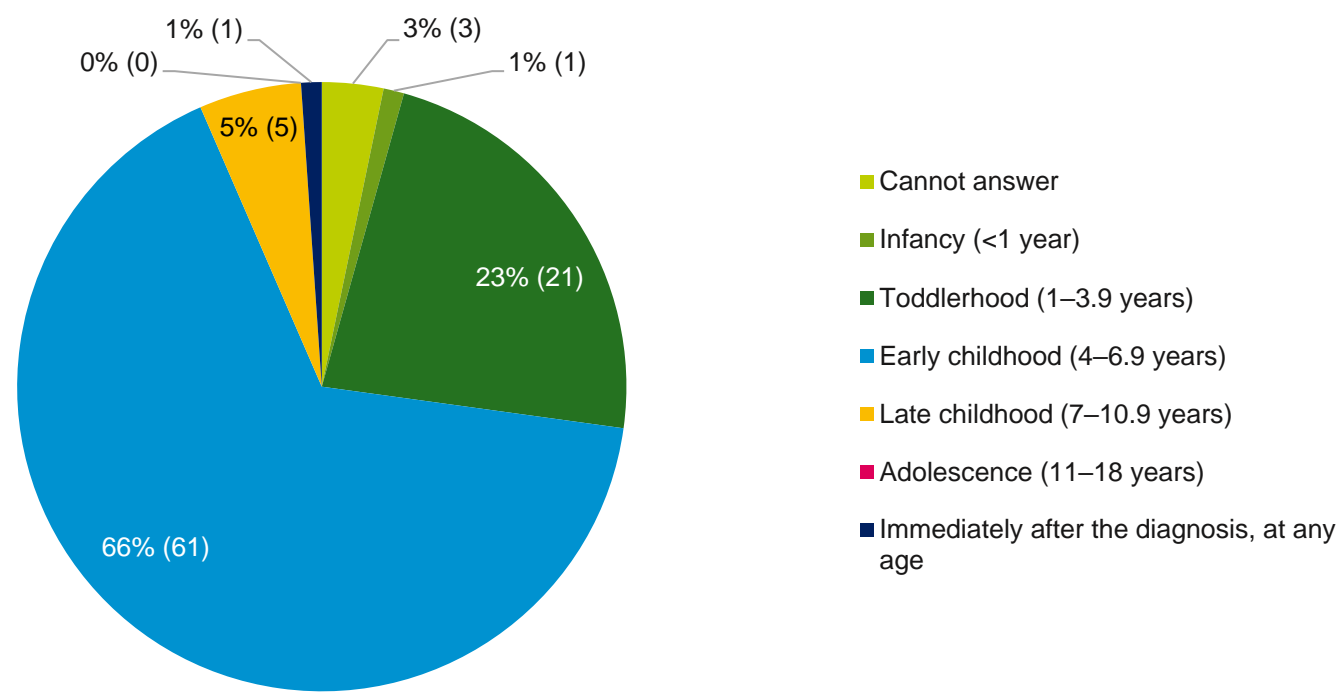
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