ACHONDROPLASIA.EXPERT CONGRESS REVIEWS ACMG 2024

Welcome to the ACMG 2024 congress review.

The 30th *American College of Medical Genetics and Genomics (ACMG) Annual Clinical Genetics Meeting* took place in Toronto, Canada, from 12th–16th March 2024. Attended by geneticists from around the world, this year's meeting saw achondroplasia on the programme in the form of a debate featuring Dr Janet Legare and Dr Julie Hoover-Fong discussing whether all patients should be started on vosoritide▼.

We have highlighted the key abstracts from the congress, focusing on achondroplasia and new clinical data on vosoritide, real-world analysis of double heterozygosity in skeletal dysplasia, and the importance of genetic counselling in helping families make informed decisions during prenatal diagnostic testing.

We hope you find this selection of summaries useful!

The Achondroplasia Team

The abstracts can be found in full here

TREAT OR NOT TREAT

Debate on treating achondroplasia with vosoritide

▸ FIND OUT MORE

VOSORITIDE CLINICAL DATA

Latest data on vosoritide in achondroplasia

▸ FIND OUT MORE

DOUBLE HETEROZYGOSITY

Cases of achondroplasia and collagen-II-opathy

▸ FIND OUT MORE

PRENATAL COUNSELLING

Panel screening and counselling

▸ FIND OUT MORE

TREAT OR NOT TREAT

A mock debate on whether or not to use vosoritide to treat individuals with achondroplasia. Janet Legare played the role of the affirmative, arguing that every child should be treated, and Julie Hoover-Fong was playing devil's advocate, and argued "just say no: all children should not be treated".

Janet Legare opened by advocating for vosoritide treatment, emphasising that it is an effective and well tolerated treatment that may improve medical sequelae associated with achondroplasia. Vosoritide has shown that it can increase annualised growth velocity (AGV). Janet highlighted that early treatment, before growth plate fusion in the spine, is crucial to maximise the benefits of vosoritide, such as reducing spinal stenosis. While height can be used as a metric to measure the efficacy of vosoritide, improved health is the ultimate goal. Legare also stressed that vosoritide has an extremely specific mode of action, targeting the inhibitory pathway of FGFR3, and has very few side effects.

Julie Hoover-Fong played devil's advocate during the debate, arguing against the use of vosoritide, proposing that there is in fact nothing to treat, and that suggesting otherwise may negatively impact the culture of dwarf pride, self-help, and support groups. She also agued that there are misconceptions about the potential effects of treatment, with some patients not responding as well as others and not enough data on co-morbidities being available. Hoover-Fong also proposed that a better alternative may be available in future, as the daily injections of vosoritide can be difficult for parents to administer to their children and an oral medication would be preferred.

Legare responded by stating that the use of medication does not detract from having achondroplasia, or the need for regular care of the associated health issues. She also reiterated that most data shows that vosoritide is well tolerated and effective for increasing AGV. However, Janet suggested that an improvement in FMS score is the main goal, not increased height, and that if vosoritide can reduce medical sequelae, even just for FMS then it will be worth it for young patients.

Julie countered that height should be considered as height is part of our identity. There is also no data yet available on whether vosoritide treatment results in any change in the spine or FMS. It's also not possible to discuss treatment with a child at the age before the closure of their growth plates; they may not have wanted to be treated with vosoritide. Hoover-Fong also reiterated that oral medication may be an option in future.

Janet closed with a reminder that time is of the essence, and vosoritide is not an attempt to treat a disease, but a condition. She concedes that due to the need for vosoritide treatment to be initiated at a young age, we won't know the full impact for decades, but gives a reminder that vosoritide is the only approved medication to treat growth in achondroplasia. People who have been treated with vosoritide have been followed for overall care and psychological assessment of families and patients are showing an increase in empowerment. Support groups are also becoming more welcoming to patients receiving achondroplasia treatment, and continued support from groups like the Little People of America can be key to whether patients continue to pursue treatment. Legare finished with the reminder that height may be the metric, but better health is the goal.

Julie stated that many patients may think that if they start treatment, they don't need to continue with their health routine surveillance or management, which could have some long-term consequences. While it is true that the Little People of America are changing their stance on vosoritide, they aren't "rolling out the red carpet" for it. There is also the view that a person with achondroplasia is still an important individual and that they may feel their identity is negatively impacted.

The debate concluded with a poll for the audience: How confident are you in recommending treatment for all patients?

The poll resulted in 70% for and 30% against vosoritide treatment in all patients.

NEW VOSORITIDE DATA IN ACHONDROPLASIA

Vosoritide is indicated for the treatment of achondroplasia in patients 4 months of age and older whose epiphyses are not closed.[1]

Hoover-Fong *et al.* presented data on vosoritide's prolonged effect in an ongoing 52-week Phase 2 open label extension (OLE) study (BMN 111-205) conducted in children aged 5–14 years with achondroplasia (ACH). Safety and efficacy findings were reported after a mean of 80.95 months (SD 17.73, max. 106.7), representing the longest clinical experience with vosoritide to date. Comparative analysis was conducted for all participants who reached 7 years follow up (N=17), and cross-sectional analysis was performed with untreated subjects who were matched to each of the subjects in the vosoritide arm at baseline (N=390) and at the 7-year timepoint (N=173) by age and sex. The primary endpoint was safety and tolerability of vosoritide (15 or 30 µg/kg/day).[2]

Vosoritide demonstrated a well-tolerated safety profile, with no evidence of accelerated skeletal maturation or serious events over 7 years of treatment. Injection site reactions were the most common adverse event (3.3%) and no serious adverse events led to discontinuation of vosoritide and were generally attributed to underlying ACH.[2]

After 7 years, children who underwent treatment with vosoritide (15 µg/kg or 30 µg/kg) exhibited an additional height gain of 11.03 cm in comparison with untreated age and sex-matched ACH controls. Mean differences in AGV between treated versus untreated participants across integer age groups from 6 to 16 years was 1.63 (0.57) cm/year for boys and 1.33 (0.58) cm/year for girls.

At Month 84 (n=15), change from baseline in height z-score was +1.67 (0.67) relative to an untreated ACH population (CLARITY[3]) and change in upper:lower body ratio was -0.21 (0.12).

Mean AGVs of treated children were comparable to that of average stature children prior to puberty and were maintained over a longer duration. Vosoritide's durability, growth-promoting effects and well tolerated safety profile were maintained over an extended period of 7 years, demonstrating its potential to offer significant therapeutic benefit to individuals with ACH.[2] ▶ [P144]

Savarirayan *et al.* presented results from a Phase 2 extension study (111-208), exploring vosoritide's effect in young children with achondroplasia aged 3 months–<5 years (n=73). Long-term safety and efficacy results were assessed to understand the impact of vosoritide on growth over 4 years of treatment. Primary endpoints included vosoritide safety and tolerability and height/body length Z-scores.[4]

Mean 12-month interval AGV in children treated with vosoritide is higher compared to age-matched untreated children

ACH untreated reference derived from CLARITY[3]
Average stature reference is non-African American data from Kelly A *et al.* J Clin Endocrinol Metab. 2014.

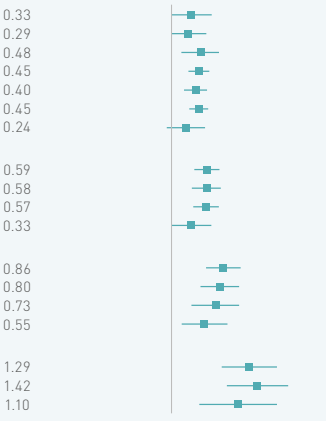
Hoover-Fong J, *et al.* [P144]

Height Z-score consistently increased over time in treated children vs controls

Children ≥ 2 years at start of treatment

Timepoint Studies	Comparator	Number of subjects Vosoritide	Number of subjects Comparator	Treatment difference
1 year				
Study 111-206 (FAS randomized)	111-206 placebo	15	16	0.33
Study 111-206 (FAS)	111-206 placebo	19	16	0.29
Study 111-206 (FAS randomized)	AchNH longitudinal	15	124	0.48
Study 111-206/111-208	AchNH longitudinal	34	198	0.45
Study 111-206/111-208	AchNH cross-sectional	34	761/701	0.40
Study 111-206/111-208	Obs/Pbo longitudinal	34	72	0.45
Study 111-206/111-208	Obs/Pbo cross-sectional	34	77/134	0.24
2 year				
Study 111-206/111-208	AchNH longitudinal	30	146	0.59
Study 111-206/111-208	AchNH cross-sectional	30	725/614	0.58
Study 111-206/111-208	Obs/Pbo longitudinal	30	55	0.57
Study 111-206/111-208	Obs/Pbo cross-sectional	30	80/163	0.33
3 year				
Study 111-206/111-208	AchNH longitudinal	22	107	0.86
Study 111-206/111-208	AchNH cross-sectional	22	672/484	0.80
Study 111-206/111-208	Obs/Pbo longitudinal	22	21	0.73
Study 111-206/111-208	Obs/Pbo cross-sectional	22	80/167	0.55
4 year				
Study 111-206/111-208	AchNH longitudinal	8	30	1.29
Study 111-206/111-208	AchNH cross-sectional	9	444/254	1.42
Study 111-206/111-208	Obs/Pbo cross-sectional	9	79/109	1.10

Treatment difference (95% CI) Vosoritide minus comparator

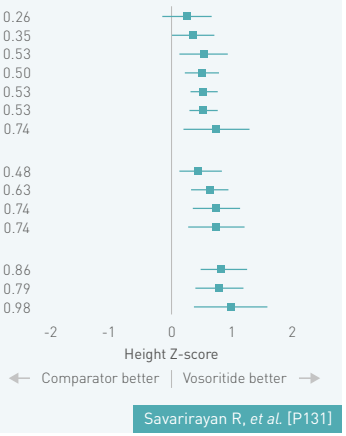


Consistent and sustained treatment effect with mean height Z-score gain > 1 SDS after 4 years

Children < 2 years at start of treatment

Timepoint Studies	Comparator	Number of subjects Vosoritide	Number of subjects Comparator	Treatment difference
1 year				
Study 111-206 (FAS randomized)	111-206 placebo	17	16	0.26
Study 111-206 (FAS)	111-206 placebo	24	16	0.35
Study 111-206 (FAS randomized)	AchNH longitudinal	16	216	0.53
Study 111-206/111-208	AchNH longitudinal	32	287	0.50
Study 111-206/111-208	AchNH cross-sectional	32	788/716	0.53
Study 111-206/111-208	Obs/Pbo longitudinal	32	31	0.53
Study 111-206/111-208	Obs/Pbo cross-sectional	28	49/56	0.74
2 year				
Study 111-206/111-208	AchNH longitudinal	25	223	0.48
Study 111-206/111-208	AchNH cross-sectional	25	767/638	0.63
Study 111-206/111-208	Obs/Pbo longitudinal	25	20	0.74
Study 111-206/111-208	Obs/Pbo cross-sectional	25	55/64	0.74
3 year				
Study 111-206/111-208	AchNH longitudinal	14	150	0.86
Study 111-206/111-208	AchNH cross-sectional	14	715/509	0.79
Study 111-206/111-208	Obs/Pbo cross-sectional	14	61/85	0.98

Treatment difference (95% CI) Vosoritide minus comparator



Consistent and sustained treatment effect with mean height Z-score gain > 0.79 SDS over 3 years

AchNH reference derived from CLARITY[3]

Savarirayan R, *et al.* [P131]

Participants were grouped based on age at the start of vosoritide treatment: children aged ≥2 years at the start of vosoritide treatment (4 years follow-up) or children aged <2 years at vosoritide treatment initiation (3 years follow-up). Treated children consistently demonstrated greater height gain compared with placebo and matched untreated children from CLARITY.[3] Children in the ≥2-year cohort experienced a mean height z-score increase ranging from 0.55–0.86 SDS after 3 years and 1.10–1.42 SDS after 4 years. Children in the >2-year group saw 0.79–0.98 SDS after 3 years. Mean height gains increased by 3.0– 4.12 in the ≥2-year cohort compared with 3.45–3.87 in the <2-year cohort, after 3 years.[4] Gains in absolute height, relative to those of matched children of average stature, were 86% at Year 3 and 90% at Year 4 for children in the ≥2-year cohort and 80% in the <2-year cohort at Year 3.

Safety profiles were comparable across age groups, with the most common adverse events being mild and self-limiting injection site reactions. No treatment-limiting adverse events or new safety issues emerged, affirming vosoritide's tolerability. The study reinforced the benefit of early treatment initiation, with no worsening in body proportions over time, highlighting the consistent and durable effect of vosoritide on growth in young children with ACH who began treatment before the age of 5 years. Participants >5 years of age were not included.[4] ▶ [P131]

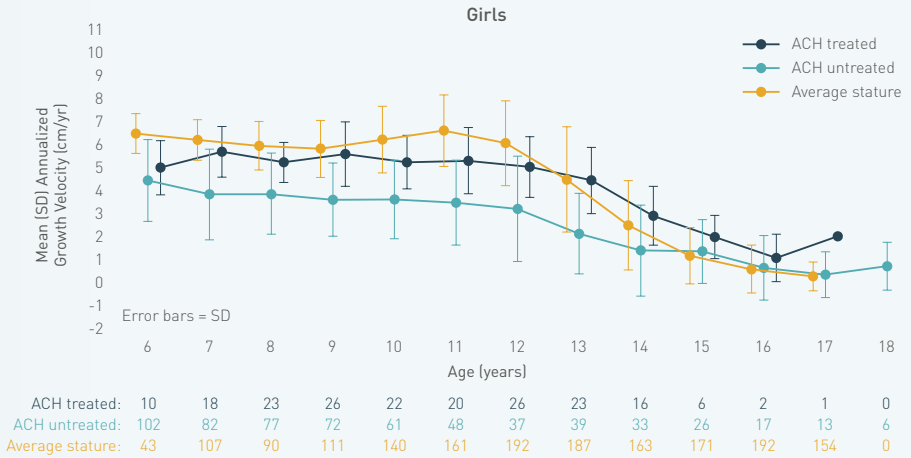
Savarirayan *et al.* presented data from an OLE of a Phase 3 trial that demonstrated improvements in AGV with vosoritide compared with placebo (111 301/302).[5,6] The OLE was initiated to investigate long-term safety and efficacy of vosoritide in children aged 5–18 years (n=119; 15 µg/kg/day of vosoritide). A comparative analysis was conducted for all participants who completed 3 years of treatment (n=111) compared with a matched untreated control; and cross-sectional analysis in which untreated subjects were matched to each of the subjects in the vosoritide arm at baseline (N=690) and at the 3-year timepoint (N=520) by age and sex. The primary endpoint was AGV, and secondary endpoints included height z-score and upper:lower body segment ratio.[7]

Vosoritide demonstrated persistent growth-promoting effects in children with achondroplasia for up to 3 or 4 years with extensive follow-up. The mean (SD) AGV between treated and untreated children aged 6–17 years was 1.46 (0.61 cm/year in girls; 1.73 (0.52) cm/year in boys). Mean (SD) change from baseline height z-score was +1.17 (0.42) at Week 208 (n=53) compared with an untreated ACH population.[3] Mean (SD) upper:lower body segment ratio improved from baseline by -0.15 (0.14) at Week 208 (n=52). Moreover, treated children demonstrated an additional height gain of 5.75 cm (95% CI: 4.94–6.57) over 3 years compared with untreated children with ACH matched by age and sex.[7]

The safety profile was favourable, with only 31.1% of adverse events being treatment related. Serious adverse events (n=22, 18.5%) were generally attributed to underlying achondroplasia, with no new safety issues emerging. Importantly, there was no evidence of accelerated bone age, suggesting that vosoritide does not lead to pathological growth patterns.[7]

Overall, vosoritide was consistently associated with higher AGV and a continuous increase in height Z-score compared to age and sex matched untreated children with achondroplasia. These results demonstrate durable efficacy of vosoritide over 3 years in promoting growth in children with achondroplasia, with no new safety concerns. The consistent and long-term benefits highlight the potential of early treatment initiation.[7] ▶ [P139]

Annualised growth velocity in children receiving vosoritide compared with age-matched untreated children with ACH[1]



AchNH derived from CLARITY[3]

Savarirayan R, *et al.* [P139]

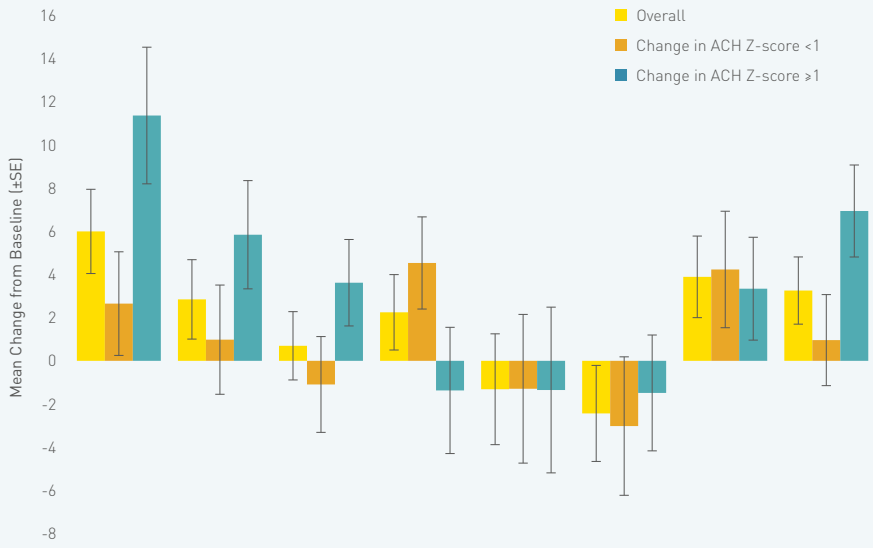
Savarirayan *et al.* showed further data from a Phase 3 OLE trial (111-301/302) demonstrating efficacy of vosoritide in promoting growth in children with ACH compared with placebo (15 µg/kg/day of vosoritide).[7] In an exploration of the long-term effects of vosoritide on health-related quality of life (HRQoL), this study utilised the Quality of Life in Short Stature Youth (QoLISSY) questionnaire in children who participated in the OLE (n=119) compared with an untreated group (n=150).[8]

Participants and their caregivers completed the QoLISSY questionnaire at baseline and every 6 months thereafter, focusing on various domains such as physical, social, and emotional.

After 3 years, mean (SD) change in the physical domain score was 6.0 (19.4) for caregiver reported (n=99) and 6.3 (20.2) for self-reported (n=60). Changes to other domains were less pronounced after 3 years (change in total score was 3.3 (15.5) for caregivers and 5.4 (17.7) for self-reported). Greater improvement in the physical domain was noticed in children with ≥1 SD increase in ACH height z-score where mean changes in the physical domain scores were 11.4 (19.5) for caregiver-reported (n=38) and 8.5 (21.8) for self-reported (n=28).[8]

The study found that after 3 years of treatment, there was a notable improvement in QoLISSY total scores, with even greater enhancements observed in children who showed significant growth improvements. These findings suggest that vosoritide improves HRQoL among children with ACH, particularly for the physical domain score.[8] [P141]

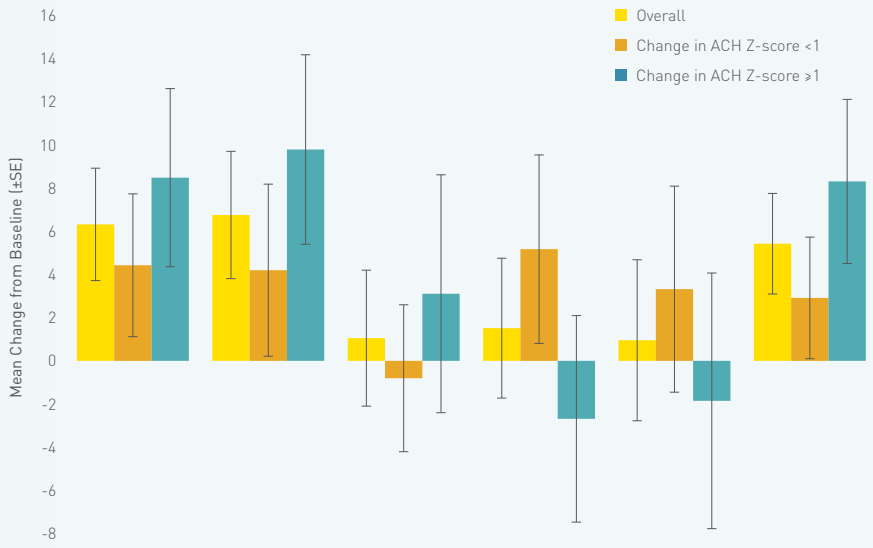
Mean change from baseline in caregiver reported QoLISSY scores at Year 3 in the treated population[8]



	Physical Score	Social Score	Emotional Score	Coping Score	Beliefs Score	Future Score	Effects on Parent Score	Total Score
Overall	99	99	100	93	95	97	99	99
Change in ACH Z-score <1	61	61	62	57	58	60	61	61
Change in ACH Z-score ≥1	38	38	38	36	37	37	38	38

Savarirayan R, *et al.* [P141]

Mean change from baseline in self-reported QoLISSY scores at Year 3 in the treated population[8]



	Physical Score	Social Score	Emotional Score	Coping Score	Beliefs Score	Total Score
Overall	60	59	59	58	59	58
Change in ACH Z-score <1	32	32	31	31	32	31
Change in ACH Z-score ≥1	28	27	28	27	27	27

Savarirayan R, *et al.* [P141]

DOUBLE HETEROZYGOSITY IN SKELETAL DYSPLASIA

Double heterozygosity occurs when individuals inherit two distinct dominant genetic conditions within the skeletal dysplasia spectrum. Historically, cases of double heterozygosity have been associated with severe life-limiting or fatal outcomes. However, advancements in medical technology have challenged the traditional prognosis associated with this condition.[9]

Schelhaas *et al.* aimed to address the unique phenomenon of double heterozygosity in two children with molecularly confirmed ACH and collagen-II-opathy, now aged 2 and 6 years. The younger child has undergone neurosurgical management of foramen magnum stenosis, and an elevated risk of hydrocephalus has been observed in the first 2–3 years of life in ACH.[9]

Both children have undergone extensive medical interventions, including tracheostomy, ventilator support, and neurosurgical procedures to manage complications such as tracheomalacia, spinal cord compression, cervical instability, and hydrocephalus. Despite the lack of existing literature on the medical management of individuals with dual dysplasia diagnoses, these cases underscore the importance of multidisciplinary care involving genetics, neurosurgery, orthopaedics, pulmonology, otolaryngology, craniofacial plastic surgery, and speech therapy.[9]

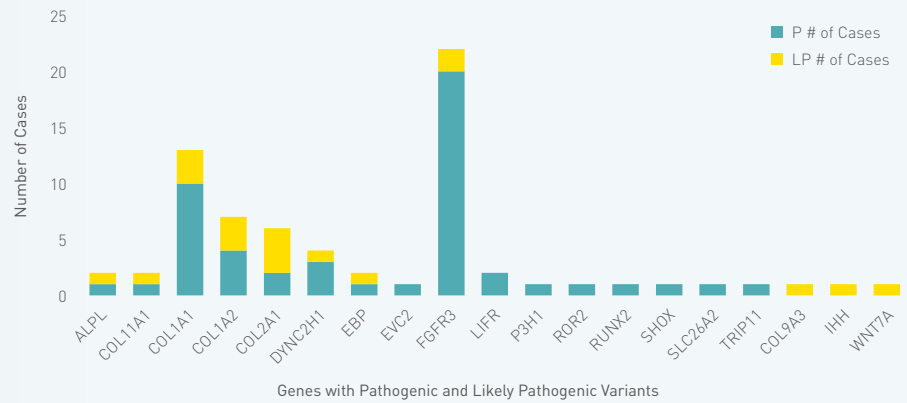
The successful management of these cases challenges the historically poor prognosis associated with double heterozygosity. The children have surpassed previous expectations and are thriving under specialised medical care. This study highlights the necessity of updated prenatal counselling protocols that incorporate the possibility of life-sustaining interventions and the value of specialised care from experienced providers in managing rare dysplasia diagnoses. By acknowledging the potential for positive outcomes and providing comprehensive support, healthcare professionals can better guide parents facing similar diagnoses, offering hope and improving the quality of care for affected individuals.[9] ▶ [P814]

PRENATAL COUNSELLING IN SKELETAL DYSPLASIA

Skeletal dysplasia encompasses a spectrum of congenital conditions affecting bone and cartilage, stemming from genetic variations. Estimated incidence is 1 in every 5000 newborns and 5 in every 1000 pregnancies. Identification of prenatal skeletal dysplasia holds critical importance in facilitating family planning options, tailored perinatal care, delivery at specialised hospitals, psychological support, and informed decision-making involving termination of pregnancy. The effective management of prenatal testing via genetic counsellors or medical geneticists are pivotal in aiding families to comprehend outcomes and make informed decisions.[10]

Shaw *et al.* presents a retrospective analysis of prenatal skeletal dysplasia panel cases conducted at a commercial laboratory between October 10, 2018, and August 2, 2023. The panel included 177 genes with associations to a range of skeletal dysplasia phenotypes.[10] 142 skeletal dysplasia panels were completed on prenatal specimens. 69 cases were positive, yielding a 48.2% positivity rate for diagnostic results consistent with skeletal dysplasia; 51 of these cases were pathogenic and 18 were likely pathogenic. A total of 19

Genes with pathogenic and likely pathogenic variants identified[10]



Shaw J, *et al.* [P779]

unique diagnostic genes were discovered, eight of which are known to lead to lethal forms of skeletal dysplasia (*COL1A1, COL1A2, EBP, LIFR, FGFR3, SLC26A2, TRIP11,* and *DLL3*). These findings underscore the necessity of offering prenatal testing options when abnormal ultrasound findings are present, as many skeletal dysplasia cases are hypothesised to be lethal either in the prenatal or perinatal period. However, termination of affected pregnancies, while an option for some individuals, may present logistical challenges depending on gestational age and legal considerations.[10]

Overall, the findings support the need for comprehensive prenatal care and informed decision-making processes for families affected by skeletal dysplasia. By providing access to prenatal testing and genetic counselling, healthcare professionals can better support patients and promote optimal outcomes for both mothers and newborns.[10] [P779]

LIST OF ABBREVIATIONS

ACH – achondroplasia

AGV – annualised growth velocity

FGFR3 – fibroblast growth factor receptor 3

HRQoL – health-related quality of life

OLE – open label extension

QoLISSY – Quality of Life in Short Stature Youth

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