Clinical Utility of a Sponsored, No-cost Skeletal Dysplasia Gene Panel Testing Program: Results from 850 Tests

Guillermo Seratti[1], Vikram Pansare[1], Tiffany Yar Pang[1], Emanuela Izzo[1], William Mackenzie[2], Cathleen Raggio[3], Klane White[4], Rebecca Truty[5], Britt Johnson[5], Swaroop Aradhya[5]

[1]BioMarin Pharmaceutical Inc., Novato, CA; [2]Nemours Alfred I. duPont Hospital for Children, Wilmington, DE; [3]Hospital for Special Surgery, Uniondale, NY; [4]Seattle Children's Hospital, Seattle, WA; [5]Invitae, San Francisco, CA

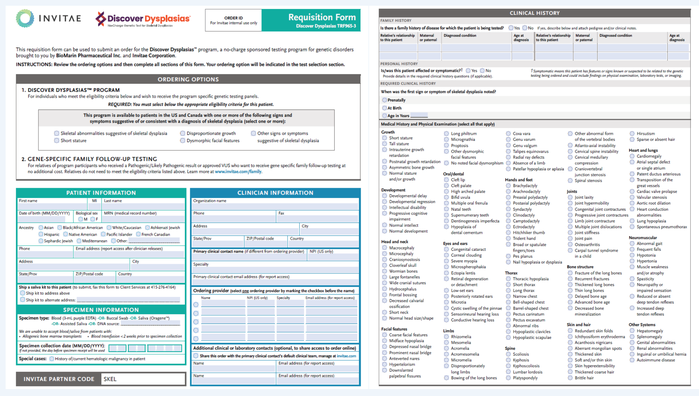
Introduction

- Rare diseases, such as mucopolysaccharidosis IVA (MPS IVA; Morquio A syndrome) and mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome), are often misdiagnosed as another type of skeletal dysplasia (SD) or may go undiagnosed for extended periods, potentially resulting in delayed intervention and irreversible disease progression[1-3]
- The Discover Dysplasias™ program provides a sponsored, no-cost, focused SD gene panel to patients suspected of having a skeletal dysplasia with the goal of achieving timely diagnoses[4]
- The program uses a gene panel comprising 109 genes associated with SD, as well as MPS disorders that are not typically included in clinically available SD panels
- Reflex biochemical enzyme testing is offered for cases in which molecular results for MPS genes are inconclusive
- Genetic counseling is provided as part of the program to help clinicians, patients and their families understand the results

Methods

- Program design, including gene selection, was based on recommendations from a multi-specialty advisory board held in June 2019
- Patients eligible for testing through the program were based in the US and had one or more of the following: skeletal abnormalities suggestive of SD, short stature, disproportionate growth, dysmorphic facial features or other signs or symptoms suggestive of SD **(Figure 1)**

Figure 1. Discover Dysplasias™ Requisition Form



https://discoverdysplasias.com/wp-content/themes/Dysplasias/pdf/Discover-Dysplasias-Requisition-Form-US-Canada.pdf

- Variants were classified according to ACMG standards[5]:
  - Pathogenic (PATH), Likely Pathogenic (LPATH), Variant of Uncertain Significance (VUS), Benign (BEN), Likely Benign (LBEN)
- Molecular diagnosis (MDx) was defined as:
  - 1 variant in a gene (PATH or LPATH) with autosomal dominant inheritance, X-linked dominant, X-linked recessive (male) *OR*
  - 2 variants (PATH or LPATH) in a gene with autosomal recessive inheritance

Results

- A total of 850 tests were conducted through the Discover Dysplasias program between December 2019 and August 2020
- The mean (SD) age at time of testing was 11.9 (15.3) years; median: 7 years; range: 0-90 years **(Figure 2)**
- Initial symptom onset was noted prenatally for 23% of patients, at birth for 33%, and after birth for 44% **(Figure 3)**
  - Median age at symptom onset among patients presenting after birth was 5 years

Figure 2. Age at Testing

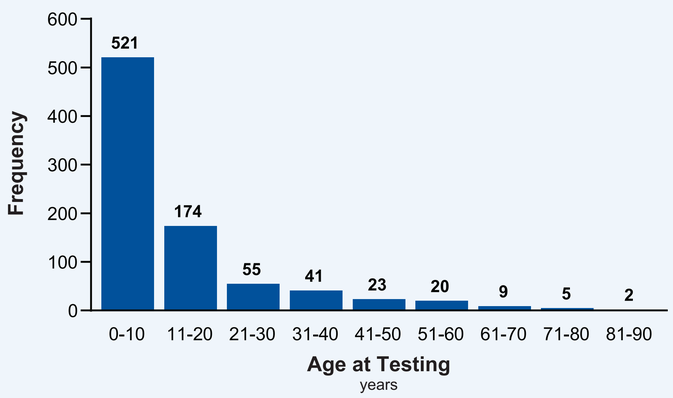
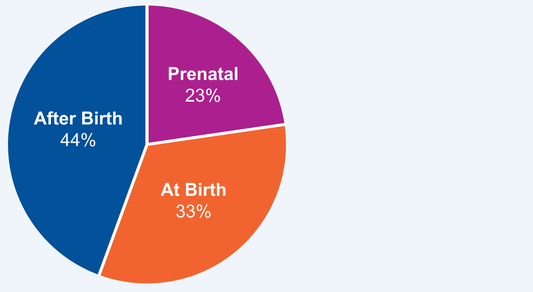


Table 1. Frequent Molecular Diagnoses and Management Implications

Gene	Inheritance	Conditions	Current or Future Pharmacologic Therapies (approved disease-modifying treatments and clinical trial enrollment opportunities)
FGFR3	AD	Achondroplasia; Camptodactyly, tall stature, and hearing loss (CATSHL) syndrome; Crouzon syndrome with acanthosis nigricans; Hypochondroplasia; Muenke syndrome; Severe achondroplasia with developmental delay and acanthosis nigricans (SADD); Thanatophoric dysplasia	Observational and interventional clinical trials open for enrollment[6]
COL2A1	AD	Achondrogenesis type II; Stickler syndrome, type I; Multiple forms of dysplasia, including Kniest dysplasia, Platyspondylic lethal skeletal dysplasia Torrance type, and Spondyloepimetaphyseal dysplasia; Spondyloepiphyseal dysplasia congenita	Observational clinical trial open for enrollment[6]
COMP	AD	Multiple epiphyseal dysplasia (MED); Pseudoachondroplasia (PSACH)	Interventional clinical trials open for enrollment[6]
RUNX2	AD	Cleidocranial dysplasia (CCD); Metaphyseal dysplasia with maxillary hypoplasia and brachydactyly	No disease modifying treatment available[7]
LMX1B	AD	Nail-patella syndrome (NPS)	No disease modifying treatment available[7]
ALPL	AD	Hypophosphatasia	Asfotase alfa (Strensiq) approved in US for the treatment of perinatal/infantile- and juvenile-onset hypophosphatasia and the EU for long-term enzyme replacement therapy in people with paediatric-onset hypophosphatasia to treat bone manifestations of the disease[8,9]
MATN3	AD	Multiple epiphyseal dysplasia (MED); Spondyloepimetaphyseal dysplasia (SEMD)	No disease modifying treatment available[7]
SLC26A2	AR	Achondrogenesis, type IB (ACG1B); Atelosteogenesis type 2 (AO2); Diastrophic dysplasia (DTD); Multiple epiphyseal dysplasia 4 (EDM4)	No disease modifying treatment available[7]
COL10A1	AD	Metaphyseal chondrodysplasia, Schmid type (MCDS)	No disease modifying treatment available[7]
FLNB	AD	Atelosteogenesis type I (AO1); Atelosteogenesis type III (AOIII); Boomerang dysplasia; Piepkorn osteochondrodysplasia; Larsen syndrome; Spondylocarpotarsal synostosis syndrome (SCT)	No disease modifying treatment available[7]
GDF5	AD	Brachydactyly and symphalangism, Grebe syndrome, Acromesomelic dysplasia, Hunter-Thompson type (AMDH), Du Pan syndrome	No disease modifying treatment available[7]
LEMD3	AD	Buschke-Ollendorff syndrome (BOS); Osteopoikilosis, with or without melorheostosis	No disease modifying treatment available[7]
TRPV4	AD	Skeletal dysplasias, including Spondylometaphyseal dysplasia, Kozlowski type	No disease modifying treatment available[7]
FBN1	AD	Marfan syndrome; Weill-Marchesani syndrome; Geleophysic dysplasia; Acromicric dysplasia	Interventional clinical trials open for enrollment[6]
SOX9	AD	Campomelic dysplasia	No disease modifying treatment available[7]
COL11A1	AD	Stickler syndrome; Marshall syndrome; Fibrochondrogenesis	Observational and interventional clinical trials open for enrollment[6]
DLL3	AR	Spondylocostal dysostosis	No disease modifying treatment available[7]
FLNA	XLD	Periventricular heterotopia with or without Ehlers-Danlos features; Otopalatodigital spectrum disorders; Frontometaphyseal dysplasia; Melnick-Needles syndrome; Terminal osseous dysplasia	No disease modifying treatment available[7]
GALNS	AR	Mucopolysaccharidosis type IVA (MPS IVA; Morquio A)	Elosulfase alfa (Vimizim) indicated for patients with MPS IVA[10,11]; Observational clinical trials open for enrollment[6]
MESP2	AR	Spondylocostal dysostosis	No disease modifying treatment available[7]

Figure 3. Timing of Symptom Onset



- A genetic diagnosis was established for 210 patients (35 genes), for an overall molecular diagnostic yield of 24.7% **(Figure 4)**
  - One MPS VI patient and two MPS IVA patients were identified, where the latter were confirmed by reflex enzyme testing
- Several of the conditions diagnosed most freqently (2 or more molecular diagnoses) have an approved disease-modifying treatment available or opportunity for clinical trial enrollment **(Table 1)**

Figure 4. Molecular Diagnosis Genes

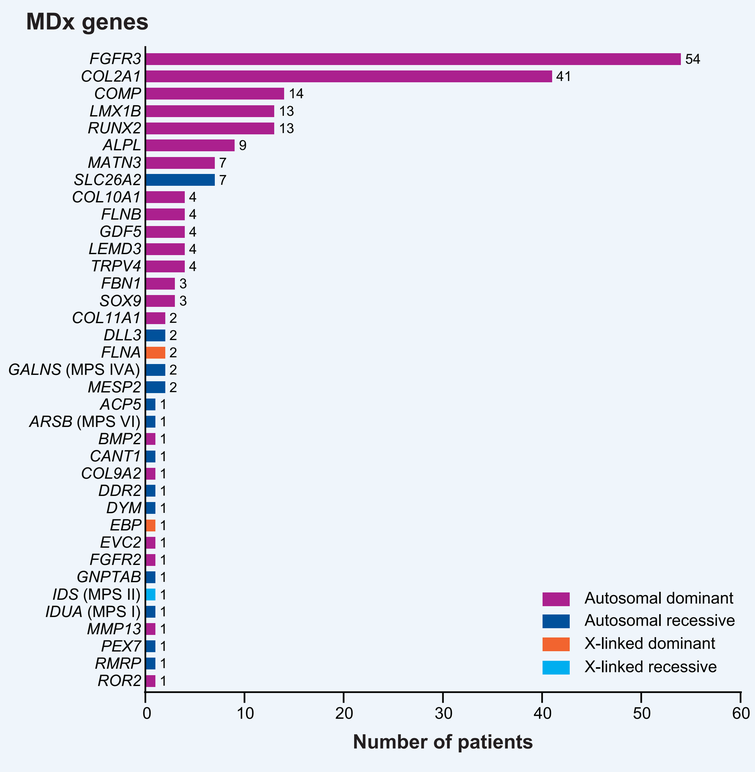
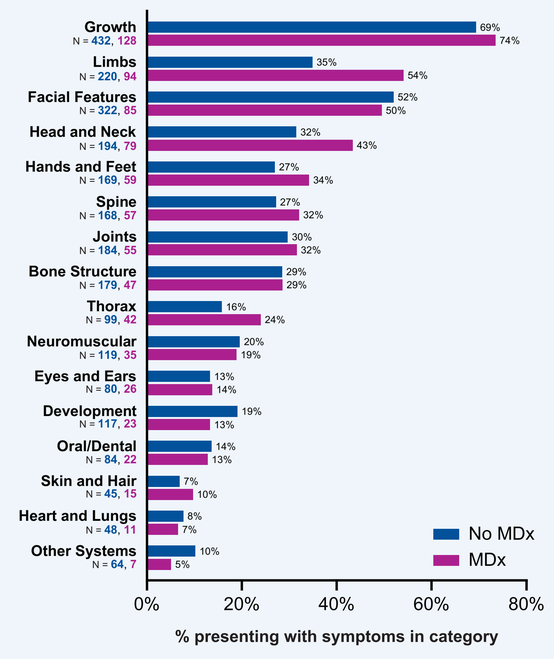


Figure 5. Clinical Presentation by Outcome Group



N's represent number of patients with available clinical data in each category

- Clinical presentation data was available for 792 patients (93%)
  - Compared with patients for whom no molecular diagnosis was determined, patients receiving a molecular diagnosis were more likely to have clinical features relating to limbs (54.1% vs 34.9%), head and neck (43.4% vs 31.5%), and thorax (24.0% vs 15.8%) **(Figure 5)**

Conclusions

- Use of a gene panel program, with genetic counseling support and MPS reflex enzyme testing as required, may help provide a timely end to the diagnostic journey of patients with skeletal dysplasias
- This targeted, multi-gene testing approach has clinical utility in identifying the genetic etiology of SD and may subsequently allow for disease-specific interventions and proactive treatment plans

Acknowledgements

The authors would like to thank Abigail Hunt (BioMarin) for poster graphic editing and design.

References

1. Wood TC et al. Diagnosing mucopolysaccharidosis IVA. *J Inherit Metab Dis.* 2013;36:293–307 **2.** Wood TC et al. Expert recommendations for the laboratory diagnosis of MPS VI. *Mol Genet Metab.* 2012;106:73-82. **3.** Choy B et al. Identifying the need for a multidisciplinary approach for early recognition of mucopolysaccharidosis VI (MPS VI). *Mol Genet Metab.* 2015; 115:41-47. **4.** Discover Dysplasias™. https://www.invitae.com/en/discover-dysplasias **5.** Richards S et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17(5):405. **6.** ClinicalTrials.gov. https://clinicaltrials.gov/ **7.** Adam MP et al. GeneReviews®. University of Washington, Seattle; 1993-2019. **8.** Strensiq (asfotase alfa) solution for subcutaneous injection. U.S. Food and Drug Administration. Accessed 15 January 2021. **9.** Strensiq EPAR. European Medicines Agency (EMA). Accessed 15 January 2021. **10.** Vimizim (elosulfase alfa) Package Insert. U.S. Food and Drug Administration. Accessed 15 January 2021. **11.** Vimizim EPAR. European Medicines Agency (EMA). Accessed 15 January 2021.