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

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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 progression¹⁻³

- 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 diagnoses⁴
- 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,

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 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 |

patients and their families understand the results

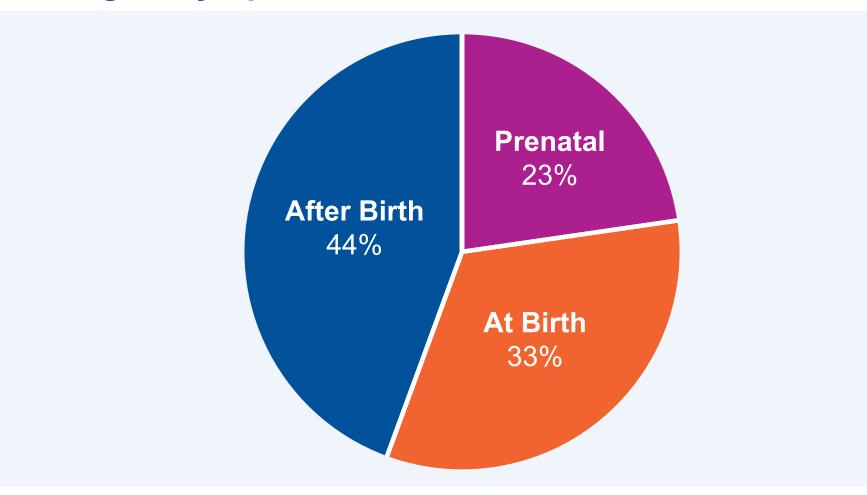
Methods

- 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

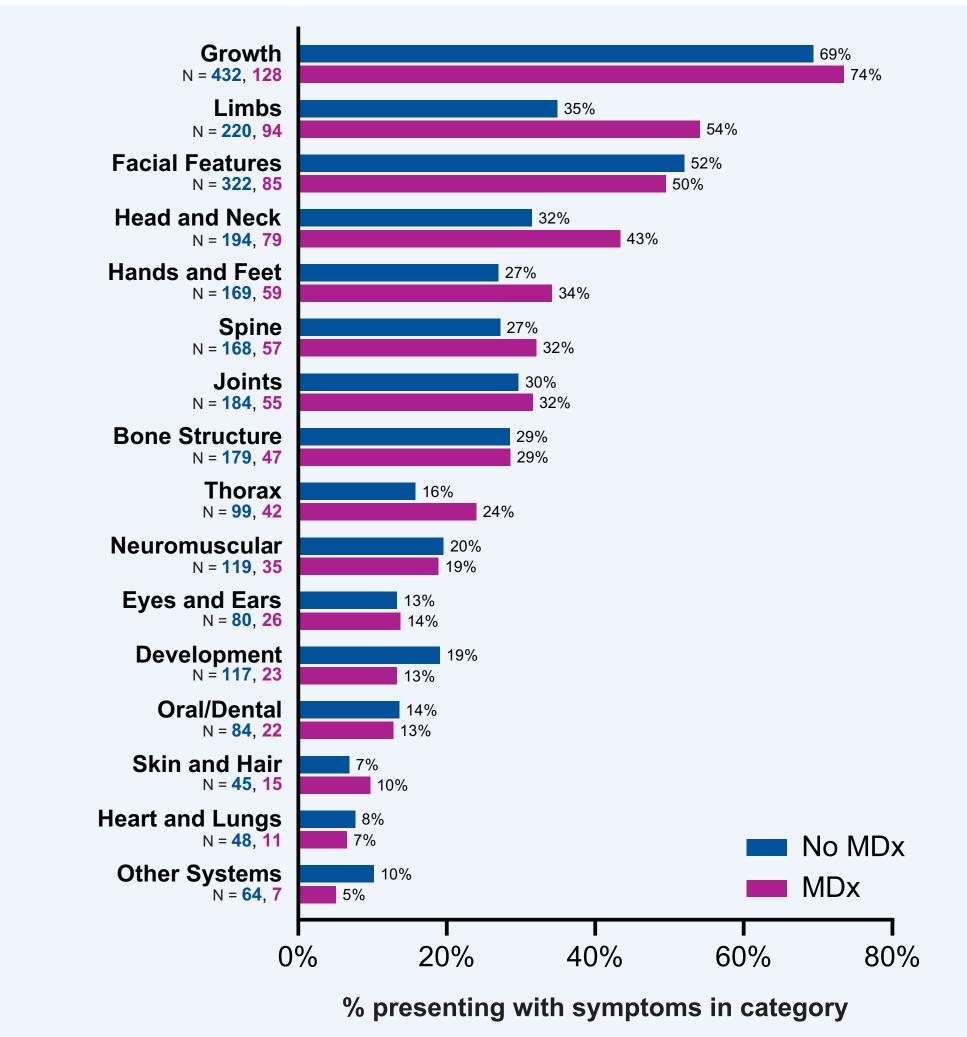
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| | Discover Dysplasias | For Invitae internal use | amb | | FAMILY HISTORY | | | | | | | | |
| F | No-Charge Genetic Test for Skelletal Dysplasias | | D | Discover Dysplasias TRF965-3 | Is there a family histe | ory of disease | for which the patient is being tested? | ○Yes ○No | If yes, describe below a | and attach pedigree | e and/or clinical no | otes. | |
| | | | | | Relative's relationship to this patient | Maternal or paternal | Diagnosed condition | Age at diagnosis | Relative's relationship to this patient | Maternal Di or paternal | Diagnosed condition | n | Age dia |
| requisition form can be use | ed to submit an order for the Discover Dysplasi | as™ program, a no-charge s | ponsored testing prog | ram for genetic disorders | | | | | | | | | |
| ght to you by BioMarin Pha | irmaceutical Inc. and Invitae Corporation. | | | - | | | | | | | | | |
| RUCTIONS: Review the orde | ering options and then complete all sections of th | is form. Your ordering option | will be indicated in the | test selection section. | PERSONAL HISTOR | | | | | | | | |
| | | | | | | | nptomatic?† 🔘 Yes 🔘 No I history questions (if applicable). | | Symptomatic means this p sting being ordered and cou | | | | |
| | ORDERING | OPTIONS | | | REQUIRED CLINICA | | | | | | | | |
| DISCOVER DYSPLASIAS | ™ PROGRAM | | | | When was the first | sign or sympto | om of skeletal dysplasia noted? | | | | | | |
| For individuals who meet the eligibility criteria below and wish to receive the program specific genetic testing panels. | | | | | | • • • | | | | | | | |
| | REQUIRED: You must select below the ap | propriate eligibility criteria for | this patient. | | O Prenatally | | | | | | | | |
| т | his program is available to patients in the US and C | Canada with one or more of the | e following signs and | | Age in Years | | | | | | | | |
| | symptoms suggestive of or consistent with a diag | | | | | Physical Exa | mination (select all that apply) | | | | | | _ |
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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)

Figure 5. Clinical Presentation by Outcome Group



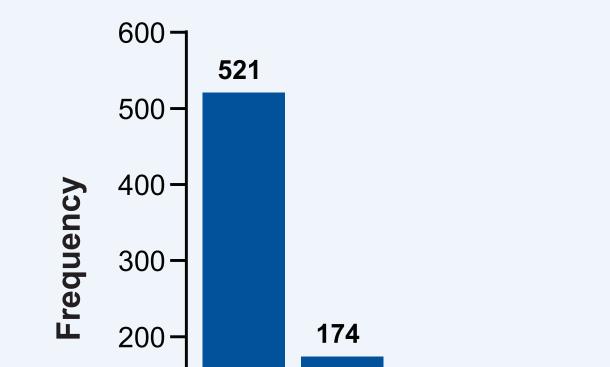
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- Variants were classified according to ACMG standards⁵:
- Pathogenic (PATH), Likely Pathogenic (LPATH), Variant of Uncertain Significance (VUS), Benign (BEN), Likely Benign (LBEN)
- Molecular diagnosis (MDx) was defined as:
- 1 variant in a gene (PATH 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

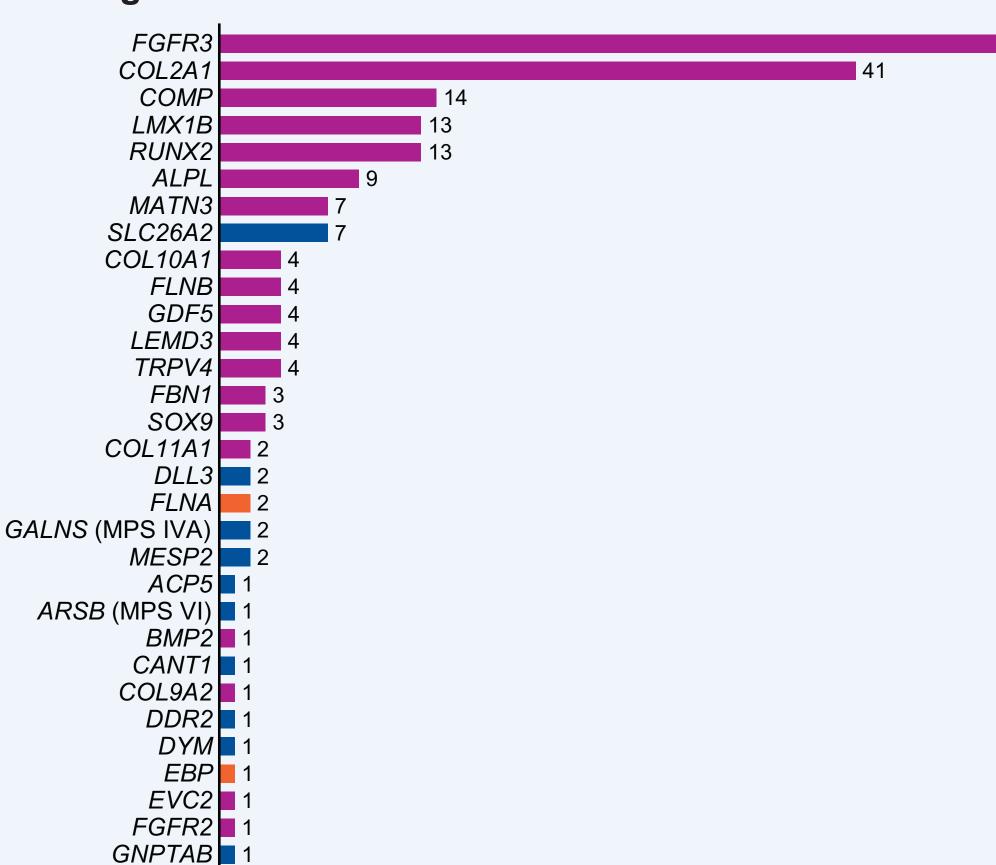
Figure 2. Age at Testing



- 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

MDx genes



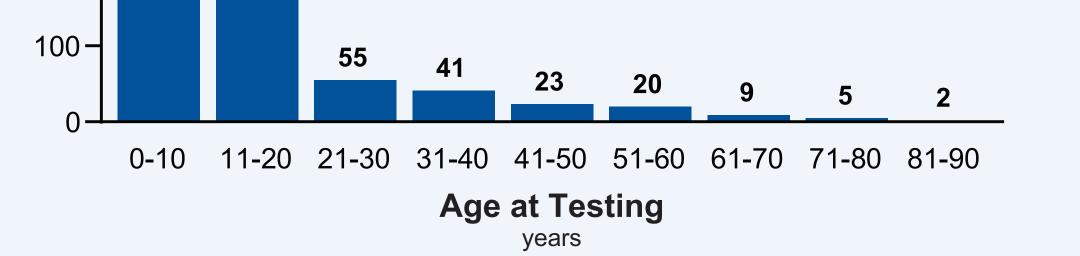
N's represent number of patients with available clinical data in each category

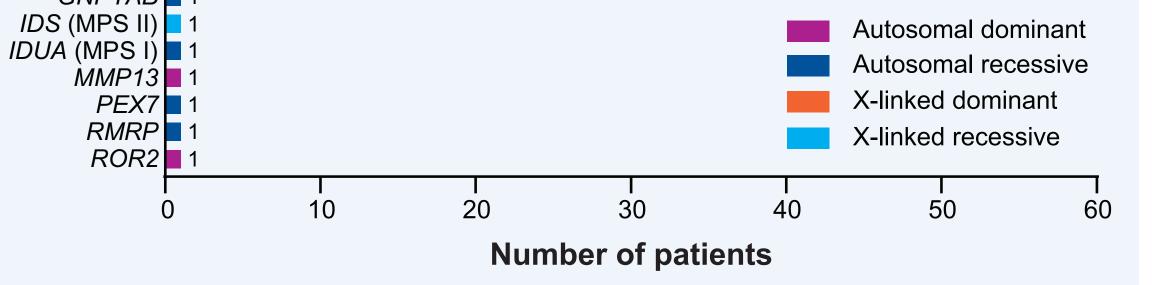
- Clinical presentation data was available for 792 patients (93%)
- Compared with patients for whom no molecular diagnosis was determined, patients receiving a molecular diagnosis were more likely to have clinical features relating to limbs (54.1% vs 34.9%), head and neck (43.4% vs 31.5%), and thorax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

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