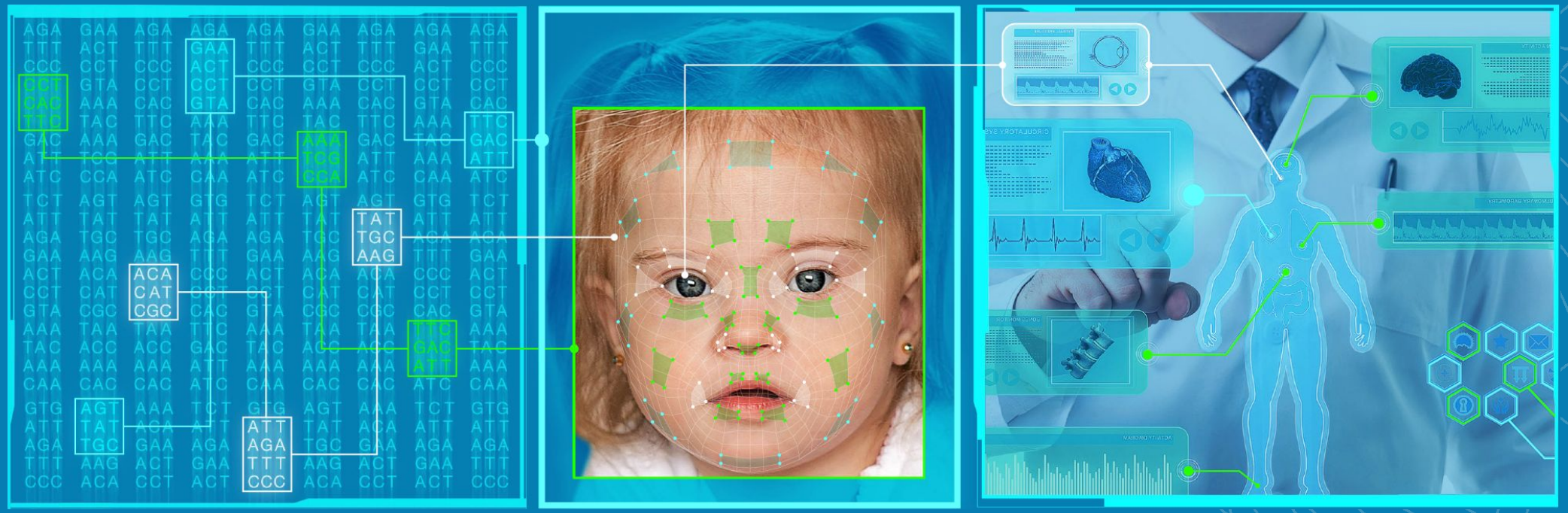


Next Generation Phenotyping using DeepGestalt in Clinic, Research and Variant Analysis

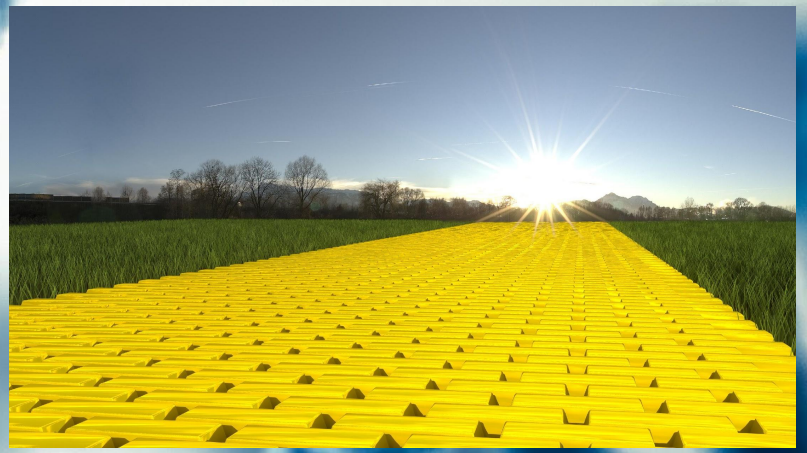
Yaron Gurovich

FACE2GENE

FACE2GENE

FACE2GENE

HNRNPH2



350 MILLION PEOPLE WORLDWIDE SUFFER FROM RARE DISEASES

(Global Genes, https://globalgenes.org/rare-diseases-facts-statistics/)

= 10M

280M

5600+

80 PERCENT OF RARE DISEASES ARE GENETIC

(Bavisetty S, et al. Emergence of pediatric rare diseases. Rare Diseases 2013, volume 1. Available at: http://www.tandfonline.com/doi/full/10.4161/rdis.23579)

7000+ RARE DISEASES HAVE BEEN DEFINED

(Global Genes. Rare diseases: facts and statistics, 2014. Available at: http://globalgenes.org/rare-diseases-facts-statistics)

= 100

FACE2GENE

Phenotype

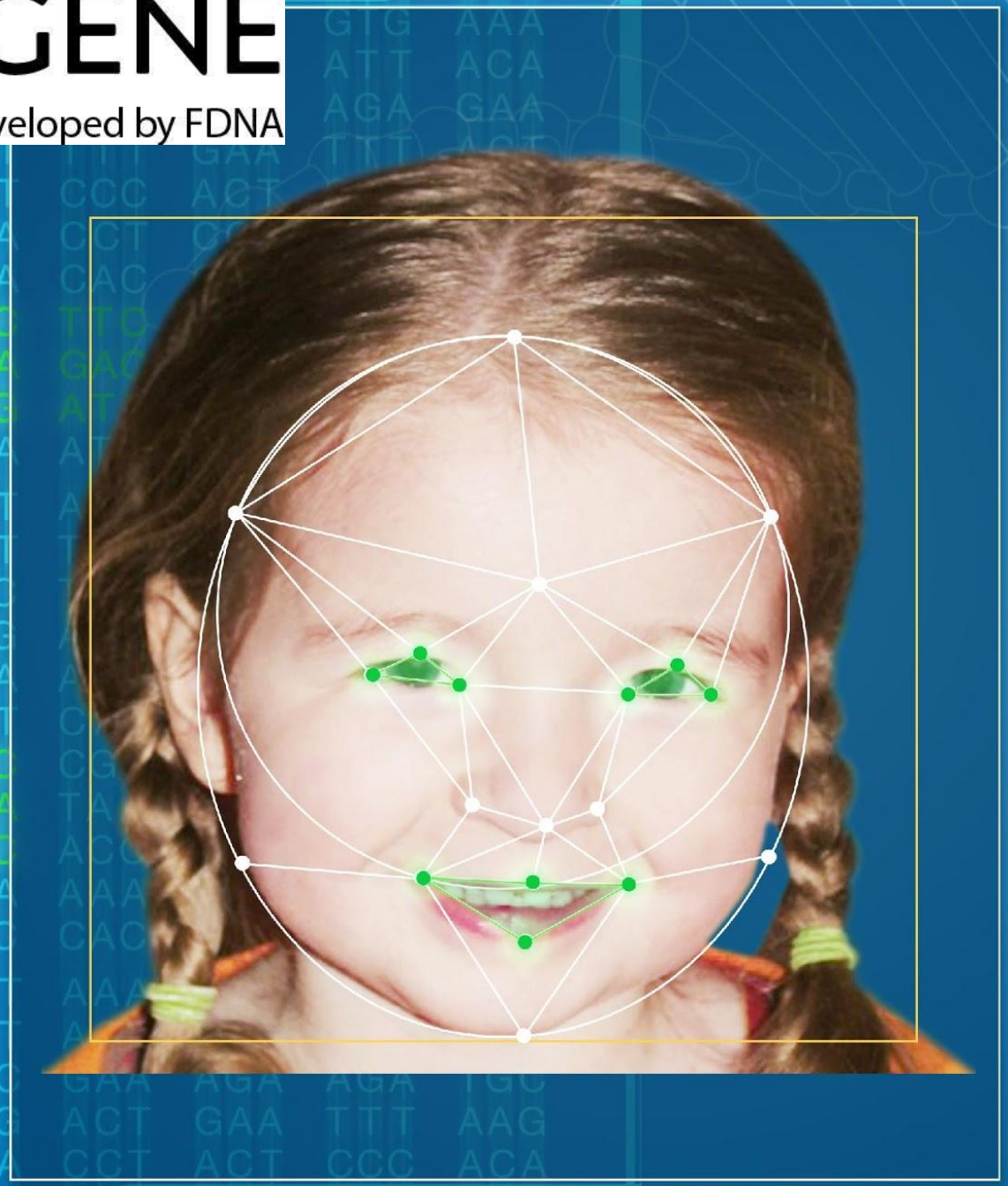
Phenotype

The set of **observable characteristics** of an individual resulting from the interaction of its **genotype** with the environment.

FACE2GENE

FACE2GENE

Developed by FDNA



SUGGESTED SYNDROMES (30)

HNRNPH2
OMIM: 190685
Gestalt
LOW | MED | HIGH
Feature

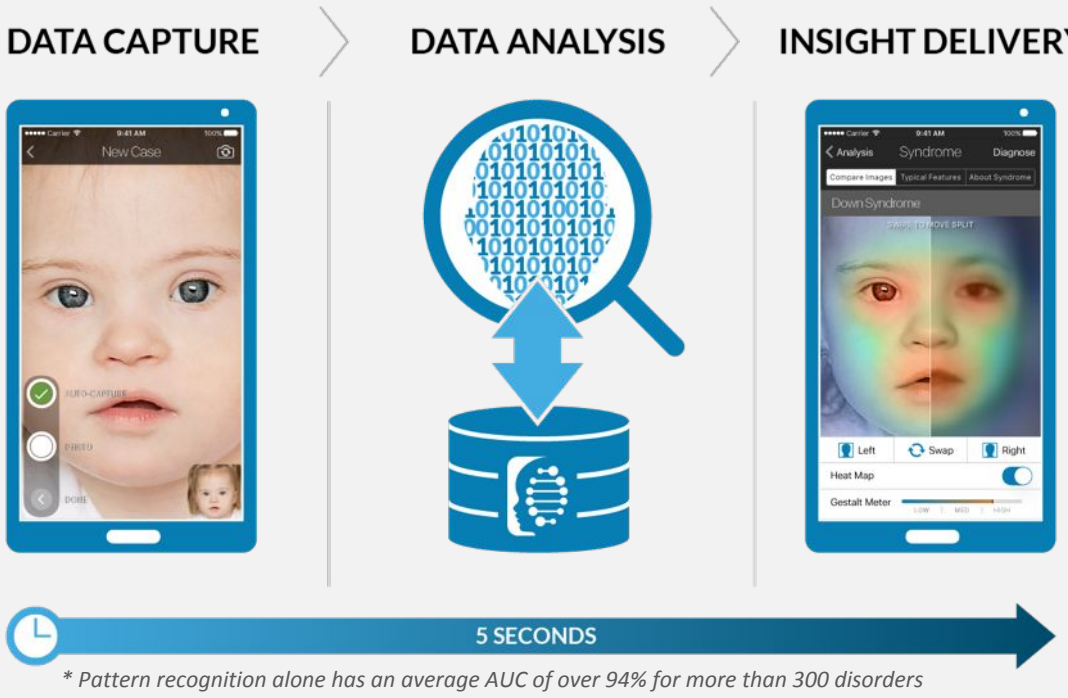
Branchiooculofacial Syndrome; BOFS
OMIM: 113620
Gestalt
LOW | MED | HIGH
Feature

Kaufman Oculocerebrofacial Syndrome; KOS
OMIM: 244450
Gestalt
LOW | MED | HIGH
Feature

Hutchinson-Gilford Progeria Syndrome; HGPS
OMIM: 176670
Gestalt
LOW | MED | HIGH
Feature

FACE2GENE | Accessible Phenotyping through Cloud

Face2Gene makes our Next-generation Phenotyping technologies accessible through the cloud on mobile devices and web browsers, allowing better and faster clinical evaluation of patients in real-time.



** Pattern recognition alone has an average AUC of over 94% for more than 300 disorders*

NBC NEWS — *"the latest medical technology that leverages the power of big data to make better diagnoses"*

WIRED — *"a breakthrough method of diagnosis based on facial recognition algorithms…the most promising to deliver AI's 50-year old promise to revolutionize medicine"*

FORTUNE — *"AI and deep learning could help doctors figure out a patient's disease simply by analyzing a face"*

STAT — *"[FDNA's] partnerships could contribute to precision medicine efforts or help companies develop new therapies for rare diseases."*

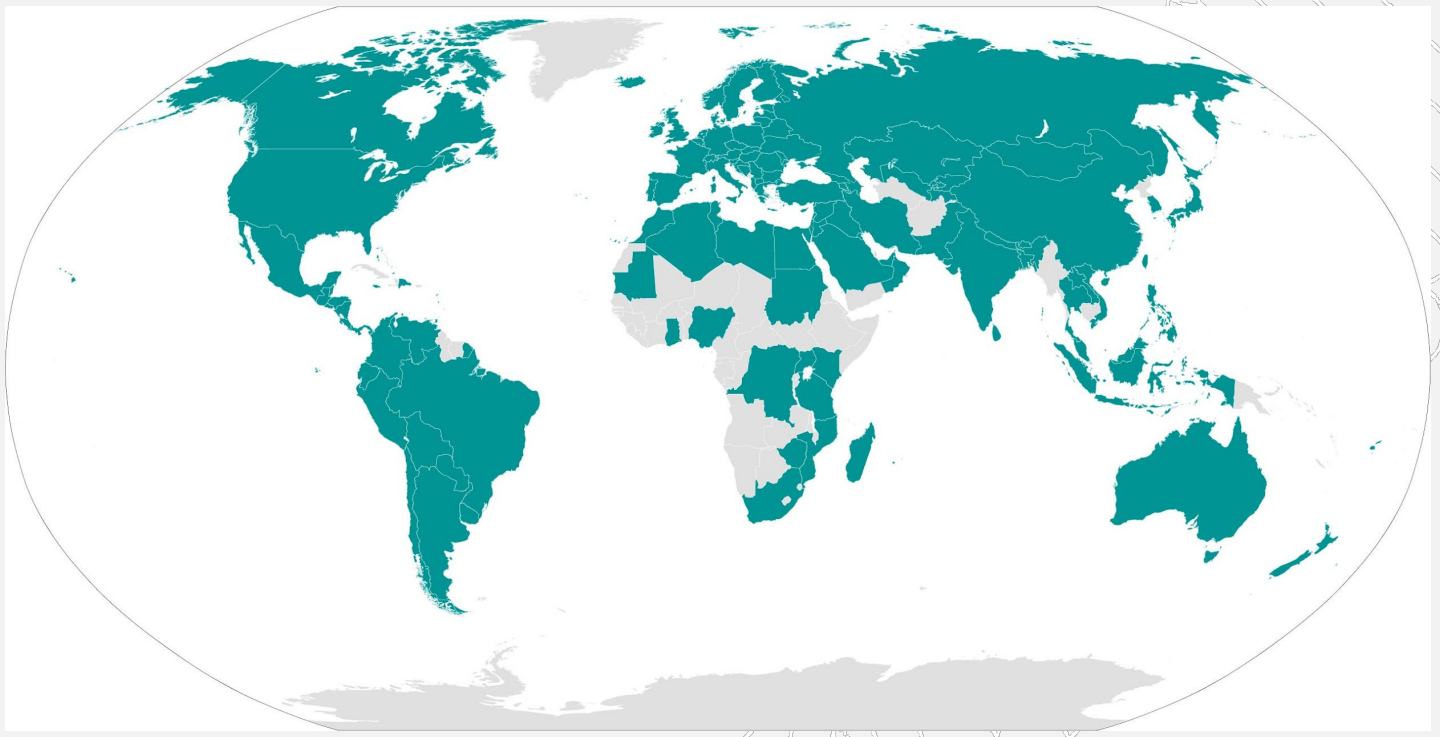
The Economist — *"[FDNA is] analyzing faces to provide automated diagnoses of rare genetic conditions... far earlier than would otherwise be possible"*

FDNA

Face2Gene on a Global Scale

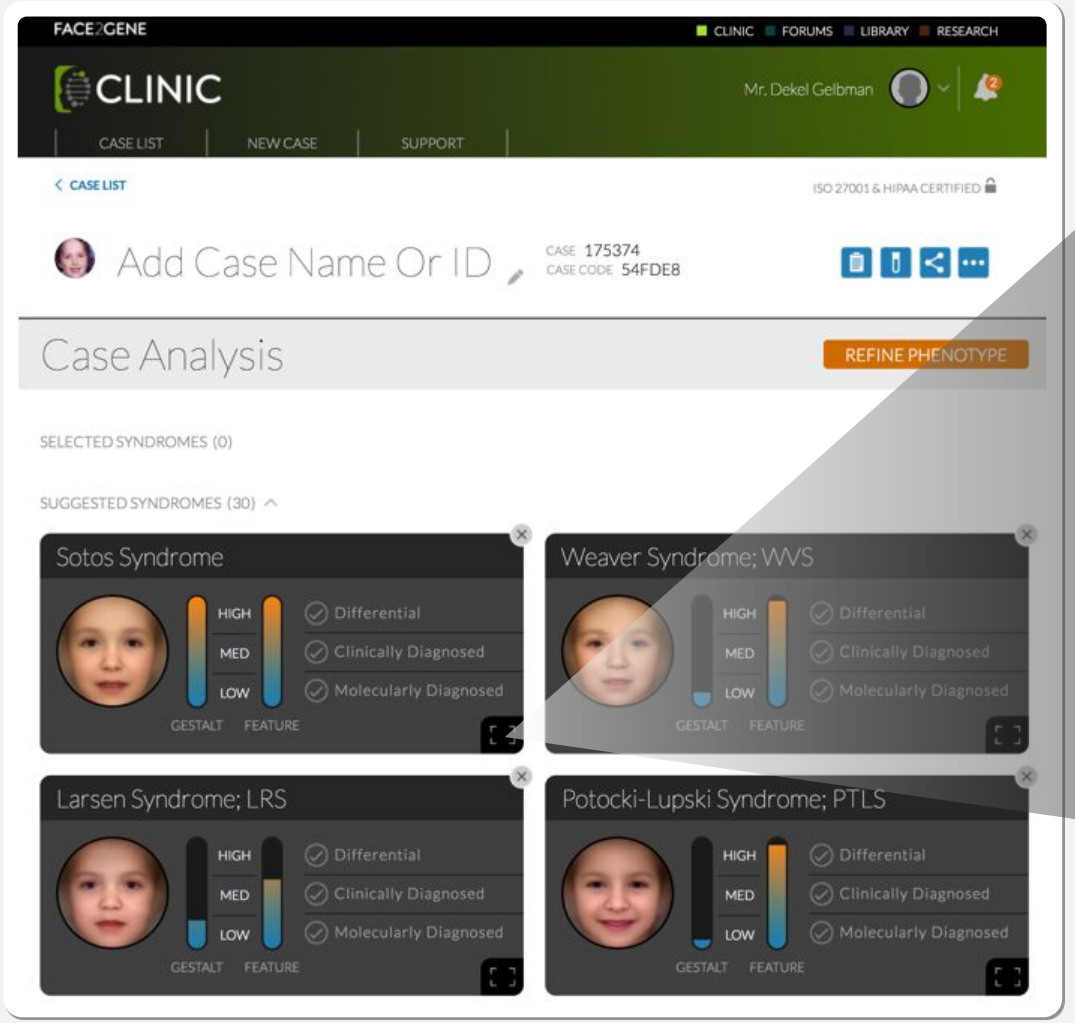
Face2Gene's user base is the largest network in the space of clinical genetics, facilitating data sharing

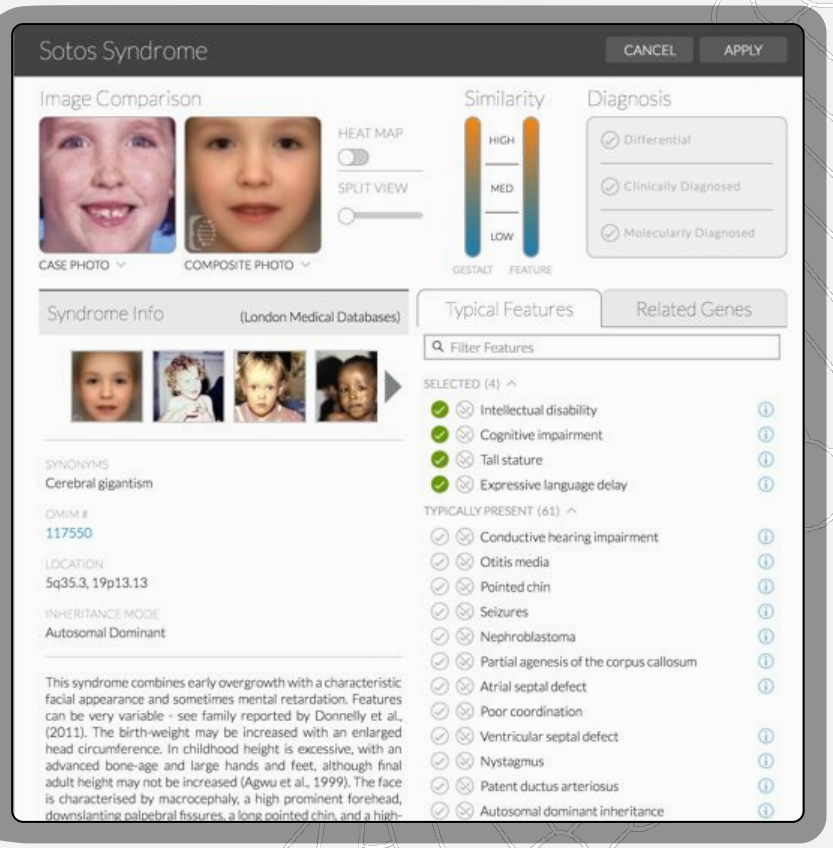
- **70%+ Clinical Geneticists Worldwide**
- **2,000+ Clinical and research sites**
- **130+ Countries**



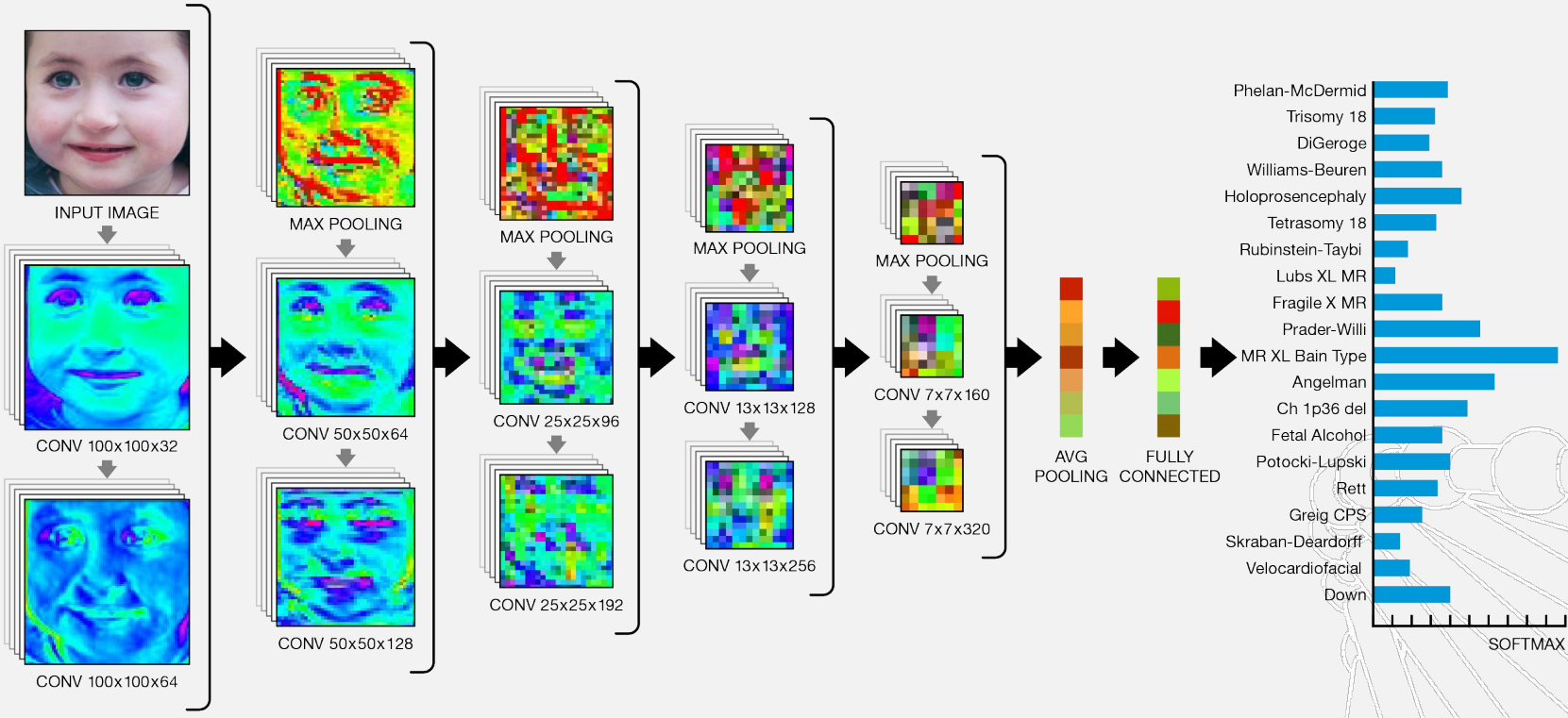
FDNA

Face2Gene CLINIC





DeepGestalt



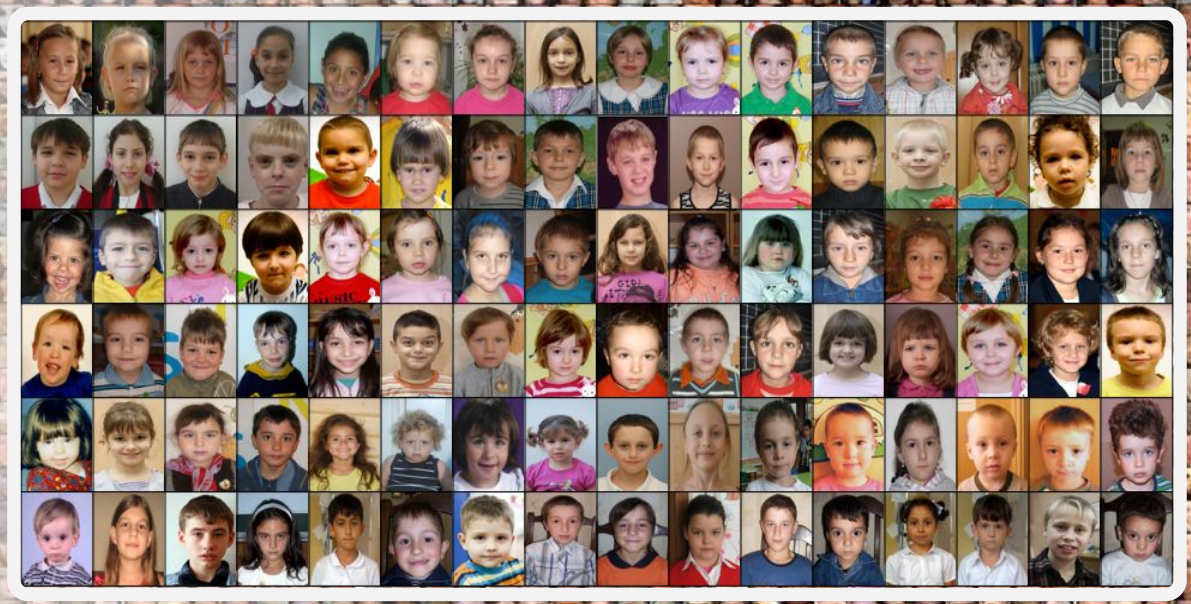
Using deep learning convolutional neural networks to analyze facial photos.

Gurovich et al. (Jan 2019) *Identifying rare genetic syndromes using deep learning*.

nature medicine

Database Challenges

- Small dataset
- Large variation in number of patients per disorder
- Ethnic diversity within disorders
- Need to support thousand of disorders



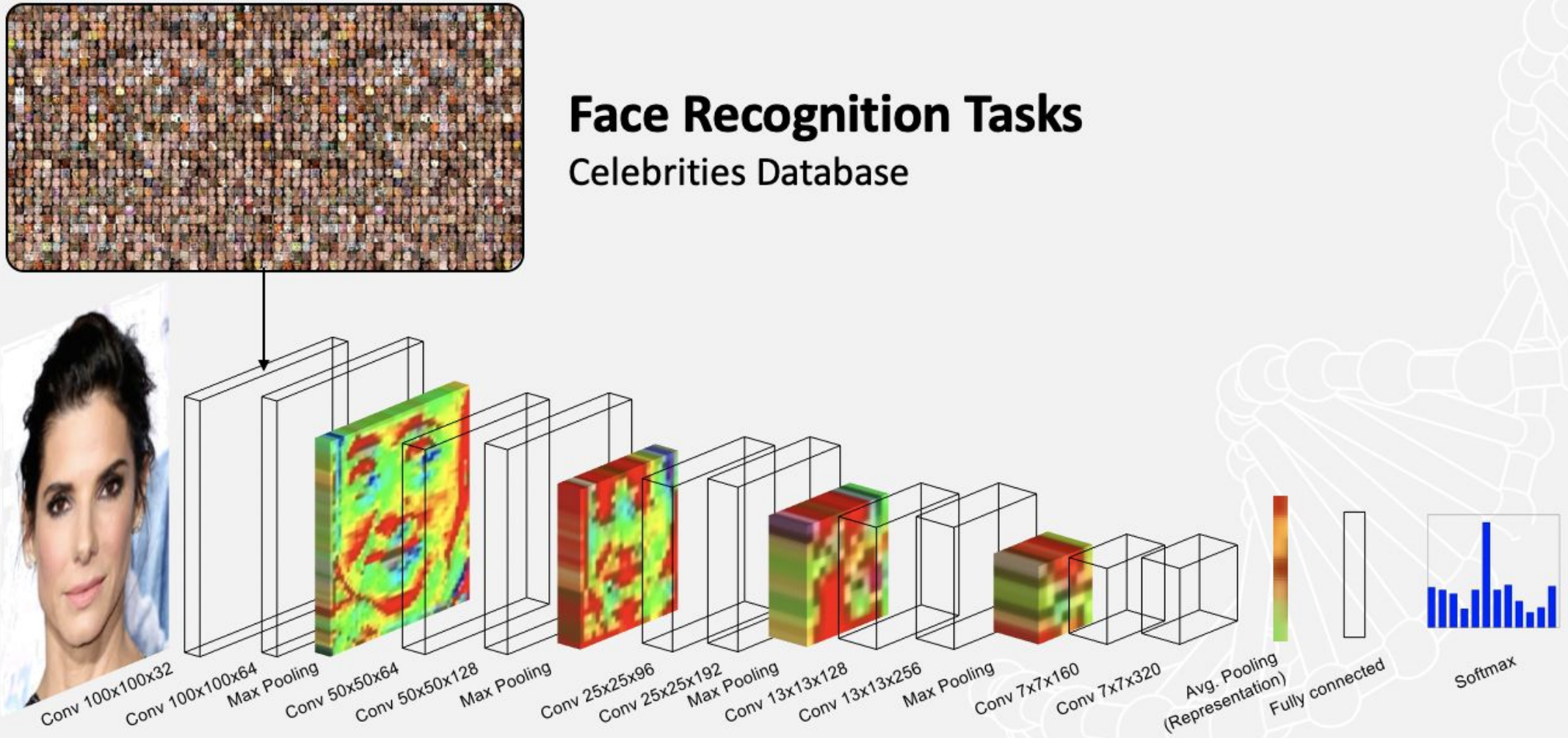
Types of Face Recognition

Intra-Person

Intra-Syndrome

FDNA

Initial Training

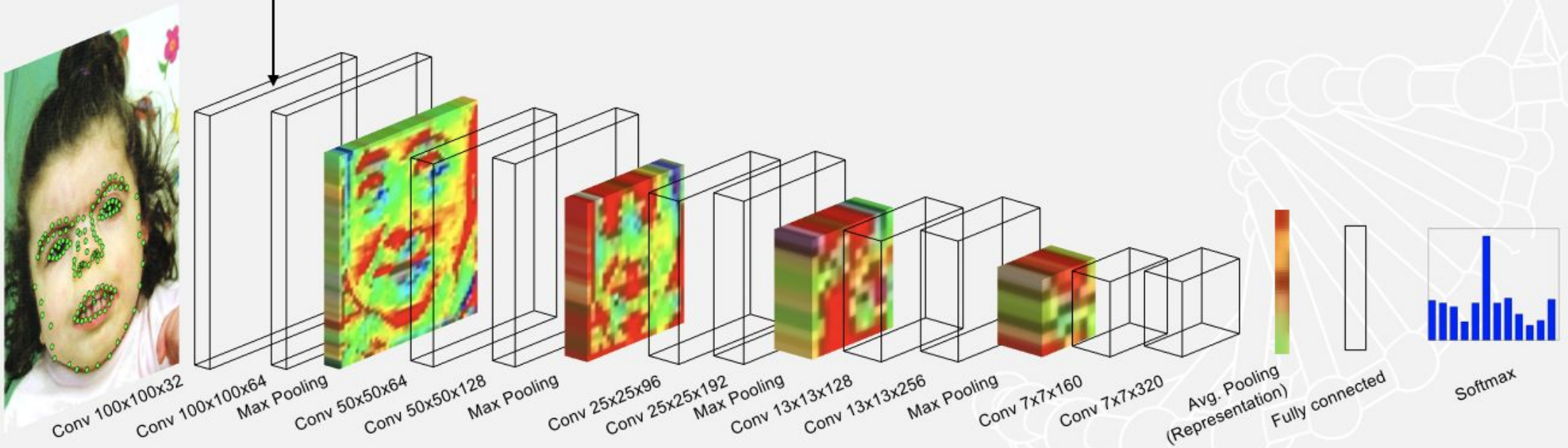


FDNA

Transfer Learning

Phenotype Recognition

Affected Children Database



FDNA

DeepGestalt - Results

Binary Cornelia de Lange Syndrome

Method	Accuracy % (95% CI)	P-Value
Rohatgi et al. (34)	75 (NA)	NA
Basel-Vanagaite et al. (5)	87 (NA)	0.22
DeepGestalt	**96.88 (90.1-100.1)**	**0.01**

Binary Angelman Syndrome

Method	Accuracy % (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)
Bird et al. (35)	71 (NA)	60 (NA)	78 (NA)
DeepGestalt	**92 (80-100)**	**80 (50-100)**	**100 (100-100)**

Multi-Class Gestalt Model

Facial Area	Clinical-Test (Top-10 Accuracy %)	Publications-Test (Top-10 Accuracy %)
Face Upper Half	82.0	82.4
Middle Face (Ear to Ear)	81.0	80.2
Face Lower Half	76.8	77.2
Full Face	88.2	87.5
Aggregated Model	**90.6**	**89.4**

Specialized Gestalt Model

KRAS PTPN11 RAF1 SOS1 RIT1

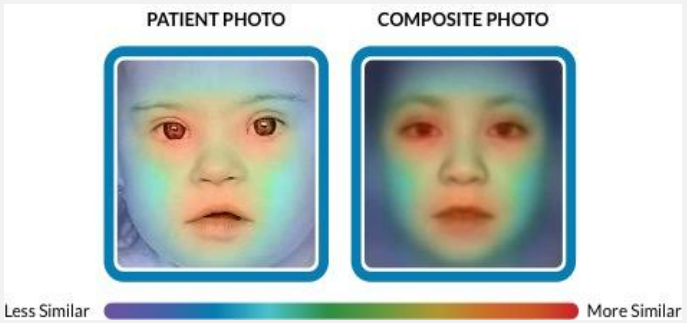
Top-1-accuracy of 64%, Random 20%

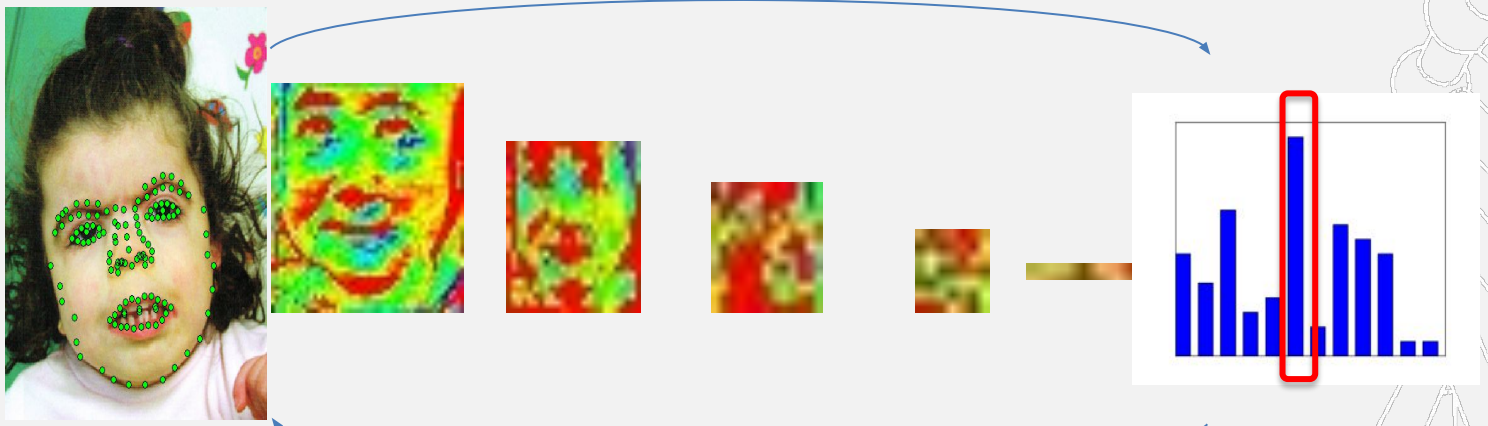
- *Source: Gurovich, Y. et al. DeepGestalt - Identifying Rare Genetic Syndromes Using Deep Learning. Nature Medicine.*

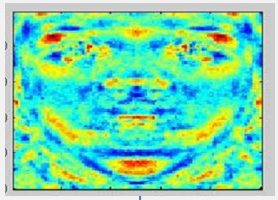
FDNA

Insights Delivery

Insights Delivery





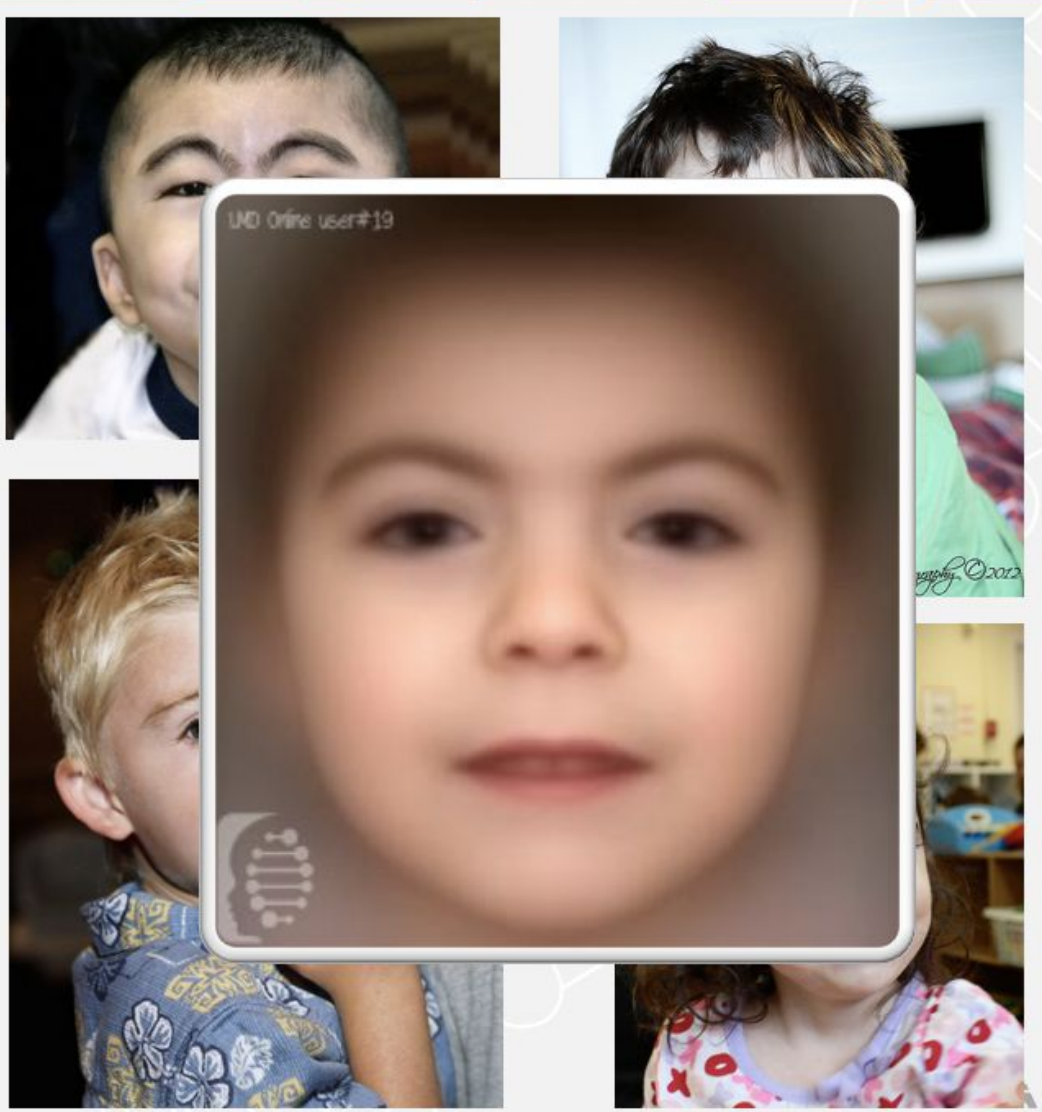


PRIOR KNOWLEDGE

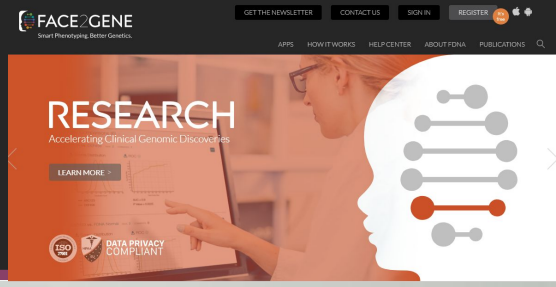
FDNA

Insights Delivery

Insights Delivery



Research Application



FACE2GENE CLINIC FORUMS LIBRARY LABS RESEARCH ACADEMY

RESEARCH

Dr. John Doe

PROJECT LIST | NEW PROJECT | SUPPORT

< PROJECT

HIPAA & EU DATA PRIVACY COMPLIANT

Project 123456

ACTIONS

Composite Photos

Dr. Kerry's cases
33 Cases | 33 Images

Unaffected controls
24 Cases | 24 Images

Other syndromes controls
20 Cases | 20 Images

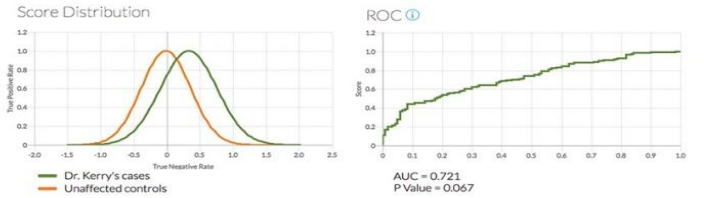
Multiclass Comparison

Confusion Matrix

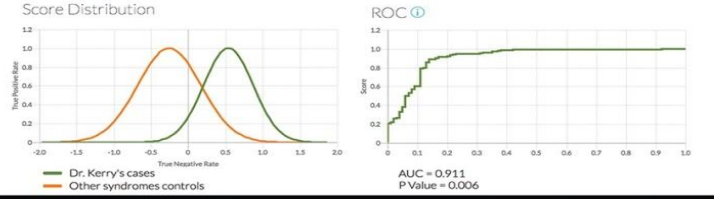
Actual \ Predicted	DR. KERRY'S CASES	UNAFFECTED CONTROLS	OTHER SYNDROMES CONTROLS
DR. KERRY'S CASES	0.71	0.23	0.06
UNAFFECTED CONTROLS	0.38	0.47	0.14

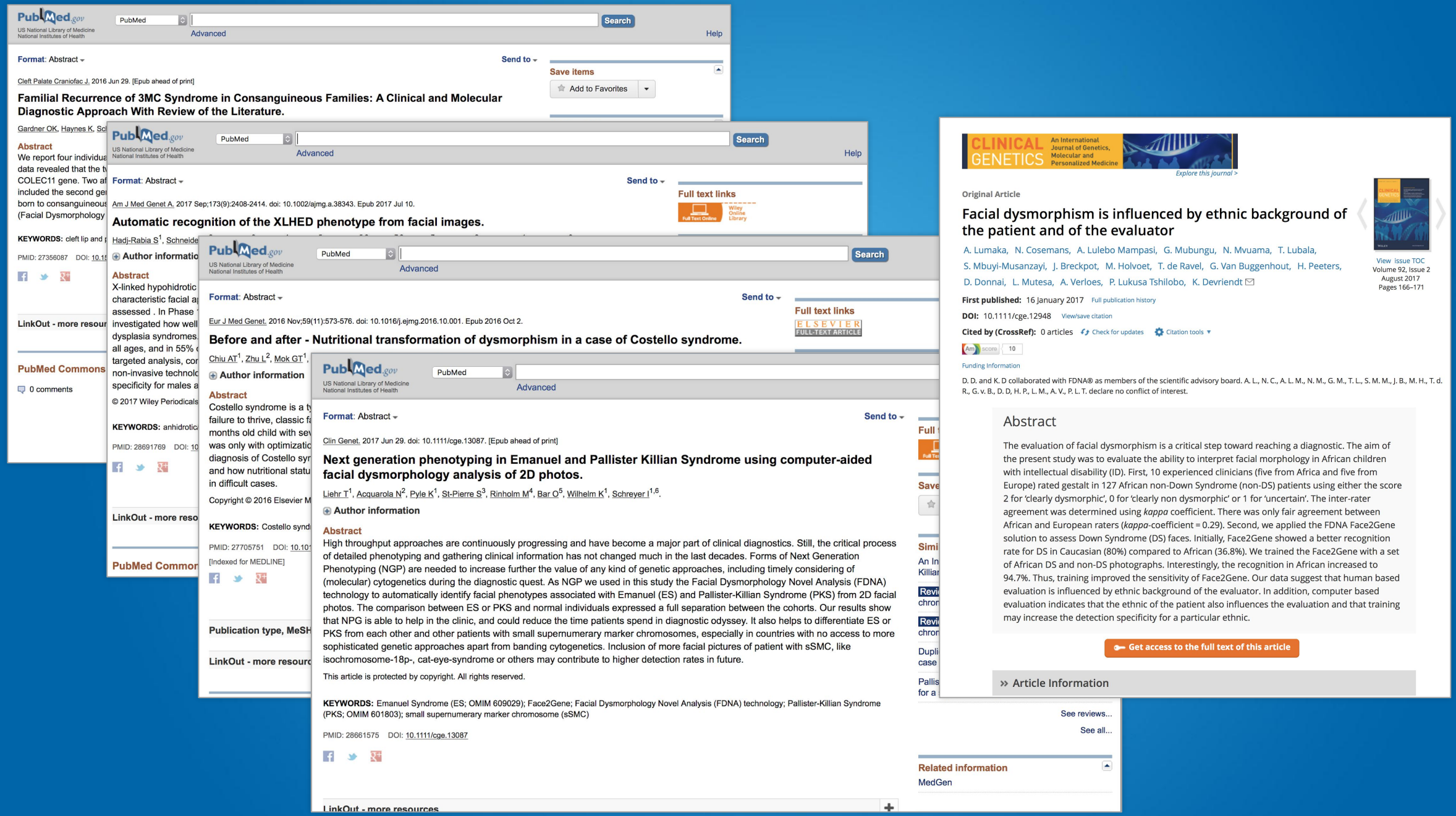
Binary Comparisons

Dr. Kerry's cases vs. Unaffected controls



Dr. Kerry's cases vs. Other syndromes controls





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Cleft Palate Craniofac J. 2016 Jun 29. [Epub ahead of print]
Familial Recurrence of 3MC Syndrome in Consanguineous Families: A Clinical and Molecular Diagnostic Approach With Review of the Literature.
Gardner OK, Haynes K, Sc
Abstract
We report four individua
data revealed that the t
COLEC11 gene. Two af
included the second ge
born to consanguineous
(Facial Dysmorphology
KEYWORDS: cleft lip and p
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Am J Med Genet A. 2017 Sep;173(9):2408-2414. doi: 10.1002/ajmg.a.38343. Epub 2017 Jul 10.
Automatic recognition of the XLHED phenotype from facial images.
Hadj-Rabia S[1], Schneide
Author informatio
Abstract
X-linked hypohidrotic
characteristic facial a
assessed . In Phase
investigated how well
dysplasia syndromes,
all ages, and in 55%
targeted analysis, cor
non-invasive technolo
specificity for males a
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PMID: 28691769 DOI: 10
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Eur J Med Genet. 2016 Nov;59(11):573-576. doi: 10.1016/j.ejmg.2016.10.001. Epub 2016 Oct 2.
Before and after - Nutritional transformation of dysmorphism in a case of Costello syndrome.
Chiu AT[1], Zhu L[2], Mok GT[1],
Author information
Abstract
Costello syndrome is a t
failure to thrive, classic f
months old child with se
was only with optimizatio
diagnosis of Costello syn
and how nutritional statu
in difficult cases.
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KEYWORDS: Costello syndr
PMID: 27705751 DOI: 10.10
[Indexed for MEDLINE]
Publication type, MeSH
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Clin Genet. 2017 Jun 29. doi: 10.1111/cge.13087. [Epub ahead of print]
Next generation phenotyping in Emanuel and Pallister Killian Syndrome using computer-aided facial dysmorphology analysis of 2D photos.
Liehr T[1], Acquarola N[2], Pyle K[1], St-Pierre S[3], Rinholm M[4], Bar O[5], Wilhelm K[1], Schreyer I[1,6].
Author information
Abstract
High throughput approaches are continuously progressing and have become a major part of clinical diagnostics. Still, the critical process of detailed phenotyping and gathering clinical information has not changed much in the last decades. Forms of Next Generation Phenotyping (NGP) are needed to increase further the value of any kind of genetic approaches, including timely considering of (molecular) cytogenetics during the diagnostic quest. As NGP we used in this study the Facial Dysmorphology Novel Analysis (FDNA) technology to automatically identify facial phenotypes associated with Emanuel (ES) and Pallister-Killian Syndrome (PKS) from 2D facial photos. The comparison between ES or PKS and normal individuals expressed a full separation between the cohorts. Our results show that NPG is able to help in the clinic, and could reduce the time patients spend in diagnostic odyssey. It also helps to differentiate ES or PKS from each other and other patients with small supernumerary marker chromosomes, especially in countries with no access to more sophisticated genetic approaches apart from banding cytogenetics. Inclusion of more facial pictures of patient with sSMC, like isochromosome-18p-, cat-eye-syndrome or others may contribute to higher detection rates in future.
This article is protected by copyright. All rights reserved.
KEYWORDS: Emanuel Syndrome (ES; OMIM 609029); Face2Gene; Facial Dysmorphology Novel Analysis (FDNA) technology; Pallister-Killian Syndrome (PKS; OMIM 601803); small supernumerary marker chromosome (sSMC)
PMID: 28661575 DOI: 10.1111/cge.13087
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Original Article
Facial dysmorphism is influenced by ethnic background of the patient and of the evaluator
A. Lumaka, N. Cosemans, A. Lulebo Mampasi, G. Mubungu, N. Mvuama, T. Lubala, S. Mbuyi-Musanzayi, J. Breckpot, M. Holvoet, T. de Ravel, G. Van Buggenhout, H. Peeters, D. Donnai, L. Mutesa, A. Verloes, P. Lukusa Tshilobo, K. Devriendt
View issue TOC
Volume 92, Issue 2
August 2017
Pages 166–171
First published: 16 January 2017 Full publication history
DOI: 10.1111/cge.12948 View/save citation
Cited by (CrossRef): 0 articles Check for updates Citation tools
Funding Information
D. D. and K. D collaborated with FDNA® as members of the scientific advisory board. A. L., N. C., A. L. M., N. M., G. M., T. L., S. M. M., J. B., M. H., T. d. R., G. v. B., D. D, H. P., L. M., A. V., P. L. T. declare no conflict of interest.
Abstract
The evaluation of facial dysmorphism is a critical step toward reaching a diagnostic. The aim of the present study was to evaluate the ability to interpret facial morphology in African children with intellectual disability (ID). First, 10 experienced clinicians (five from Africa and five from Europe) rated gestalt in 127 African non-Down Syndrome (non-DS) patients using either the score 2 for 'clearly dysmorphic', 0 for 'clearly non dysmorphic' or 1 for 'uncertain'. The inter-rater agreement was determined using *kappa* coefficient. There was only fair agreement between African and European raters (*kappa*-coefficient = 0.29). Second, we applied the FDNA Face2Gene solution to assess Down Syndrome (DS) faces. Initially, Face2Gene showed a better recognition rate for DS in Caucasian (80%) compared to African (36.8%). We trained the Face2Gene with a set of African DS and non-DS photographs. Interestingly, the recognition in African increased to 94.7%. Thus, training improved the sensitivity of Face2Gene. Our data suggest that human based evaluation is influenced by ethnic background of the evaluator. In addition, computer based evaluation indicates that the ethnic of the patient also influences the evaluation and that training may increase the detection specificity for a particular ethnic.
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Article Information

Research Application - Ethnic Diversity

- Vorravanpreecha N, Lertboonnum T, Rodjanadit R, Sriplienchan P, Rojnueangnit K, (2018) Studying Down syndrome recognition probabilities in Thai children with de-identified computer-aided facial analysis American Journal of Medical Genetics Am J Med Genet Part A. 2018;1–6. https://doi.org/10.1002/ajmg.a.40483

"We present a scientific basis for this novel tool, useful in the clinic where patients are of a different ethnicity unfamiliar to the evaluator. "

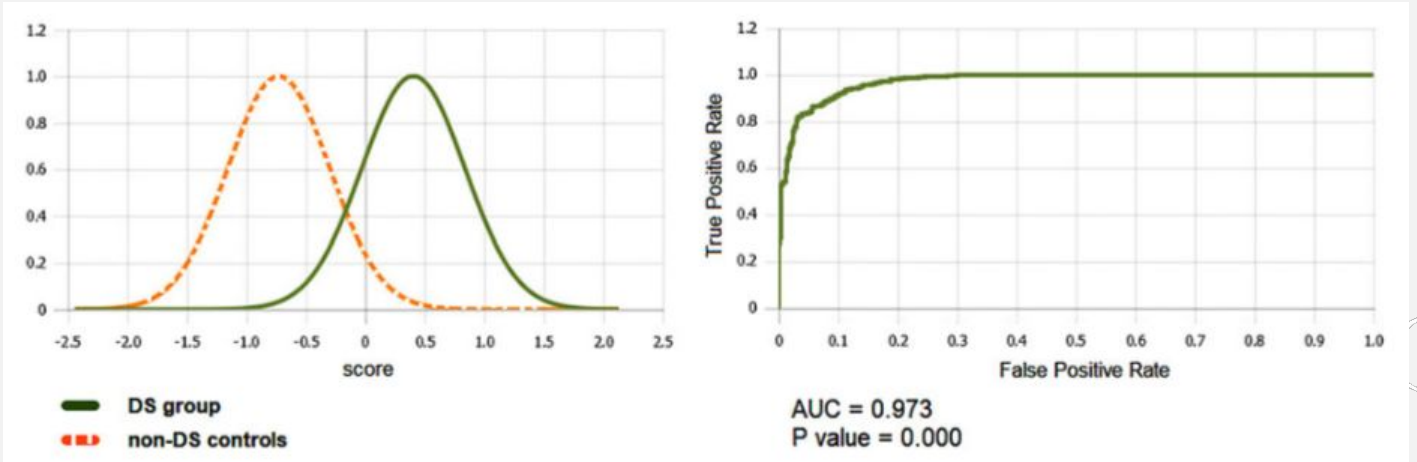

TABLE 1 Demographic data of study and control groups

	Children with DS (n = 30)	Non-DS controls	
		Unaffected children (n = 94)	Other-syndromes children (n = 46)
Male; n (%)	17 (56%)	52 (55.3%)	25 (54.34%)
Mean age (±SD) in years	3.22 ± 2.96	4.37 ± 3.09	5.53 ± 2.11
Age range	2 months to 11 years	2 months to 11 years	6 months to 9 years

Research Application - Ethnic & Age Diversity

- Pantel JT., Zhao M., Mensah MA., Hajjir N., Hsieh TH., Hanani Y., Fleischer N., Kamphans T., Mundlos S., Gurovich Y, Krawitz PM. *Advances in computer-assisted syndrome recognition by the example of inborn errors of metabolism* J Inherit Metab Dis (2018). ttps://doi.org/10.1007/s10545-018-0174-3

"Our results show that DeepGestalt, the next-generation-phenotyping technology within **Face2Gene, is not confounded by sex or ethnic background** for the studied phenotypes. "

n=40	MPS I	MPS II	ML	SLOS	NCBRS
MPS I	**0.39**	0.35	0.17	0.07	0.02
MPS II	0.17	**0.59**	0.19	0.03	0.02
ML	0.16	0.2	**0.49**	0.15	0.0
SLOS	0.04	0.04	0.13	**0.75**	0.03
NCBRS	0.06	0.05	0.02	0.05	**0.82**

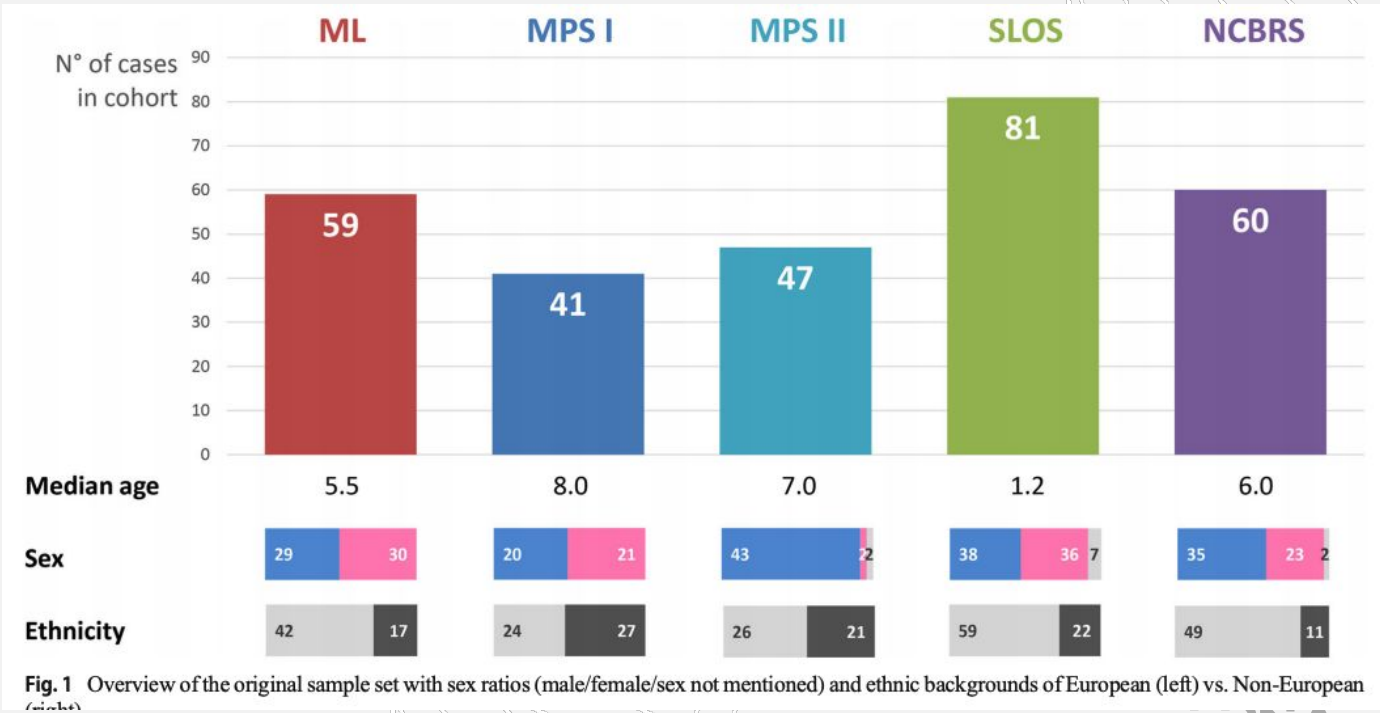

Fig. 1 Overview of the original sample set with sex ratios (male/female/sex not mentioned) and ethnic backgrounds of European (left) vs. Non-European (right)

Research Application - Genotype-Phenotype correlation

- Martinez-Monseny A,Cuadras D, Bolasell M, et al. (2018) *From gestalt to gene: early predictive dysmorphic features of PMM2-CDG* J Med Genet doi:10.1136/jmedgenet-2018-105588

  - PMM2, Angelman and control cohorts.
  - PMM2 age groups cohorts.
  - “At present, Face2Gene is useful to suggest PMM2-CDG.”