ESPR
European Society of Paediatric Radiology

56th Annual Meeting & 42nd Post Graduate Course

June 06 - 10, 2022
MARSEILLE - FRANCE

Palais du Pharo

espr2022.org

Disclosure

- Funding, honoraria, expenses
  - Alexion
  - BioMarin
  - Newlife Foundation
  - Skeletal Dysplasia Group for Teaching and Research

Acknowledgements

A BIG THANK YOU

- Professor Philippe Petit
  - Mentors (Professor Christine Hall)
  - Patients and families

dREAMS

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“ERA”

A date or event marking the beginning of a new and distinct period of time

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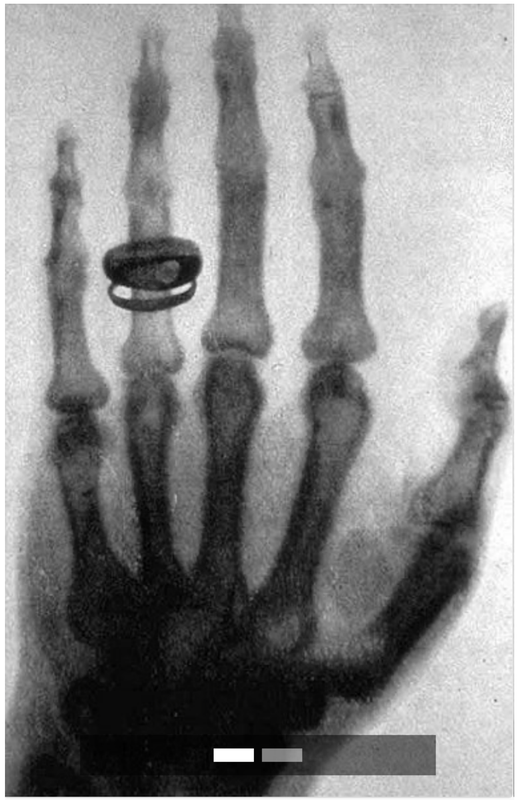
Eras Leading to This Talk (1)

"Era": A date or event marking the beginning of a new and distinct period of time

- 8th November 1895
  - Wilhelm Conrad Röntgen
  - Discovery of X-rays

Anna Röntgen: "I have seen my death!"



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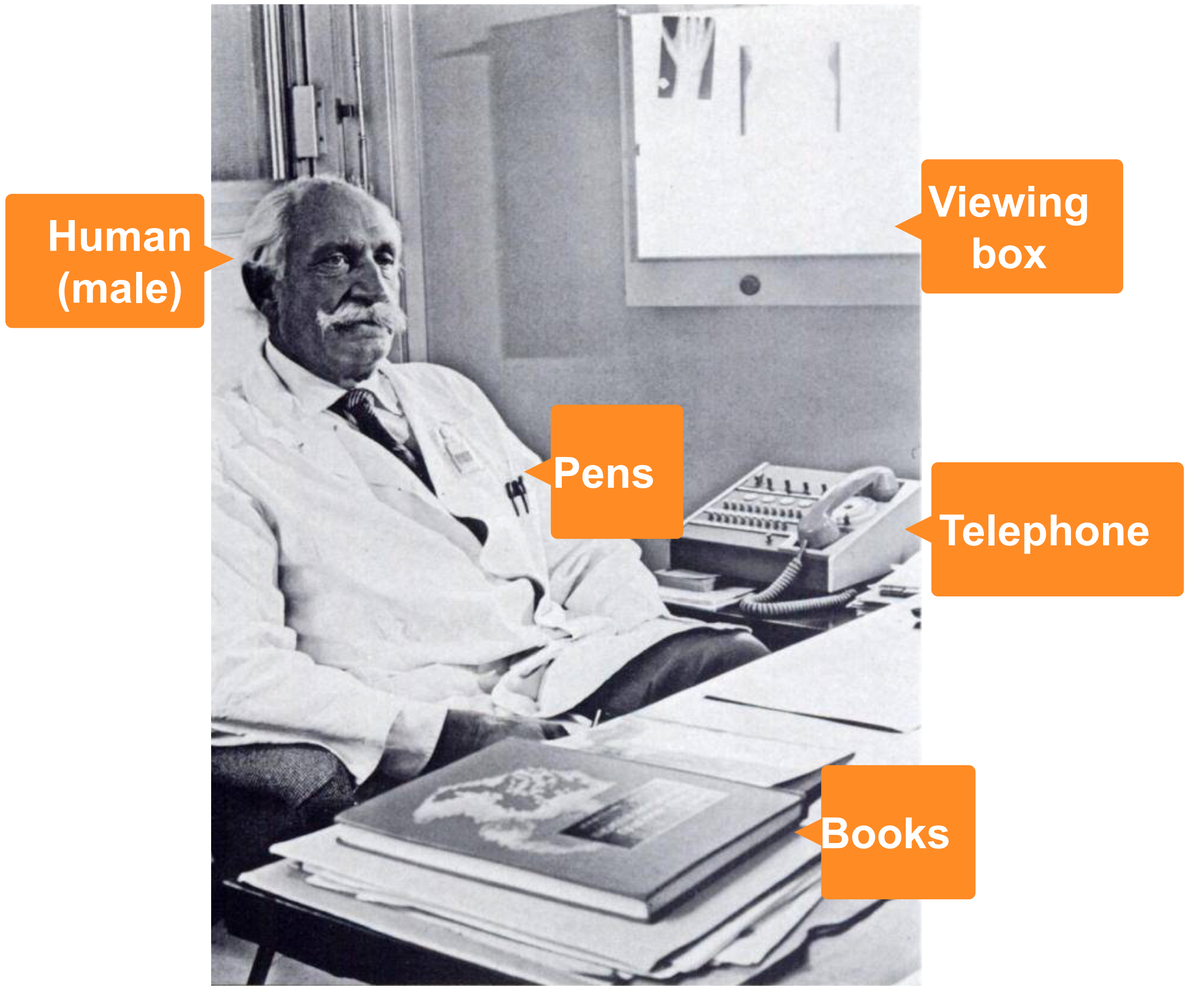
Eras Leading to This Talk (2)

"Era": A date or event marking the beginning of a new and distinct period of time

- 1907 - 1974
  - Professor Jacques Lefebvre
  - First meeting of European paediatric radiologists (ESPR) in 1963

doi: 10.2214/ajr.123.4.853



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Eras Leading to This Talk (3)

"Era": A date or event marking the beginning of a new and distinct period of time

- Paris, November 6th to 9th 1969
  - Pierre Maroteaux: International Skeletal Dysplasia Society (ISDS)
    - Ann de Radiol 1970 13:455-464
    - Leonard Langer & Maroteaux
      - Radiology 1971 99:699-702
    - 3 groups of dysplasias
    - 3 other groups (including storage)
    - 134 named conditions
    - No genes

- ISDS Nosology 2019
  - 461 different diseases (134)
  - 42 groups (9)
  - 437 genes (0)

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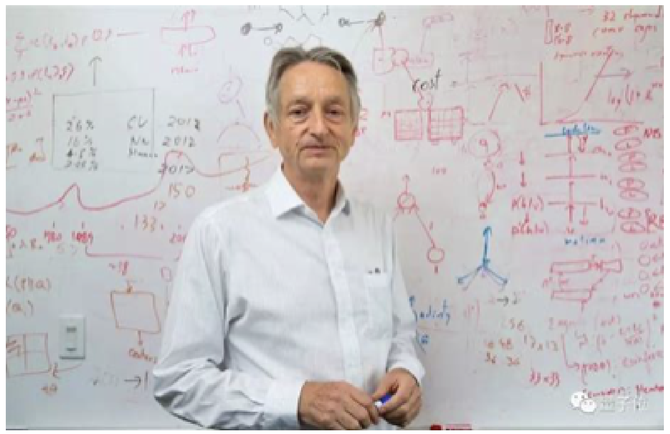
Eras Leading to This Talk (4)

"Era": A date or event marking the beginning of a new and distinct period of time

- Godfathers of artificial intelligence:

Geoffrey Hinton

1947 -



Jim Goodnight

1943 -

Alan Turing

1912 - 1954

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Eras Leading to This Talk (5)

"Era": A date or event marking the beginning of a new and distinct period of time

- 1869-2003
  - Deoxyribonucleic acid (DNA)
    - Johann Friedrich Miescher (1869)
    - Rosalind Franklin & Maurice Wilkins (1950s)
    - James Watson & Francis Crick (1953)
    - Human genome project (completed in 2003)

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Radiological Diagnosis of Skeletal Dysplasias

ESPR 2002 (Bergen, Norway)

Pediatr Radiol (2003) 33: 153–161
DOI 10.1007/s00247-002-0855-8

REVIEW

Amaka C. Offiah
Christine M. Hall

Received: 6 September 2002
Revised: 4 November 2002
Accepted: 6 November 2002
Published online: 20 December 2002

Originally presented as a workshop at the 39th Annual Congress of the ESPR, Bergen, June 2002

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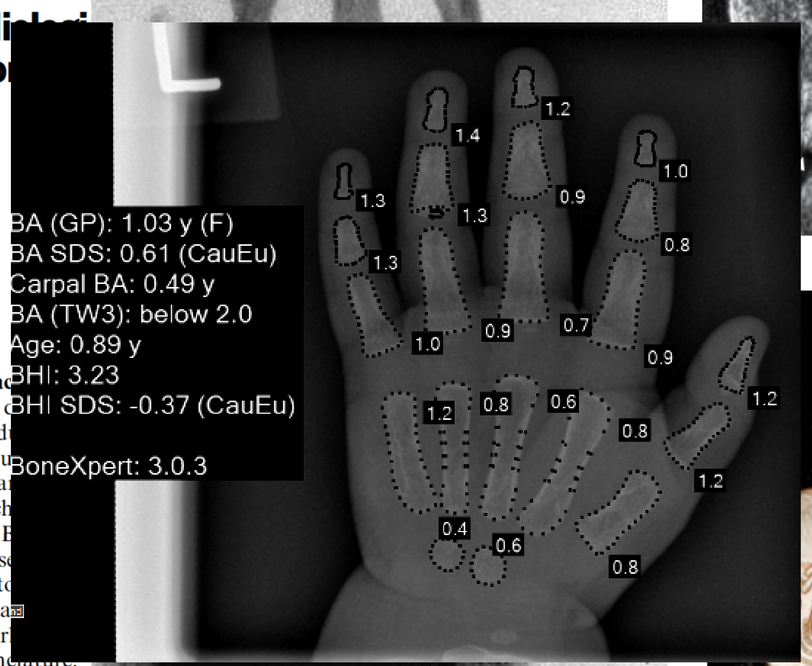

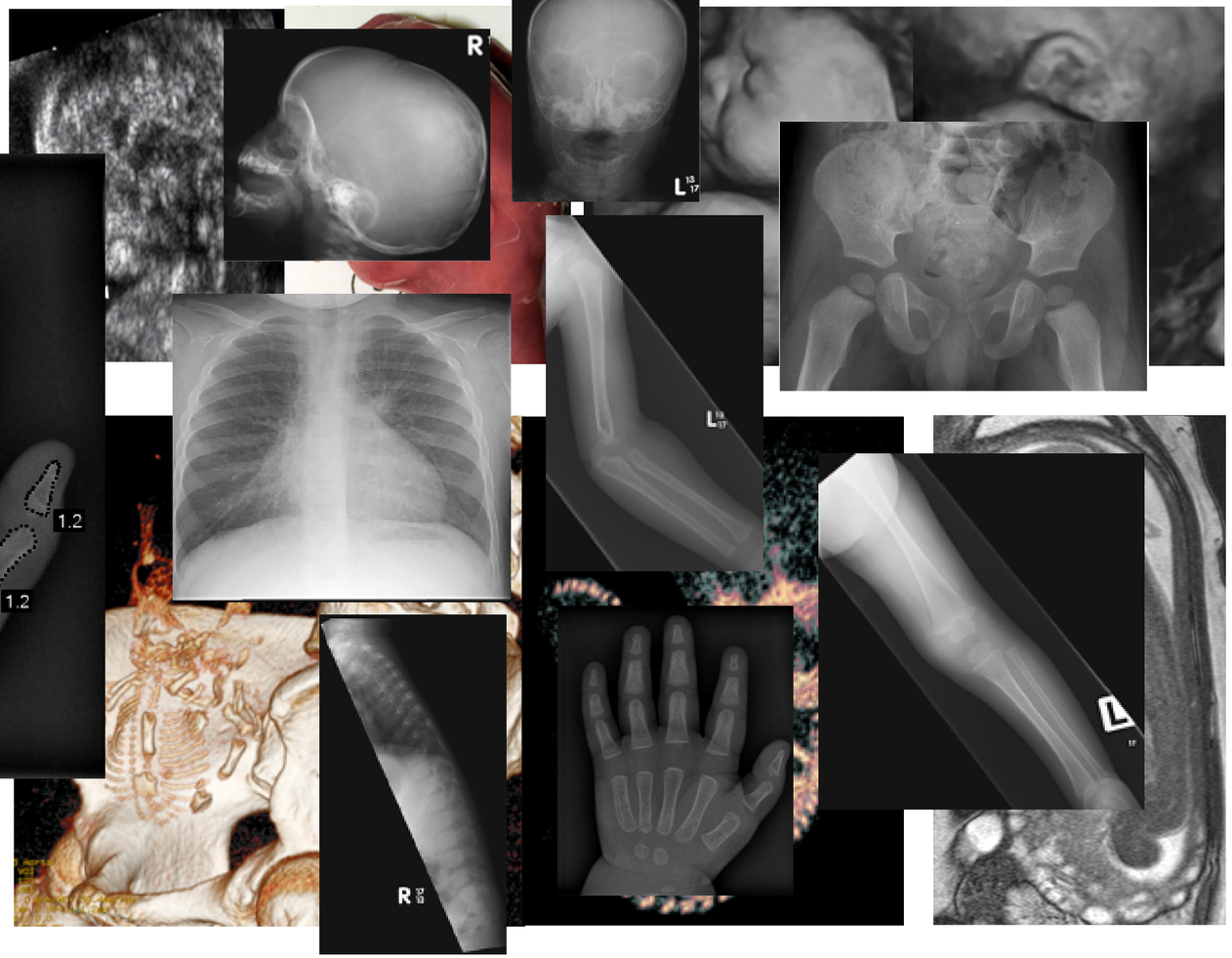

Ha… …etal & Perinatal Skeletal Dysplasias Radcliffe Publishers 2012

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Radiological Diagnosis of Skeletal Dysplasias

Bone Age Assessment: BoneXpert

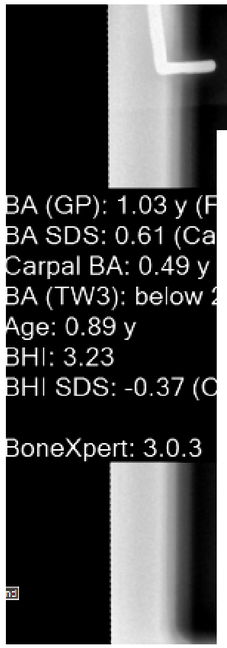
Pediatric Radiology
https://doi.org/10.1007/s00247-022-05295-w

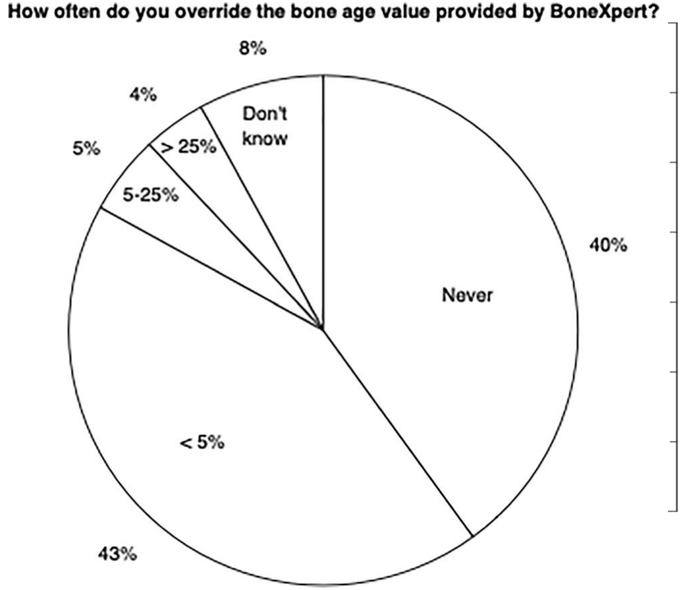
ORIGINAL ARTICLE

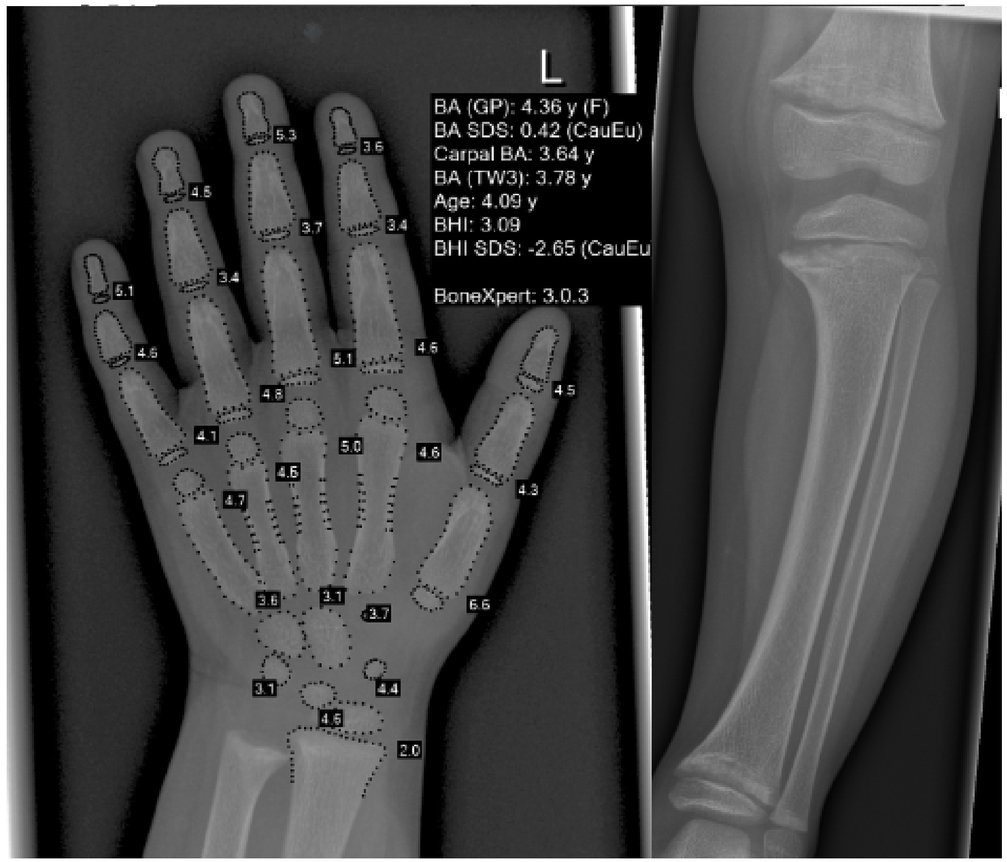
Autonomous artificial intelligence in pediatric radiology: the use and perception of BoneXpert for bone age assessment

Hans Henrik Thodberg[1] · Benjamin Thodberg[1] · Joanna Ahlkvist[2] · Amaka C. Offiah[3]

Received: 15 June 2021 / Revised: 23 December 2021 / Accepted: 19 January 2022







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Radiological Diagnosis of Skeletal Dysplasias

Artificial Intelligence: Shape & Pattern Recognition

Pediatr Radiol (2003) 33: 153–161
DOI 10.1007/s00247-002-0855-8

REVIEW

Amaka C. Offiah
Christine M. Hall

Radiological diagnosis of the constitutional disorders of bone. As easy as A, B, C?

Received: 6 September 2002
Revised: 4 November 2002
Accepted: 6 November 2002
Published online: 20 December 2002

Originally presented as a workshop at the 39th Annual Congress of the ESPR, Bergen, June 2002

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Abstract Although many constitutional disorders of bone are individually rare, collectively they make up a large group of disorders. They are broadly classified into osteochondrodysplasias and dysostoses. Because of the rarity of some of these conditions, they can be difficult to diagnose. Members of the International Dysplasia Group meet regularly to update and clarify the nomenclature. The last meeting was in Oxford in 2001. This article attempts to highlight the differences between the osteochondrodysplasias and the dysostoses, and provides a systematic approach to their radiological diagnosis.

Keywords Osteochondrodysplasia · Dysostosis · Nomenclature Radiological diagnosis

Wafer thin
Rectangular shaped
Hooked

Spondyloepiphyseal dysplasia congenita
Thanatophoric dysplasia
Mucopolysaccharidoses

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Radiological Diagnosis of Skeletal Dysplasias

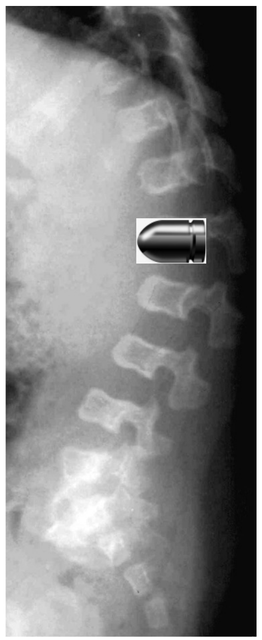
Artificial Intelligence: Shape & Pattern Recognition

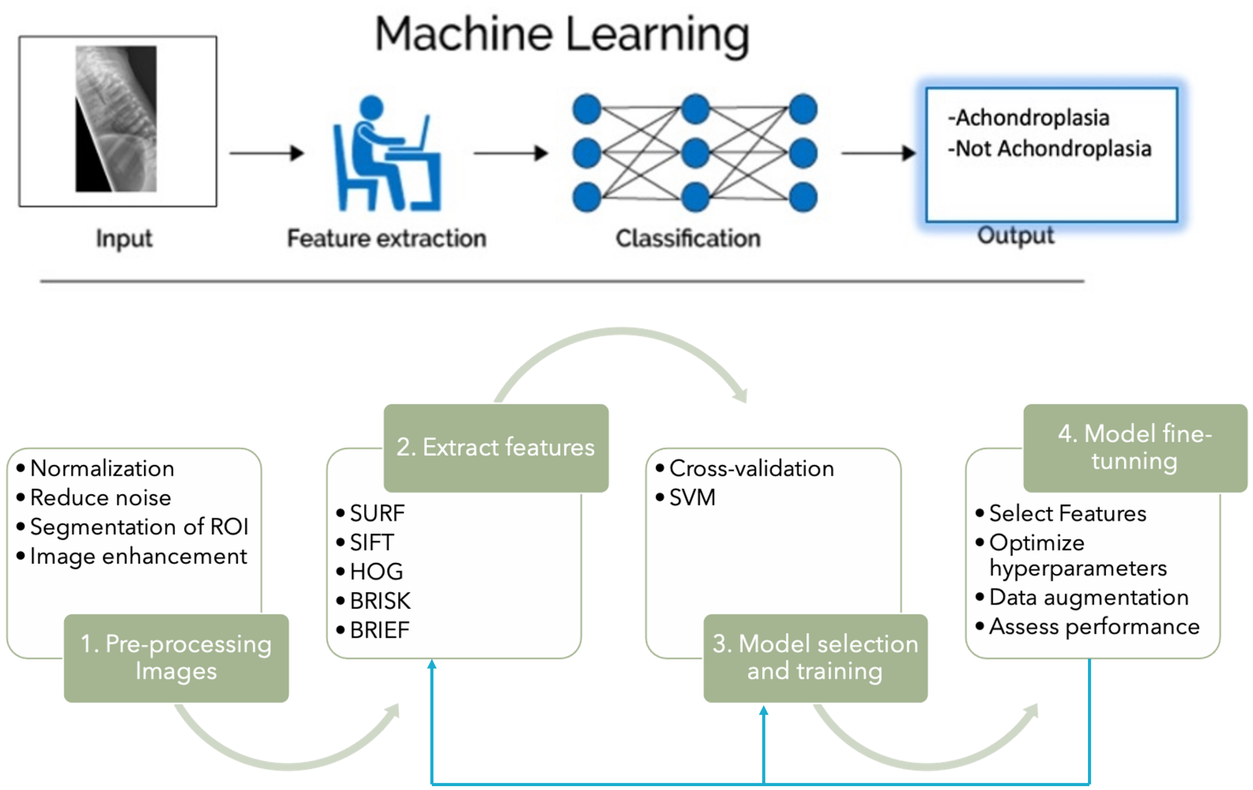
Offiah A, Lanfranchi V, Davila Garcia ML, Villa-Uriol M, Yang P

40 lateral spine, 16 AP spine, 26 chests: Achondroplasia and Normal (all infants) from the dREAMS collection

(MRC Confidence in Concept Fund: Project No 16068)

Bullet-shaped





Feature	Size of Feature Vector	% Average Accuracy	Body Part
SURF	168,000	75	Spine Lat
HOG	63,936	87.5	Spine Lat
SURF	72,000	68.0	Spine AP
HOG	63,936	75	Spine AP
SURF	120,000	88	Chest
HOG	63,936	87.5	Chest

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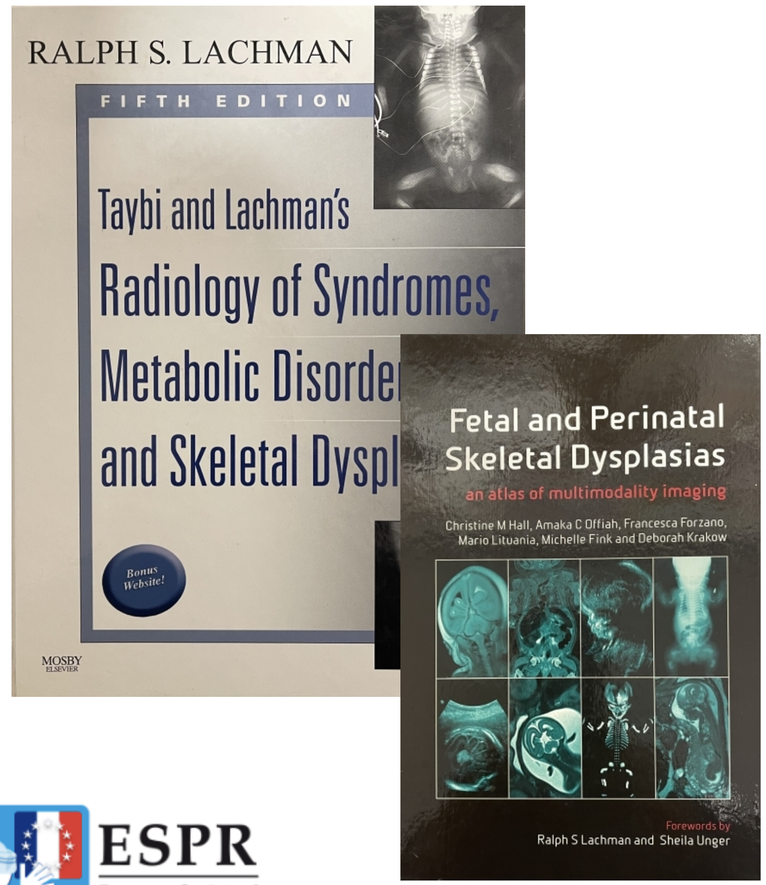
Radiological Diagnosis of Skeletal Dysplasias

Teaching Aids

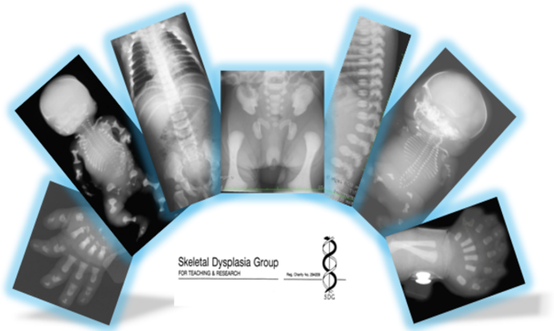


Skeletal Dysplasia Group
for teaching and research
Reg. Charity No. 294209

Name.....

Spring Instructional Course
Sheffield
May 16th – 18th 2022

THE RADIOLOGICAL AND CLINICAL DIAGNOSIS OF SKELETAL DYSPLASIAS



ISDS
www.isds.ch

ABOUT THE EVENT

We are pleased to announce that the "*15th International Skeletal Dysplasia Society Meeting*", will be held in Santiago, Chile, on August 24 - 27, 2022, and for the first time in Latin America

MEETING VENUE & LOCATION
Best Western Premier Marina Las Condes Hotel
Av. Alonso de Córdova N° 5727
Santiago, 7560927
Chile

Hotel website
*Reduces rates are available for meeting attendees - "Limited vacancies"

We look forward to seeing you in Santiago!

EARLY BIRD REGISTRATION
Until
15th June 2022

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Radiological Diagnosis of Skeletal Dysplasias

REAMS ic Radiological Electronic Atlas of Malformation Syndromes

Hall CM, Offiah AC

Certus Tech Ltd.

- Online electronic diagnostic & teaching aid for skeletal dysplasias
- >12,000 images (> 500 patients, > 400 conditions)

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Radiological Diagnosis of Skeletal Dysplasias

dREAMS: dynamic Radiological Electronic Atlas of Malformation Syndromes

Phase 1: Quality Assurance (Funders: Newlife Foundation, SDG)

- Import images (identify source - REAMS, ESDN, Gorlin, Bristol etc.)
- Anonymise
- Quality control
  - Positioning
  - Cropping
  - Contrast/brightness
  - Age group allocation
  - Diagnosis

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Radiological Diagnosis of Skeletal Dysplasias

dREAMS: dynamic Radiological Electronic Atlas of Malformation Syndromes

Phase 2: Image Annotation (Funders: SDG, Alexion)

- Based on a defined ontology
  - A knowledge framework in a specific domain (radiology of skeletal dysplasias)
    - Describes characteristics
    - Describes relationships

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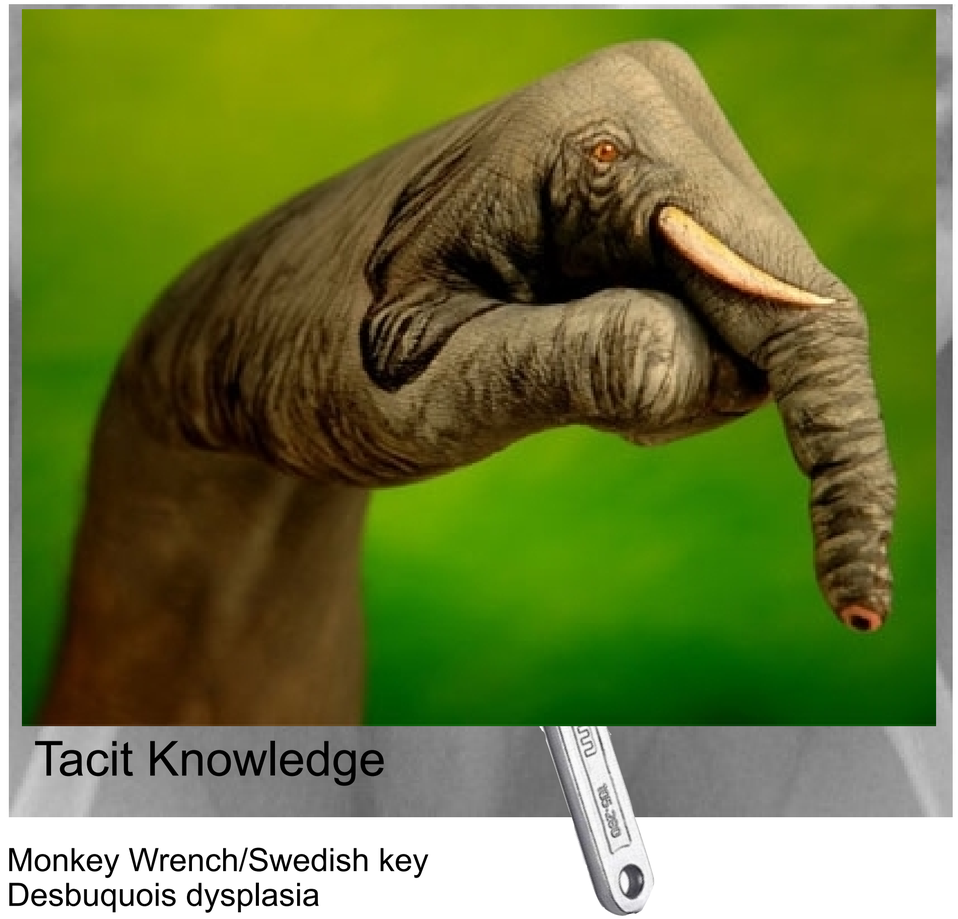
Radiological Diagnosis of Skeletal Dysplasias

dREAMS: dynamic Radiological Electronic Atlas of Malformation Syndromes

Phase 2: Image Annotation

- Importance of an ontology?
  - Stippling = chondrodysplasia punctata
  - Fragmented = epiphyseal dysplasia
  - Advanced ossification = ciliopathy, Desbuquois

1. Descriptors
2. Associated diagnoses



Monkey Wrench/Swedish key
Desbuquois dysplasia

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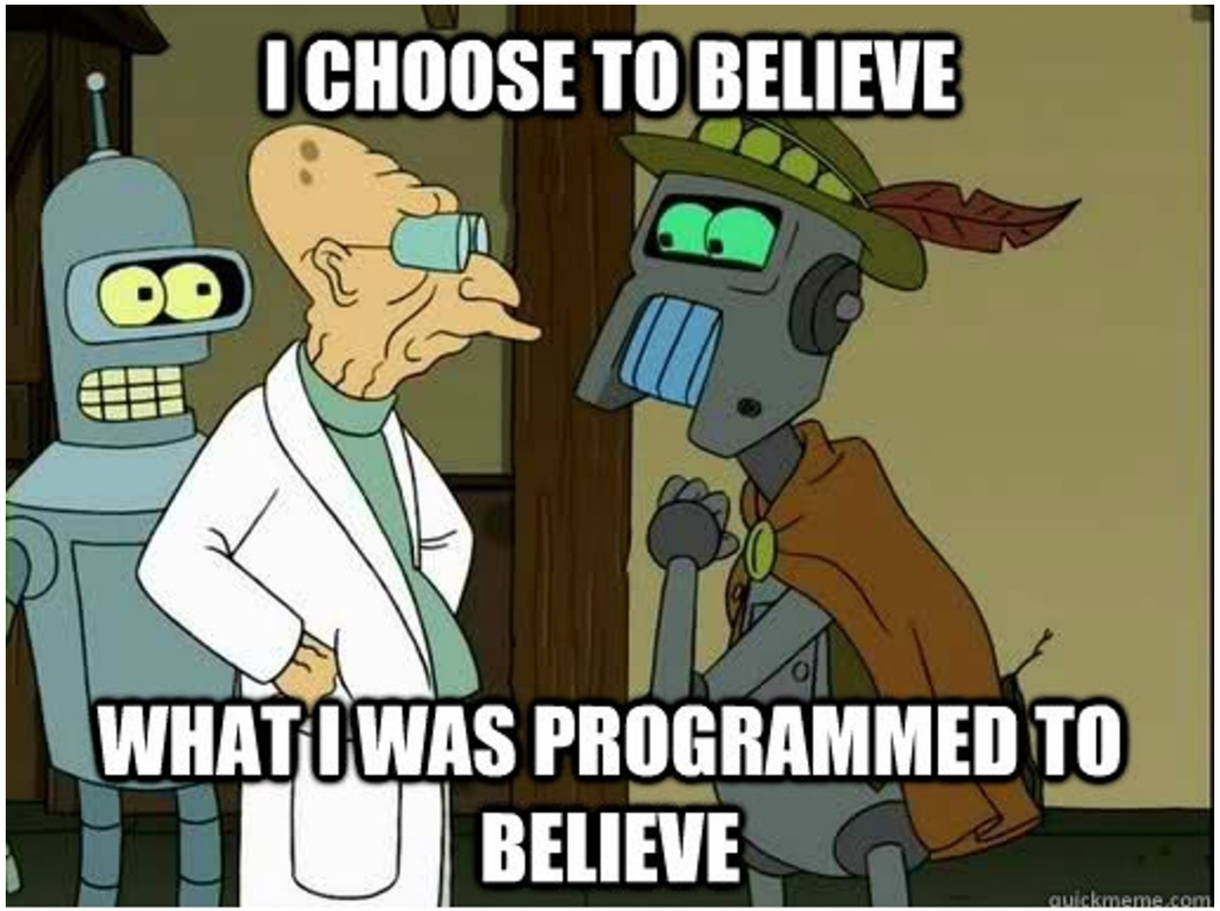
Radiological Diagnosis of Skeletal Dysplasias

dREAMS: dynamic Radiological Electronic Atlas of Malformation Syndromes

Phase 2: Image Annotation

1. Descriptors
2. Associated diagnoses



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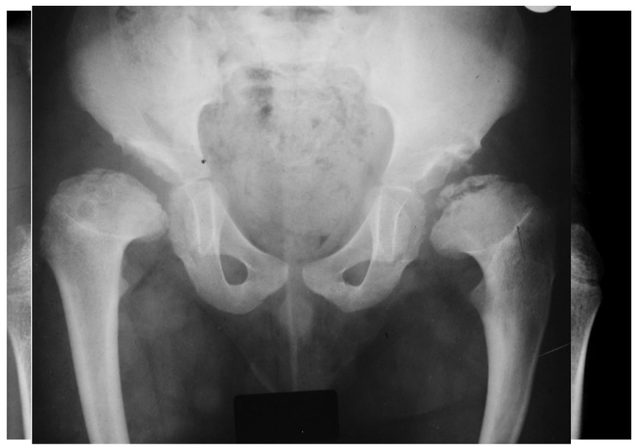
Radiological Diagnosis of Skeletal Dysplasias

dREAMS: dynamic Radiological Electronic Atlas of Malformation Syndromes

Phase 2: Image Annotation

- dREAMS ontology
  - Abnormality
  - Abnormality may have a qualifier
  - Location
  - Abnormality + Location = Feature
  - Each feature has a unique dREAMS identifier

Avoid Tautology:
Hypoplasia of the odontoid peg
Platyspondyly
Posterior scalloping of lumbar vertebral bodies
"Loss of height of" vertebral bodies = "platyspondyly"
"Loss of height of" capital femoral epiphyses = "flattening"



Brachyolmia
Spondyloepiphyseal dysplasia with progressive arthropathy

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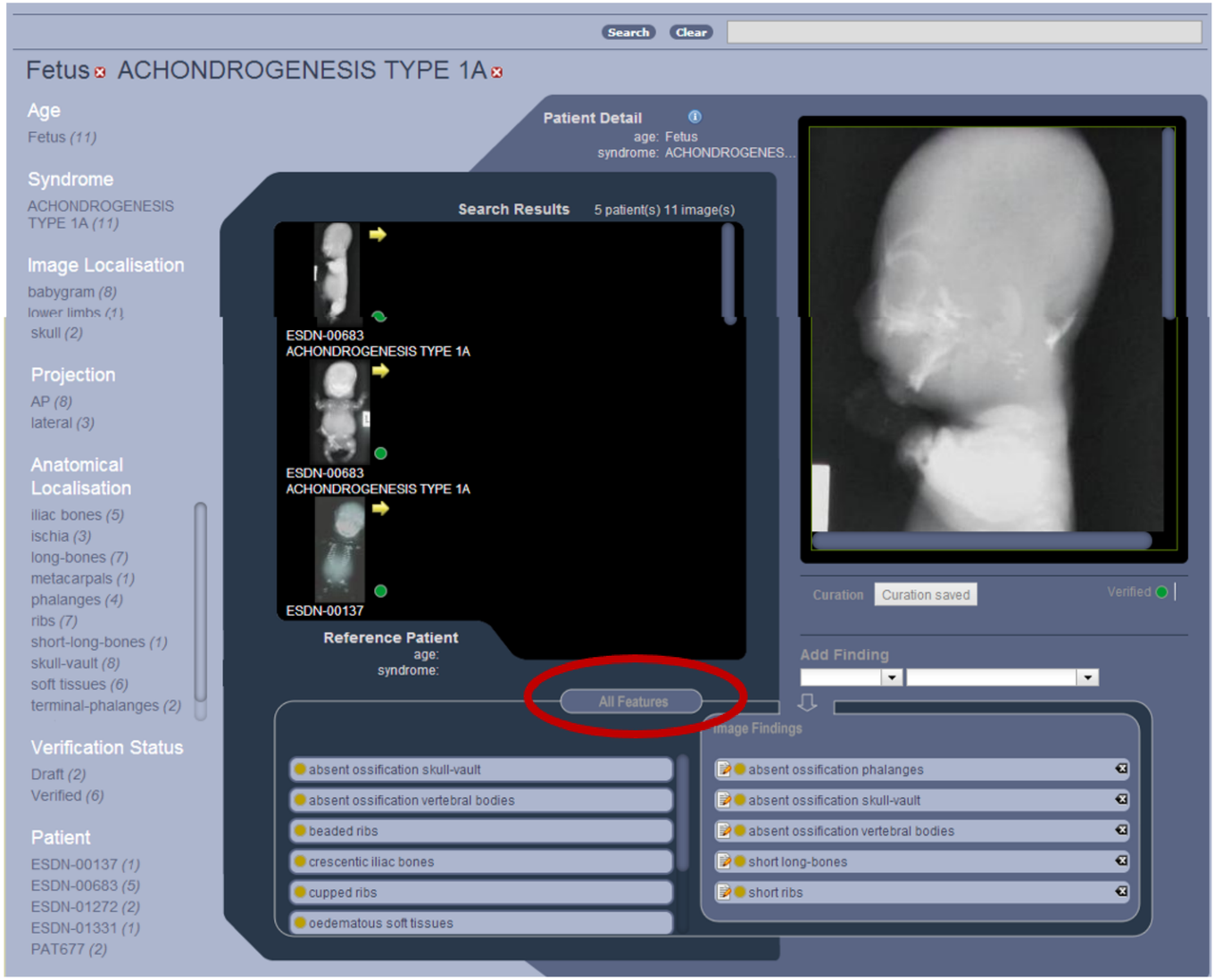
Radiological Diagnosis of Skeletal Dysplasias

dREAMS: dynamic Radiological Electronic Atlas of Malformation Syndromes

Phase 2: Image Annotation



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Radiological Diagnosis of Skeletal Dysplasias

dREAMS: dynamic Radiological Electronic Atlas of Malformation Syndromes

Phase 3: Maintenance and prospective population

- Clinical
- Research
  - Alexion (hypophosphatasia)
  - 100,000 genome project

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Radiological Diagnosis of Skeletal Dysplasias

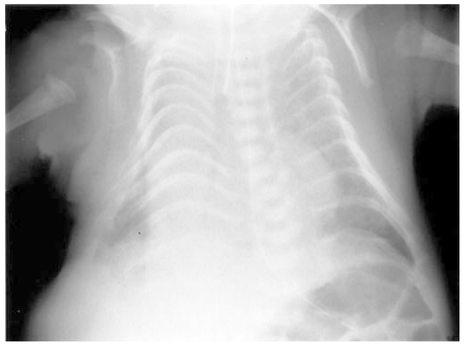
Genetic Analysis as the Gold Standard

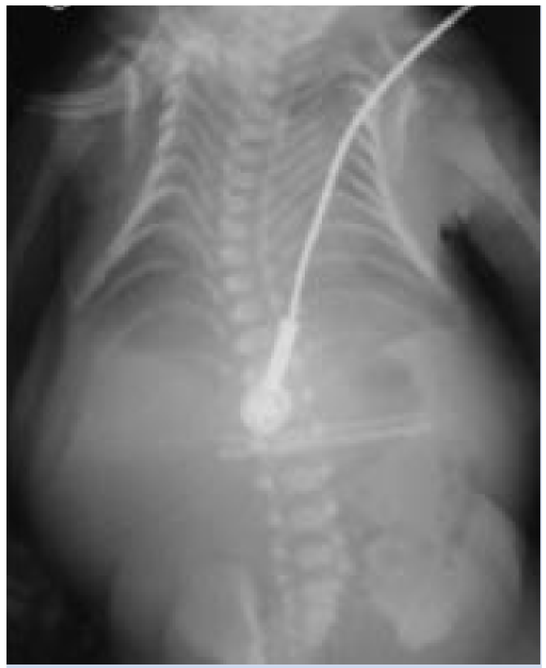
Pediatr Radiol (2003) 33: 509–512
DOI 10.1007/s00247-003-0931-8

CASE REPORT

Amaka C. Offiah
Luc Cornette

Paternal uniparental disomy 14: introducing the 'coat-hanger' sign





RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Segmental Paternal Uniparental Disomy (patUPD) of 14q32 With Abnormal Methylation Elicits the Characteristic Features of Complete patUPD14

Melita D. Irving,[1]* Karin Buiting,[2] Deniz Kanber,[2] Celia Donaghue,[3] Reiner Schulz,[4] Amaka Offiah,[5] Shehla N. Mohammed,[1] and Rebecca J. Oakey[4]

[1]Department of Clinical Genetics, Guy's Hospital, London, UK
[2]Institut für Humangenetik, Universitätsklinkum Essen, Essen, Germany
[3]Department of Cytogenetics, Guy's Hospital, London, UK
[4]Department of Medical and Molecular Genetics, King's College London, Guy's Hospital, London, UK
[5]Academic Unit of Child Health, Sheffield Children's NHS Foundation Trust, Sheffield, UK

Received 18 August 2009; Accepted 22 March 2010

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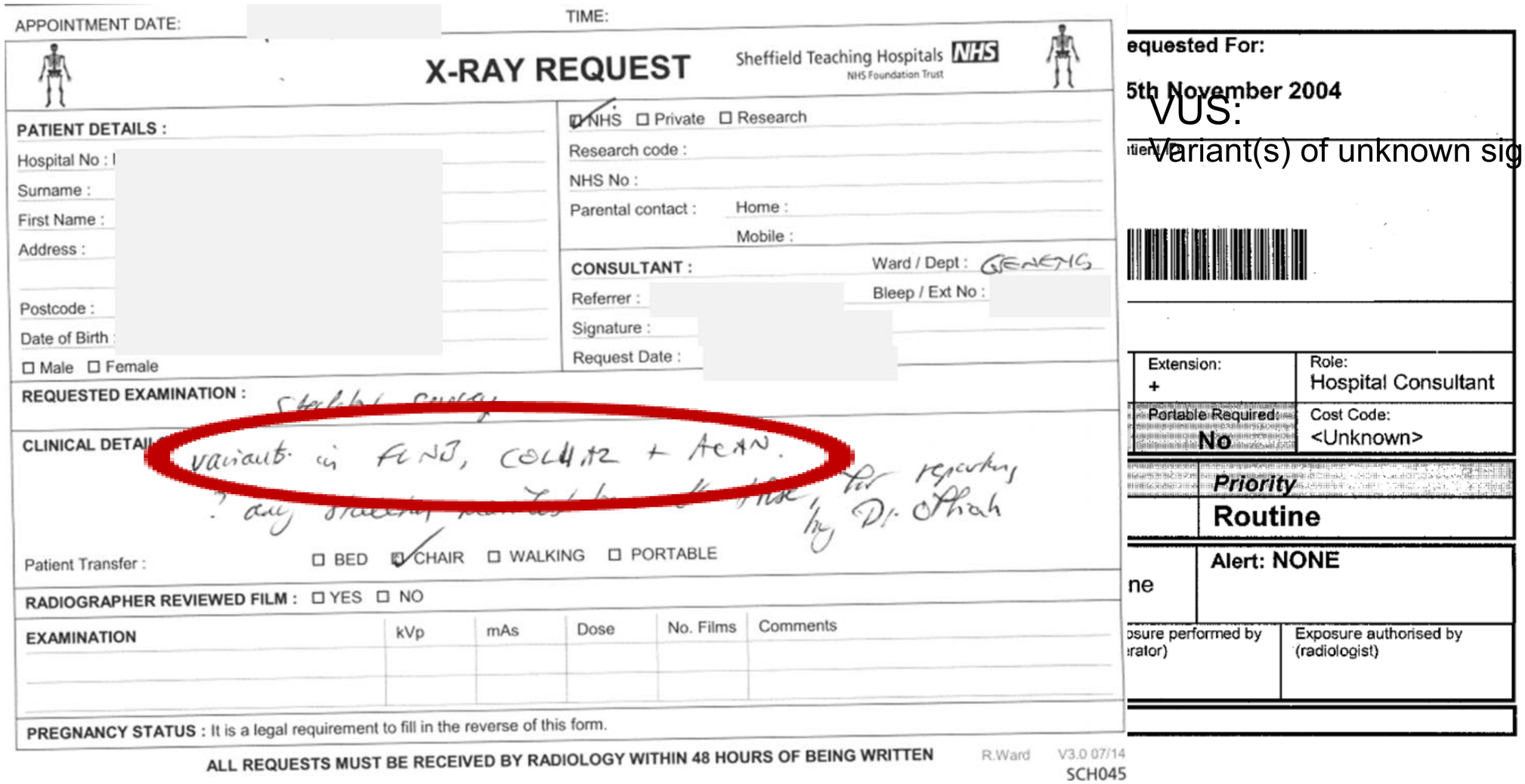
Radiological Diagnosis of Skeletal Dysplasias

"Reverse Radiology"



APPOINTMENT DATE: TIME:

X-RAY REQUEST Sheffield Teaching Hospitals NHS NHS Foundation Trust

PATIENT DETAILS :

Hospital No :
Surname :
First Name :
Address :
Postcode :
Date of Birth :
☐ Male ☐ Female

☑ NHS ☐ Private ☐ Research
Research code :
NHS No :
Parental contact : Home :
Mobile :

CONSULTANT : Ward / Dept : GENETICS
Referrer : Bleep / Ext No :
Signature :
Request Date :

REQUESTED EXAMINATION :

CLINICAL DETAIL

variants in FLNJ, COL4A2 + ACAN.
for reporting
by Dr. Shah

Patient Transfer : ☐ BED ☑ CHAIR ☐ WALKING ☐ PORTABLE

RADIOGRAPHER REVIEWED FILM : ☐ YES ☐ NO

EXAMINATION	kVp	mAs	Dose	No. Films	Comments

PREGNANCY STATUS : It is a legal requirement to fill in the reverse of this form.

ALL REQUESTS MUST BE RECEIVED BY RADIOLOGY WITHIN 48 HOURS OF BEING WRITTEN R.Ward V3.0 07/14 SCH045

equested For:
5th November 2004
tient)

Extension: +
Role: Hospital Consultant
Portable Required: No
Cost Code: <Unknown>

Priority
Routine

Alert: NONE

ne

osure performed by
rator)

Exposure authorised by (radiologist)

VUS:
Variant(s) of unknown significance

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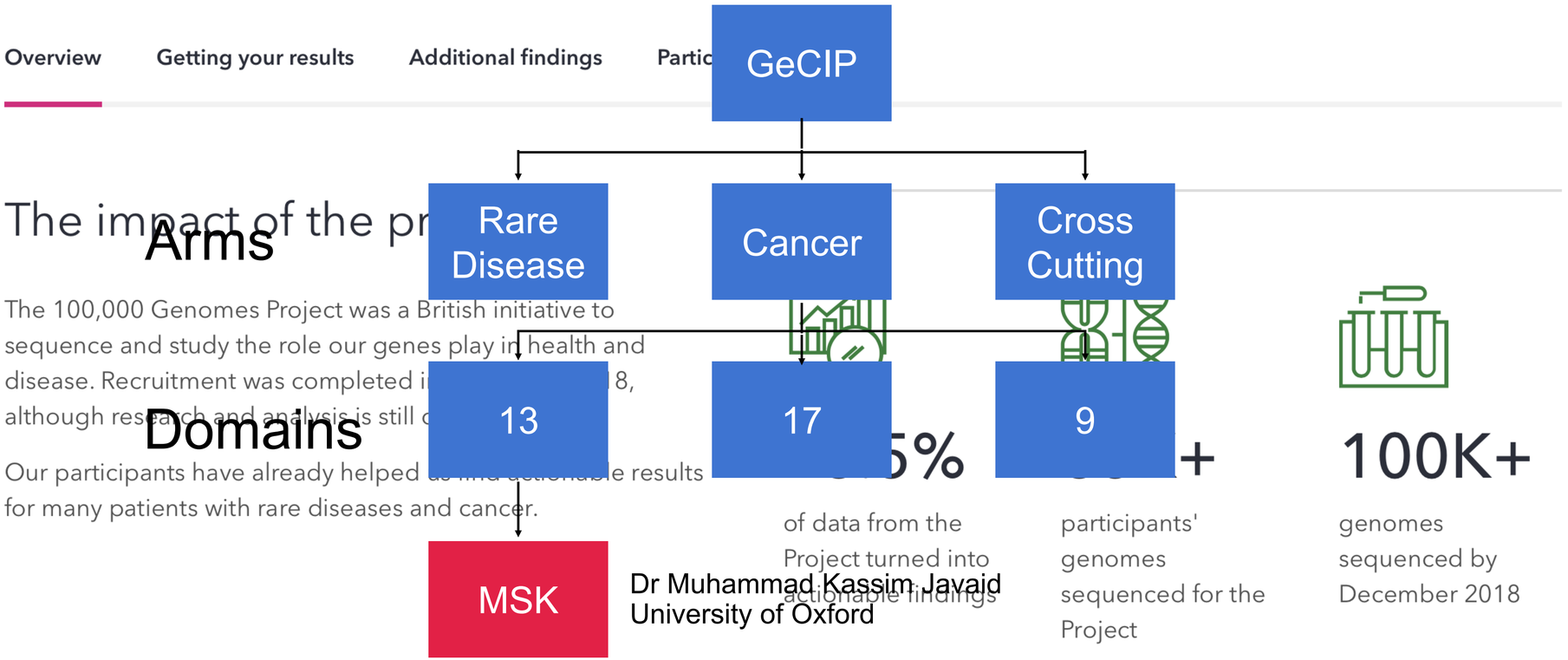
Radiological Diagnosis of Skeletal Dysplasias

Collaboration is Key: 100K Genomes (MSK GeCIP) Project

- GeCIP - Genomics England Clinical Interpretation Partnership
  - Approved researchers with access to the Genomics England Research Environment



Dr Muhammad Kassim Javaid
University of Oxford

Radiological Diagnosis of Skeletal Dysplasias

Collaboration is Key: 100K Genomes (MSK GeCIP) Project

MSK GeCIP

Dr Muhammad Kassim Javaid
University of Oxford

- £1.2M MRC-funded project
  - “Identifying new disease genes & mechanisms for MSK disorders in 100K genomes project using bioinformatics, phenotyping & machine learning”
    - Prof Jenny Taylor (Laboratory genetics)
    - Dr Muhammad Javaid (Adult rare MSK)
    - Dr Melita Irving (Paediatric rare MSK)
    - Prof Amaka Offiah (Radiology)
    - Prof David Clifton (Engineering Science)

Radiological Diagnosis of Skeletal Dysplasias

Collaboration is Key: 100K Genomes (MSK GeCIP) Project

MSK Specific Disease subtype	No. Cases	Solved	Unsolved
Osteogenesis Imperfecta	363	132	231
Unexplained Skeletal Dysplasia	237	40	197
Classical Ehlers-Danlos syndrome	116	11	105
Kyphoscoliotic Ehlers-Danlos syndrome	50	10	40
Multiple Epiphyseal Dysplasia	33	12	21
Stickler syndrome	26	7	19
Radial Dysplasia	25	2	23
Choanal atresia	17	1	16
Chondrodysplasia punctata	9	1	8
Thoracic dystrophies	8	2	6
Total	**884**	**218**	**666**

430 trios
162 duos
223 singletons
69 larger families

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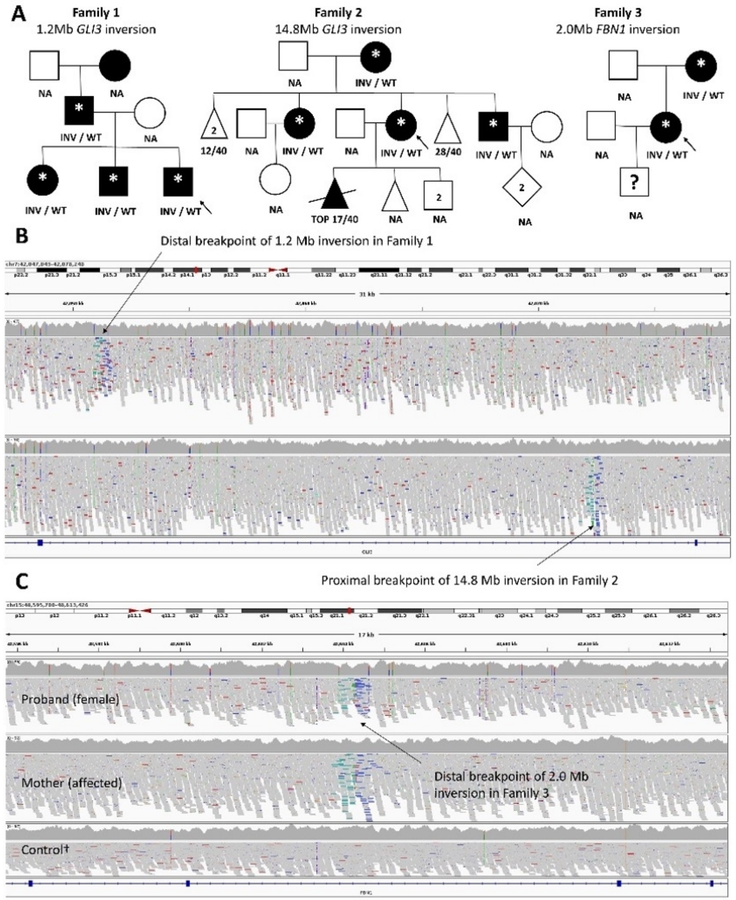
Radiological Diagnosis of Skeletal Dysplasias

Collaboration is Key: 100K Genomes (MSK GeCIP) Project



Work Package 2: Bioinformatics

Work Package 3: Phenotyping

59 cases solved
34 genes

MDT clinical suspicion >20 years
Greig syndrome *GLI3*
Kantaputra mesomelic dysplasia *HOXD*
Marfan's *FBN1*

Novel /near novel genes

SCUBE3 – novel gene (Lin *at al* 2021)
PRKG2 – novel for phenotype, (Pagnamenta *et al* 2021)
PKDCC –3 GEL Px, novel gene for phenotype.
Only 2 prior reported cases for *PKDCC, PRKG2*

Structural variants

Inversions (15 families)
FBN1 (5), *GLI3* (2), *EFTUD2*, *PHEX*, *EXT2*, *EP300-TCF20*, *HOXD*
Translocated duplication *PHEX*
Deletions
TCOF, TRPS1, EFTUD2(2), FBN1(4), EXT1(2), COL1A1 (2), IHH(2), KDELR2(2), TBX4,

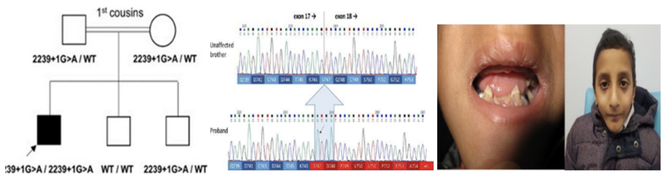
Non-coding variants

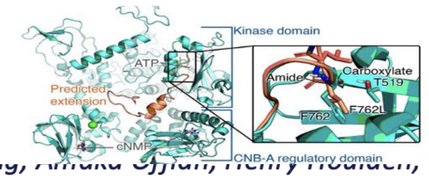
COL1A1
Splice site variant
6/511 cases – 1% yield
5' UTR pathogenic variant

IFITM5
5'UTR in 5 unrelated OI cases (further 1% yield)

Blended phenotypes

GLI3 & HOXA
skeletal & urogenital features
EP300-TCF20
Rubinstein Taybi, ILD
EXT2 & MITF
multiple bone exostoses & deafness





Alistair Pagnamenta
Jing Yu

Kassim Javaid, Melita Irving, Ajitha Gijsan, Henry Houlden, Patricia Osborne, MSK MDT & GeCIP

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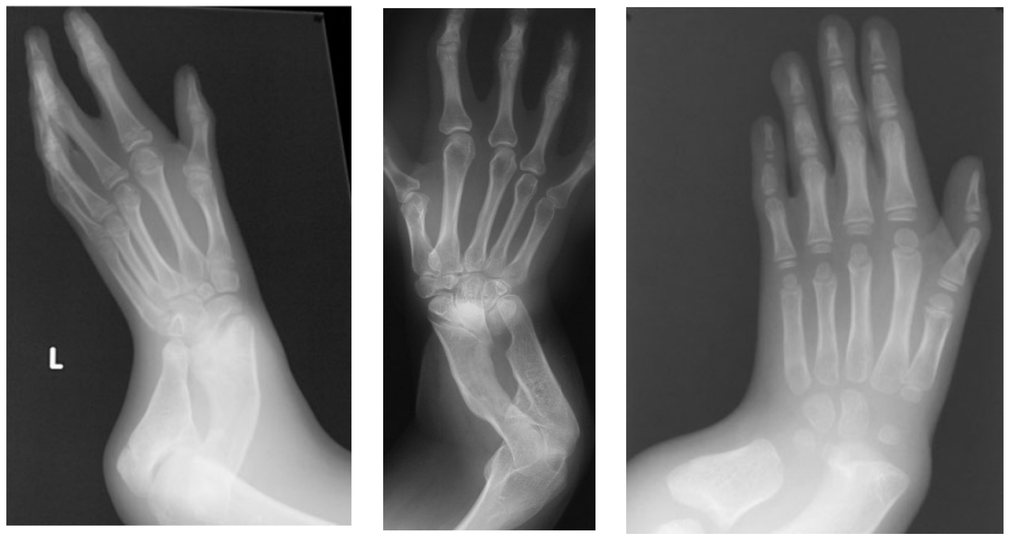
Radiological Diagnosis of Skeletal Dysplasias

Collaboration is Key: 100K Genomes (MSK GeCIP) Project

American Journal of Medical Genetics 128A:6–11 (2004)

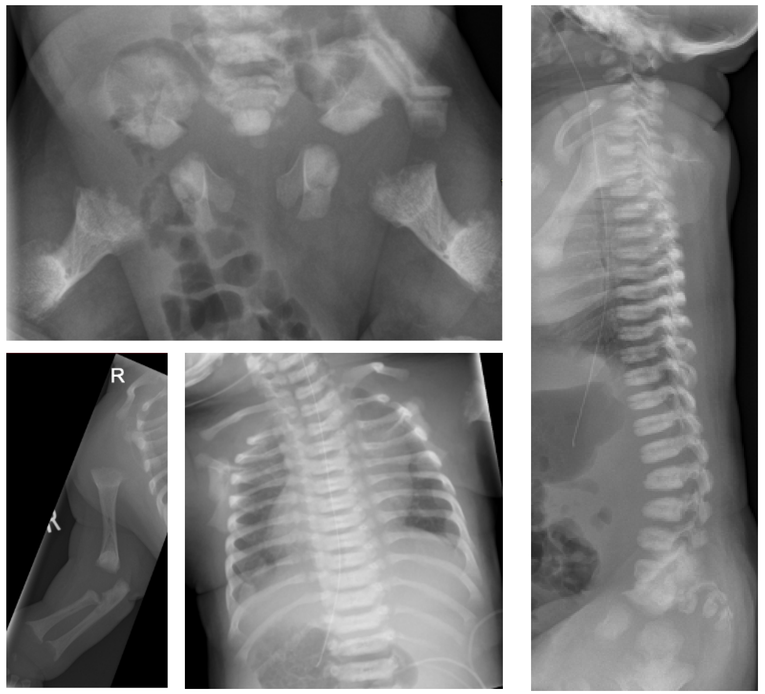
Kantaputra Mesomelic Dysplasia:
A Second Reported Family

Deborah J. Shears,[1] Amaka Offiah,[2] Paul Rutland,[1] Tony Sirimanna,[3] Maria Bitner-Glindzicz,[1]* and Christine Hall[2]



2-day-old male
Dumbbell long bones:
1. Polland Desbuquois (spine does not fit)
2. Metatropic dysplasia (no myotonia) BUT
Reverse femoral bowing

Homozygous *HSPG2* mutation = Schwartz-Jampel



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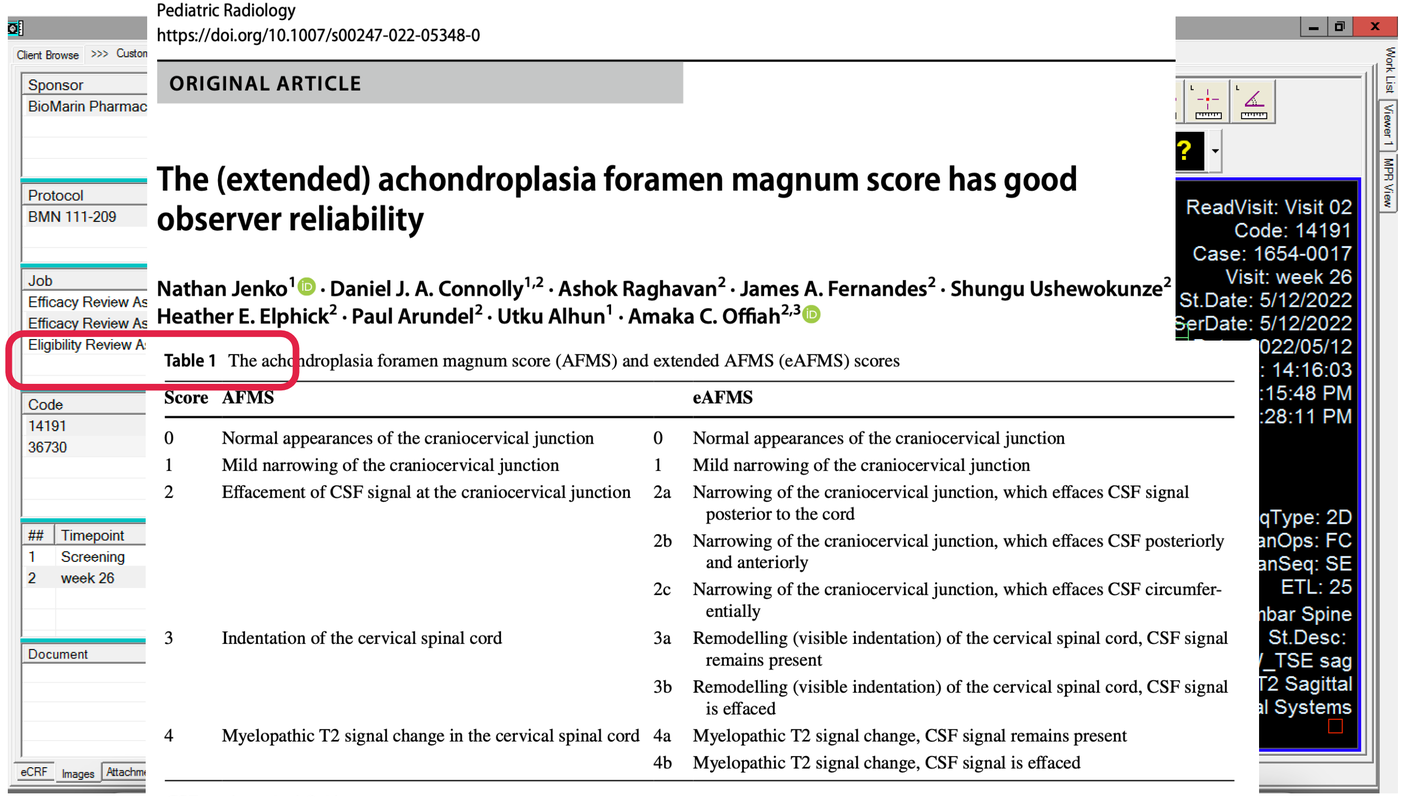
Radiological Diagnosis of Skeletal Dysplasias

Radiological Parameters as Objective End Points in Drug Trials

Identification of genes = Identification of pathways = Drug repurposing/novel drugs



Pediatric Radiology
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ORIGINAL ARTICLE

The (extended) achondroplasia foramen magnum score has good observer reliability

Nathan Jenko[1] · Daniel J. A. Connolly[1,2] · Ashok Raghavan[2] · James A. Fernandes[2] · Shungu Ushewokunze[2] · Heather E. Elphick[2] · Paul Arundel[2] · Utku Alhun[1] · Amaka C. Offiah[2,3]

Table 1 The achondroplasia foramen magnum score (AFMS) and extended AFMS (eAFMS) scores

Score	AFMS		eAFMS
0	Normal appearances of the craniocervical junction	0	Normal appearances of the craniocervical junction
1	Mild narrowing of the craniocervical junction	1	Mild narrowing of the craniocervical junction
2	Effacement of CSF signal at the craniocervical junction	2a	Narrowing of the craniocervical junction, which effaces CSF signal posterior to the cord
		2b	Narrowing of the craniocervical junction, which effaces CSF posteriorly and anteriorly
		2c	Narrowing of the craniocervical junction, which effaces CSF circumferentially
3	Indentation of the cervical spinal cord	3a	Remodelling (visible indentation) of the cervical spinal cord, CSF signal remains present
		3b	Remodelling (visible indentation) of the cervical spinal cord, CSF signal is effaced
4	Myelopathic T2 signal change in the cervical spinal cord	4a	Myelopathic T2 signal change, CSF signal remains present
		4b	Myelopathic T2 signal change, CSF signal is effaced

CSF cerebrospinal fluid

achondroplasia. It is not known whether final adult height will be increased, or what the harms of long-term therapy might be.

Lifetime impact of achondroplasia: Current evidence and perspectives on the natural history.
Hoover-Fong J, Cheung MS, Fano V, Hagenas L, Hecht JT, Ireland P, Irving M, Mohnike K, Offiah AC, Okenfuss E, Ozono K, Raggio C, Tofts L, Kelly D, Shediac R, Pan W, Savarirayan R.
Bone. 2021 May;146:115872. doi: 10.1016/j.bone.2021.115872. Epub 2021 Feb 3.
PMID: 33545406 Free article. Review.

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Savarirayan R, Ireland P, Irving M, Thompson D, Alves I, Baratela WAR, Betts J, Bober MB, Boero S, Briddell J, Campbell J, Campeau PM, Carl-Innig P, Cheung MS, Cobourne M, Cormier-Daire V, Deladure-Molla M, Del Pino M, Elphick H, Fano V, Fauroux B, Gibbins J, Groves ML, Hagenäs L, Hannon T, Hoover-Fong J, Kaisermann M, Leiva-Gea A, Llerena J, Mackenzie W, Martin K, Mazzoleni F, McDonnell S, Meazzini MC, Milerad J, Mohnike K, Mortier G, Offiah A, Ozono K, Phillips JA 3rd, Powell S, Prasad Y, Raggio C, Rosselli P, Rossiter J, Selicorni A, Sessa M, Theroux M, Thomas M, Trespedi L, Tunkel D, Wallis C, Wright M, Yasui N, Fredwall SO.
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PMID: 34837063 Review.

Rationale, design, and methods of a randomized, controlled, open-label clinical trial with open-label extension to investigate the safety of vosoritide in infants, and young children with achondroplasia at risk of requiring cervicomedullary decompression surgery.
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Sci Prog. 2021 Jan-Mar;104(1):368504211003782. doi: 10.1177/00368504211003782.
PMID: 33761804 Free article. Clinical Trial.

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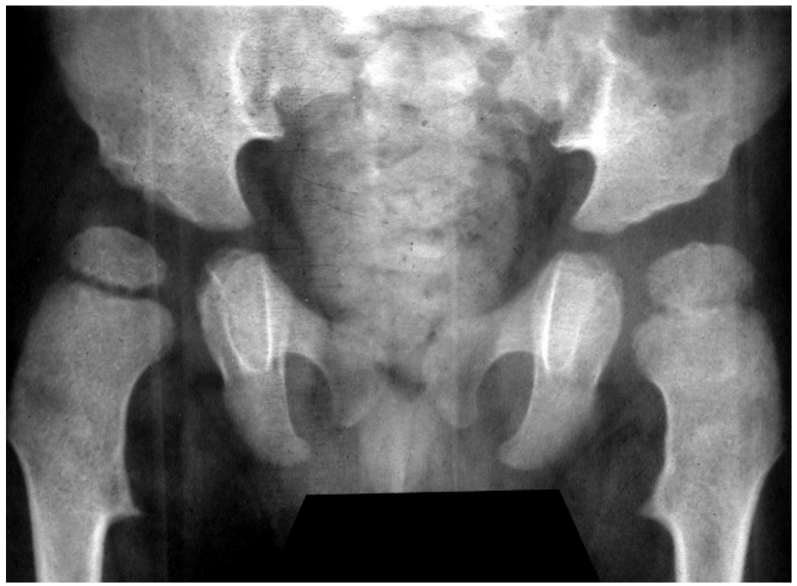
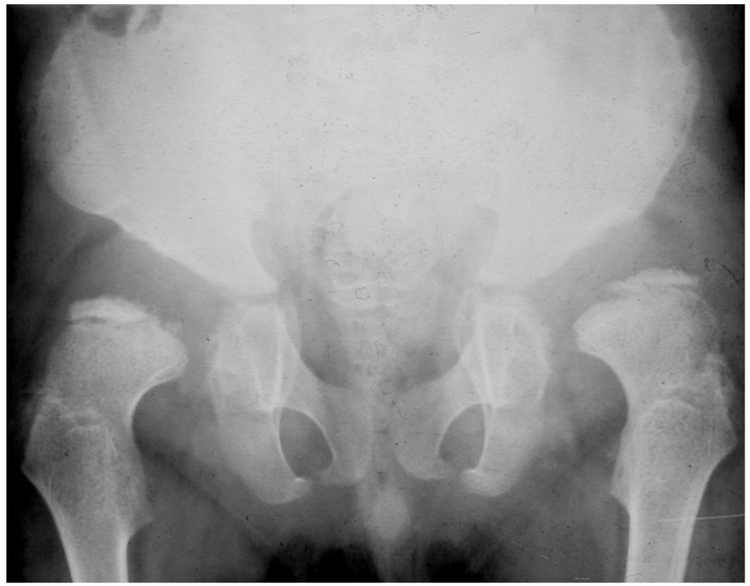
- Elosulfase alfa for Morquio

2 years



10 years



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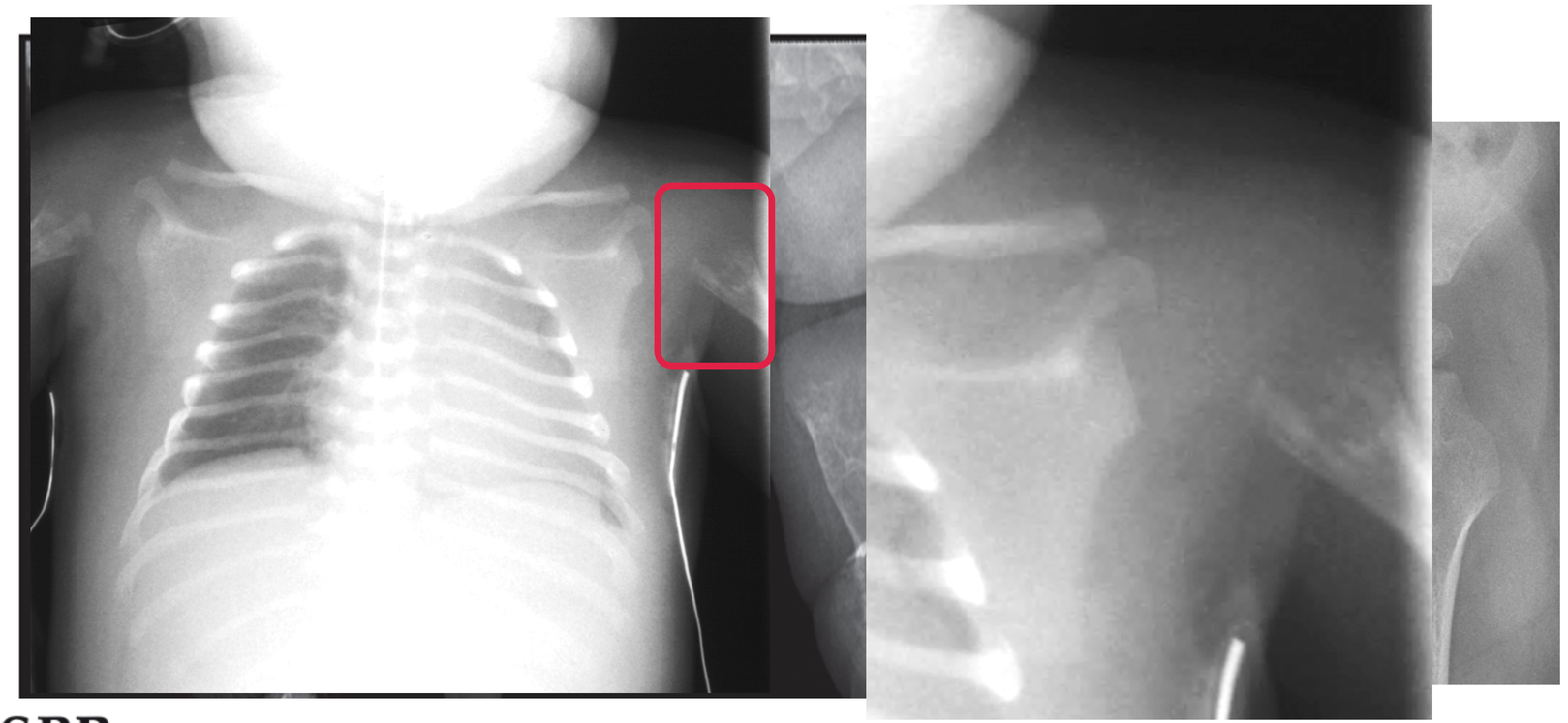
- Asfotase alfa for hypophosphatasia



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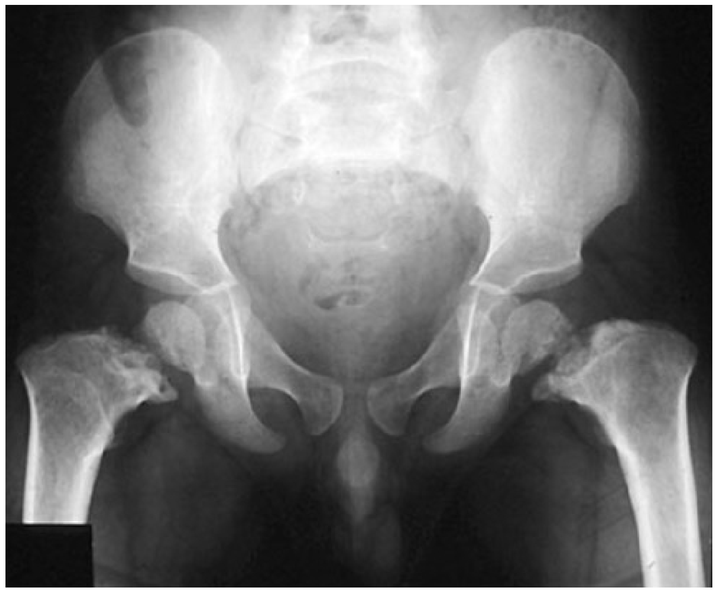
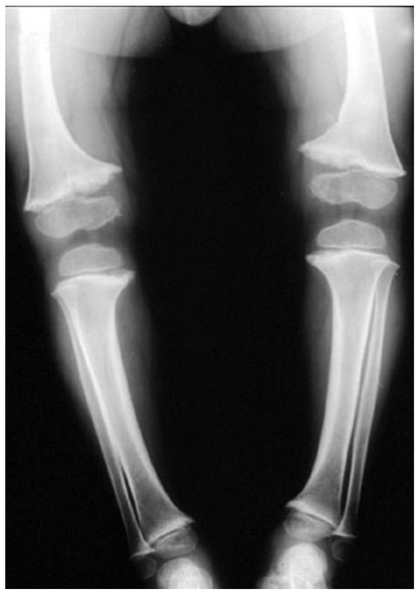
- Carbamezapine for metaphyseal chondrodysplasia type Schmid
  - Phase I/IIa open-label in 40 children with confirmed *Col10A1* mutation





› Hum Mol Genet. 2018 Nov 15;27(22):3840-3853. doi: 10.1093/hmg/ddy253.

Carbamazepine reduces disease severity in a mouse model of metaphyseal chondrodysplasia type Schmid caused by a premature stop codon (Y632X) in the Col10a1 gene

Mitra Forouhan [1], Stephan Sonntag [2], Raymond P Boot-Handford [1]

Affiliations + expand

PMID: 30010889 PMCID: PMC6216233 DOI: 10.1093/hmg/ddy253

Free PMC article

Pre-clinical data → Orphan drug → Clinical trial

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Radiological Diagnosis of Skeletal Dysplasias

In the Era of Whole Genome/Exome Sequencing, AI & Drug Trials

- More challenging
- More rewarding
  - Clinical Perspective
    - Genetic confirmation
    - Collaborative approach
  - Research Perspective
    - Design of studies/study end points
    - Artificial intelligence

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Diagnosis of Skeletal Dysplasias in the era of Whole Genome/Exome Sequencing, AI & Drug Trials

“Reverse Radiology”

dREAMS

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