Medical Genetics services and role in diseases affecting multiple systems

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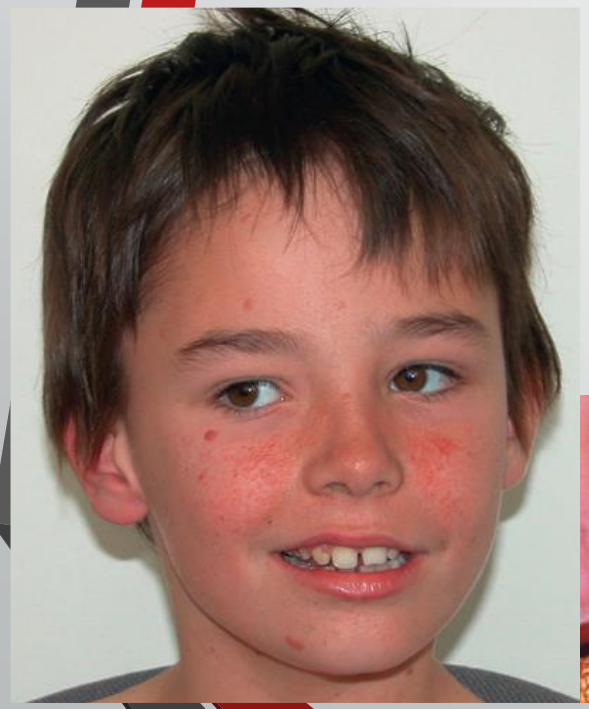
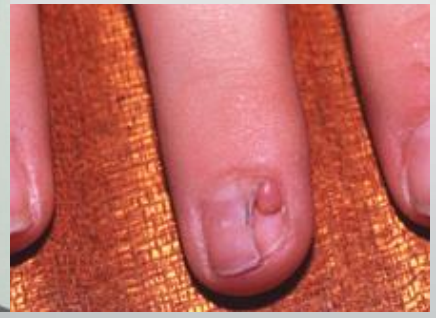
Overview

- Define terminology
- Domains of care
- Examples
- Conclusion

PLEIOTROPY





- Autosomal dominant disorders manifest in different systems of the body in a variety of ways. This is **pleiotropy**—a single gene that may give rise to two or more apparently unrelated effects affecting different parts of the body or organs.
- In tuberous sclerosis, affected individuals can present with a range of problems:
  - learning difficulties,
  - Subependymal nodules, SEGAs
  - epilepsy,
  - a facial rash known as adenoma sebaceum
  - subungual fibromas
  - Renal cysts, angiomyolipomas
  - Cardiac rhabdomyomas, conduction defects
  - All features or very few may be present.

REDUCED (NON) PENETRANCE

- Some individuals, affected by certain autosomal dominant disorders, may display very few abnormal clinical features and they demonstrate **reduced penetrance**.
- This may be the result of the modifying effects of other genes, as well as interaction of the gene with environmental factors.
- An individual with no features of a disorder despite being heterozygous for a particular gene mutation is said to demonstrate **non-penetrance**; in lay terms the condition 'skips a generation'.

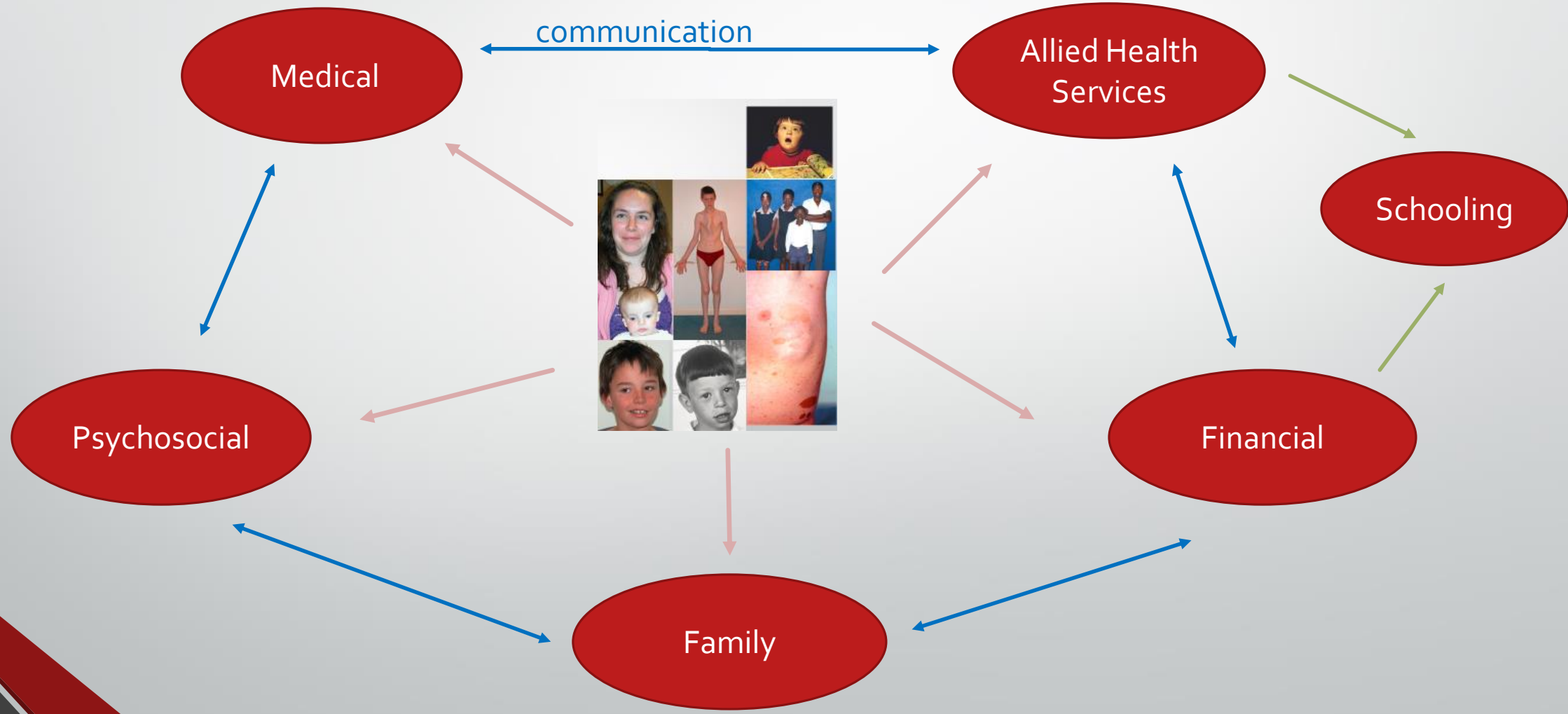
VARIABLE EXPRESSION

- The clinical features in autosomal dominant disorders can show striking variation from person to person, even in the same family. This difference between individuals is referred to as **variable expressivity**.
- In autosomal dominant polycystic kidney disease, some affected individuals develop renal failure in early adulthood whereas others only have a few renal cysts that do not affect renal function.
- Several X-linked disorders are known in which heterozygous females have features of the disease, usually presenting at a later age and less severe than the males.

HETEROGENEITY

- Different mutations in a single gene can cause a variety of diseases or phenotypes. Mutations in *LMNA* gene cause Emery-Dreifuss muscular dystrophy, dilated cardiomyopathy and a from of Charcot-Marie-Tooth disease). Called phenotypic heterogeneity.
- Mutations in different genes cause a single clinical disease. Retinitis pigmentosa is caused by mutations in different genes with different inheritance patterns. Called genetic or locus heterogeneity.

Domains of care



Medical

- Diagnostic odyssey
- Investigations to determine organ involvement
- Planning of care –referral to appropriate specialists
- Medical treatment
- Anticipatory guidance
- Monitoring for complications

Allied health care services

- Care – Occupational, Speech, Physiotherapy, Dietician,
- Rehabilitation
- Integration into society – communication skills
- Safety in home environment

Psychosocial

Genetic Alliance SOUTH AFRICA

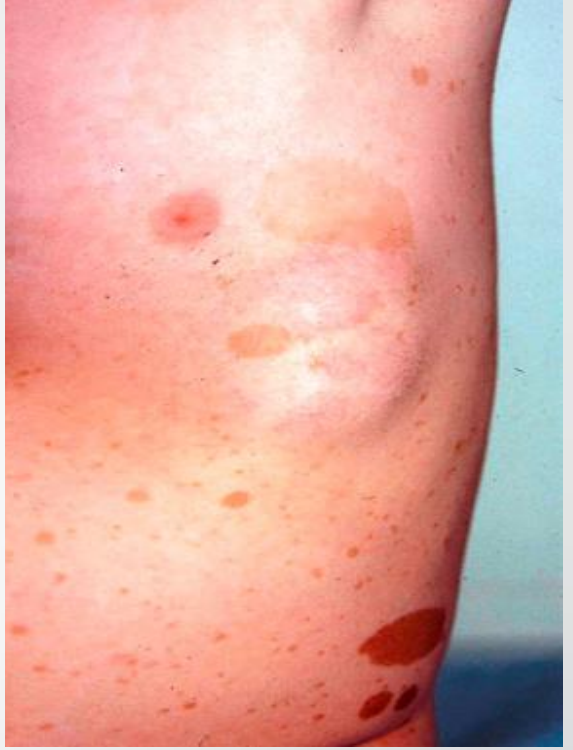
Rare Diseases South Africa — Empowerment through navigation, advocacy and engagement

- Support groups and Social Worker
- Psychology
- Genetic counselling
- Child feels different, needs to take medication chronically
- Cannot do what peers do
- Anxiety/depression affects child, parents and other family members

Financial

- Adaptation to disability
- Planning for continuation of care
- Special schooling and needs

Family involvement



- Other affected individuals (reduced penetrance)
- Manifesting heterozygotes (cardiomyopathy in Duchenne carriers, menorrhagia in haemophilia carriers)
- Recurrence risks
- Maintain family unity, attention to healthy children

Down Syndrome

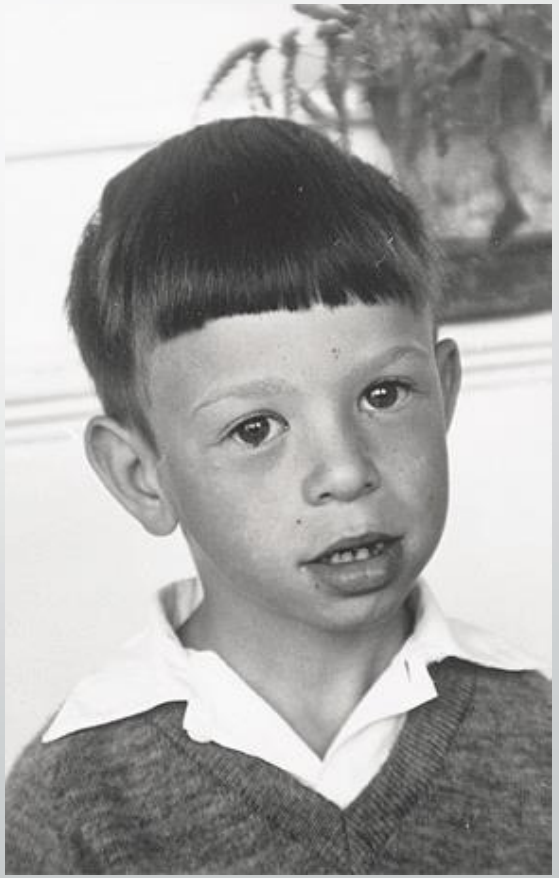
TABLE 1 Medical Problems Common in Down Syndrome

Condition	%
Hearing problems	75
Vision problems	60
Cataracts	15
Refractive errors	50
Obstructive sleep apnea	50–75
Otitis media	50–70
Congenital heart disease	40–50
Hypodontia and delayed dental eruption	23
Gastrointestinal atresias	12
Thyroid disease	4–18
Seizures	1–13
Hematologic problems	
Anemia	3
Iron deficiency	10
Transient myeloproliferative disorder	10
Leukemia	1
Celiac disease	5
Atlantoaxial instability	1–2
Autism	1
Hirschsprung disease	<1

Pediatrics 2011;128;393
Marilyn J. Bull and the Committee on Genetics
Health Supervision for Children With Down Syndrome

Williams Syndrome

Interval/Age	Test/Measurement
Annual	• Medical evaluation • Vision screening to monitor for refractive errors and strabismus • Monitoring of blood pressure in both arms • Measurement of calcium/creatine ratio in a random spot urine and urinalysis
Every 2 years	• Serum concentration of calcium
Every 3 years	• Thyroid function and TSH level
Every 5 years	• Audiologic examination
Every 10 years	• Renal and bladder ultrasound examination
In adults	• Oral glucose tolerance test (OGTT) starting at age 30 years to evaluate for diabetes mellitus 1 • Evaluation for mitral valve prolapse, aortic insufficiency, and arterial stenoses • Evaluation for cataracts



Marfan

Marfan Syndrome Diagnostic History and Physical Form

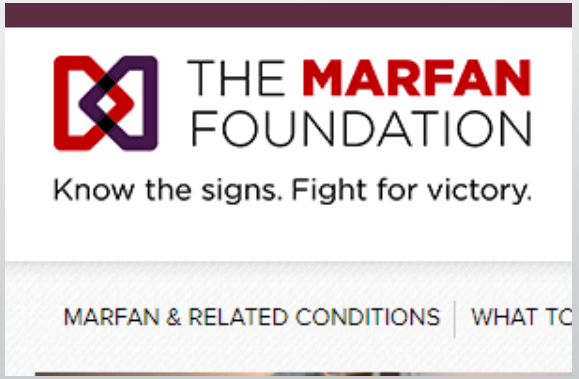
Patient Sticker

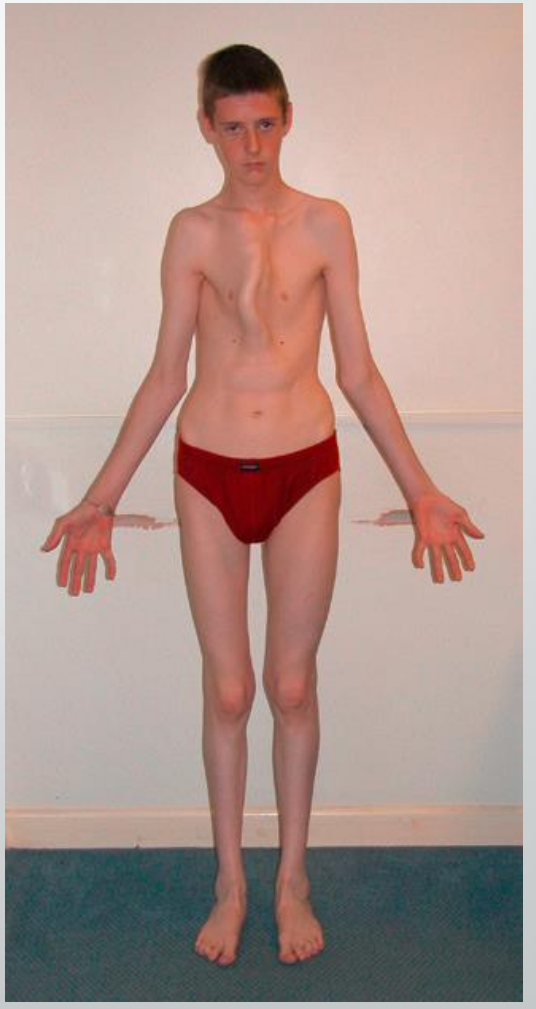
I. INTAKE INFORMATION	
Name of Patient:	
Date of Birth:	Current Age:
Referring Physician:	
Reason for Referral: (i.e., signs and symptoms of connective tissue disorder)	

II. PERTINENT PAST MEDICAL HISTORY	
CARDIOVASCULAR:	Comments:
☐ Thoracic Aortic Aneurysm	
☐ Abdominal Aortic Aneurysm	
☐ Other Aortic Aneurysm	
☐ Tortuosity of Vessels	
☐ History of Dissection	
☐ Valvular Disease	
EYE, SKIN & PNEUMOTHORAX:	Comments:
☐ Dislocated Lenses	
☐ Retinal Detachment	
☐ Myopia	
☐ Poor Healing	
☐ Abnormal Scars	
☐ Striae	
☐ Pneumothorax	
PAST SURGICAL HISTORY:	Comments:
☐ Cardiovascular	
☐ Ocular	
☐ Skeletal	
☐ Hernia	
☐ Other	

III. FAMILY HISTORY
For 1st degree relatives (parents, children, siblings) or 2nd degree relatives (grandparents, aunts, uncles, half-sibling, etc):
☐ Aortic Conditions (e.g., aneurysms or dissections):
☐ Ectopia Lentis (dislocated lenses):
☐ Marfan Syndrome or Related Disorders:

Prepared by The Marfan Foundation | marfan.org

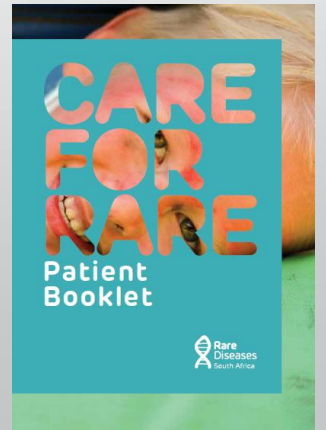


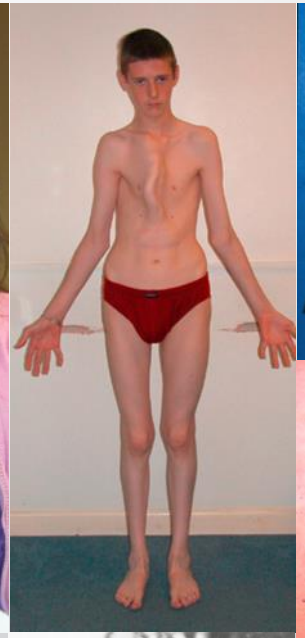


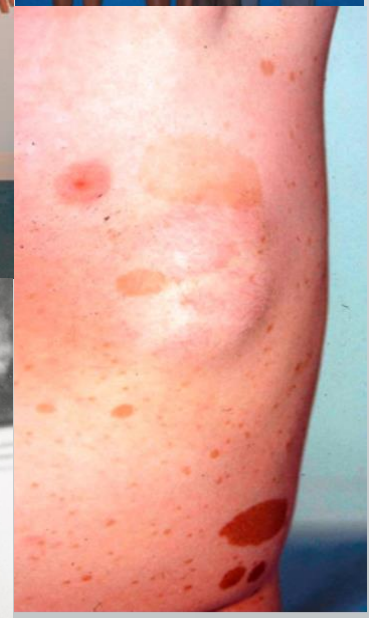
Conclusion

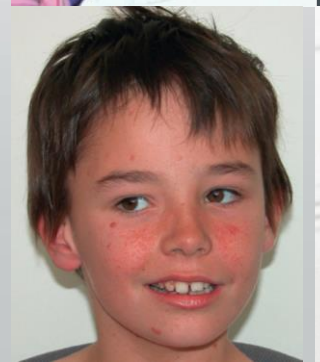
- Clinical Geneticist probably best suited to
  - co-ordinate aspects of care
  - Provide proper counselling
  - Provide effective monitoring
  - Provide ongoing support and advice
  - Arrange family screening and referral

- Patient diary being developed by RDSA









Thank you