

Information MD! 2008

Genetic Testing and Genetic Counselling

Types of tests, results, implications and benefits

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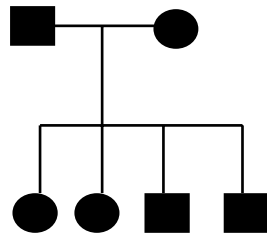
Overview

- What is genetic counselling?
 - DMD
 - SMA
- What is genetic testing?



Medical Genetics

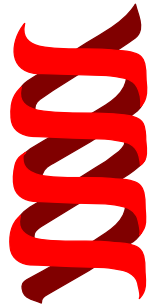
- Understanding inheritance of genetic diseases



- Developing treatment for genetic diseases



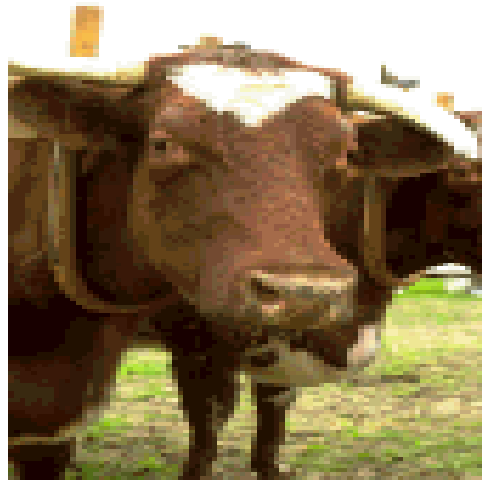
- Investigating molecular basis (causes) of genetic diseases



- Providing genetic counselling for families



How the media portrays genetics



What we do not do!

- » genetically modify food
- » clone anyone
- » weird experiments in a laboratory
- » grow babies in test tubes
- » grow organs
- » paternity testing

- » replace body parts
- » create super humans

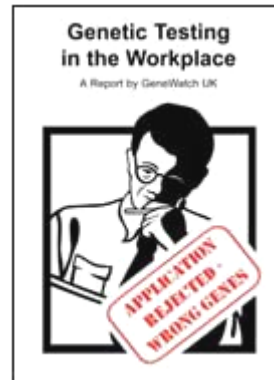


Genetics, the general public and the internet

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Why do people have genetic counselling?

- to receive information on a particular genetic condition & information on the chances of other family members possibly being affected with that condition
- Genetic counselling is often 'risk assessment' counselling



Why is Genetics different?

- Because we regularly see ‘families’ and not just the individual
- Genetic information is often “shared” information





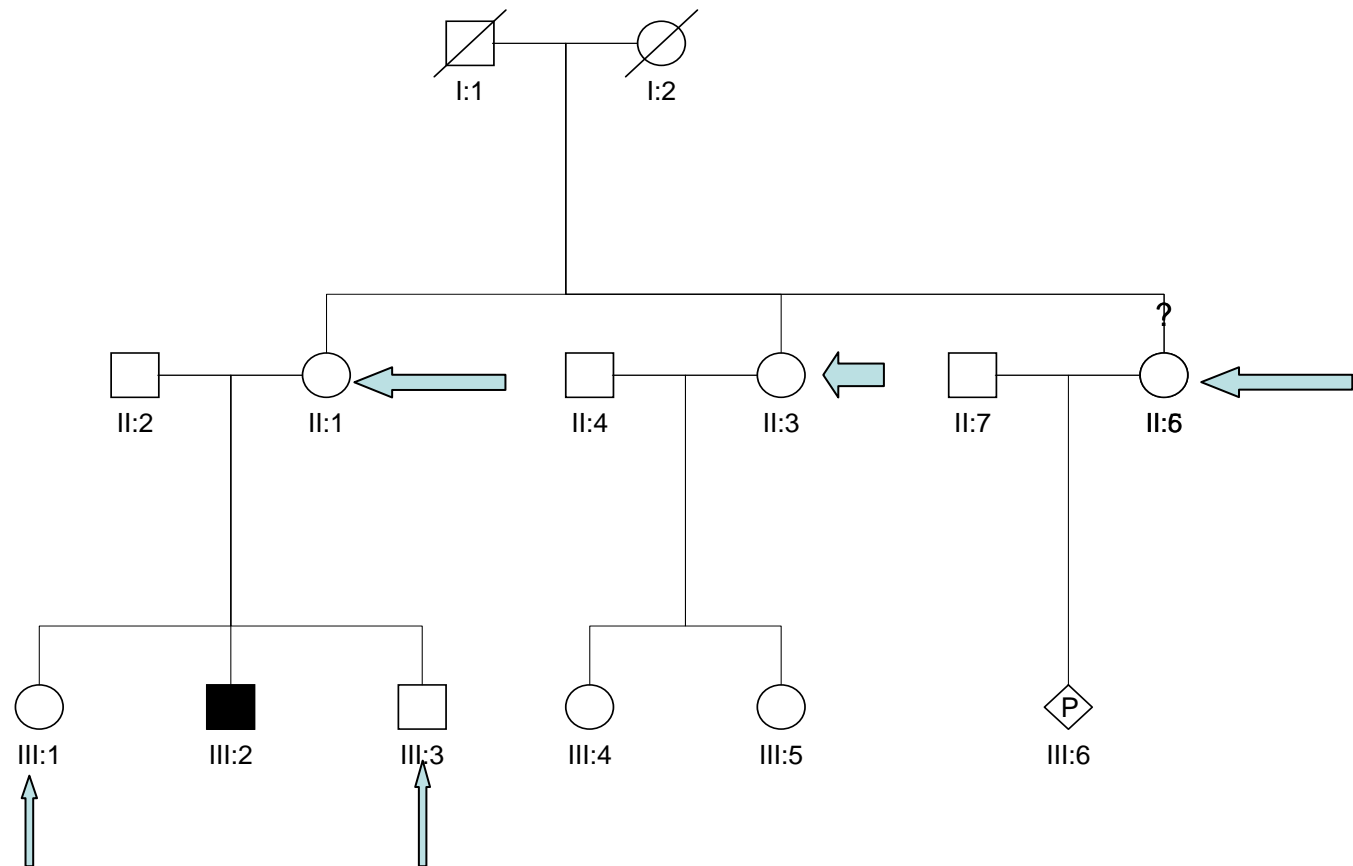
What do we do when we provide genetic counselling?

We aim to

- Provide accurate information
- Help families with interpretation of this information
- Give families options
- Provide support - practical & emotional
- Enable informed choice
- Facilitate decision making



Duchenne muscular dystrophy



Duchenne & Becker Muscular Dystrophy

- X-linked recessive disorder
- Affects:
 - 1/3500 live male births (DMD)
 - 1/30,000 live male births (BMD)

Deletions, duplications and point mutations in the DMD gene can cause either Duchenne Muscular Dystrophy (DMD) or Becker Muscular Dystrophy (BMD).

The DMD gene is located on the short-arm (p) of the X chromosome and spans 79 exons.

Approximately 65% of dystrophies in the DMD gene are a result of partial gene deletions or duplications.

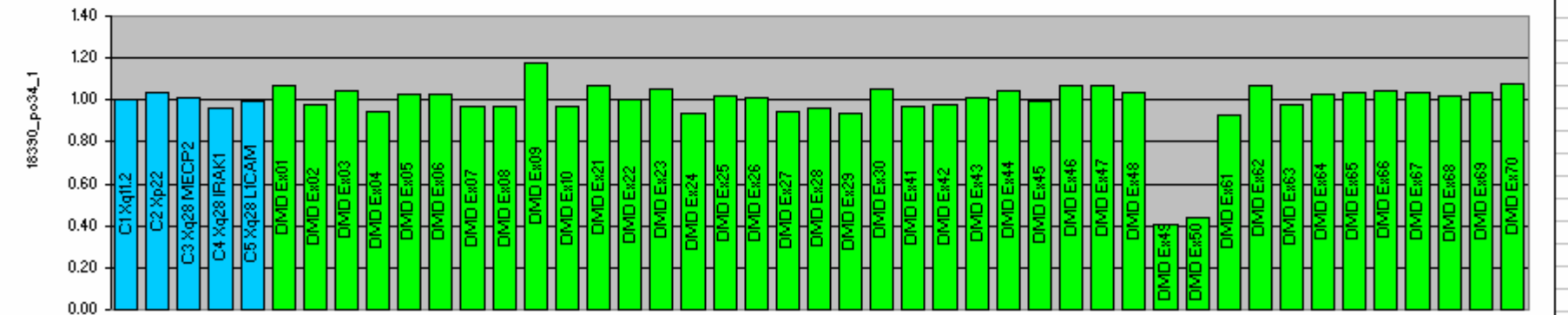
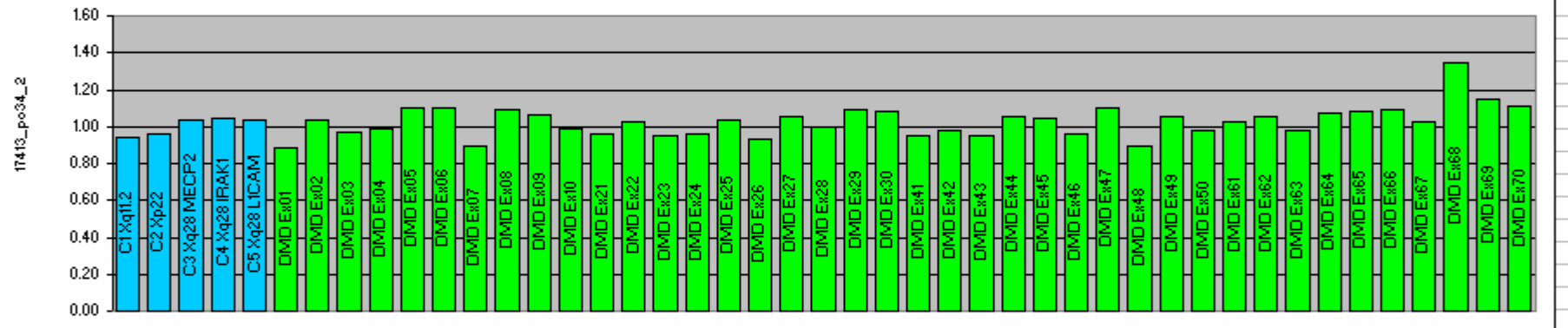
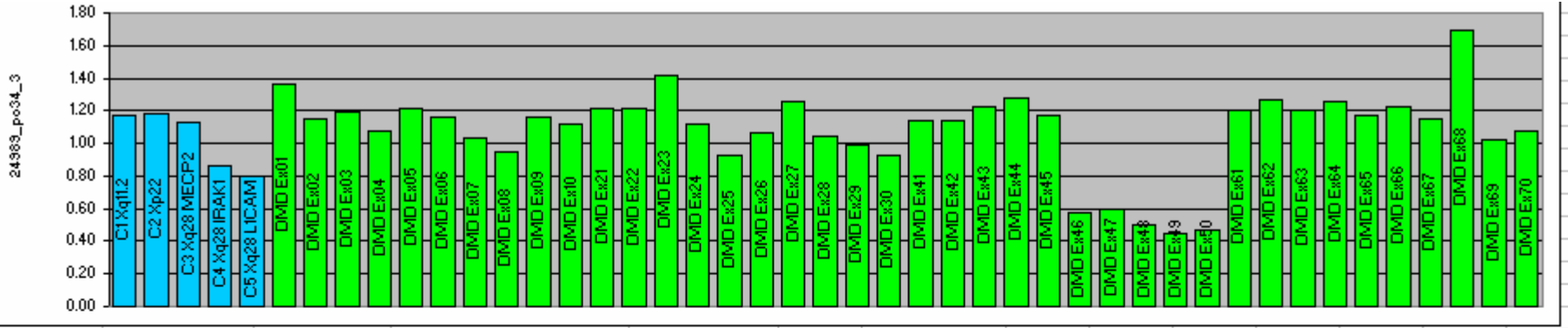
The remaining patients have point mutations or small insertions.

Diagnostic and Carrier testing

- Deletions and duplications can be detected using Multiplex Ligation-dependant Probe Amplification (MLPA).
- This assay provides the unique ability to hybridize several probes for the target region and control sequences in a single experiment
- MLPA kits are developed by MRC-Holland for DMD/BMD testing
 - Enables detection of deletions and duplications in all 79 exons in both male and female carriers.

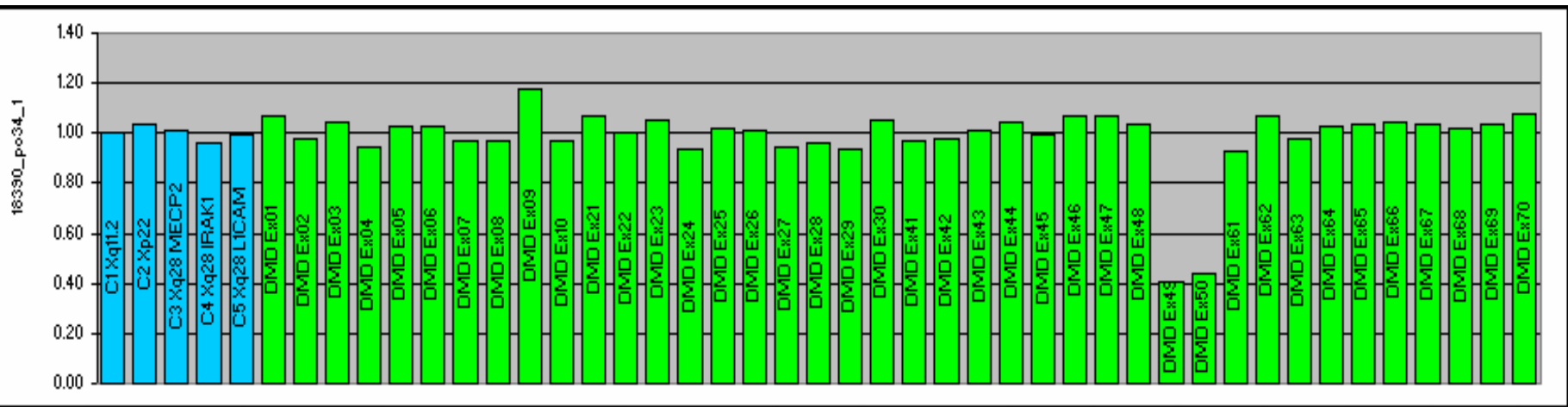


MLPA results

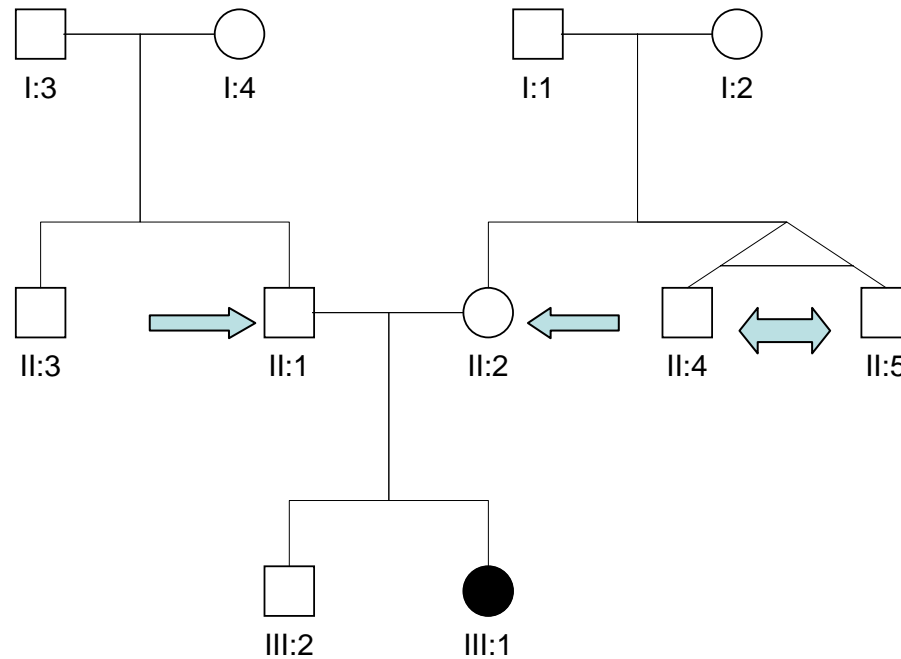


Duchenne Muscular Dystrophy MLPA

Test 2	Lab No		DMD Ex46	DMD Ex47	DMD Ex48	DMD Ex49	DMD Ex50	DMD Ex61	DMD Ex62	DMD Ex63
	18390_po34_1	C1 Xq11.2	1.06	1.06	1.03	0.41	0.44	0.92	1.06	0.97
	Operator	C2 Xp22	1.03	1.03	1.01	0.40	0.43	0.90	1.03	0.95
	Dean	C3 Xq28 MECP2	1.05	1.05	1.02	0.40	0.44	0.91	1.05	0.97
	Worksheet	C4 Xq28 IRAK1	1.11	1.11	1.08	0.42	0.46	0.96	1.11	1.01
	1	C5 Xq28 L1CAM	1.08	1.08	1.05	0.41	0.45	0.93	1.08	0.99
Quality	0.03	MEAN	1.07	1.07	1.04	0.41	0.44	0.93	1.07	0.98
	FEMALE ODDS NORMAL	:DEL	2562:1	15517:1	2856:1	1:64	1:367	1925:1	68833:1	35614:1
	FEMALE ODDS NORMAL	:DUP	17:1	74:1	29:1	2:1	3:1	88:1	284:1	660:1
	MALE ODDS NORMAL	:DUP	85:1	462:1	133:1	3:1	4:1	318:1	1942:1	2947:1
	PROB OF DEVIATION	NORMAL	46.2120%	19.1922%	67.9164%	0.0588%	0.0075%	29.6087%	0.1258%	62.9496%
	PROB OF DEVIATION	FEM DELETED	0.0180%	0.0012%	0.0238%	3.7939%	2.7567%	0.0154%	0.0000%	0.0018%
	PROB OF DEVIATION	FEM DUP	2.7859%	0.2603%	2.3522%	0.0263%	0.0030%	0.3349%	0.0004%	0.0953%
	PROB OF DEVIATION	MALE DUP	0.5427%	0.0415%	0.5099%	0.0185%	0.0020%	0.0932%	0.0001%	0.0214%



SMA



Introduction

- Spinal Muscular Atrophy (SMA) is a common autosomal recessive disorder that is characterized by degeneration of the anterior horn cells of the spinal cord
- SMA has an estimated incidence of 1/10 000 live births with a carrier frequency of approximately 1/35 - 1/40
- SMA patients are subdivided into Types I, II, III & IV according to age of onset and achieved motor abilities



SMA Types

- **Type I (Werdnig Hoffmann)**
 - Severe type, onset in the first six months of life, unable to sit or walk, and usually patients die of respiratory failure within 2 years.
- **Type II**
 - An intermediate type, onset > 6 months, patients can sit but never walk unaided, life expectancy is significantly reduced.
- **Type III (Kugelberg-Welander)**
 - Milder form of the disease, patients show first symptoms after 18 months and are able to stand and walk, but often become wheelchair bound as the disease progresses during their youth or adulthood.
- **Type IV**
 - Onset of weakness in the second or third decade of life. Motor impairment is mild without respiratory or nutritional problems, and patients are able to walk in adult years



SMN gene

- The gene involved is Survival Motor Neuron (SMN)
- The SMN gene is localized to chromosome region 5q13 within a highly complex region of DNA
- Two highly homologous genes
 - SMN1 (telomeric)
 - SMN2 (pseudogene, centromeric)
- SMN consists of nine exons (exons 1, 2a, 2b and 3 - 8)
- SMN1 and SMN2 differ by a single nucleotide in exon 7
- The severity of SMA is determined by the SMN1 mutations on both chromosomes and the SMN2 copy number



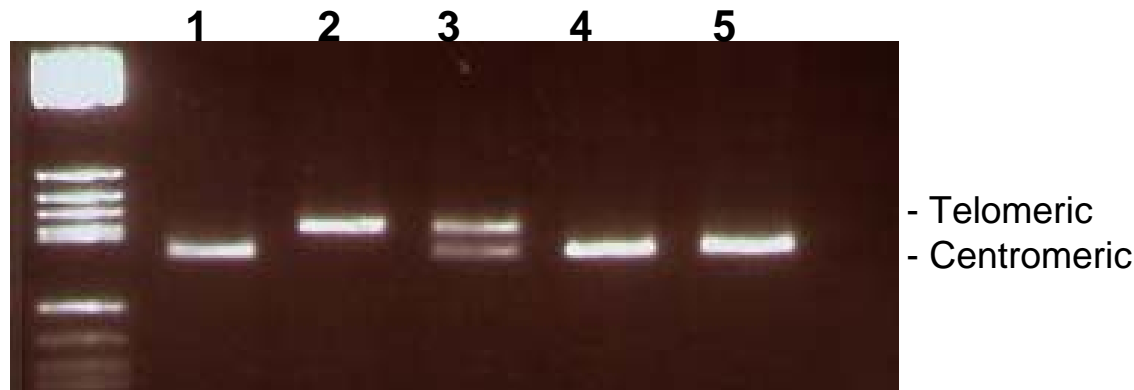
SMA carrier testing

- A Quantitative Real Time PCR assay is used to measure the copy number of the SMN1 (telomeric) gene
- The Real Time assay enables specific copy number of the SMN gene to be determined (0, 1, 2, 3, 4+ copies)
- The copy number of SMN1 varies greatly in different individuals
 - SMA carriers: 1 SMN1 copy
 - Non carriers: 2 or more SMN1 copies



SMA testing of diagnostic patients

- In 95% of patients with SMA, there is a deletion of both copies of SMN1
- The assay for diagnostic patients involves amplifying exon 7 of the SMN gene, followed by restriction enzyme digestion and gel electrophoresis



What we do....

If we do our job well:

Enable families to make decisions based on accurate information, and that families know they will be supported whatever their decisions may be.



DMD, SMA and the genetic counsellor

- The genetic counsellors role is not with the child who has been diagnosed – they are managed and cared for by a multidisciplinary team
- Genetic counsellors have a duty of care to other family members who may be at risk of passing on or being carriers of a genetic condition



Genetic Counselling

- Impact of diagnosis
- Reproductive options
- Implications for other family members
 - Who to tell?
 - When to tell?
 - What to tell?
 - How to tell?



Communication of genetic information within families

- First degree relatives more likely to be informed
- Communication more often carried out by females
- Individuals often report 'moral obligation' to inform
- Socially and emotional closeness
- Responsibility – 'head of family'



Communication of Genetic risk in families

- Difficult to comprehend & communicate
- May be hindered by:
 - Feeling guilty about passing on what may be perceived as bad news to family
 - Estranged family members
 - Social, geographical or emotional distance between relatives
 - Family members sick or pregnant



Carrier testing in children

- Limitation of child's future right to make an autonomous decision
- Loss of confidentiality of child's carrier status
- Possible stigmatization of the child
- Right of a parent to request a test
- Determining the maturity of the child in decision making process



Genetic Counselling

- Dramatic advances in genetics
- Complex information
- Clear and concise – must be relevant
- Varied
- Challenging



Genetic testing

- Genetic testing – not a panacea



Family expectations

- Living with uncertainty
- Family dynamics/Family conflict
- Loss and Grief
- Guilt/blame/shame
- Ethical issues
- Internet



We are aware that Genetic information and technology are powerful tools, and that we must never underestimate the impact of this on individuals and families.



Acknowledgments

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