Neurological examination

- Neurological examination:
- Vital signs: normal
- General: normal
- Spine: very slightly exaggerated lumbar lordosis
- Mental status and cranial nerves: normal
- Motor examination: enlargements of both calves
- Sensory examination: normal
- Gait: mild difficulties
- Muscle stretch reflexes: decreased

Laboratory investigations

- Echocardiogram i Electrocardiogram
- CT brain
- MRI brain
- Creatine kinase
- EMG
- DNA analysis
- RNA analysis
- Sural nerve biopsy
- Nerve conduction studies
- Western blot
- Muscle biopsy
- IQ score
- Karyotype of the mother of the proband?

Results of laboratory investigations

- **Laboratory findings:**
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- Echocardiogram: normal
- EKG: normal
- Nerve conduction studies: normal
- Needle electromyography: Myogenic changes, fibrillation potentials and short-duration, low amplitude, rapidly recruiting motor unit potentials.
- Cranial CT scan: normal
- Brain MRI: normal
- DNA analysis: deletion of the exons 45-47 of the *DMD* gene on chromosome Xp21.
- RNA analysis –not performed
- Sural nerve biopsy: normal Creatine kinase (CK): 14.250 IU/L (normal 0-300)
- Karyotype of mother of the proband: 45, XX, der(14;21)(p10;q10)

Diagnosis ?

Genetic counselling

- All daughters of Robert will receive the abnormal gene-life expectancy
- All daughters of Robert will be carriers of Duchenne muscular dystrophy
- The risk to sons of women who are definite carriers is 1 in 2 (50%)
- Is there mother of Robert carrier of the mutation in the *DMD* gene?
- Will Robert transmit the disease to his sons ?
- Are the sisters of Robert carriers of DMD gene mutation ?
- What is life expectancy in Duchenne dystrophy ?
- Lifespan is markedly reduced in DMD.
- Should be karyotype be performed in the sisters of proband?
- Prenatal diagnosis is available to carriers of a known dystrophin mutation by chorionic villus sampling (CVS) at 11 weeks gestation
- Prenatal diagnosis is available to mothers of an apparently de novo *DMD* mutation (germline mosaicism)
- If *DMD* mutation is unknown high risk X may be identified by linkage studies.

Medical menagement

- Loss of ambulation usually between 7 and 13 years, rehabilitation, prednisolon under the control of the neurologist
- -Scoliosis (90% of patients, surgery if necessary should be performed in specialist centre) Note that prior to intervention rigorous cardiac assessment should be performed.
- -Nocturnal hypoventilation (night- time facial or nasal mask ventilation)
- -Cardiac problems (ECG every two years to age 10 years and annually thereafter)
- Echo should be repeated before any surgery.

Questions

- X-linked disease is not transmitted from male to male- a problem of phenocopies

- Karyotype of mother of the proband:
- 46, XX, der(14;21)(p10;q10)
- Which investigations are necessary ?

Results of DNA analysis

- A deletion removing exons 45-47 from the mature mRNA leaving all the other exons of the *DMD* gene intact

In frame and out of frame mutations in the *DMD* gene

Exon	Size (bp)	Frame	Phenotype
41	183/3=61	0	BMD
42	195/3=65	0	BMD
43	173/3=57.6	-1	DMD
44	148/3=49.3	+1	DMD
45	176/3=58.6	-1	DMD
46	148/3=49.3	+1	DMD
47	150/3=50	0	BMD
48	186/3=62	0	BMD
49	109/3=36.3	+1	DMD

Results of DNA analysis

- A deletion removing exons 45 (-1)+ 46(+1)+ 47 (0)= 0 from the mature mRNA leaving all the other exons of the *DMD* gene intact

Diagnosis

- Duchenne muscular dystrophy ?
- Becker muscular dystrophy ?

Laboratory investigations

- Echocardiogram and Electrocardiogram
- Cranial CT scan
- Muscle CT scan
- Brain MRI
- Creatine kinase
- Needle electromyography
- DNA analysis
- RNA analysis
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- IQ score
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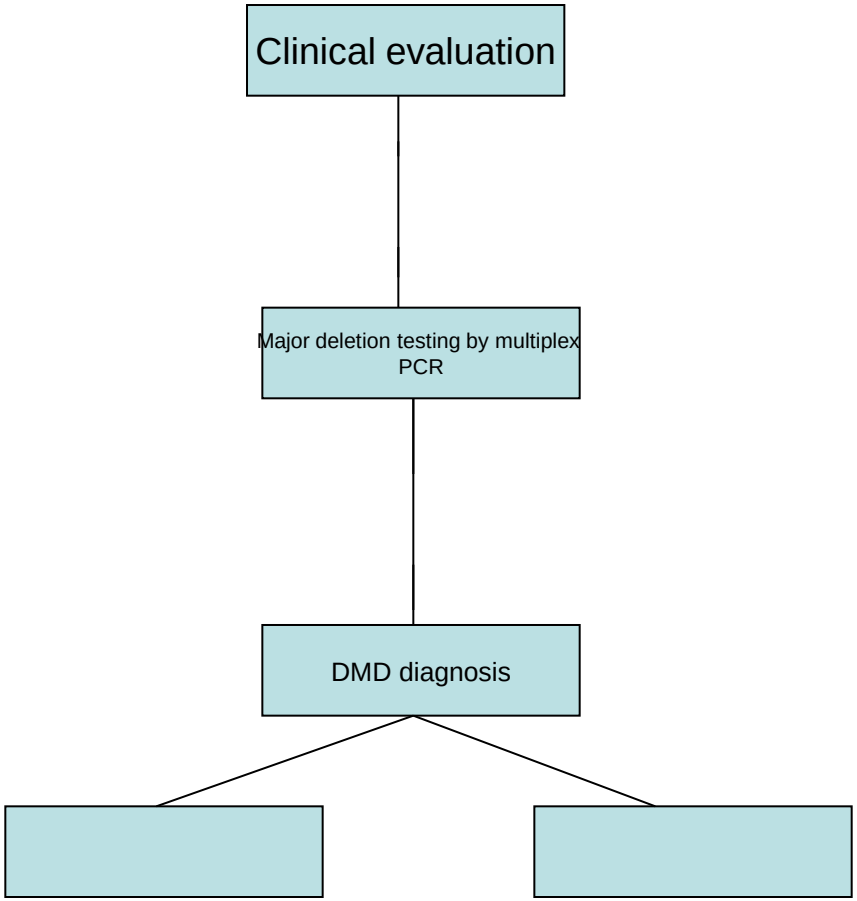
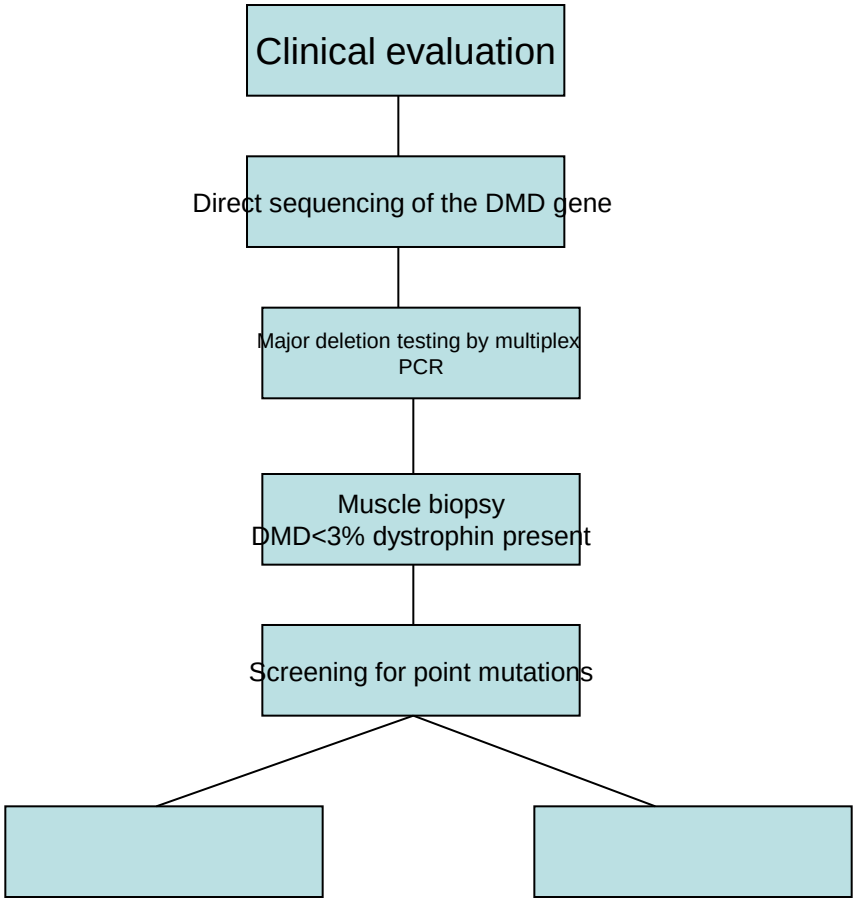
Bayes' theorem to establish the risk

Probability	She is a Carrier	She is not a carrier
Prior	1/2	1/2
Conditional (3 affected sons)	1/8	1
Joint	1/16	1/2
Odds	1	8
Final probability	1/9	-
Final probability	-	8/9

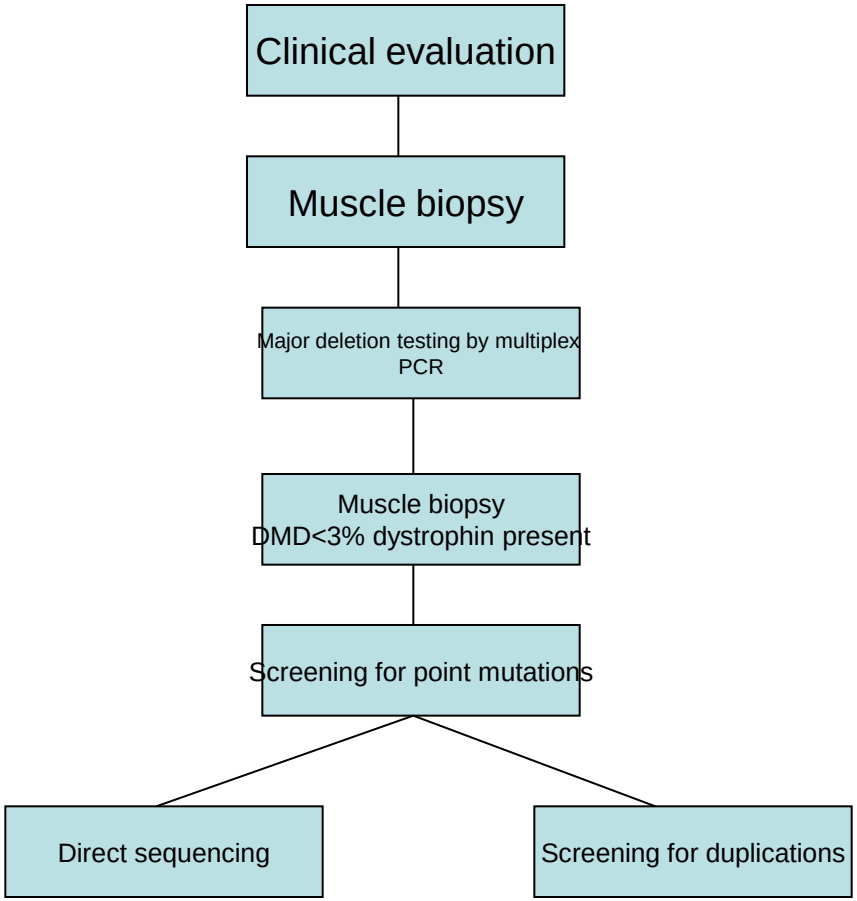
Current diagnostics procedure in DMD/BMD (1)



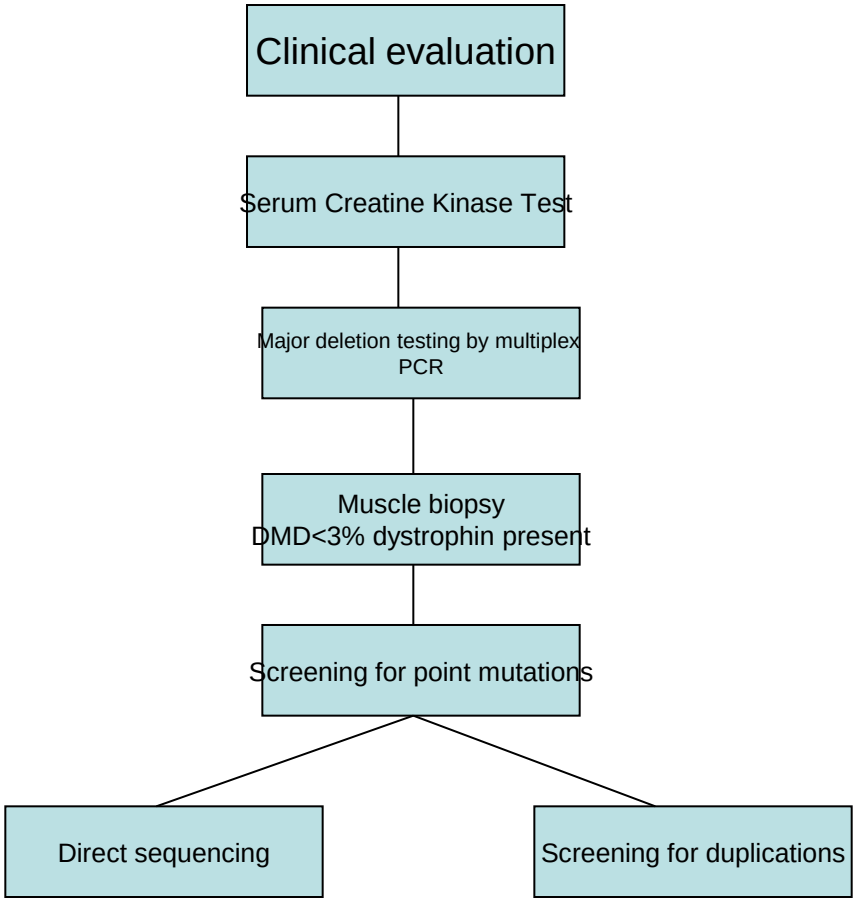
Current diagnostics procedure in DMD/BMD (2)



Current diagnostics procedure in DMD/BMD (3)



Current diagnostics procedure in DMD/BMD (4)



Current research for DMD/BMD therapies

- Aminoglycoside antibiotic read-through of stop codons (translational infidelity)-the patients with nonsense mutations
- Induced exon-skipping to yield a BMD phenotype from a DMD mutation (antisense oligoribonucleotides directed against splice sites)
- Regulation of other genes to ameliorate the DMD/BMD phenotype (upregulation of utrophin, a dystrophin homolog)
- Myostatin has been shown to act as a negative regulator of muscle growth