Increased NT with normal karyotype: Is termination justified?

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Introduction

- Measuring NT during the first trimester scan in combination with PAPP-A and B-HCG can predict 80 – 90% of chromosomal abnormalities
- Abnormal NT can also predict structural defects especially cardiac defects.
- It is also used as an early marker of twin-to-twin transfusion in monochorionic twins
- Furthermore some syndromes have been described to have abnormal NT's

Incidence of chromosomal defects according to NT measurement

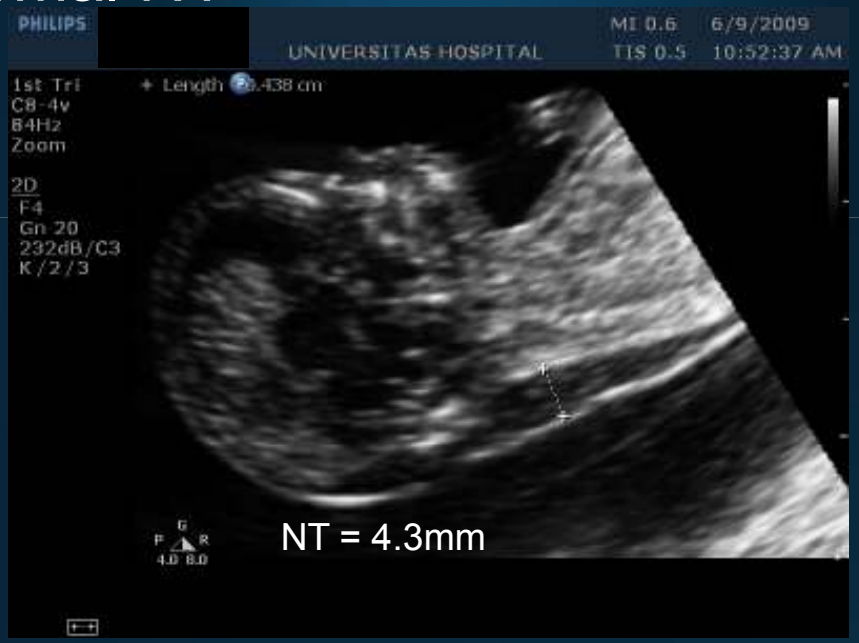
Nuchal translucency	Chromosomal defects
≤3.4 mm	0.33 %
3.5 – 4.4 mm	21.1 %
4.5 – 5.4 mm	33.3 %
5.5 – 6.4 mm	50.5 %
≥ 6.5 mm	64.5 %

Souka et al. 2001

The dilemma!

- Parents counselled
- We measure an abnormal NT
- Karyotyping is done
- Results: NORMAL

SO WHAT NEXT?

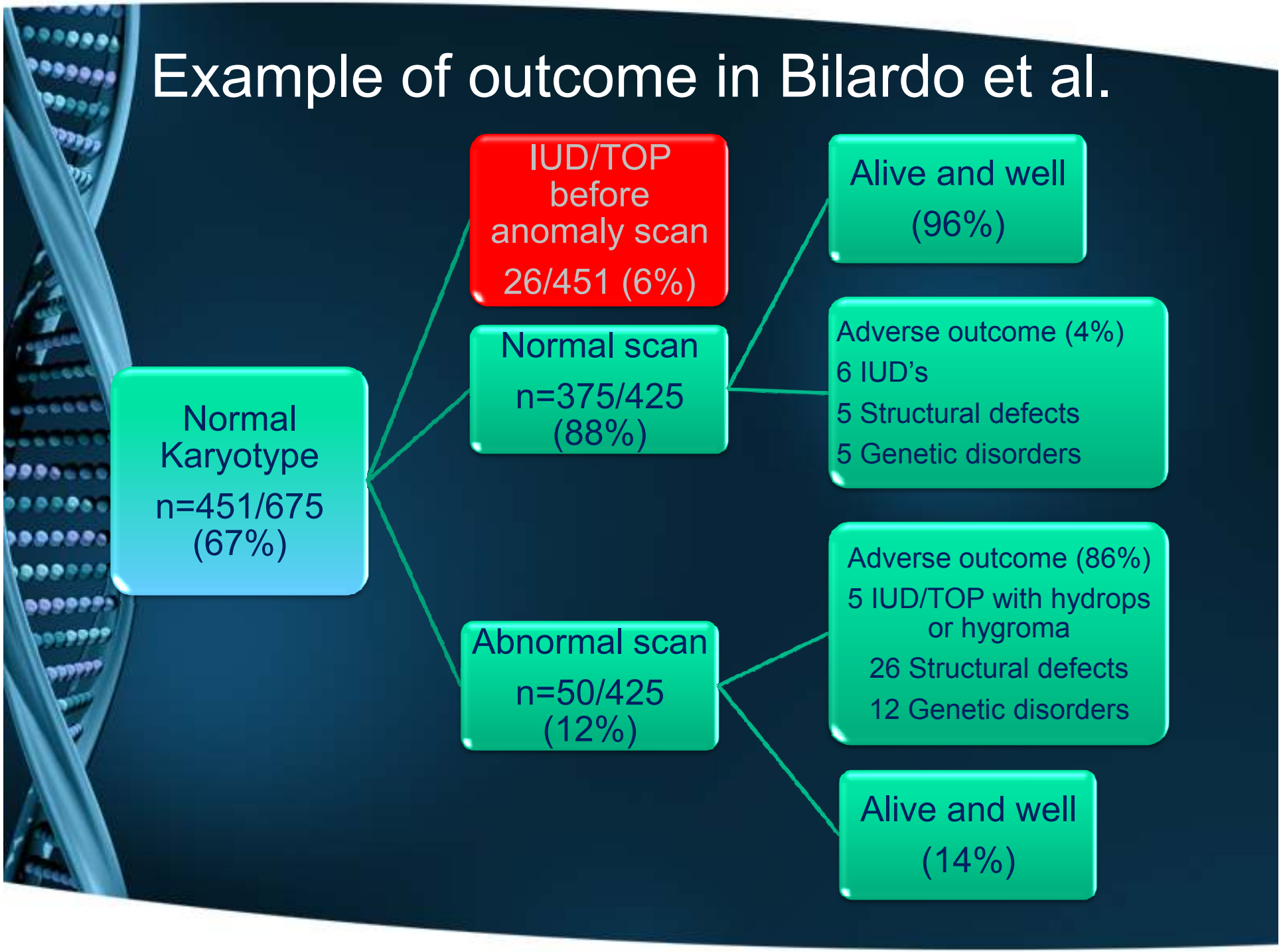


What can we expect if karyotype is normal?

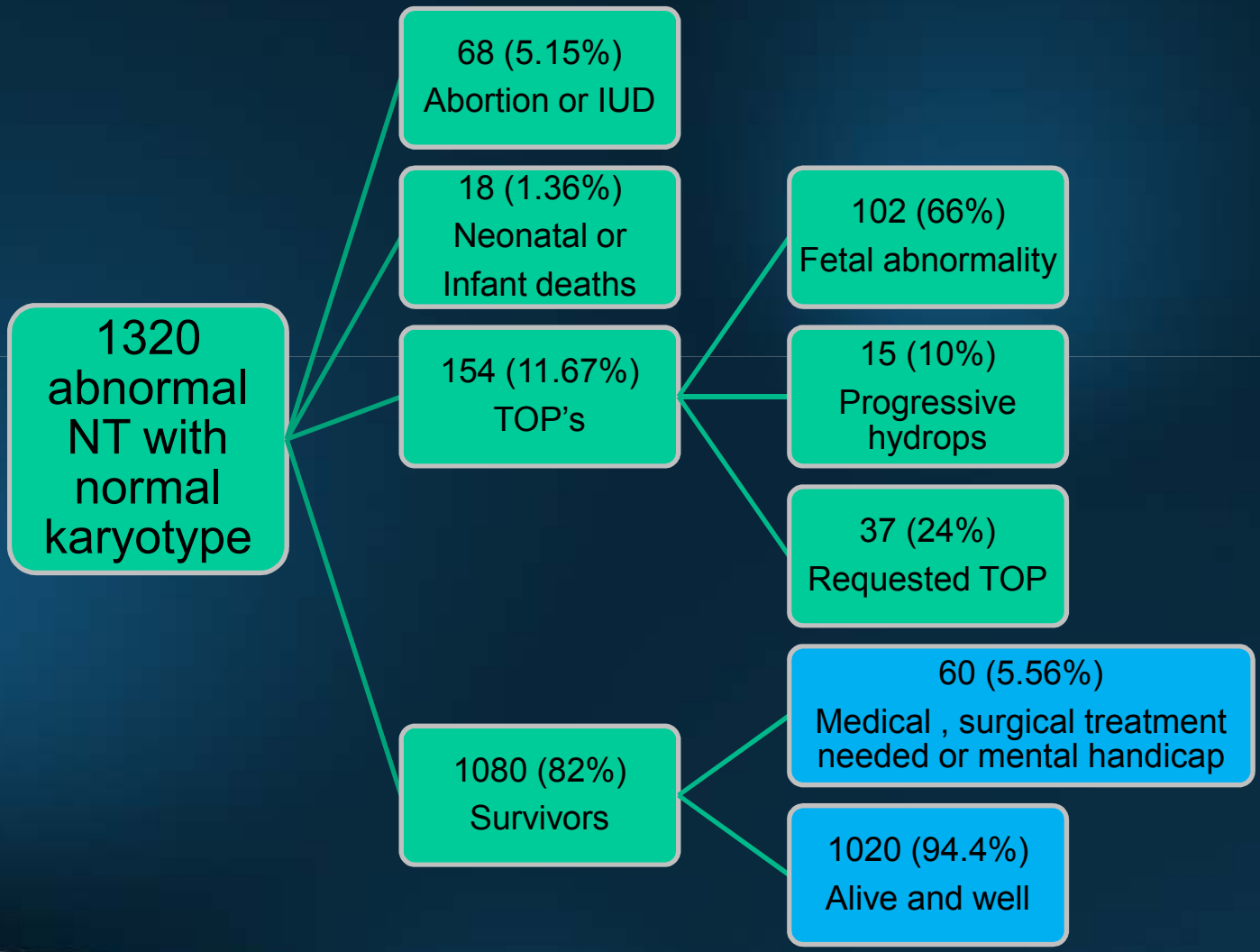
As NT increases the chance for a normal fetus decreases

NT (mm)	Live births, no defects (Bilardo et al. 2007)	Live births, no defects (Souka et al. 2001)
95th centile – 3.4	92 %	
3.5 – 4.4	83 %	85.9 %
4.5 – 5.4	71 %	77.3 %
5.5 – 6.4	58 %	66.7 %
≥6.5	20 %	31.2 %

Example of outcome in Bilardo et al.



Outcome in Souka et al.



So why the increase in NT?

Proposed meganisms:

- Cardiac dysfunction due to abnormalities of the heart or great arteries
- Venous congestion of the head and neck
  - Amnio rupture sequence
  - Diaphragmatic hernia
  - Narrow chest in skeletal abnormalities
- Failure of lymphatic drainage
  - Delayed development of lymphatic tissue
  - Impaired fetal movements
- Fetal anaemia or hypoproteinemia
- Altered composition of subcutaneous tissue

Souka et al. 2001

Fetal abnormalities and genetic syndromes reported in association with increased NT

Central nervous system defect

Anencephaly	Joubert syndrome
Craniosynostosis	Microcephaly
Dandy-Walker malformation	Macrocephaly
Diastematomyelia	Spina Bifida
Encephalocele	Iniencephaly
Holoprosencephaly	Trigonocephaly C
Hydrolethalus syndrome	Ventriculomegaly

Fetal abnormalities and genetic syndromes reported in association with increased NT

Facial defect

Agnathia/micrognathia

Facial cleft

Microphthalmia

Treacher-Collins syndrome

Nuchal defect

Cystic hygroma

Neck lipoma

Cardiac defect

Multiple lesions – VSD, ASD, DORV, Epstein's, AVSD etc.

Fetal abnormalities and genetic syndromes reported in association with increased NT

Pulmonary defect

Cystic adenomatoid malformation

Diaphragmatic hernia

Fryn syndrome

Abdominal wall defect

Cloacal extrophy

Exomphalos

Gastrochisis

Fetal abnormalities and genetic syndromes reported in association with increased NT

Gastrointestinal defects

Crohn's disease
Duodenal atresia
Esophageal atresia
Small bowel obstruction

Genitourinary defect

Ambiguous genitalia
Hydronephrosis
Hypospadias
Infantile polycystic kidneys
Muticystic dysplastic kidneys
Renal agenesis

Souka et al.

Fetal abnormalities and genetic syndromes reported in association with increased NT

<u>Skeletal defect</u>

Achondrogenesis

Achondroplasia

Asphyxiating thoracic dystrophy

Campomelic dwarfism

Jarco-Levin syndrome

Kyphoscoliosis

Limb reduction defect

Osteogenesis imperfecta

Roberts syndrome

Short rib polydactyly

VACTER assosciation

Fetal abnormalities and genetic syndromes reported in association with increased NT

Fetal anemia

Blackfan-Diamond anemia

Fanconi

Parvo B19 virus infection

Neuromuscular defect

Fetal akinesia deformation sequence

Myotonic dystrophy

Spinal muscular atrophy

Metabolic defect

Beckwith- Weidemann syndrome

Other

Severe development delay

Noonan syndrome

Souka et al.

What should our management be?

- Reassure the parents:
  - Overall adverse outcome quoted in most studies around 18%
- Follow up anatomy scan at 16 and 20 weeks (should include extensive cardiac evaluation)
- If this scan is normal, the chance of a live birth with no defects increases to **96-98%** (Adverse outcome in 2.24%)
- Adverse outcome can be expected in 18% if nuchal edema persists

If chromosomal defects are included

- The chance of an adverse outcome, including chromosomal defects increase with nuchal translucency

Nuchal Translucency (mm)	Adverse outcome including chromosomal abnormalities
3.5 – 4.4	32%
4.5 – 5.4	49%
5.5 – 6.4	67%
≥6.5	89%

Severe development delay

- 1.2 % if nuchal edema persists
- 0.4% if follow-up scans was normal

What about added diagnostic techniques for genetic/developmental syndromes?

- Studies up to now has failed to show added benefit (Schou et al. 2009)

What we do know……

Of the known 99 genetic/developmental syndromes associated with increased NT:

- Only 49 have genes identified
- Only 36 have reported mutations (400 in all)

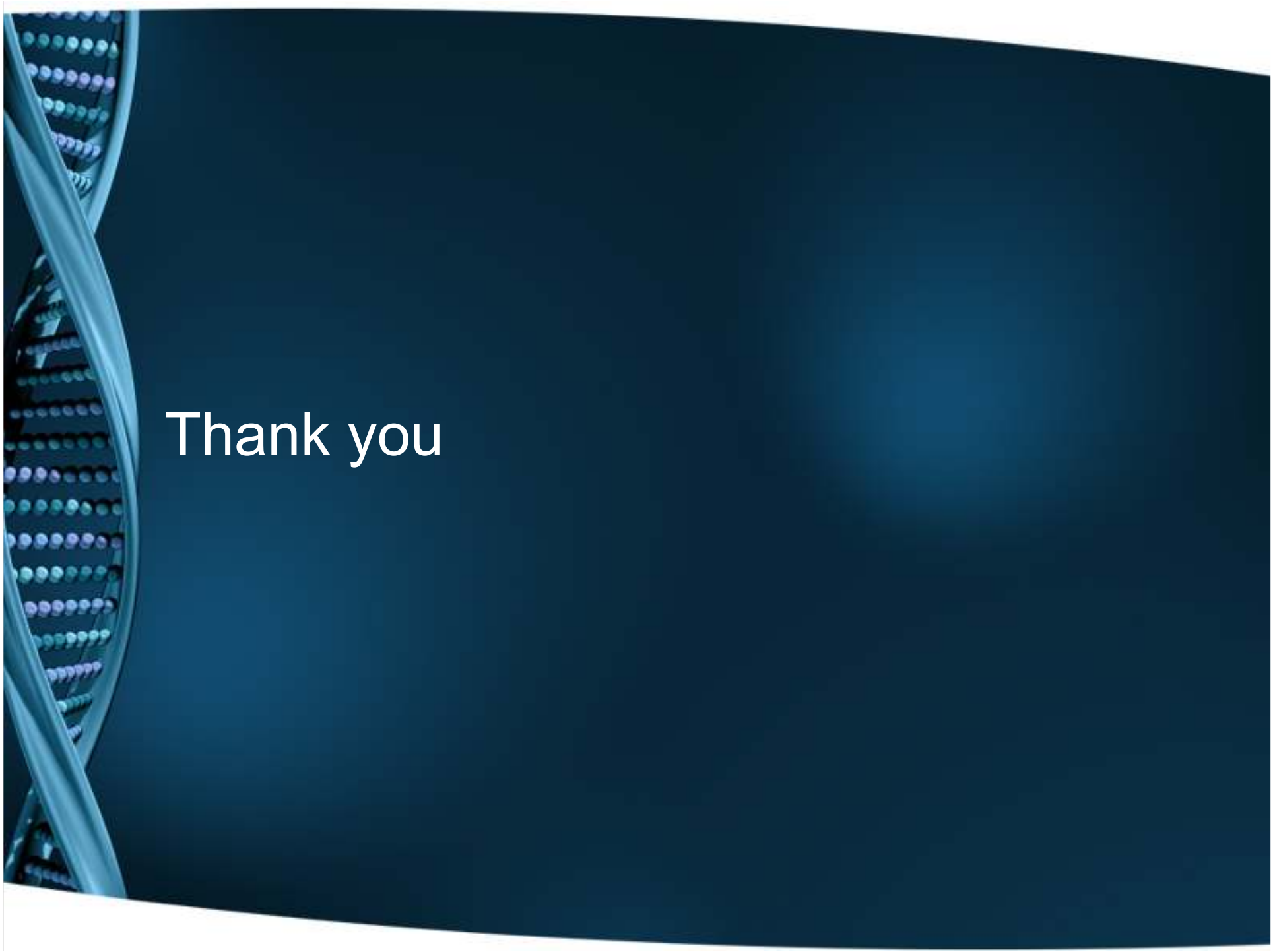
5 Diseases most prominent

1. DiGeorge: 7 genes with 17 mutations
2. Noonan syndrome: 5 genes with 108 mutations
3. Smith-Lemli Opizt: 1 gene with 130 mutations
4. Congenital adrenal hyperplasia: 1 gene with 25 mutations
5. Spinal muscle atrophy: 1 gene with 1 mutation

Should we identify common syndromes in our population associated with increased NT and test for those, if testing is available?

Conclusion

- Outcome not so poor
- With a good and thorough mid trimester scan we can identify most of the 18% that will have an adverse outcome.
- With a normal follow-up scan the outcome can be expected to be favourable in 96 – 98% of cases.
- We need to counsel our patients accordingly to let them make an informed decision.


Thank you