LEIDEN UNIVERSITY MEDICAL CENTER

Risks and considerations of N=1 trials

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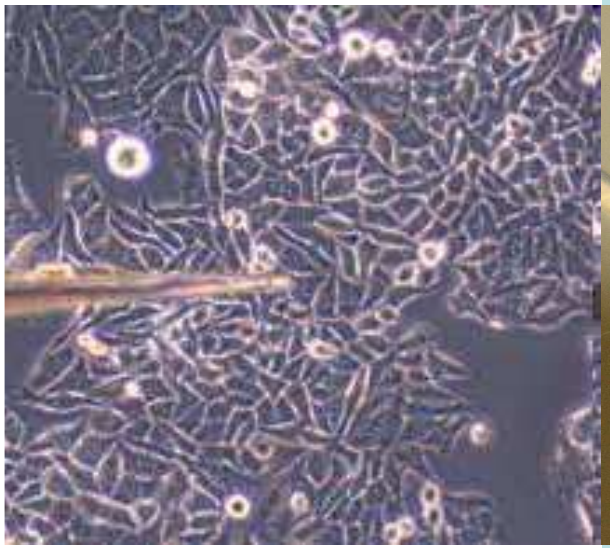
London

Test procedure therapeutic approaches

Cell culture → Animal models → Patients



- First test
- Does it work?
- Few cells
- No circulation
- No immune system
- No organs

- *Mdx* mouse
- Lacks dystrophin
- Organs & immunity

Limitation:

- Efficient regeneration
- High metabolism

Phase I/II:

- Primarily: safety
- No control group

Phase II/III:

- Effective?
- Long term safety?

Drug testing in patients

- **Test compound properties**
  - Taken up by tissues efficiently?
  - How quickly cleared from the body?
- **Test compound for efficacy**
  - Does it work?
  - At which dose?
- **Test compound for safety**
  - Are there side effects?
  - At which dose?
  - Are they tolerable?

Drug testing in groups of patients

Boys with Duchenne are all unique!

- Variation in response to drug
  - Compound uptake and processing by body
  - Beneficial/intended effect
  - Side effects
- Variation in disease progression
  - Stable phase or progressive
  - Speed of progression

➔ All influence response to compound

N=1 trials

Compare two drugs for certain amount of time

A → washout → B

➔ Were symptoms better/worse/similar for A/B?

➔ Side effects?

Conditions

- For chronic conditions with a **stable** course
- Treatment effects quickly identifiable

DMD

- Progressive disease
- Therapeutic approaches aim to slow down progression
- Difficult to pick up effect

N=1 trials

Example:

Patient takes compound x for 6 months

6 MWT before: 250 m

6 MWT after: 180 m

➔Patient became worse

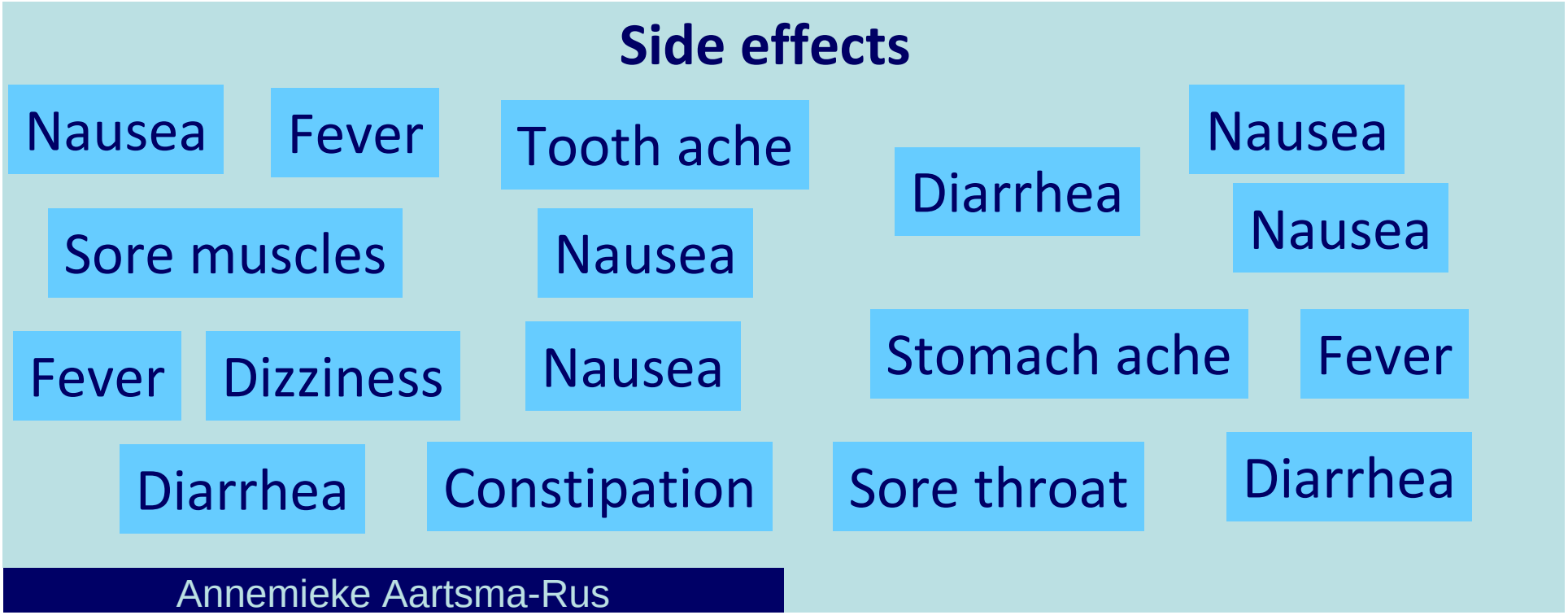
Unknown what would have happened without compound

- Did compound x make patient progress quicker?
- Would progression have been same without compound x?
- Would progression have been worse without compound x?

Drug testing in groups of patients

Boys with Duchenne are all unique!

- Need groups of patients to assess
  - **Safety**
  - Efficacy



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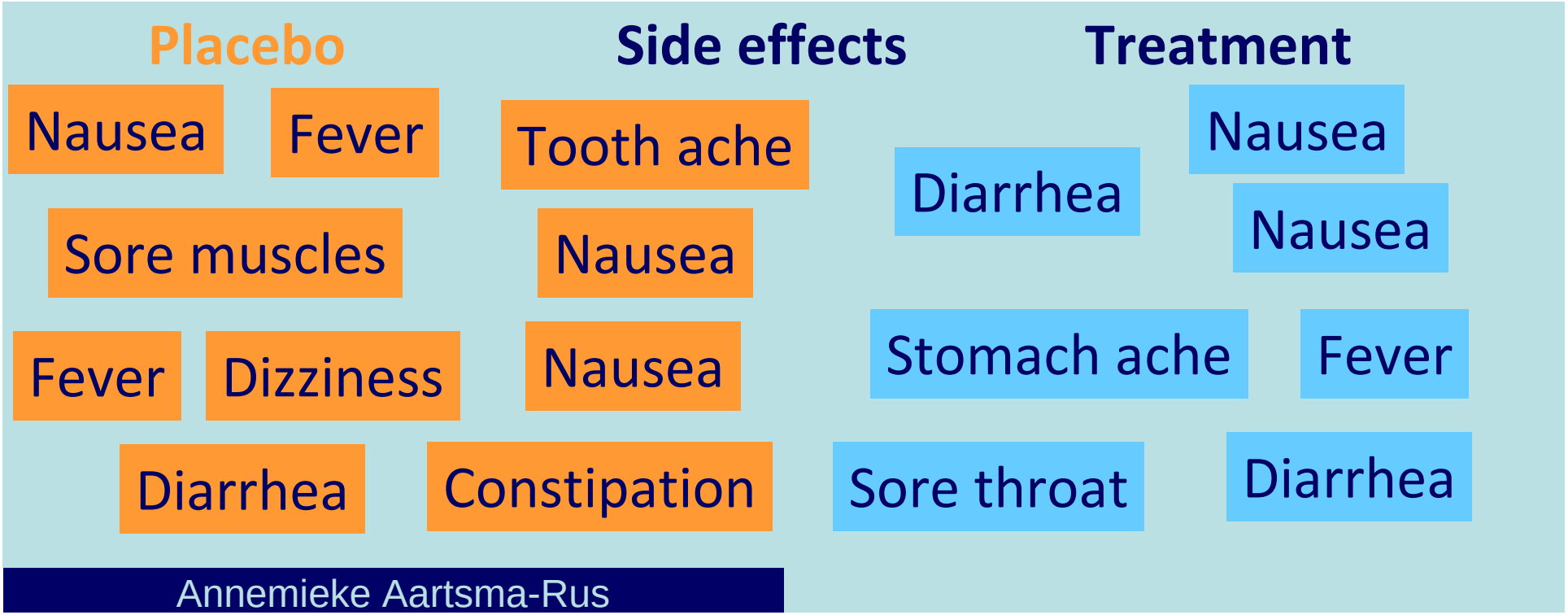

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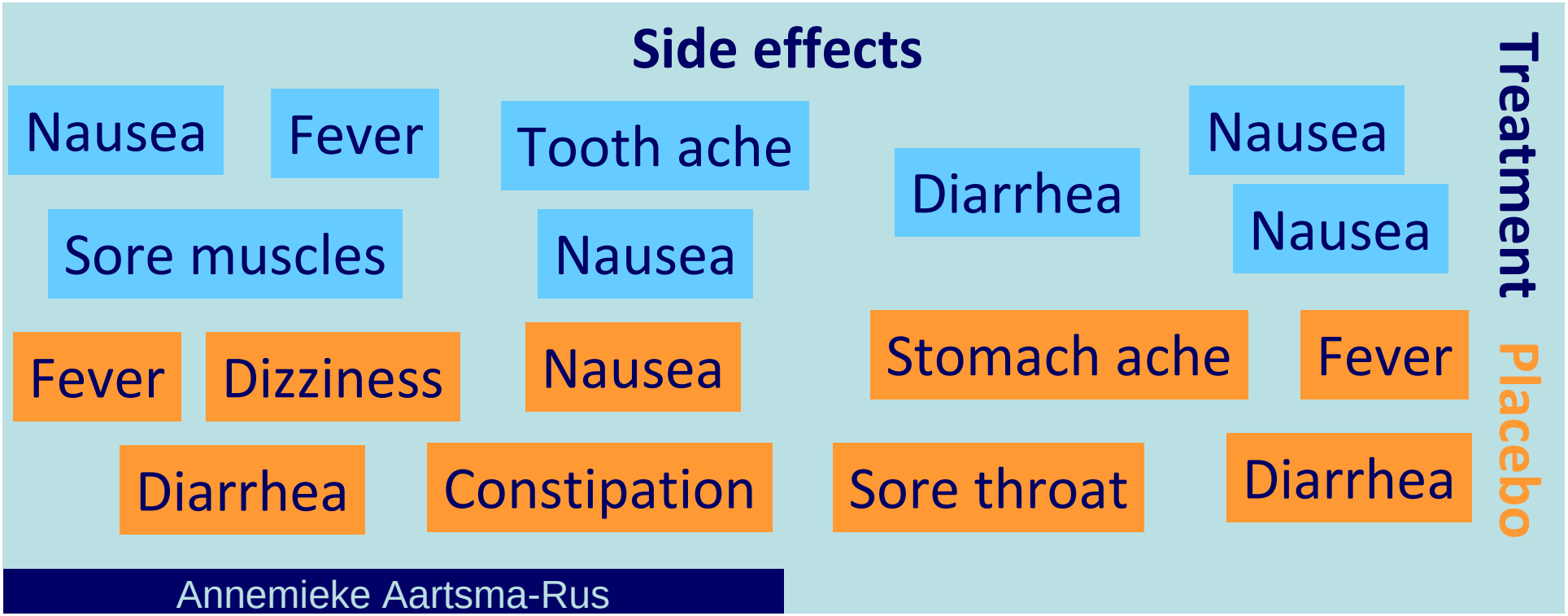

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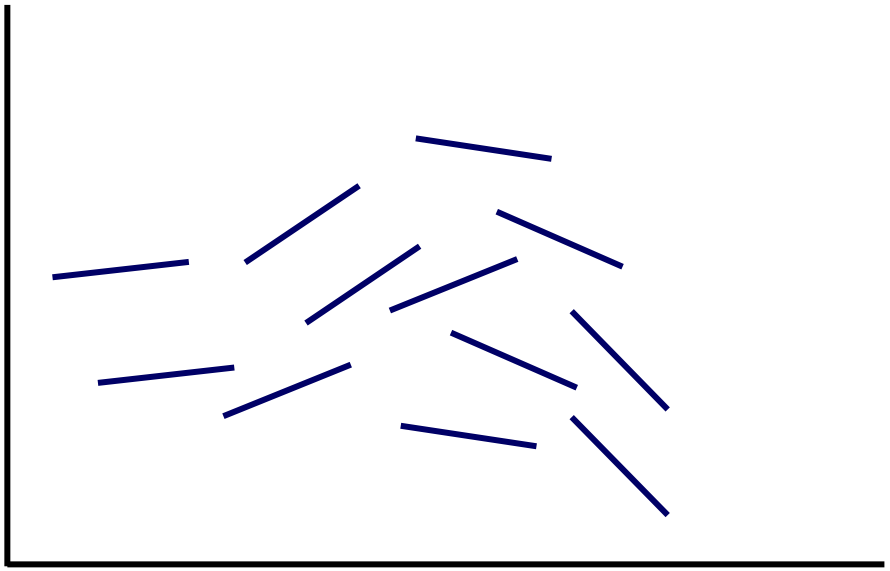

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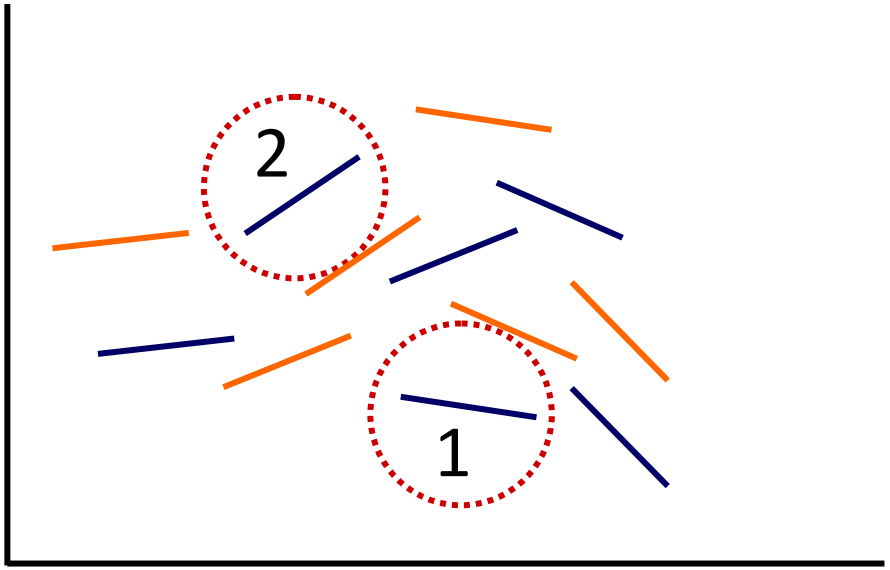


Conclusion:

Overall: No effect

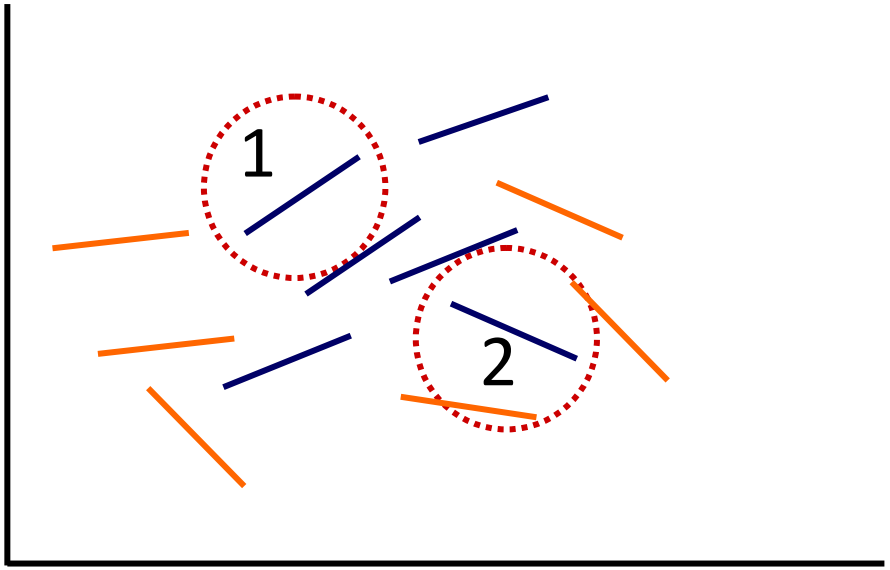
1: No effect

2: Effect

Drug testing in groups of patients

Boys with Duchenne are all unique!

- Need groups of patients to assess
  - Safety
  - **Efficacy**



Conclusion:

Overall: Effect

1: Effect

2: No effect

Drug testing in individual patients

Boys with Duchenne are all unique!

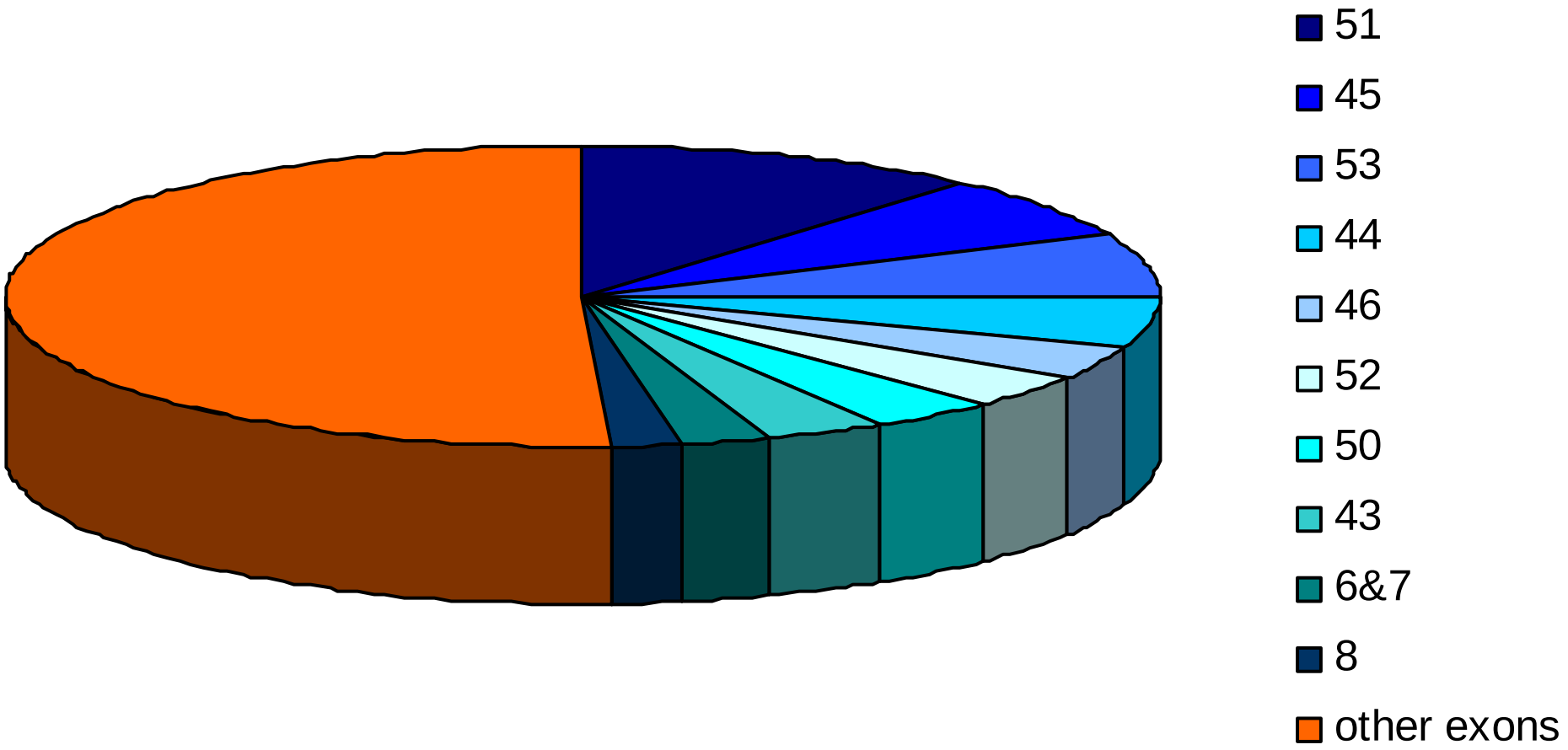
- Need groups of patients to assess drugs
- Based on individual patients risk
  - Conclude compound is safe when it is not
  - Conclude compound is not safe when it is
  - Conclude compound is effective when it is not
  - Conclude comopund is not effective when it is

Exon skipping challenge

- Mutation specific approach
- Exon 51 skipping tested in placebo-controlled trials
  - 180 patients
  - Assess safety and efficacy
- Trials for exon 44 skipping ongoing
  - Dose finding
- Trials for exon 53 and 45 skipping planned for 2012
  - Dose finding

➔Does not apply to majority of patients

Exon skipping challenge



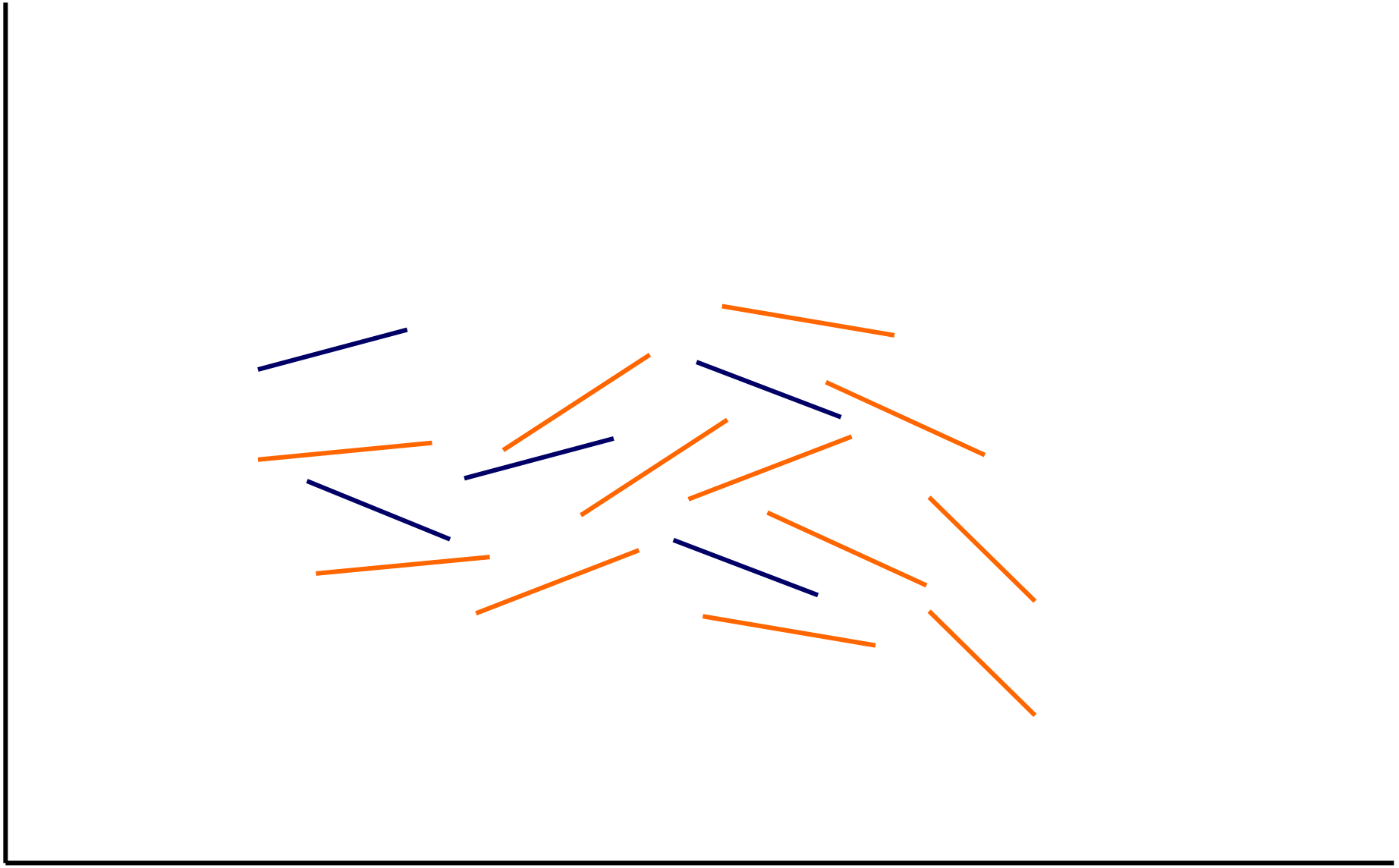
Challenge of exon skipping trials

- All AONs are considered new drugs
- Have to go through all stages of clinical testing
- AONs of same chemistry
  - Same building blocks
  - Different order

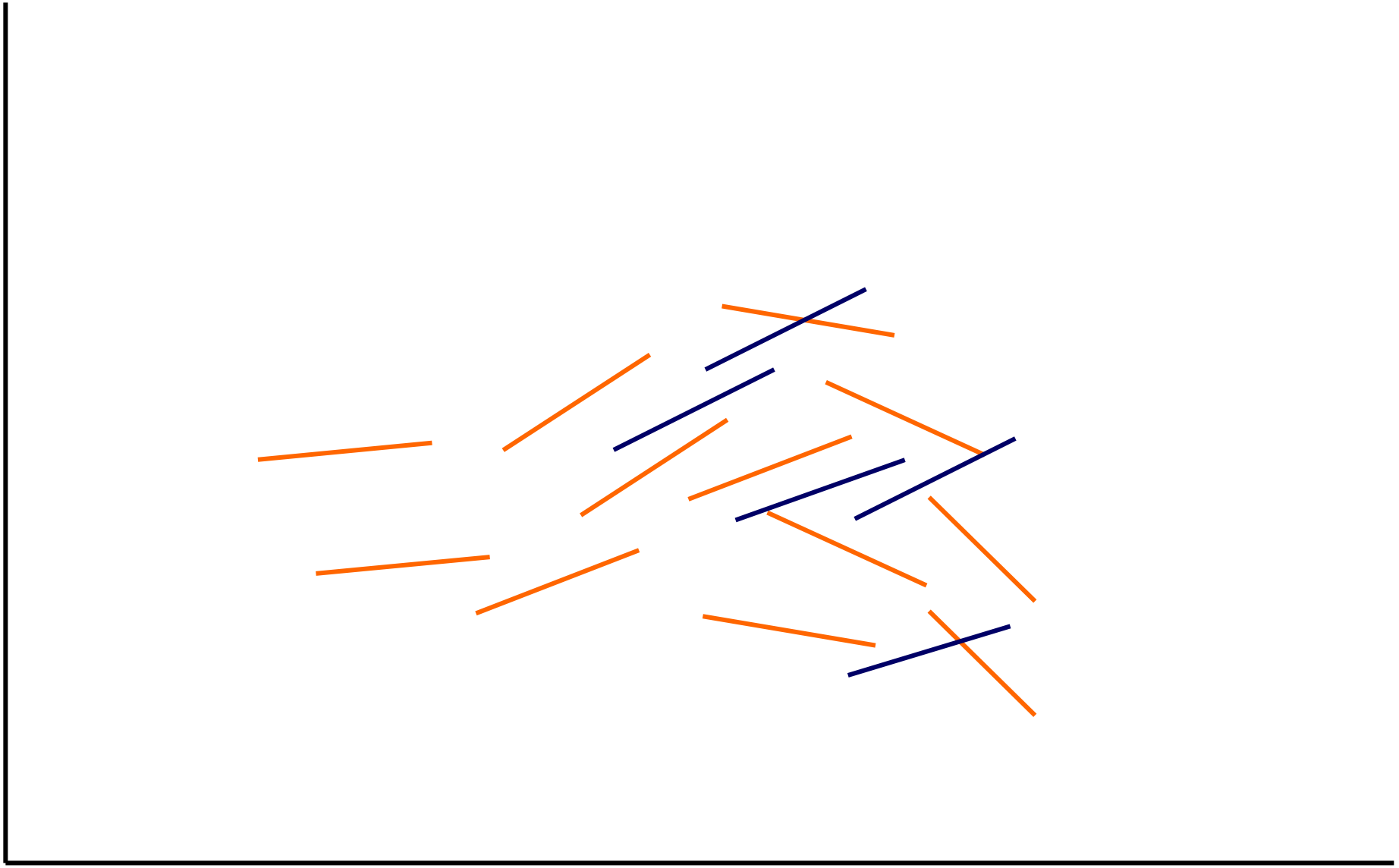
Future for exon skipping

- Need results exon 51 placebo-controlled trial
  - Safe and effective?
- Quicker development path for future compounds
  - Cannot do large trials for all exons
- Toxic screening
  - Confirm compound behaves as expected
  - Identify toxic compounds in early stage
- Tests in smaller groups of patients
- Good natural history data

Natural history data



Natural history data



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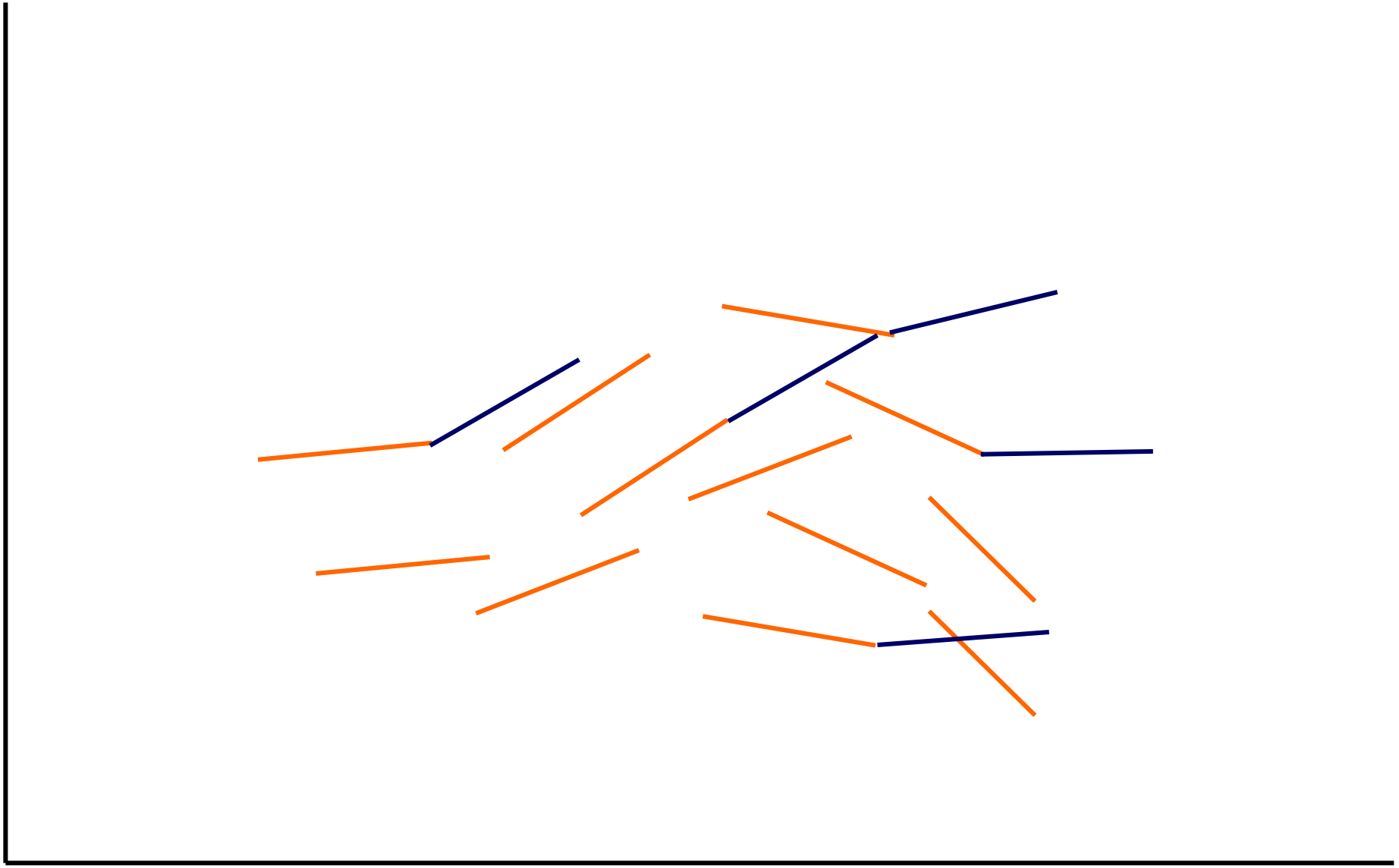

Summary

- Due to variation between patients need more than 1 patient in trial
- Usually large groups → impossible for DMD
- Better use of natural history data
  - Placebo effect
  - Also need other outcome (e.g. dystrophin)
- For similar compounds (e.g. exon skipping)
  - Tools to identify abnormally behaving compounds