The genomic timeline of testicular germ cell tumour (TGCT)

**Pre-cancer: TGCT predisposition**
- FRR of TGCT is high (4 to 8 fold)
- 49% of all TGCT risk is inherited
- Susceptibility is highly polygenic
- Pathways implicated: KIT signalling, male germ cell development, sex determination, genomic integrity

**Precursor state: tumour origin**
- TGCTs can arise from a non-invasive precursor lesion, called ITGCN
- ITGCN likely forms during fetal development
- ITGCN has high expression of OCT3/4 & NANOG
- ITGCN is malignant equivalent of PGC

**Progression to cancer: tumour subtypes**
- ITGCN lies dormant until puberty
- Following puberty ITGCN cells begin to proliferate, due to hormonal influences
- i(12p) likely acts as a triggering event, causing invasive growth
- ITGCN transforms to either seminoma / non-seminoma tumour histologies

**Presentation with malignant tumour**
- TGCTs have a low rate of somatic mutations
- KIT and KRAS are most frequent driver genes
- wt p53 retained
- High level of i(12p) - hallmark CNV
- seminoma = mKIT, hyper-triploid
- non-seminoma = wtKIT, hypo-triploid

**Post-treatment: platinum resistance**
- TGCTs are typically platinum-sensitive with high >95% 5-year survival.
- Small minority are resistant to platinum
- Mechanisms of platinum resistance are poorly understood but may include DNA repair genes, p53 activity and methylation patterns

**Post-cancer: long term survivorship issues**
- TGCT survivors can experience a number of platinum-based side effects: neurotoxicity, hypogonadism, infertility, increased risk cardiovascular disease and secondary cancer.
- Certain germline polymorphisms, e.g. variants in GSTP1, increase patient risk

Features:
- Early adulthood
- Late adulthood

Time:
- Pre-conception
- Fetal development
- Post natal development
- Post pubertal development
- Early adulthood
- Late adulthood