14. **The Cancer Genome Atlas** (TCGA) is a comprehensive and coordinated effort to accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies.
15. It has identified 33 cancer types from 11,000 samples. Its findings include:
    - Molecular basis of cancer – improved our understanding of the genomic underpinnings of cancer.
    - Tumour subtypes – revolutionized how cancer is classified.
    - Therapeutic targets – identified genomic characteristics of tumours that can be targeted with currently available therapies or used to help drug development.

16. **The International Cancer Genome Consortium** aims to identify all the genetic faults in large numbers of individual cancers.
17. It has identified more than 46 million somatic mutations in all cancers. There are therefore more mutations than the number of human genes: each gene is **mutated ~3 times.** There are thus many different mutation combinations between individuals, explaining the heterogeneous nature of cancer and the need for personalised medicine.

18. **Summary:** Genome instability *varies among and within cancer types.* I.e. some breast cancer types have few mutations due to different lifestyles, stage of the disease, predispositions (i.e. susceptibility).
19. Many mutations are found within the **coding portions** of the genome, such as introducing stop codons into the frame. This impacts the protein, causing different amino acid sequences and causing early termination or short frames.
20. Silent mutations are redundant and have no impact on the protein.
21. Some tumours have a high frequency of non-silent mutations per tumour due to accumulations during mismatch repair mechanisms caused by environmental factors such as sun exposure or smoking.

Not All Mutations Contribute to Cancer:

1. **Driver mutations** are mutations that confer a *selective growth advantage* to the tumour. i.e. a driver mutation could lead to cells overcoming the selective barrier that causes apoptosis – "just right instability" – thus resulting in cell immortality.
2. **Passenger mutations** are mutations that have *no effect* on the neoplastic process. I.e. mutations that introduce early stop codons that have no effect on the protein.

3. **Inactivating driver mutations** lead to the *loss-of-function* of the encoded protein – **tumour suppressor genes.**
4. ~95 tumour suppressor genes have been identified so far.
5. **Activating** driver mutations (oncogenes) lead to the *gain-of-function* of the encoded protein.
6. Proto-oncogenes do not lead to tumour formation unless overexpressed or mutated.
7. ~120 oncogenes have been identified thus far.