1. **Your name:** ZZZ

2. **Paper Title:** Characterizing genetic intra-tumor heterogeneity across 2,658 human cancer genomes

3. **Paper Authors:** Dentro*, Leshchiner*, Haase*, Wedge, Loo

4. **Journal:** Journal

5. **Date Published:** April 15, 2021

6. **Link to paper PDF:** 10.1016/j.cell.2021.03.009

7. **Link to supplementary information:** 10.1016/j.cell.2021.03.009

8. **Link to accompanying website:** 10.1016/j.cell.2021.03.009

10. **Broad Topic:** Cancer Genomics, Whole Genome Sequencing

11. **Most relevant lecture:** Lecture 22: Cancer genomics

12. **Keywords:** Cancer genomics, branching evolution; cancer driver genes; cancer evolution; whole-genome sequencing

13. **Abstract:** Intra-tumor heterogeneity (ITH) is a mechanism of therapeutic resistance and therefore an important clinical challenge. However, the extent, origin, and drivers of ITH across cancer types are poorly understood. To address this, we extensively characterize ITH across whole-genome sequences of 2,658 cancer samples spanning 38 cancer types. Nearly all informative samples (95.1%) contain evidence of distinct subclonal expansions with frequent branching relationships between subclones. We observe positive selection of subclonal driver mutations across most cancer types and identify cancer type-specific subclonal patterns of driver gene mutations, fusions, structural variants, and copy number alterations as well as dynamic changes in mutational processes between subclonal expansions. Our results underline the importance of ITH and its drivers in tumor evolution and provide a pan-cancer resource of comprehensively annotated subclonal events from whole-genome sequencing data.

14. **What is the major take-home point of the paper:**
   - Each subclone within the same tumor can often have different activities in terms of mutation signatures, which implies that subclonal expansions are involved in temporally and spatially changing mutations.
   - Aside from several exceptions, it is confirmed that confirm that mutational processes are relatively stable between the clone and subclones.
   - Some of chromosomal and genetic instable neoplastic cells’ daughter cells acquire mutations to obtain further selective advantages and start new subclonal lineages.

15. **What datasets did the paper generate / assemble / reprocess:**
   - Builds on the ICGC-TCGA Pan-Cancer Analysis of Whole Genomes (PCAWG) dataset
     - 2,778 cancer samples from these 2,658 distinct donors, comprising 2,605 primary tumors and 173 metastases

16. **What new methodologies/frameworks/algorithms/ML techniques did the paper introduce:**
   - Novel method for determining consensus segment breakpoints
     - Utilized the insight that a method’s uncertainty is indicated by where the breakpoint delineating change in copy number state lies
• cloneHD: reconstructs evolutionary history of genomes of clones with single-nucleotide variants (SNVs) from bulk DNA sequencing. The authors further extended the method to apply a tree structure on SNVs to discover relationships between subclones.
• Sclust: builds on DPlust to derive the cancer cell fraction of each mutation from copy number states, estimated purity, and variant allele frequency

17. Is the code of the paper easily accessible / well-organized / well-documented / with examples:
   • The code for the methods is listed in github: https://github.com/PCAWG-11/Heterogeneity
     o Includes code for pipelines, architectures, and methods, such as Sclust, clondHD, Ccube, etc.

18. Why did you select this paper to highlight:
   • The paper investigates intra-tumor heterogeneity (ITH) and its origins. ITH has important clinical significance because it provides genetic variation that has the potential to drive cancer progression and lead to drug resistance.
   • The paper develops a novel consensus to characterize ITH utilizing whole genome sequencing for a relative comprehensive set of cancers (38 cancers) with high-quality data of indels, SNVs, and mutations provided from the PCAWG.

19. What new analyses / methods / integrations can you imagine you could build on this paper:
   • The methods to detect mutations can be applied to a series of longitudinal and multi-sample datasets to investigate into the temporal dynamics of mutational processes/
   • We can also further explore the subclone drivers in localized cancers since the study was done on subclonal expansions
   • We can also investigate the tumor drivers’ metastatic potential since there is evidence that specific subclones harbor private driver mutations.