Inferring sub-clonal events using liquid biopsies

Liquid biopsies, primarily the analysis of cell-free DNA (cfDNA) present in blood samples, offer the potential of minimally invasive monitoring of cancer evolution. Hence, liquid biopsies provide a cost-effective way to longitudinally track tumour composition and to monitor clinical outcomes. cfDNA analysis can be performed using somatic copy number aberrations (SCNAs). SCNA profiles have been routinely utilised to infer the proportion of all tumour-derived DNA in blood. Such analysis allows to detect and diagnose a tumour, guide treatment, monitor treatment response and periods with no symptoms (remission of cancer).

However, a more granular analysis could be advantageous. For example, deriving quantitative information on the proportion of tumour sub-populations (sub-clonality) could have important clinical implications. For instance, it would allow better understanding and controlling therapy-induced resistance. However, distinguishing between all tumour-derived and subclone-derived DNA using SCNA profiles is challenging. This has been recently addressed by a new method, liquidCNA, which allows to infer and track sub-clonal populations from longitudinally collected cfDNA samples.

Aim: This project aims to infer sub-clonal events (applying the liquidCNA algorithm) in a cohort of advanced breast cancer patients and investigate its clinical utility in monitoring response to therapy.

Outcome: This research will investigate the use of sub-clonality estimation in predicting clinically relevant outcomes in breast cancer.

The project can be divided into 2 parts:

- **Part 1**: estimation of sub-clonal fraction
- **Part 2**: predict outcomes based on sub-clonal fraction

Part 1

We will implement the LiquidCNA paper. (You can start here to get familiar with the main concepts and code.)

Part 2

We will use the estimated sub-clonal fraction from Part 1 to predict:

- Time-to-progression
- Time-to-death
- Or other outcomes

Progression evaluation is currently primarily based on radiological assessments according to response evaluation criteria in solid tumours (RECIST).

See Bratman et al, 2020 for an example.

Data

We will be using data from metastatic breast cancer patients (about 200) measured in multiple timepoints during the course of their treatment (about 1000 samples in total). We have shallow whole-genome sequencing (sWGS) (0.1x) for these patients and survival/disease progression information.

Additional reading

- Wan, Jonathan CM, et al. "Liquid biopsies come of age: towards implementation of circulating tumour DNA." Nature Reviews Cancer (2017) - *Fig. 5 is a nice summary of the main idea behind monitoring response to treatment using liquid biopsies.*

- Corcoran, Ryan B., and Bruce A. Chabner. "Application of cell-free DNA analysis to cancer treatment." New England Journal of Medicine (2018) - *an overview of the potential applications of cfDNA in cancer management.*

- Merker et al, 2018 - *considerations on how to show clinical validity and utility of biomarkes (such as tumour fraction, subcloncal fraction etc)*

- Siravegna et al, 2017 - *a review on liquid biopsies*

- García-Saenz et 2017- *a study on cfDNA and imaging in advanced breast cancer*