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Sommario	Acute Myeloid Leukaemia (AML) is a cancer of the myeloid lineage of blood cells characterised by rapid growth of undifferentiated myeloid precursors that accumulate in the bone marrow and suppress normal haematopoiesis. It is the most common adult leukaemia with an estimated number of more than 60’000 new cases for the US in 2016. Despite the high rates of complete remissions achieved after treatment (60-80% in young adults), the number of patient that will result cured after induction and consolidation therapy is very low (~12%). The molecular basis of relapsing disease is still unclear and the small number of identified predictive factors has small predictive power. To date, chemotherapy induction treatment is similar for all patients and consists in the administration of mainly three drugs (fludarabine, cytarabine, and idarubicin). Prediction markers for the outcome of chemotherapy would instead reduce useless treatments and direct research through new possible therapeutic targets that would enhance AML treatment. In three successive studies, Ding et al., Corces-Zimmerman et al. and Krönke et al., described four possible behaviours for relapse patients: the return of the first leukaemia (dominant clone or a subclone), with or without additional evolution, or the emergence of ancestral clones, also in this case, with or without additional mutations. In this thesis, endowed of the

	NGS technologies advancement, we decided to delineate the possible process of relapse formation in order to be able in the future to predict which patients are more susceptible to relapse. Our experimental plan includes the whole exome analysis of 30 pairs of primary/relapsed AML samples using NGS to identify relapse-specific mutations, the bioinformatics analysis of the clonal evolution of the disease and the identification of pathways that correlate with the relapsing disease.?The methods for the analysis of NGS data, at present, are still in a refinement phase, especially for the high level analysis (detection of variants and definition of their role in the pathogenesis). We broadly analysed the existing methods for the treatment of NGS data (aligners, mutation callers, CNV callers and methods to reconstruct clonal composition) in order to determine those better fitting to our cohort of patients and purposes: occasionally, we had the possibility to choose the best tool meeting our investigative needs, discovering that other methods were valuable as well, in other cases we verified that more improvements are needed to obtain reliable results. Our analysis shows that the genomic landscapes of primary and relapse AMLs are similar and in the majority of the patients (76%) some relapse clones were already present in the primary tumour and reappeared after chemotherapy at similar or augmented cellular frequencies. We also identified some functional gene categories (DNA methylation pathway, cohesin complex and chromatin modifiers) more prone to resistance and peculiar genes (e.g. ASXL1, TET2) presenting growing VAFs at relapse. In 4 out of 29 patients (14%) we were able to identify driver mutations in the blood sample of the complete remission at low frequency; we hypothesise that more sophisticated diagnostic tools, based on NGS analysis, would help in driving the treatment to obtain better outcomes for patients.
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