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Predicting survival of cancer patients by chromosomal copy number heterogeneity

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ABSTRACT

We recently introduced a method to derive intra-tumor heterogeneity (ITH) from a single copy number measurement. This method stratifies patients for survival and could potentially help to identify low and high-risk patients with clinical relevance.

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The time that patients live after diagnosis with cancer varies from days to decades. This large variation in survival times can be partially understood from the location and stage of disease at diagnosis. Improving prediction of survival rates could have significant clinical relevance, e.g. for the identification of patients with good prognosis that do not benefit from chemotherapy and can thereby be saved from the side-effects that come with these agents.[1] Identification of prognostic "biomarkers" based on the molecular characteristics of cancers is therefore a topic of great interest.

New measurement techniques have allowed high-throughput studies to identify biomarkers over the last decades. Such studies are often data-driven and involve large scale measurements without specific hypothesis.[2] The consequence of this approach is that a biological rationale for identified biomarkers is typically missing, perhaps partially explaining why a large portion of biomarkers fail to make it to the clinic.[3] We opted for a different approach, by asking ourselves what a possible cause for worse patient prognosis could be and designing a method to quantify precisely that.[4]

From Darwinian evolution theory it is well-known that more diverse populations are more likely to adapt to new circumstances and survive. Applying this evolutionary perspective to oncology one can argue that intra-tumor heterogeneity (ITH) of the malignant cell population increases the chances that at least one of the cancer cells can adapt to new circumstances (upon metastasis or during treatment), through which the cancer progresses and the prognosis for patient survival becomes poor. A biomarker that quantifies ITH hence in theory could stratify patients for survival.

Indeed, previous studies have reported that ITH is important for survival in several cancer types.[5,6] Current measurements of ITH, however, rely on the analysis of multiple bulk samples or multiple single cells per cancer and hence cannot easily be scaled or transferred to the clinic.[6,7] Single-sample ITH measurements are scalable and methods based on variant allele frequencies (VAFs) do exist.[5] However, VAFs are subject to substantial technical noise and the reliability and reproducibility of ITH methods based on VAFs is under debate.[8,9]

We recently introduced a single-sample measurement of ITH that leverages variations in chromosomal copy numbers rather than in point-mutations.[10] The rationale behind this measurement of chromosomal copy number heterogeneity (CNH) is that individual cells and homogeneous cell populations always have integer (i.e. 0, 1, 2, 3,. . .) copies of each base-pair, and deviation from integer values in a bulk sample reflects genetic heterogeneity in the malignant cell population (Figure 1). Chromosomal copy number variations occur in all cancer types. Hence by design CNH is a scalable biomarker with potential to stratify patients for survival, independent of the tissue of origin.

Before turning to survival data, however, we first validated and characterized our method in detail. Using single-cell data, multi-region sequencing data and simulations we demonstrated that CNH accurately quantifies ITH from a single copy number measurement. Next, we correlated CNH measurements to gene expressions for more than 8,000 cancers which indicated that cancers that have a high CNH score express genes that cause chromosomal instability. In other words, analysis of gene expression data suggested that ongoing chromosomal instability underlies CNH. This finding was further substantiated by the observation that tumors with a high heterogeneity often have mutations in *P53* (also known as *TP53*), a gene which protects the stability of the genome. Importantly, also by live imaging of cell divisions in organoids we found that chromosomally instable cancers have high CNH. The observed relation with chromosomal instability both substantiated the biological relevance of CNH and questions whether ITH can be properly understood as the coexistence of a small number of genetically distinct clones.[5,7]

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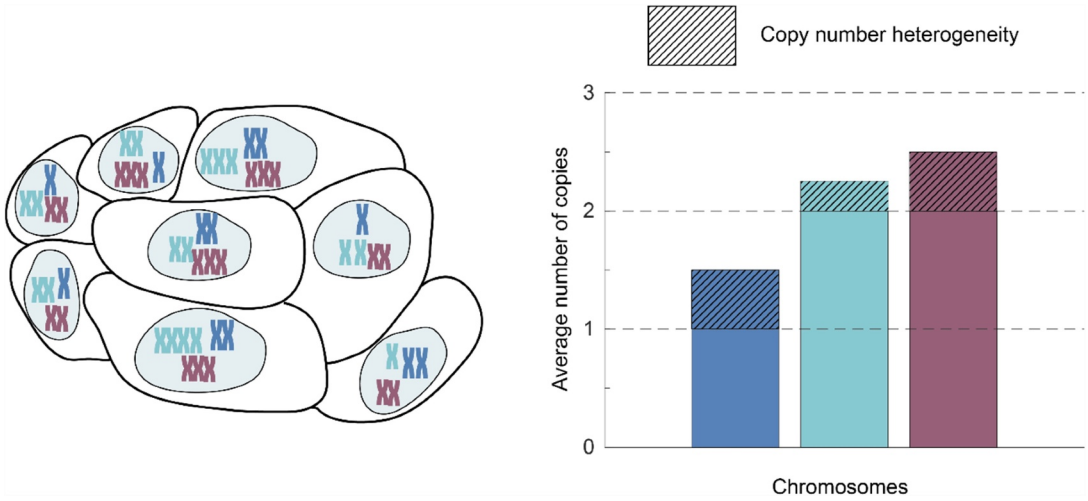

Figure 1. Chromosomal copy number heterogeneity in cancers. The number of copies of chromosomes in cancers frequently deviates from the diploid configuration of healthy cells. Also within a cancer malignant cells can have different karyotypes: this type of intra-tumor heterogeneity (ITH) we call copy number heterogeneity (CNH). CNH is reflected by non-integer values in the average number of copies of a chromosome in a bulk measurement.

Having validated and characterized the method, we next assessed the ability of CNH as a prognostic biomarker in The Cancer Genome Atlas (TCGA) pan-cancer cohort, consisting over 10,000 primary cancers with copy number data from 33 distinct cancer types. We found that patients with low CNH in the large majority of cancer types had a better prognosis than CNH high cancers, exactly as we expected for the Darwinian evolution of diverse populations.

Interestingly, also in a tissue-of-origin agnostic analysis CNH stratifies patients for survival, which we believe reflects the universality of our approach. Moreover, CNH identifies low and high-risk patients both in microsatellite stable and instable cancers, showing the applicability of this method across molecular subgroups. Importantly, also when controlling for known confounders such as age and stage we found in multivariate analysis that CNH is an independent prognostic biomarker for survival.

In summary, the CNH method we recently introduced was designed as a biomarker with a clear biological rationale: patients with a CNH low cancer are expected to do better than patients with a CNH high cancer because diversity in the malignant cell population is bad news for the patient. After careful validation of our method, and showing that chromosomal instability underlies CNH, we indeed found that high CNH in the primary malignancy indicates poor prognosis in the majority of cancer types. We hence propose that CNH can be a biomarker of clinical relevance to identify low- and high-risk patients for many types of cancer. Dedicated follow-up studies are warranted to demonstrate the clinical relevance in specific clinical scenarios.

Disclosure Statement

E.v.D., L.V. and D.M.M. are listed as inventors in a pending patent application (NL82151) filed by Oncode Institute on behalf of the Academisch Medisch Centrum, covering the content of the paper. T.v.d. B. declares no conflict of interest.

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