QUESTIONS INSPIRE2LIVE, ANSWERS HARTWIG MEDICAL FOUNDATION

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HOW OFTEN DOES WGS OF A CASE OF CANCER OF **UNKNOWN PRIMARY** LEAD TO

A) FINDING THE PRIMARY CANCER AND

If the primary tumor is unknown, the cancer cannot be treated properly. A comprehensive DNA test of a tumor biopsy leads in 65% of all cases to a strong clue about the origin of the tumor. In 70% of all cases we find indications for personalised medicine.

B) FINDING TARGETABLE/TREATABLE DNA-DEFECTS?

In general, we do find an indication for targeted treatment in 62% of **all patients**. In 18% of cases this concerns a registered standard treatment (on-label), in 13% a treatment with a drug registered for another tumor type (off-label) and in 32% an experimental drug (Nature 2019) (Nature (2019) 575: 210-216). For the PTO patient subgroup (n=175 in the Hartwig medical database) we do find actionable mutations in 53% of patients.

2. COULD YOU GIVE SOME EXAMPLES OF HOW HARTWIG'S NATIONAL TUMOR DATABASE HAS SUCCESSFULLY BEEN USED IN RESEARCH?

Using computer algorithms and based on genome-wide mutation characteristics from the database of breast and prostate cancer patients, researchers have been able to divide these patients into subgroups. The patients in these subgroups can benefit from more differentiated treatments based on tumor characteristics (Nature Genetics 2019) (Nature Communications 2019) (Nature Genetics (2019) 51:1450-1458; Nature Comm. (2019) 10:5251). Together with Erasmus University Medical Center, the Hartwig Medical Foundation is exploring the possibility of establishing prospective trials using this method to stratify patients in comparison with regular protocol-based treatments.

A few of the quotes of researchers who used the Hartwig Medical database:

- Hans Clevers, Hubrecht Institute: ‘We have identified a novel mutational signature caused by a bacterial species and could show that the resulting mutations contribute to known cancer driver gene alterations using the HMF database. These results are currently validated in several follow-

up projects to determine the consequences of infection with these bacteria early in life. This research has for the first time firmly linked a bacterium to the induction of specific mutations. We expect it to pave the way to better identification of people at risk of developing colorectal cancer and inspire interventions targeted at oncogenic bacteria.

- Harmen van de Werken, Erasmus MC Cancer Computational Biology Center (CCBC): 'In collaborations with many scientist and clinicians we can now better stratify prostate cancer patients (1), find the effects of drug therapies at DNA level in breasts cancer patients (2) and see different genomic subtypes in neuroendocrine patients (3).'
  (1) van Dessel, L. F et al. Nat. Commun. 10, 5251 (2019).
  (2) Angus, L et al.. Nat. Genet. 41, 1450–1458 (2019).
  (3) Van Riet et. al. preprint DOI: 10.21203/rs.3.rs-50333/v1 (2020)

- Simon Grund Sørensen, Aarhus University Hospital, Skejby: 'We have studied DNA damage deficiencies using the HMF data and have are developing predictive models of potential clinical relevance. For this purpose, the size and quality of HMF has been absolute key.'

3. HOW DOES HARTWIG'S TUMOR DATABASE CONNECT INTO INTERNATIONAL DATABASES IN ORDER TO CREATE FURTHER RELEVANCE?

The HMF database is worldwide unique and is the largest for research accessible resource of its kind (containing whole genome sequencing, rna-sequencing and clinical data for over 5,000 patients).

A few of the quotes of researchers who used the Hartwig Medical database does illustrate this:

- Hans Clevers, Hubrecht Insitute: 'The HMF database provides a unique resource of metastatic cancer whole genome sequencing data.'
- A researcher at Harvard Medical School, Boston: 'HMF uniquely was able to harness an extraordinarily valuable clinical cohort of patients with metastatic cancers and leapfrog traditional academic approaches to generate the most valuable whole genome cancer data set for the field.'
- Nuria Lopez Bigas, CRG Barcelona: 'There are not so many datasets with large numbers of tumor whole-genomes, and in addition Hartwig dataset is focused on metastatic tumors and contains a very rich clinical annotation.'
- Peter van Loo, Crick Institute, London: 'No-one else has anything else that comes close to this large-scale pan-cancer series of whole-genome sequenced cancer metastases.'
- A researcher at Weil Cornell, New York: 'It is an unparalleled resource, about an order magnitude larger than any other metastasis WGS dataset.'
- Carlos Caldas, University of Cambridge: 'By directly comparing Hartwig, ICGC and PBCP we will have a very detailed characterization of the genomic and trancsriptomic features of primary and metastatic breast cancer.'

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