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Machine learning algorithm predicts treatment response in MM

ROTTERDAM, the Netherlands and SAN DIEGO, USA, August 1, 2018: Renowned scientific journal Nature Communications published July 27th, 2018 a research paper by Joske Ubels about a novel machine learning concept that derives predictive treatment classifiers when applied to gene expression datasets with two treatment arms and survival data. During the validation on Multiple Myeloma (type of blood cancer) datasets with extensive follow-up, two classifiers were found that are able to predict if a Multiple Myeloma patient could specifically benefit substantially from a bortezomib (Velcade[®]) or a lenalidomide (Revlimid[®]) treatment at moment of diagnosis¹.

“Multiple Myeloma treatments are associated with serious side effects and are often only beneficial for a subgroup of patients. There is an urgent clinical need for diagnostic means that help physicians selecting the right treatment for their patients at the moment of diagnosis”, says Dharminder Chahal, CEO SkylineDx. “Constructing classifiers that can achieve true treatment benefit prediction poses a unique challenge, as it is impossible to know how a patient would have responded to an alternative treatment”, explains Joske Ubels. “To address this, we introduce Simulated Treatment Learning (STL). The unique approach behind STL is that patients who received different treatments, but have similar genetic profiles in the tumor cells, can be used to model each other’s response to those treatments. We implemented the STL concept in the algorithm GESTURE^{TM2}”. Joske Ubels wrote this research paper in collaboration with the research group of Jeroen de Ridder, Associate Professor in the Center for Molecular Medicine at UMC Utrecht (the Netherlands) and the research group of Professor Pieter Sonneveld at Erasmus Medical Center (the Netherlands and SkylineDx, a high-tech commercial-stage company in the field of (cancer) diagnostics.

GESTURETM found predictive gene expression classifiers for treatments bortezomib and lenalidomide.

“Using rigorous cross-validation, we find that GESTURETM is successful in predicting treatment benefit for both treatments and was robust across validation folds”, continues Joske Ubels. The authors combined data from three randomized phase III clinical trials comprising of 910 patients with multiple myeloma. For each patient gene expression profiles were generated from purified myeloma plasma cells at diagnosis. The results in this bortezomib dataset show a subgroup of 180 patients (19.8% of population, HR = 0.50, p =

0.0012) that benefit substantially more from this treatment than the population as a whole (HR = 0.74, p = 0.0029). In an independent dataset obtained from the CoMMpass database, the STL was also successful in identifying a predictor for treatment benefit with lenalidomide. The results in this lenalidomide dataset (n = 662) show a subgroup of 206 patients (31.1% of population, HR = 0.36, p = 0.0031) that benefit substantially more than the population as a whole (HR = 0.59, p = 0.0042).

“If a patient falls into one of these subgroups, in comparison with the other treatment arm within the identified subgroup, the risk of disease progression can be reduced by 50% for bortezomib and 64% for lenalidomide. By further developing this predictive classifier and making it available at the moment of diagnosis, we help physicians and patients with this debilitating disease in creating much needed tailored treatment plans”, concludes Dharminder Chahal.

GESTURE™ can play an important role in rescuing treatments that do not achieve a significant effect.

The implementation of STL in the algorithm GESTURE™ is a method to derive classifiers that can predict treatment benefit from any gene expression dataset with two treatment arms and survival data. Furthermore, GESTURE™ was successfully tested across different gene expression platforms, different treatments and different study types. Demonstrating GESTURE™'s generic applicability can be of use in clinical phase III studies where treatments do not achieve a significant effect in the entire patient population but may still benefit a subset of patients.

Links

1. Ubels et al. Predicting treatment benefit in multiple myeloma through simulation of alternative treatment effects. Nature Communications. 2018. (visit online: <https://www.nature.com/articles/s41467-018-05348-5>)
2. GESTURE™ is the acronym for ‘Gene Expression-based Simulated Treatment Using similaRity between patiEnts’

About Multiple Myeloma

Multiple Myeloma (MM) is a cancer that arises from plasma cells, a type of white blood cell made in the bone marrow. In patients with MM, the plasma cells become abnormal, multiply uncontrollably, and release only one type of antibody – known as M-protein – which has no useful function. According to the World Cancer Research Fund International, an estimated 114,000 people around the world are diagnosed with MM annually, and the disease represents 0.8% of all cancers globally. For more information about MM, visit www.hematon.nl/myeloom (information available in Dutch only), www.themmr.org, www.myeloma.org.uk, www.mpeurope.org or www.myeloma.org.

About SkylineDx

SkylineDx is a high-tech commercial-stage biotech company headquartered in Rotterdam, the Netherlands and a commercial office and laboratory in San Diego, California, USA. The company uses its expertise to bridge the gap between academically discovered gene expression signatures and commercially available diagnostic products with high clinical utility. With the focus on diagnostics, SkylineDx assists healthcare professionals in accurately

determining the type or status of the disease or to predict a patient's response to a specific treatment. Based on the test results, healthcare professionals can tailor the treatment to the individual patient. MMprofiler™ with SKY92 is the company's lead product. To learn more, please visit www.skylinedx.com.