Precision medicine in pancreatic cancer — fact or fiction?

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Late diagnosis and an inability to personalize treatment are major problems preventing reductions in pancreatic cancer mortality. In 2015, the identification of a highly discriminatory exosomal biomarker, culture systems that recapitulate human disease and new methods of analysing large data sets to identify prognostic markers have improved the future outlook for patients with this cancer.

Pancreatic cancer is projected to be the third leading cause of cancer-related death by 2030. Multiple factors contribute to the dismal prognosis for patients with pancreatic cancer, but two clinical problems are a major concern: late diagnosis and treatment resistance or lack of personalized treatment stratification. These aspects have been addressed in research published in 2015, and considerable progress has been made towards the use of precision medicine for the treatment of pancreatic cancer (FIG. 1).

An association between cancer survival and 22 distinct leukocyte subsets has been revealed...

Pancreatic cancer has a very poor prognosis, with a 5-year survival rate of only 6% and 80–85% of patients with pancreatic cancer diagnosed at a stage when the tumour is unresectable. Early detection is projected to increase survival by 30–40%.

Serum levels of carbohydrate antigen 19–9 (CA19–9) above 37 U/ml are the best established blood test for the detection of pancreatic cancer. CA19–9 can discriminate between patients with pancreatic cancer and healthy individuals with a sensitivity of 80.3% (95% CI 77.7–82.6) and a specificity of 80.2% (95% CI 78.0–82.3), and between malignant and benign pancreatic disease with a sensitivity of 78.2% (95% CI 72.3–80.4) and a specificity of 82.8%. However, to reduce health-care expenditure and prolong patients’ survival, an assay for early diagnosis would have to perform with a minimum sensitivity of 88% at a specificity of 85%. Aiming to identify a marker with a higher diagnostic accuracy than CA19–9, Melo and co-workers established that the detection of the cell surface proteoglycan glypican-1 on circulating exosomes isolated from patient plasma samples enables the discrimination between patients with early-stage and late-stage pancreatic cancer, benign pancreatic disease and healthy individuals. Using a cut-off of 7.6% glypican-1-positive exosomes, patients with pancreatic ductal adenocarcinoma (PDAC) could be distinguished from healthy individuals and those with benign pancreatic disease with a previously unmet sensitivity and specificity of 100%. Identification and isolation of cancer-specific exosomes in body fluids enables a diagnostic marker to be detected without contamination by noncancer proteins, therefore increasing diagnostic accuracy. Questions to be answered in 2016 include whether these findings can be validated independently in a larger set of patients, and whether exosomal glypican-1 is just a marker of pancreatic cancer or whether it has a function in exosome generation or tumour growth and progression.

Isolating exosomes from patients’ serum samples is a difficult task in clinical practice; however, a new approach of performing next-generation sequencing on easily obtainable cell-free media, such as plasma, might be more feasible for the detection of cancer-related gene expression in the clinic. In a prospective proof-of-concept study, Zill and colleagues analysed 54 genes concomitantly in tumour tissue and cell-free DNA isolated from a 1 ml plasma sample. The diagnostic accuracy of cell-free DNA sequencing was 97%, with 92.3% mean sensitivity and 100% specificity, over a preselected panel of five genes. If replicated in a larger study, this approach opens new avenues for a tailored and personalized treatment strategy for patients with pancreatic cancer.
In summary, although the predominant question in pancreatic cancer research in 2014 was whether stroma was friend or foe, the focus of research in 2015 has been the identification and validation of diagnostic biomarkers. If the findings reported in 2015 can be reproduced in the clinical setting, tests based on glypican-1 hold promise for the early detection of pancreatic cancer, at least in high-risk cohorts. Organoid models of PDAC are an improvement on previous preclinical models for the study of disease pathogenesis and treatment response. In addition, pooling large data sets enables the identification of cancer-specific signatures that are predictive of disease outcome, potentially paving the way to precision medicine. It remains to be seen whether these research efforts will be able to alter the pessimistic projections for the burden of pancreatic cancer.

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doi:10.1038/nnrgastro.2015.215
Published online 15 Jan 2016


Acknowledgements
The authors are supported by funding from the Deutsche Krebsforschung/ Dr. Mildred-Scheel-Stiftung (109102), the Deutsche Forschungsgemeinschaft (DFG GRK1947-13, MA 41151-1/2-3) and the European Union (EU-FP-7: EPC-TM and EU-FP7-REGPOT2010-1).

Competing interests statement
The authors declare that there are no competing interests.