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Immunovia interview with Prof. Stephen Pereira, Gastroenterologist and Hepatologist, *BSc, PhD, FRCP, FRCPE,* at the London Clinic (UCL), Principle Investigator for Immunovia´s PanSYM study in London, UK, in regard to the clinical utility of diagnostic tests in pancreatic cancer:

1. **Do you think there is a clinical unmet need in the area of Pancreatic Cancer diagnosis?**

   Globally, 400,000 cases of pancreatic cancer are diagnosed each year with only a marginally lower number of deaths, pancreatic cancer is expected to become the third commonest cause of cancer death in the UK and second in the US by 2030. PDAC is an aggressive cancer which is mostly resistant to chemo and radiotherapy with high rates of recurrence. Surgical resection offers best chance for a cure, however, only about a quarter of patients are at a surgically resectable disease stage at diagnosis, with roughly 25% of these actually found to be fit for major resection. Those that do no undergo surgical resection of their cancer, are not expected to live longer than 14 months overall. With respect to direct costs spent on hospital care and interventions (including diagnostic, surgical and chemotherapy), these stand around 20,000 euros per patient (Europe). Loss of productivity due to mortality stands around 240,000 euros per patient (Carrato et al., 2015). Having a non-invasive blood test to differentiate non-PDAC from PDAC individuals with a high probability at an early stage will be invaluable.

2. **Regarding early detection of PDAC in the early symptoms risk group, and based on the data available to date, do you foresee that this test would deliver clinical utility in a clinical setting? Please elaborate.**

   Several population based studies showed a clear link between certain non-specific symptoms that occur months or even years before the diagnosis of pancreatic cancer (i.e. abdominal pain, weight loss, change in bowel habits). Unfortunately, due to their non-specific nature, these often go either unnoticed or are subject to a lengthy diagnostic with repeated visits and tests before a final diagnosis is made. International healthcare and clinical governance authorities already recognised the need for early identification of red-flag symptoms and certain clinical features, that will trigger accelerated diagnostic pathways for cancer detection. Patients who are identified as at higher risk, will most often be further assessed using one or more imaging modalities (such as CT, MRI, EUS, PET-CT), however, waiting times and pre-existing workload may delay patients having a prompt assessment. These modalities which are heavily used for a variety of other indications, could be prioritised based on criteria such as early warning symptoms and signs, shortening the time from presentation to surgery. Early identification of warning signs and symptoms which could be linked with a potential diagnosis of PDAC, has the potential to accelerate such diagnostic pathways, especially if supported by a minimally invasive and accurate test to support further urgent investigations.

3. **How important would it be with a blood-based test for early detection of pancreatic cancer for this risk group?**

Although several blood based biomarker tests have previously been reported to have high diagnostic values for the detection of PC, the only cancer biomarker used in clinic is CA19-9. CA19-9 however, performs less than ideal in terms of being able to identify a malignant process not to mention accurately rule out the presence in patients who don't actually have pancreatic cancer (sensitivity of 79-81% at best, specificity of 90%; Hasan et al 2019, Advances in pancreatic cancer biomarkers) CA19-9 is mostly used for assessing treatment response and prognostication. Imaging modalities have similar or only slightly better rates of PC detection, however, come with logistical complexities. Surgery can also be used as a diagnostic modality, however, is complicated by potential complications and further delay due to the need of pre-operative workup. Having a minimally invasive, point of care test that is highly accurate, will help prioritise patients for urgent intervention and support the decision making process in less equivocal cases.

4. **What more would you require in terms of data and proofs to use Immunovia´s test in the clinical setting (PanSYM)?**

In order to prove clinical utility, the accuracy of the IMMray-PanCan-d assay will have to be assessed in a clinical environment where the test is designed to be used. Clinicians who will be using the test would like to know whether using the assay results in lower use of other more complex tests such as additional imaging, which are also more expensive to use. What would also be important to know, is whether the test made a difference in the decision making process of whether to proceed with (or avoid) scans, surgery or even chemotherapy compared to decisions made based on currently available standard of care tools. Not to mention the costs involved. Most of these questions will be answered in a study that is currently being designed to evaluate the role of the assay in a high risk population, in secondary care.

5. **Will the reported test performance be appropriate for the presented risk groups according to your assessment? If not, what parameter would you like to see improved, and to what level?**

Non or minimally invasive standard of care tests that are currently in use include blood tests and imaging modalities (such as CT/PET-CT, MRI, EUS). Accuracy for detecting pancreatic cancer is around 90% at best.
While the sensitivity of the test in correctly identifying PC (in those that truly have it) is comparable to existing tests, the issue with testing someone for a relatively rare disease, is the rate at which it wrongly detects it in patients who are actually healthy. This is important in terms of preventing associated anxiety for patients who are told they might have cancer, but also in saving them from undergoing unnecessary tests. The IMMray PanCan-d test has so far shown to be able to rule out over 99% of negative cases, while the best performance for other modalities is reported only around 90%. Meaning that in every 100 people, 10 will be wrongly told to have cancer. Based on a survey we recently did in patients and clinicians

in the UK, the acceptable test accuracy for testing for PC in UK patient populations was a 70% sensitivity at 90% specificity.

Apart from improving the sensitivity of the test, perhaps by using it together with another modality, some other important considerations would be a short time to obtain the results of the assay, the technical reliability and costs of the assay.

6. **How is the biomarker CA 19-9 used in the diagnosis of PDAC? How is IMMray™ PanCan-d differentiated and what benefits would it offer for early detection?**

CA19-9 is the only pancreatic cancer biomarker used in clinic, apart from CEA in certain cases. CA19-9 (and CEA) are however non-specific to pancreatic cancer and have only proven beneficial for assessing treatment response and to predict the prognosis. The IMMray PanCan-d test has shown to have higher accuracy in differentiating those with early stage (I and II) pancreatic cancer from healthy individuals or those with symptoms suggestive of PC. The assay could potentially be used at points of care, to support further investigation or accelerate the workup for surgery by being highly suggestive of a pancreatic cancer diagnosis. This could be used in specific settings, where high volume of patients with gastro-intestinal symptoms are being investigated for pancreatic cancer and prioritise their management. Since several symptoms have been associated with higher overall risk for pancreatic cancer, specifically testing patient with these symptoms for pancreatic cancer with an accurate, readily available blood test, could suggest a diagnosis of pancreatic cancer sooner. Diagnosing pancreatic cancer a few months or even weeks earlier, is often crucial in terms of disease resectability and patient survival.