Multiple factors beyond the selection of a diagnostic development partner impact the drug, diagnostic co-development process. These include *epidemiological factors*, such as biomarker prevalence and prognostic significance; *operational* factors, such as development of sufficiently broad informed consent design for screening and CDx development purposes, country specific regulations for handling tissue or DNA samples, and recruitment of biomarker negative individuals for treatment with study drug; as well as *technical* factors, such as the types of samples to be analyzed (e.g. surgical resections, cytological specimens, plasma), global differences in tissue handling and interpretation of results obtained from an FDA approved platform. However, the co-development process does not end with approval of the CDx and drug. What happens with existing laboratory developed tests already in the marketplace − but perhaps designed for use in annotative testing rather than patient selection-quality clinical tests?
A significant, non-incremental, treatment benefit of the drug under development can be a powerful driver for regulatory interactions as well as investigator interest and patient enthusiasm. Crizotinib, being developed for the treatment of ALK-positive NSCLC, has provided a tremendous opportunity to put into clinical and regulatory practice the process of simultaneous submission of therapeutic and diagnostic regulatory packages relating CDx performance with clinical efficacy.

Scientific Symposium (Mon, 26 Sep, 14:45−16:45) **Joint ECCO, EASD and EASO Session On Diabetes, Obesity and Cancer**

333 INVITED

Obesity, Diabetes, Treatments for Diabetes and Their Effect on Cancer Incidence and Mortality − an Overview

S. Wild[1]. [1]*University of Edinburgh, Centre for Population Health Sciences, Edinburgh, United Kingdom*

The association between type 2 diabetes and some types of cancer is well established and the complexity of this association is receiving increasing recognition. Many factors influence the risk of both diabetes and cancer including age, sex, ethnicity, socioeconomic status, obesity/insulin resistance, diet (including alcohol intake), physical activity levels and smoking history. The presence of diabetes may influence the uptake of cancer screening. Diabetes treatments may influence the risk of cancer independently of their effect on glycaemia and complicate investigation of the association between diabetes and cancer. Both observational and experimental study designs have a place in investigating the association between treatment of diabetes and cancer but both approaches also have limitations. The aim of the presentation is to introduce the complexity involved in attempting to clarify the factors that contribute to the associations between obesity, diabetes, hyperglycaemia, diabetes treatment and cancer.

334 INVITED

Are There Early Common Origins of Obesity, Diabetes and Cancer?

T.I.A. Sørensen[1], T.L. Berentzen[1], M. Gamborg[1], C. Holst[1], J.L. Baker[1]. [1]*Copenhagen University Hospital, Institute of Preventive Medicine, Copenhagen, Denmark*

Obesity, diabetes and cancer do have early origins defined as conditions influencing level of risk later in life. Occurrence of obesity early in life is undoubtedly associated with increased risk of later type 2 diabetes and of various cancers (postmenopausal breast, endometrial, colon, kidney, oespohagus). The associations will be illustrated by results of studies based on linkage between large registers of records from the school health examinations and draft board examinations, carried out since 1936 and 1943, respectively, in the Copenhagen area in Denmark, and providing information about early body sizes at birth, during school ages and in young adulthood, and registers including data on hospitalization, diabetes and cancer. Main questions are at what age these associations are established, and especially what the role the prenatal, the prepubertal and the pubertal period have, and if the associations can be considered as consquences of one causal pathway such as that passing through the metabolic syndrome with different effects. Although the answers to these questions may inform the search for early common targets for preventive actions, there are currently no available applicable unified solution.

335 INVITED

Diabetes and the Cancer Patient Pathway

H.C.J. Yeh[1]. [1]*Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University, Baltimore, Maryland, USA*

A number of epidemiologic studies have identified a positive association between type 2 diabetes and cancer incidence and mortality for a variety of cancers. Meta-analyses also found that pre-existing diabetes was associated with increased risk of postoperative mortality and reduced survival after cancer diagnosis.
There are a variety of pathways by which diabetes might influence the risk of mortality in cancer patients: First, previous studies and meta-analyses noted obese and diabetic women were less likely to receive cancer screening, which may lead to advanced stage at cancer diagnosis. Second, patients with diabetes often have other diabetes-related comorbid conditions that may influence clinical decision-making. Some studies found cancer patients with diabetes were treated less aggressively than those without diabetes. Third, previous clinical studies have observed patients with diabetes had increased risks of cancer recurrence and second cancer. Fourth, some studies suggested when cancer occurs in an adult with diabetes, it can divert attention and resources, leading to inadequate diabetes care and increased risk of diabetic complications. However, the findings were not consistent. Finally, diabetes is a well established risk factor for infection-related mortality and cardiovascular disease death.

336 INVITED

Diabetes, Metformin and Clinical Studies in Cancer

L. Lipscombe[1]. [1]*University of Toronto, Medicine Women's College Hospital, Toronto Ontario, Canada*

It is increasingly recognized that patients with diabetes have an increased risk of cancer and poorer cancer-related outcomes. Furthermore, emerging evidence suggests that insulin-modifying therapies used to treat diabetes may influence cancer outcomes. Treatment with insulin and insulin secretagogues has been associated with increased cancer incidence and mortality. Conversely, there is growing evidence that metformin, an insulin sensitizer, may play a beneficial role in cancer, both through insulin-dependent and insulin-independent mechanisms. In animal studies, metformin inhibits tumour growth, decreases tumour burden and even prevents tumour development. Insulin, IGF-I and hyperglycemia are known to be growth promoters and are reduced in diabetic patients taking metformin. Hyperinsulinemia has specifically been shown to be an adverse prognostic factor in breast cancer, and metformin treatment in non-diabetic breast cancer patients reduces circulating insulin levels. Metformin also has direct effects on the AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) pathways, which are involved in cellular proliferation. This effect may also contribute to lower cancer incidence and better cancer outcomes.
Observational studies in humans also suggest a protective effect of metformin on cancer-related outcomes. Several large studies have shown that metformin treatment in diabetic patients is associated with a significant reduction in cancer incidence and mortality, when compared to no metformin or to sulphonylurea treatment. Specific reductions in the incidence of breast, pancreatic, and hepatic cancers have been documented with metformin use, while effects on prostate cancer are inconsistent. Metformin may also affect cancer prognosis. One clinical study reported that metformin treatment in breast cancer patients receiving neoadjuvant chemotherapy was associated with significantly higher pathologic complete response rates.
While the data for metformin and cancer are promising, the interpretation of these findings is difficult due to the observational nature of these studies. It is still unclear to what extent metformin is truly protective or whether the apparent benefit is relative to the potential harmful effects of other, insulin-promoting diabetes treatments. We also do not know whether these benefits will translate into similar effects in non-diabetic patients. There are currently several ongoing randomized controlled trials that will help to resolve these issues. The registered trials are individually studying breast, prostate, pancreatic, and other cancers, and involve both patients with early and advanced stages of disease. Most of the trials are being conducted in non-diabetic patients. The results of these trials will help to elucidate the true impact of metformin on specific cancers and among the non-diabetic population.