Conclusions: These results highlight the importance of QA in routine tissue banking for research. However, it should not be forgotten that biomarkers that will prove to be clinically useful must be reliable on less than perfect specimens, and, preferably, on formalin fixed, paraffin embedded tissue. This may limit the clinical utility of some biomarkers discovered in the research setting.

S7

Are size-based response criteria appropriate in the era of targeted therapy?

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Introduction: The standard way to assess a patient's response to chemotherapy is to use computed tomography (CT) to measure tumor size using uni-dimensional (RECIST) or bi-dimensional (WHO) criteria. This methodology has changed little in the past 30 years despite the emergence of new therapies and advances in imaging technology.
Main Message: We and others have found that measuring the changes in the size of tumors in one or two dimensions does not adequately capture the effects of novel therapies on primary tumors and metastases. Radiographic changes in the size of tumors treated for instance with epidermal growth factor receptor tyrosine kinase inhibitors such as gefitinib or erlotinib or inhibitors of angiogenesis such as bevacizumab do not necessarily occur at the same magnitude or speed as observed in those individuals treated with standard cytotoxic therapies. With these newer agents, tumors respond by undergoing cystic change, central necrosis, and density changes that may not be captured by conventional measurements of the largest lesion diameter.
Conclusions: In summary, our early experience with volumetric CT calculations, measurements of necrosis or cystic change, "ghosting" of tumors as they change with therapy suggests that these may be promising biomarker technologies to measure response and could replace be an adjunct to other surrogates such as unidimensional tumor measurements, or even more functional biomarkers.

S8

Value of FDG-PET as a marker of treatment response

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PET imaging with the glucose analog fluorodeoxyglucose (FDG-PET) has been evaluated in numerous studies to monitor tumor response in patients undergoing chemo- and radiotherapy. The clinical value of FDG-PET for differentiation of residual or recurrent viable tumor and therapy-induced fibrosis or scar tissue has been documented for malignant lymphomas and various solid tumors. Furthermore, there are now several reports suggesting that quantitative assessment of therapy-induced changes in tumor FDG-uptake may allow prediction of tumor response and patient outcome very early in the course of therapy. Thus treatment may be adjusted according to the individual chemo- or radiosensitivity of the tumor tissue. Since the number of alternative treatments is continuously increasing, early prediction of tumor response to therapy by FDG-PET has an enormous potential to "personalize" treatment and to reduce the side effects and costs of ineffective or unnecessary therapy. Recent studies have demonstrated the feasibility of PET-guided chemotherapy in lymphoma and esophageal cancer. In addition, FDG-PET imaging may shorten clinical trials of new drug candidates, by providing an earlier and more accurate readout for tumor response to therapy. The usefulness of FDG-PET in drug development has been demonstrated in the development of c-kit inhibitors for treatment of gastrointestinal stromal tumors, where metabolic changes preceded a reduction of tumor size by several weeks.
Patient preparation and acquisition of PET have been standardized and simplified in recent years allowing FDG-PET studies for treatment monitoring to be performed outside of specialized research centers. Furthermore, criteria for assessment of tumor response by FDG-PET have been defined by the "International Harmonization Project in Lymphoma". Response assessment by FDG-PET is now an integral part of the "International Working Group Criteria" for response assessment in lymphomas.

S9

PET Biomarkers: beyond FDG

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Introduction: Molecularly targeted therapy holds great promise for improving cancer treatment; however, it creates new demands for tools to guide treatment selection. While treatment selection has traditionally depended upon tissue-based biomarkers, functional and molecular imaging can play an important and complementary role in directing targeted cancer therapy and monitoring early response [1]. PET imaging is modality that is well suited to this task, given its ability to probe multiple facets of pharmacology and tumor biology, and it quantitative capabilities. Most clinical imaging to date has been done using [F-18]-fluorodeoxyglucose (FDG) PET, which has demonstrated its value as a biomarker for measuring response [2]. However, other PET radiopharmaceuticals beyond FDG will also play an important role in directing therapy [3,4].
Main Message: Energy metabolism is associated with tumor growth, but also with a variety of other biological processes, including inflammation and tissue repair in response to damage. As cancer treatment becomes more targeted and individualized to patient and tumor characteristics, more specific PET radiopharmaceuticals will help guide treatment selection by (1) quantifying the therapeutic target, (2) identifying resistance factors, and (3) measuring early response to therapy [4]. Early studies has shown the ability of PET to measure the regional expression of therapeutic targets such as the estrogen receptor (ER), androgen receptor (AR), and HER2 molecule, all established therapeutic targets for breast or prostate cancer, using radiopharmaceutical such as [F-18]-fluoro-

estradiol (FES), [F-18]-fluorodihydrotestosterone (FDHT), and [Ga-68]-labeled F(ab′)2 fragments of trastuzumab.
PET can measure tumor hypoxia using probes such as [F-18]-fluoromisonidazole. Hypoxia is a well-established resistance factor for radiotherapy, increasingly also recognized as a factor that mediate resistance to systemic therapy through the activation of pathways, such as the VEGF pathway, that mediate tumor growth and metastasis. PET can also measure drug resistance arising from barriers to drug delivery to the tumor, for example, by using [C-11]-verapamil to measure regional P-glycoprotein transport.
Finally, PET can detect early changes in response to therapy, for example by measuring tumor proliferation, using tracers such as [F-18]-fluorothymidine and/or cell death, using [F-18]-fluoroannexin. This approach can identify at an early stage which drugs have had a pharmacokinetic effect on the tumor and likely response, and importantly, which drugs are not likely to be effective.
Conclusions: These new radiopharmaceuticals, combined with conventional imaging and established PET procedures using FDG, hold great promise for directing effective, targeted cancer therapy. Further development of the new PET imaging probes will require development of rigorous and robust methods of image quantification, and careful study design to validate the information provided by PET imaging compared to both in vitro assay and to well-defined patient outcomes [5].
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S10
DCE-MRI as a biomarker of tumor angiogenesis

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Introduction: Several randomized trials have demonstrated in a range of tumours the clinical benefit associated with augmenting conventional chemotherapy with inhibitors of Vascular Endothelial Growth Factor (VEGF). This class of drug has been extensively evaluated with Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI), largely during trials conducted in the phase I/II setting.
Main Message: DCE-MRI is an attractive biomarker for drugs that inhibit VEGF because the cytokine is the major mediator of vascular permeability. Thus agents that inhibit VEGF should reduce vascular permeability, a feature of the malignant vasculature, and this impacts on the rate of egress of contrast from the vasculature into the interstitial space. This transfer of contrast has been measured in several studies as the Ktrans, the endothelial surface area $\times$ permeability constant. By far the majority of studies have demonstrated that broad spectrum VEGF inhibitors impact on Ktrans and that the degree of change of this parameter correlates with the dose of the drug and with clinical benefit. However, in a recent phase I study of a pure VEGFR2 inhibitor we have seen evidence of an active drug that does not impact on Ktrans, suggesting that the latter parameter is regulated by a more widespread effect on the VEGF system. We have therefore carried out a detailed time course study of patients receiving the monoclonal anti-VEGF antibody, bevacizumab and the data will be presented.
Conclusions: One of the difficulties with DCE-MRI and imaging in general is heterogeneity. We have demonstrated that the vascular enhancing fraction of ovarian cancer and the histographical distribution of other MRI parameters have clinical significance, highlighting the importance of detailed and comprehensive image analysis. This is of continued relevance as the new targets of anti-angiogenic drugs are likely to have effects that are detected through DCE-MRI, confirming the importance of this biomarker in early clinical trial evaluation of new drugs.

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S11
The functional diffusion map (fDM): an early predictive biomarker of tumor response

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Introduction: Diffusion MRI measurements can be used to quantify water diffusion values within tumors. Diffusion of water molecules are sensitive to celluar density/structures and as such, therapeutic-induced changes in tumor architecture can be detected through alterations in tumor diffusion values thus the diffusion imaging approach can be used as a sensitive surrogate for early detection of treatment response. Applications of this technology in grade III/IV gliomas, head and neck tumors, breast and metastatic prostate cancer to the bone will be shown.
Main Message: Diffusion MRI (D-MRI), which measures changes in cellular water mobility, has been proposed as an early surrogate for treatment response. Previously we reported that using a functional diffusion map (fDM) at 3 weeks D-MRI was closely associated with RR, time to progression, and OS. Data on fDM in 60 patients with MG are now reported. Sixty patients were recruited for this study. There were no differences in pre-treatment variables between groups (age, KPS, pathologic grade, or surgical resection (all $p > 0.05$, Fisher's Exact Test)). Mean change in ADC, as well as the percentage of