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Precision Medicine & PET/CT: Challenges and Implementation

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National Institutes of Health (NIH) defines precision medicine as “an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.” This approach will allow doctors and researchers to predict more accurately which treatment and prevention strategies for a particular disease will work and in which groups of people. *It’s about selecting the right type of treatment for the right disease, at the right time and for right patient.* The focus is on identifying which approach will be effective for which patient based on genetic, environmental and life style factors. It is in contrast to our current therapy paradigm of ‘one-size-fits-all’ approach, in which disease treatment and prevention strategies are developed for the ‘average’ patient, with less consideration for the differences between patients.

‘Precision Medicine’ also can be differentiated from ‘personalized medicine’, which may imply that treatment and prevention strategies are developed uniquely for each individual. We have practiced medicine for centuries as ‘personalized medicine’ tailoring treatments to each patient. In contrast, ‘precision medicine’ is about therapies that are more precisely tailored to specific molecular targets.

In 2015, President Obama, as part of his state of the union address, announced the ‘Precision Medicine’ initiative – a research effort which focuses on bringing precision medicine to many aspects of healthcare. The budget for fiscal year 2016 included \$ 216 million in funding for the NIH, the National Cancer Institute (NCI) and Food and Drug Administration (FDA). Specifically, the funding provides \$ 130 million to the NIH to assemble a data set

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(genomic data, life style information, biologic samples linking to health care records) with a cohort of atleast 1 million volunteers, \$ 70 million to the NCI for efforts to identify genes that contributes to tumors, \$ 10 million for FDA, and \$ 5 million to the National Coordinator for Health Information Technology to develop the IT infrastructure(1). President's initiative addresses the need for multifaceted data about patients (lifestyle, environment and genomic information), the tools we need to work with large patient data sets, building infrastructure and interoperability of these systems and finally the stakeholders who will use the information.

In this context, oncology is at the forefront of precision medicine, today. There has been progress towards the discovery and development of targeted therapeutic agents with evidence in clinical trials of the improvement of therapeutic efficacy. More and more patients are receiving targeted and biologically rational therapies based on patients' cancer genome analysis and on the basis of deeper biologic understanding of the disease than unselected therapies based on a simple phenotypic marker. This avoids over or under treatment and unnecessary toxicities, morbidities and therapy failure. For example: (1) The targeting of HER2 over expression with the monoclonal antibody, trastuzumab, to improve outcome in metastatic breast cancer was the first example of targeted treatment(2) (2) the tyrosine kinase inhibitor imatinib, developed to target the BCR-ABL fusion gene, a consequence of the Philadelphia chromosome and pathognomonic of chronic myeloid leukaemia, transformed the care of patients, changing this aggressive, life-threatening disease to a manageable chronic disease(3) and (3) the epidermal growth factor receptor (EGFR) pathway has been targeted for the treatment of patients with somatic EGFR mutant non-small-cell lung carcinoma (NSCLC). EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib have confirmed significant improvements in the 'progression - free survival', in advanced EGFR mutated NSCLC(4, 5) (4) immune checkpoint inhibitors (e.g. anti-CTLA4 or PD-1 monoclonal antibody agents, ipilimumab, nivolumab, atezolizumab) for melanoma, NSCLC, renal cell cancer, Hodgkins lymphoma, head and neck Squamous cell cancer (HNSCC). Most of the therapeutic targets are in critical molecular signaling pathways associated with development of disease. Targeting specific molecular or effectors of different diseases have shown therapeutic advantages and great potential as an important aspect of precision medicine. Next-generation drugs would be designed for diseases subtypes with more specificity, efficacy and lower toxicity.

However, there are many challenges delivering the promises of precision medicine for oncologic patients. Some of these challenges, pertinent to imaging, include biomarkers for patient selection – precision diagnostics, biomarkers for tumor heterogeneity, which contributes to therapy failure, and biomarkers for early management decisions, which leads to identifying early, the therapies that are unlikely to be successful. PET/CT has a vital role in each of these domains or challenges and has potential to add value in the promise of delivery of precision medicine.

(a) Biomarker for patient selection – Precision diagnostics

Good biomarker for patient selection is key to achieve an acceptable cost / benefit ratio for any novel therapeutic agent - to avoid unnecessary side effects for patients in whom the

therapy may not be successful and to avoid the cost to patients and health care systems. It is necessary to have companion diagnostic predictive markers, when a novel targeted therapy is developed to select the right patients. Ideally, a biomarker should enable the identification of subpopulations in whom to test new agents where they have the best chance of working. This enriches the study population. For example, Tirapazamine (TPZ) is a biochemically activated, hypoxia selective antitumor agent of the benzotriazine series. For phase III trials using TPZ as therapy agent, a PET/CT with hypoxic radiopharmaceutical such as FMISO or FAZA or HX-4(6) can be deployed to enrich the study population as a companion diagnostic marker. Other examples include - enriching the metastatic breast cancer patients with ^{18}F -FES PET/CT for estrogen receptor expression before treating with hormonal therapies or enriching the neuroendocrine tumor patients with ^{68}Ga DOTATATE PET/CT, before therapy with ^{177}Lu -DOTATATE(7) or enriching the patients with ^{68}Ga -PSMA PET/CT before therapy with ^{177}Lu -PSMA therapy(8). *It is vital to develop new PET radiopharmaceuticals with specific molecular targets, which are likely to be coupled with therapy agents and facilitate the companion diagnostic-therapy paradigm that is critical for precision medicine.*

(b) Tumor Heterogeneity

Tumor heterogeneity is one of the most significant challenges for implementing precision medicine in oncology(9). Tumor heterogeneity can be (1) Inter tumoral heterogeneity within a patient – patient may have tumors or lesions which may appear similar from a histological point of view but varies significantly by molecular subtype and malignant potential (2) Intra tumor heterogeneity – cancer cells within a tumor may have varied functional heterogeneity and spatial heterogeneity. Spatial heterogeneity of sub-clones within a primary lesion or metastasis provides a challenge for precision medicine as sequencing a portion of the tumor may miss important therapeutically relevant information. Lesions may be at locations that render getting a tissue biopsy practically impossible. In addition, post therapy, clones can change with selective pressure from a targeted therapy and as a result of mutagenic activity of radiation and chemotherapy. Usually the patient outcomes are poor when biomarkers found in the primary tumor and metastatic lesions are varied. Thus, precision medicine requires the development of approaches to detect and deal with intra tumor and inter tumor heterogeneity in a patient.

PET/CT can provide information about intra tumor spatial heterogeneity as well as intra patient inter tumoral heterogeneity as it is a whole body examination and can image the primary lesion as well as metastases in a single study. In addition, the availability of multiple molecular specific PET radiopharmaceuticals provide probing of intra tumor and inter tumor heterogeneity feasible. For example, studies have shown that PET with ^{18}F -fluoroestradiol (^{18}F -FES) can be used to noninvasively assess regional ER expression(10) and has the potential to overcome the sampling errors that arise from disease heterogeneity. PET can simultaneously measure the in vivo delivery and binding of estrogens and thus ER expression at multiple tumor sites. Earlier studies showed that ^{18}F -FES uptake at a tumor site correlates with ER expression assayed in vitro by radio-ligand binding(10) and that the level of uptake predicts the likelihood of a response to tamoxifen and aromatase inhibitor treatment (11–13). FES-PET has shown promise for assessment of heterogeneity of ER expression in individual patients(14). In a recent study, the ^{18}F -fluoroestradiol (^{18}F -FES)

PET/CT resulted changed the management plan in 48.5% of patients. In detecting ER status in metastasis group (n = 27), ^{18}F -FES PET/CT showed increased ^{18}F -FES uptake in all metastatic lesions in 11 patients; absent in all lesions in 13 patients; and the remaining 3 patients had both ^{18}F -FES positive and negative lesions. In total, on the basis of the ^{18}F -FES PET/CT results, authors found changes in the treatment plans in 16 patients (48.5%, 16/33) (15). Another example is modifying radiation therapy delivery based on heterogeneity of tumor hypoxia within tumors based on fluorine-18-labeled fluoromisonidazole (^{18}F -FMISO) PET/CT(16). In this study, heterogeneous distribution of ^{18}F -FMISO within the GTV (Gross Tumor Volume) demonstrated variable levels of hypoxia within the tumor. Plans directed at performing ^{18}F -FMISO PET/CT-guided IMRT for 10 head and neck cancer patients achieved 84 Gy to the GTV(h) and 70 Gy to the GTV, without exceeding the normal tissue tolerance. Authors also attempted to deliver 105 Gy to the GTV(h) for 2 patients and were successful in 1, with normal tissue sparing(16).

(c) Early therapy assessment

Current therapy assessment methods, based on tumor anatomic changes, are insensitive or late markers for novel and targeted therapies. As identifying therapy resistance early is a priority for delivering precision medicine, PET/CT plays an invaluable role for delivering precision medicine. Using PET/CT successfully for early therapy assessment highly influenced by (1) the biology of the tumors or molecular subtypes (2) therapy selection (3) Timing of early therapy assessment PET/CT and (4) performing PET/CT in a standardized manner.

(1) Biology of the tumors / Molecular subtypes

The avidity of PET radiopharmaceutical at baseline (before any therapy) is an important determinant of how PET/CT can be deployed in early assessment of therapy. A good example is Hodgkins Disease (HD), which is intensely FDG avid and an early therapy assessment PET/CT is now standard of care, performed after 2 or 3 cycles of therapy, which predicts outcome of patients and impacts therapy decisions. Another example, most of the head and neck squamous cell cancers (HNSCC) are intensely FDG avid before therapy and the FDG avidity diminishes rapidly with successful therapy. Hence, an early therapy FDG PET/CT can be performed after two cycles of induction chemotherapy or two weeks of concurrent chemoradiation therapy and the change in FDG avidity between the baseline imaging and early therapy assessment imaging can separate the responders and non responders(17), reliably. Not all tumors are intensely FDG avid such as lobular breast cancer and bronchio alveolar cancer of the lung and it would be difficult to implement FDG PET/CT based early therapy assessment for these cancers. However, a novel PET radiopharmaceutical such as FACBC(18), which demonstrates intense uptake in lobular breast cancer can be successfully deployed. *Therefore, selecting a tumor type or molecular subtype, which has moderate to intense avidity for the PET radiopharmaceutical, is fundamentally important.*

(2) Therapy Selection

Therapies that induce an inflammatory response early can interfere with intensity of FDG uptake, which lead to errors in early therapy assessment. Radiation induced inflammatory FDG uptake can be noticeable after second week of therapy until atleast 12 weeks after therapy completion or even later(19). Inflammatory uptake due to immunotherapy can be seen early during the first two cycles and then usually subsides over many months. It has been also known chemotherapy combination with Rituximab induce inflammatory FDG uptake. In addition, rate of decline in FDG avidity depends on the effectiveness of the therapy against the tumor. Novel therapy assessment methods for immunotherapy assessment using FDG PET/CT or other novel PET radiopharmaceuticals must be developed in future. *It is important to use FDG PET/CT in appropriate therapy context for early therapy assessment.*

(3) Timing of PET/CT

The early therapy assessment PET/CT is usually performed after first or second cycle of therapy, which allows time for adaptation to modify the therapy as well as minimize the non specific inflammatory uptake induced by therapy. This is important to avoid unnecessary cost of expensive therapies and side effects associate with the therapies soon after two cycles.

(4) Standardization of PET/CT

Implementing standardized and structured qualitative therapy assessment methods such as Lugano classification for lymphoma(20) and Hopkins criteria for solid tumors(21, 22) and quantitative methods such as standardized uptake values (SUVmax or SUVpeak) or tumor volumetric markers such as metabolic tumor volume (MTV) or total lesion glycolysis (TLG) or tumor heterogeneity indices requires standardization of PET/CT procedures. The standardization of methods for PET/CT calibration, patient preparation, image acquisition, and image analysis are essential for precision therapy assessment. EANM (European Association of Nuclear Medicine) guidelines(23) or the QIBA (Quantitative Imaging Biomarker Alliance) FDG PET/CT profile (version 1.0)(24) must be followed to standardize the PET/CT procedures. EANM guidelines recommends that blood glucose level of 200mg/dl for clinical and 150mg/dl for research studies and an uptake time of 60 minutes for FDG PET/CT. When therapy assessment PET/CT is performed, the uptake time is recommended to be within 10 min of the baseline study(23). In addition, patient needs to be scanned in the same PET/CT system and same reconstruction methods and analysis are used when a patient has multiple PET/CT studies.

In conclusion, Precision Medicine is about selecting the right therapy for the right patient, at the right time, specific to the molecular targets expressed by disease or tumors, in the context of patient's environment and life style. Some of the challenges for delivery of precision medicine in oncology include: Biomarkers for patient selection for enrichment – precision diagnostics, mapping out tumor heterogeneity that contributes to therapy failures and early therapy assessment to identify resistance to therapies. PET/CT offers solutions in these important areas of challenges and facilitates implementation of precision medicine.

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References

1. Office of the Press Secretary. FACT SHEET: President Obama's Precision Medicine Initiative. The White House; 2015. <https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precisionmedicine-initiative> [Accessed August 14, 2016]
2. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001; 344(11): 783–92. [PubMed: 11248153]
3. Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2003; 349(15):1423–32. [PubMed: 14534335]
4. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol*. 2010; 11(2):121–8. [PubMed: 20022809]
5. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012; 13(3):239–46. [PubMed: 22285168]
6. Zegers CM, van Elmpt W, Szardenings K, et al. Repeatability of hypoxia PET imaging using [(1)(8)F]HX4 in lung and head and neck cancer patients: a prospective multicenter trial. *Eur J Nucl Med Mol Imaging*. 2015; 42(12):1840–9. [PubMed: 26136164]
7. Strosberg, J.; Wolin, E.; Chasen, B., et al. [Accessed August 14, 2016] 177-Lu-dotatate significantly improves progression-free survival in patients with midgut neuroendocrine tumours: results of the phase III NETTER-1 trial. https://www.nanets.net/nanets_cd/2015/pdfs/C39.pdf
8. Baum RP, Kulkarni HR, Schuchardt C, et al. 177Lu-Labeled Prostate-Specific Membrane Antigen Radioligand Therapy of Metastatic Castration-Resistant Prostate Cancer: Safety and Efficacy. *J Nucl Med*. 2016; 57(7):1006–13. [PubMed: 26795286]
9. Burrell RA, McGranahan N, Bartek J, Swanton C. The causes and consequences of genetic heterogeneity in cancer evolution. *Nature*. 2013; 501(7467):338–45. [PubMed: 24048066]
10. Mintun MA, Welch MJ, Siegel BA, et al. Breast cancer: PET imaging of estrogen receptors. *Radiology*. 1988; 169(1):45–8. [PubMed: 3262228]
11. Mortimer JE, Dehdashti F, Siegel BA, Trinkaus K, Katzenellenbogen JA, Welch MJ. Metabolic flare: indicator of hormone responsiveness in advanced breast cancer. *J Clin Oncol*. 2001; 19(11): 2797–803. [PubMed: 11387350]
12. Mortimer JE, Dehdashti F, Siegel BA, Katzenellenbogen JA, Fracasso P, Welch MJ. Positron emission tomography with 2-[18F]Fluoro-2-deoxy-D-glucose and 16alpha-[18F]fluoro-17beta-estradiol in breast cancer: correlation with estrogen receptor status and response to systemic therapy. *Clin Cancer Res*. 1996; 2(6):933–9. [PubMed: 9816253]
13. Linden HM, Stekhova SA, Link JM, et al. Quantitative fluoroestradiol positron emission tomography imaging predicts response to endocrine treatment in breast cancer. *J Clin Oncol*. 2006; 24(18):2793–9. [PubMed: 16682724]
14. Kurland BF, Peterson LM, Lee JH, et al. Between-patient and within-patient (site-to-site) variability in estrogen receptor binding, measured in vivo by 18F-fluoroestradiol PET. *J Nucl Med*. 2011; 52(10):1541–9. [PubMed: 21903739]
15. Sun Y, Yang Z, Zhang Y, et al. The preliminary study of 16alpha-[18F]fluoroestradiol PET/CT in assisting the individualized treatment decisions of breast cancer patients. *Plos One*. 2015; 10(1):e0116341. [PubMed: 25617853]

16. Lee NY, Mechalakos JG, Nehmeh S, et al. Fluorine-18-labeled fluoromisonidazole positron emission and computed tomography-guided intensity-modulated radiotherapy for head and neck cancer: a feasibility study. *Int J Radiat Oncol Biol Phys.* 2008; 70(1):2–13. [PubMed: 17869020]
17. Yu J, Cooley T, Truong MT, Mercier G, Subramaniam RM. Head and neck squamous cell cancer (stages III and IV) induction chemotherapy assessment: value of FDG volumetric imaging parameters. *J Med Imaging Radiat Oncol.* 2014; 58(1):18–24. [PubMed: 24529051]
18. Tade FI, Cohen MA, Styblo TM, et al. Anti-3-[18F] FACBC (Fluciclovine) PET-CT of Breast Cancer An Exploratory Study. *J Nucl Med.* 2016
19. Subramaniam R, Truong M, Peller P, Sakai O, Mercier G. Fluorodeoxyglucose–positron-emission tomography imaging of head and neck squamous cell cancer. *American Journal of Neuroradiology.* 2010; 31(4):598–604. [PubMed: 19910448]
20. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014; 32(27):3059–68. [PubMed: 25113753]
21. Marcus C, Ciarallo A, Tahari AK, et al. Head and neck PET/CT: therapy response interpretation criteria (Hopkins Criteria)-interreader reliability, accuracy, and survival outcomes. *J Nucl Med.* 2014; 55(9):1411–6. [PubMed: 24947059]
22. Sheikhabaie S, Mena E, Marcus C, Wray R, Taghipour M, Subramaniam RM. 18F-FDG PET/CT: Therapy Response Assessment Interpretation (Hopkins Criteria) and Survival Outcomes in Lung Cancer Patients. *J Nucl Med.* 2016; 57(6):855–60. [PubMed: 26837337]
23. Boellaard R, Delgado-Bolton R, Oyen WJ, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. *Eur J Nucl Med Mol Imaging.* 2015; 42(2):328–54. [PubMed: 25452219]
24. [Accessed on August 14, 2016] www.rsna.org/uploadedFiles/RSNA/Content/Science_and_Education/QIBA/QIBA_FDG-PET_Profile_v105_Publicly_Reviewed_Version_FINAL_11Dec2013.pdf

Key Points

- Precision Medicine is about selecting the right therapy for the right patient, at the right time, specific to the molecular targets expressed by disease or tumors, in the context of patient's environment and life style.
- Some of the challenges for delivery of precision medicine in oncology include: Biomarkers for patient selection for enrichment – precision diagnostics, mapping out tumor heterogeneity that contributes to therapy failures and early therapy assessment to identify resistance to therapies.
- PET/CT offers solutions in these important areas of challenges, and facilitates implementation of precision medicine.
- Early therapy assessment using PET/CT for precision medicine is highly influenced by (1) the biology or molecular subtype of the tumor (2) therapy selected (3) timing of early therapy assessment PET/CT and (4) standardization of PET/CT procedures.