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NRG Oncology Research Opportunities within the New National Clinical Trials Network

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NRG Oncology is a newly constituted National Clinical Trials Network (NCTN) group created through the coordinated efforts of the National Surgical Adjuvant Breast and Bowel Project (NSABP), the Radiation Therapy Oncology Group (RTOG), and the Gynecologic Oncology Group (GOG). These three legacy cancer cooperative groups have over 150 years of cumulative experience in the conduct of practice-defining, multi-institutional phase II and phase III trials supported primarily by the National Cancer Institute (NCI). As a response to the reconstitution of the NCI-supported cooperative cancer groups, the NSABP, RTOG, and GOG elected to join forces to create a new NCTN group now known as NRG Oncology (acronym NRG derived from names of parental groups). NRG leverages the unique capabilities and experiences of all three legacy groups as a foundation for innovative late-stage clinical and translational research across seven major cancer disease sites, including rare and under-studied cancers. Specifically, NRG will create a synergy greater than the sum of the three legacy groups to improve lives of adult cancer patients burdened with localized or locally advanced disease through the conduct of practice-defining clinical trials.

Discussions regarding a partnership among the three groups began first between NSABP and RTOG in 2010, with the GOG joining the discussions in the summer of 2011. The central vision held by the three groups was to create NRG as an NCTN-supported organization focused on research into seven distinct cancer disease sites:

- **a.** Adult Brain Tumors (Primary and Secondary);
- **b.** Head and Neck Cancer;
- **c.** Localized and Locally Advanced Lung Cancer (Both Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer [SCLC]);
- **d.** Breast Cancer (Focused on Localized and Locally Advanced Disease)
- **e.** Gastrointestinal (GI) Cancer (Including Colorectal and Non-Colorectal Cancers);
- **f.** Genitourinary (GU) Cancer (Emphasizing Non-Metastatic Prostate and Bladder Cancers);

g. Gynecologic Cancer (Including Ovarian, Cervix, and Endometrial Cancers)

It is anticipated that the emphasis on these seven disease sites will be complementary to the research missions and clinical trial portfolios of the other NCTN groups, particularly given NRG's unique multidisciplinary strengths in gender-specific cancers, aerodigestive malignancies, and brain tumors. In addition, the group's mission involves a focus on patients with localized and locally advanced malignancies, an emphasis that is highly relevant to all seven of NRG's cancer disease sites. The NRG scientific and administrative core committees, its non–disease site scientific committees, and the efforts of the NRG Operations Center focus on enabling its cancer disease site committees to succeed in asking and answering key clinical and translational research questions that define new diagnostic and therapeutic paradigms for both common and rare malignancies within these disease sites. In addition, NRG plans to selectively expand the outstanding portfolio of phase I and II trials conducted for women with gynecologic malignancies by GOG and for brain tumor patients by RTOG into the other five disease site committees in developing and testing novel therapies.

There are four strategic domains which are essential to NRG Oncology's research plan.

1. Innovation in Multi-Disciplinary Early-Stage Malignancy Research

All seven NRG cancer disease site committees have a history in their legacy group (s) of practice-defining trials of new multi-disciplinary approaches to localized or locally advanced cancer. Examples of these include the use of radiosurgery boost to improve survival of brain metastases patients (Lancet 2004); the addition of chemotherapy to radiotherapy for high-risk resected head and neck cancer (NEJM 2004); the concurrent delivery of chemotherapy with radiation therapy for stage III NSCLC (JNCI 2011); the value of adding oxaliplatin to 5-flourouracil/leucovorin as postoperative adjuvant therapy for stage II and III colon cancer (J Clin Oncol 2007),and adding oxaliplatin to neoadjuvant therapy for stage II and III rectal cancer (ASCO 2011); the combination of trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer (NEJM 2005); the role of sentinel lymph node resection in clinically node-negative invasive breast cancer (Lancet Oncology 2007); the optimized integration of chemotherapy and radiation therapy for pancreatic cancer (JAMA 2008); the addition of total androgen ablation to radiation therapy for early-stage prostate cancer (NEJM 2011); and the value of chemotherapy in locally advanced and maximally debulked endometrial cancer (J Clin Oncol 2006,). NRG's mission to improve the lives of cancer patients with localized or locally advanced cancer through the conduct of high-quality clinical trials is ideally suited to the significant investment in multi-modality research that NRG embraces. NRG will accomplish this mission through the clinical exploration of appropriately diverse therapeutic and diagnostic means. Currently approved or planned investigational approaches to localized malignancies within the NRG disease site committees include immunomodulation in conjunction with standard-of-care therapies (Brain Tumor, GI, and Gynecologic Cancer Committees); particle beam therapy versus photon beam therapy trial designs (Brain Tumor, Lung Cancer, and GU Cancer Committees); randomized testing of robotic surgery (Head and Neck Cancer Committee); testing of biomarker-defined chemotherapy–radiotherapy strategies (Lung Cancer and GI

Cancer Committees); and the testing of chemotherapy or radiation therapy response modifiers, such as poly (ADP-ribose) polymerase (PARP) inhibitors or histone deacetylase (HDAC) inhibitors for localized malignancies (Brain Tumor, GI Cancer, and Gynecologic Cancer Committees). The primary goal of the NRG Developmental Therapeutics Committee will be to explore new agents and new classes of agents for their potential value when integrated into the care of patients with intermediate-to-high–risk localized or locally advanced disease.

2. International Leadership in Gender-Specific Cancer Research

NRG is uniquely suited to conduct clinical trials that improve the lives of women with breast or gynecologic cancer and men with prostate cancer. Research focused on hormone-sensitive tumors exemplifies how NRG's integrated research strategy will create opportunities beyond what was feasible in its legacy groups. NRG's configuration will enable new opportunities to interrogate common pathways of hormonal resistance across these diseases, to develop interactive strategies to overcome hormonal resistance, to study populations at high risk for late disease failure, and to study populations at unique risk of developing hormone-responsive malignancies. There are also unique opportunities to study outcomes beyond survival and disease-free survival (DFS), including sexual functioning and other patient-reported outcomes as well as comparative-effectiveness research. This work will be conducted via coordinated analyses of patient outcome data with analysis of specimens from the NRG's Biorepository, through the conduct of new trials in these committees, and through the coordination of research strategies across committees, including the disease site, Translational Science and Patient Centered Outcomes Research (PCOR) Committees. NRG will effectively partner with other network groups on all these research activities.

3. Late-Phase Trial Assessment of New Technology

Many recent advances in the management of localized and locally advanced malignancies have relied on improvements in surgical, imaging, and radiation therapy technologies. NRG is fully committed to providing the scientific support necessary for the development and testing of innovative advanced radiation oncology technology across the NCTN through its Center for Innovation in Radiation Oncology (CIRO). This center's capabilities will allow NRG to expand the transformational work conducted in its legacy groups to systematically evaluate new methods of planning and delivering therapeutic radiation. Specifically, NRG will assume primary responsibility within the NCTN to design and execute trials that evaluate new radiation oncology approaches to cancer treatment. When a new radiation technology is identified for testing, this center, working closely with NRG committees including the PCOR Committee, will facilitate the testing of this approach's feasibility, reproducibility, cost effectiveness, and its impact on tumor control, tumor symptom reduction, and treatment-related toxicity (via patient-reported outcomes,). Examples of radiation technologies to be evaluated include robotic guidance systems, image-guided radiation, radiation therapy dose "painting" (radiation therapy dose-intensification to regions of interest as defined by molecular imaging), particle beam therapies, and motion

management systems. NRG trials also will assess new image-guided surgical systems, robotic surgical techniques, and imaging techniques.

4. Translational Research Informing the First Three Domains

An outstanding cadre of investigators who develop primary and secondary research endpoints for group trials in all disease sites lead NRG translational science efforts. Landmark translational science results from the group's legacy committees include the creation and verification of a robust molecular and clinical profile (MCP) grading system for glioblastoma patients (ASCO 2011 and 2012); clarification and analysis of the strong association of human papilloma virus status with outcome of oropharyngeal cancer patients (NEJM 2010); development of Oncotype Dx as a predictive and prognostic test for early stage breast cancer (NEJM 2006) and as a prognostic test for stage II and III colon cancer (J Clin Oncol 2011); identification of prognostically relevant gene signatures of high-grade serous ovarian carcinoma (J Clin Inv 2013); and the discovery of human equilibrative transporter-1 (hENT-1) protein as a predictive marker for gemcitabine sensitivity for previously resected pancreatic cancer (Gastroenterology 2009). NRG trials will emphasize the employment of biomarkers to stratify patients with potentially curable malignancies to therapeutic regimens that are designed to truly reflect both the risk of tumor recurrence and the risk of therapy-related toxicities. NRG's translational science is strengthened by outstanding tumor and tissue procurement, processing, and storage procedures in conjunction with NRG's Biorepository sites in Pittsburgh, San Francisco, and Columbus. These resources will enable the group to integrate the assessment of both integral and integrated biomarkers into its trials of novel therapeutic approaches for patients with localized or locally advanced cancer. The legacy groups have already been successful in securing Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP) awards from CTEP for their clinical trials.

NRG Oncology is continuing its practice-defining clinical and translational research arising from its three legacy groups. Its trials are expected to enroll more than 5,000 patients during the first year of NCTN activity. The results of these trials will define the management of patients afflicted with similar malignancies for years to come.