Pathways to Progress in Women's Cancer

A Research Agenda Proposed by the Society of Gynecologic Oncology

The Society of Gynecologic Oncology (SGO) and its multidisciplinary membership, have committed ourselves to eradicate women's cancers. This vision of a cancer-free environment is dependent on the development of new preventative and early screening techniques, improved treatments and survivorship support. To make our vision a reality, SGO has in this research report entitled "Pathway to Progress in Women's Cancers", identified and outlined the areas of research, by diseases, upon which the women's cancer community should focus for the next decade. From bench and translational research needs and clinical trials to training needs for experts in women's cancer care and patient education, this report is a road map for the future of women's cancer care research, and the ultimate means to improving prevention and treatment outcomes.

In 1997 the Society of Gynecologic Oncologists, in collaboration with the National Cancer Institute (NCI) and the Office of Women's Health at the Department of Health and Human Services prepared what was recognized as a definitive research plan entitled "The Ovarian Cancer Research Report." The results of that report were instrumental in a variety of major ovarian cancer research initiatives including the NCI Specialized Programs of Research Excellence (SPORE) program, the Department of Defense ovarian cancer research program and increased dedicated funding for clinical trials, research training grants and public education and awareness programming. The information in the report had an enormous impact on the ovarian cancer research community, and the results of this work are reflected in new treatment modalities, biomarker detections tests and current, ongoing clinical trials.

A decade later, members of the women's cancer community recognize the need to not only revisit the realm of ovarian cancer research needs, but also to address the broader overarching requirements needed to truly impact all gynecologic malignancies. It is our belief that the information contained in this comprehensive report will serve and direct the research into gynecologic cancers for the next decade and beyond. We believe this report will be a useful tool not only for SGO but for other organizations and advocacy groups as they set their future research and funding priorities.

We thank the countless medical and scientific professionals whose research and tireless efforts are reflected and cited in this report. In addition, we acknowledge our research partners in the public and private sector as well, whose support both past and present has been immeasurable, and to whom we look to in the future as we strive toward our vision and an ultimate cure.

Sincerely,

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President,
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EXECUTIVE SUMMARY

In 1997, the Society of Gynecologic Oncologists (now the Society for Gynecologic Oncology), the National Cancer Institute (NCI) and the Office of Women's Health convened a conference entitled "New Directions in Ovarian Cancer Research," charged with setting a national ovarian cancer research agenda for the following five years (1998-2003). The consensus of the group was that progress in ovarian cancer research would be facilitated and hastened by an investment in research infrastructure, such as tissue banking, ovarian cancer specific grant opportunities and resources for uncovering the genetic underpinnings of ovarian cancer. The group also emphasized important areas of clinical investigation, such as the search for a better screening test to add to CA125, and assessment of a population or a cohort at high genetic risk of ovarian cancer.

In addition to ovarian cancer, the spectrum of gynecologic malignancies includes cervical, endometrial, vulvar and vaginal cancers. The Centers for Disease Control (CDC) has estimated that in 2007- 80,976 women were diagnosed with a gynecologic malignancy and 27,739 died of their disease. Clearly, much more work needs to be done to ameliorate the burden of women's pelvic cancers. In 2010, the leadership of the Society of Gynecologic Oncology (SGO) organized a Research Summit on the "Pathway to Progress in Women's Cancers". The Summit brought together gynecologic oncologists, medical oncologists, radiation oncologists, basic science researchers, epidemiologists and educators to assess the landscape of gynecologic cancer research and recommend strategic goals for the next 10 years. Three working groups were organized around disease sites: ovarian cancer, endometrial cancer and cervical cancer. In recognition of the importance of translation of basic science to personalized patient care, three additional working groups focused on clinical trials, cancer survivorship and workforce training.

The working groups were additionally challenged to rank their research priorities by timeline (short, intermediate and long term) and risk (low, medium and high). These goals are summarized at the end of each chapter in a summary table with a notation that matches the relevant text for further information (ie. 1B1, Chapter 1, Section B, Bullet 1).

The strongest priority emerging from the Research Summit was the need to identify a mechanism to maintain infrastructure for clinical trials in gynecologic oncology. (4A1). Two out of three NCI clinical alerts ("Addition of Cisplatin to Radiation Therapy in Cervical Cancer", and "Prolonged Survival in Ovarian Cancer with Intraperitoneal Chemotherapy") have been issued as a direct result of the clinical trials structure in gynecologic oncology. However, it was recognized that the current clinical trials mechanism must adapt to include novel agents and new imaging endpoints. (1E1, 1B3, 1B6, Chapter 4) In addition, participation in clinical trials should be supported by legislation and regulation at both a state and federal level, requiring insurance cost coverage of clinical trials costs. (4G2) The women of America deserve to have more breakthroughs advanced by well-designed clinical trials research dedicated to gynecologic cancers.

Prior investment into the infrastructure of tissue banking has positioned gynecologic oncology research to both contribute to and benefit from national cancer resources, such as The Cancer Genome Atlas (TCGA). The Gynecologic Oncology Group (GOG) tissue bank was able to provide high quality ovarian cancer specimens as one of the first tissues in the TCGA, followed by endometrial cancers. By leveraging the TCGA and other resources, sophisticated research questions can begin to be addressed (1C2, 2C3, 3D4, 4F2 and others). These resources may be deployed to answer questions that cross biologic cancer sites, such as the mechanism of cancer cell invasion or the molecular markers of cancer initiating cells. (1A1, 1A3, 1A5, 1B2, 3E1).

Scientific innovation has provided the promise of personalized cancer therapies. Certainly, novel agents targeting specific tumor pathways are one part of personalized medicine. However, that concept does not encompass the spectrum of both treatment and survivorship, which is the ultimate goal. For instance, surgical intervention in endometrial cancer can be curative. But, the side effect of lymphedema may significantly affect the quality of a woman's life as well as her economic and social productivity. (2E4)

Women with gynecologic malignancies, as well as all cancer patients and survivors, deserve personal specialized care to identify the essential interventions required at diagnosis and/or recurrence to maximize quantity and quality of life (QOL). (5A1) In addition, the survivorship group recognized that personalized medicine must utilize multidisciplinary interventions to modify the overall trajectory of disease and evaluate their economic impact. (5G1)

In the past decade, cervical cancer became the first gynecologic cancer to be successfully prevented by a vaccine, which will continue to be refined and studied in different populations in for modifiers of efficacy. (3B1, 3C1) Prevention of cancer is also possible in endometrial cancer, where epidemiologic data supports the role of obesity in the development of this disease. Certainly education of the public about the connection between obesity and endometrial cancer (2A6) as well as study of the cancer preventative effects of obesity reduction strategies, such as bariatric surgery are warranted at this time. (2A3)

Finally, sustaining a cadre of researchers in gynecologic malignancies will require resources targeted for women's cancer. While we anticipate that established national funding mechanisms will fund our most exciting research, public-private partnerships will become increasingly important. Previously, a successful partnership between the Gynecologic Cancer Foundation (now known as the Foundation for Women's Cancer) and the NCI provided training in basic science research for budding gynecologic oncologists. Certainly creation of a similar cross-disciplinary gynecologic malignancies training grant would enhance the depth and breadth of researchers in women's cancers. (6H2) For researchers already committed to research in women's cancers, private cancer advocacy groups and professional societies might be able to partner for a Women's Cancer Bridge Program (WCBP) to sustain such investigators during a funding shortfall. (6I1)

Fifteen years ago, the roadmap defined by the "New Directions in Ovarian Cancer Research" conference spurred progress in ovarian cancer research that has directly affected patient care and saved lives. It is our hope and confidence that this "Pathways to Progress" report will prompt similar acceleration in research in all gynecologic malignancies. The women of America deserve nothing less.

Table E-1: Gynecologic Malignancies Research Priorities

	Short (0-3 years)	Intermediate (4-6 years)	Long (7-10 years)
Low Risk	***4A1)*** Maintain infrastructure for clinical trials in gynecologic oncology. ***2E4)*** Prevalence/QOL trial of lymphedema in EC. ***5A1)*** Identify the essential interventions all cancer survivors require at diagnosis and/or recurrence to maximize quantity and QOL.	***1E1, 1B3, 1B6)*** Develop new trial endpoints and biomarkers through imaging and circulating analytes.	***4F2)*** Establish collaborative teams of investigators to utilize banked specimens for gynecologic malignancies research.
Intermediate Risk	***3D5)*** Cervical cancer health disparities. ***3D4)*** Cervical cancer genetic and epigenetic susceptibility genes (TCGA).	***2E2)*** Quality outcomes of first surgery by gynecologic oncologist.	***2A3)*** Outcomes research on bariatric surgery/EC risk.
High Risk	***2A6)*** CDC educational campaign EC and obesity. ***3E1)*** Progression of CIN3-SCC (biology of invasion).	***1A1, 1A3, 1A5, 1B2)*** Define the ovarian cancer initiating stem-like cell. ***4G2)*** Ensure successful implementation of regulations at state and federal level for insurance cost coverage of clinical trial costs. ***6H2)*** Develop and implement a training grant specific to Gynecologic Oncology.	***5G1)*** Utilize multidisciplinary interventions to modify the overall trajectory of disease and evaluate their economic impact. ***6I1)*** Develop a bridge program to sustain investigators who have lost extramural funding.

CDC Centers for Disease Control; CIN3 Cervical Intraepithelial Neoplasia 3; EC Endometrial Cancer; QOL Quality of Life; SCC Squamous Cell Carcinoma; TCGA The Cancer Genome Atlas.

CHAPTER 1: OVARIAN CARCINOMA

INTRODUCTION AND BACKGROUND

Ovarian cancer is the most lethal female reproductive tract malignancy with more than 190,000 new cases diagnosed each year worldwide. In the U.S. alone, there will be nearly 22,000 new ovarian cancer cases diagnosed and approximately 14,000 women will die from the disease. The high fatality-to-case ratio is due, in part, to a lack of effective screening modalities to detect ovarian cancer at an early stage wherein rates of cure exceed 90 percent. Most patients present with advanced stage disease and the cornerstone of treatment is surgical debulking followed by platinum-based chemotherapy. The other major contributor to the high fatality-to-case ratio is the emergence of chemoresistant disease. In fact, while 80 percent of patients appear to have a complete clinical response to their primary therapy, the majority will die from disease recurrence within five years.[1-4] More than half will develop disease recurrence within 18 months. Overall, whereas the five-year survival rate of patients with other cancers continues to markedly increase, similar gains have not been seen with ovarian cancer (Figure 1).

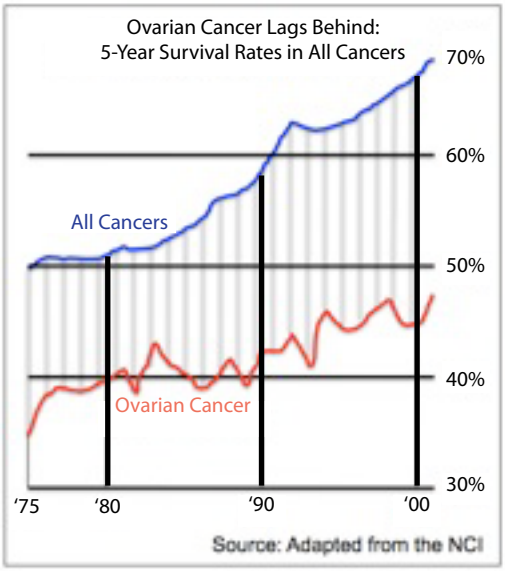

Figure 1: Survival Rate in Ovarian Cancer

Standard treatment for advanced epithelial ovarian carcinoma begins with surgical cytoreduction to remove as much tumor burden as possible, known as optimal cytoreduction. Cytoreduction theoretically results in improved blood flow to the residual tumor cells and increases the fraction of tumor cells entering the cell cycle, making them more susceptible to death from cytotoxic chemotherapy. Additionally, this surgery often alleviates symptoms associated with widespread tumor involvement within the abdomen and pelvis. Surgical cytoreduction is typically followed by six cycles of platinum and taxane-based cytotoxic chemotherapy. A number of studies have demonstrated that platinum treatment delivered via the intraperitoneal route results in improved progression-free and overall survival in women with advanced disease following optimal cytoreductive surgery.[1,5] More controversial is the role of neoadjuvant chemotherapy, which is prescribed by some centers as initial treatment instead of surgery.[6] The proposed benefit of this approach is to render surgical resection less morbid through reduction of tumor burden prior to surgery. Equivalent outcomes to those seen in cooperative group clinical trials have not yet been demonstrated with neoadjuvant chemotherapy and this remains an active area of controversy.

Recent scientific data suggest that epithelial ovarian cancer is highly heterogeneous. Understanding this heterogeneity will form the basis for developing new preventive and therapeutic strategies. BRCA1 and BRCA2 germline mutations increase the lifetime risk of ovarian cancer from 1.5 percent to approximately 20 percent or 40 percent, respectively.[7-9] Risk-reducing salpingo-oophorectomy (bilateral ovarian removal) has been shown to reduce this risk back to population levels.[10,11] From these procedures, a precursor lesion termed serous tubal intraepithelial carcinoma is found within the fallopian tube at a frequency of two to five percent with rare involvement of the ovarian surface epithelium.[12,13] This has led some scientists to question the traditional origins of ovarian carcinoma. Recent data suggest that a substantial fraction of presumed epithelial ovarian cancer may actually originate within the distal fallopian tube.[14] Morphologic and embryologic findings indicate that the ovarian surface epithelium is an unlikely site to contain a precursor lesion to epithelial ovarian carcinoma. Uncovering the true origins of ovarian cancer is likely to help advance stalled efforts at ovarian cancer screening and prevention.

RECENT DEVELOPMENTS

Mouse Models: Several mouse models of epithelial ovarian cancer have been developed within the last nine years. These models have been important for addressing some of the fundamental biological questions of ovarian cancer, such as the mechanism by which specific oncogenes and tumor suppressor genes collaborate to induce ovarian epithelial cell transformation; the correlation between initiating genetic alterations and tumor histology; pathway-targeted therapy and the comparison of gene expression between mouse and human ovarian cancer. Due to the absence of a tissue-specific promoter, surgical access to the ovaries is necessary for most of these mouse models, thus limiting their use in high-throughput drug testing.

Genomics: Molecular profiling, most commonly using gene expression, has identified a number of signatures that can differentiate normal from malignant ovarian tissues and stratify patient outcome with respect to overall and progression-free survival. Many of these signatures have been externally validated, but none have been moved into routine practice due to limitations in clinical utility and predictive accuracy. In 2006, TCGA was formally launched and ovarian cancer was selected as one of the three tumors for the pilot part of the project, which has since been deemed successful by funding agencies. TCGA had the primary goal of documenting the genomic landscape of ovarian cancer using multiple genomic and sequencing platforms. To date, however, no reliable predictor of primary resistance to platinum chemotherapy has been identified. Furthermore, no comprehensive genomic studies in recurrent tumors have been performed.

Immunology: The notion that the immune system may identify and destroy tumors is longstanding. In ovarian cancer, an improved five-year overall survival has been related to the presence of tumor infiltrating lymphocytes (TIL), or to the increased frequency of intraepithelial CD8+ TILs. To date, the majority of immune directed studies on ovarian cancer have consisted of a variety of targeted approaches designed to generate specific effectors. A variety of approaches have been evaluated, largely in phase I trials showing immunogenicity and safety. Adoptive cellular approaches with ex vivo modification of T cells such as introducing genes coding for chimeric antigen receptors have also been studied. Needed next steps include examining immunogenicity and clinical relevance of other targets, multiple targeted antigen approaches, and modification of immunosuppressive components.

Clinical Trials: Great effort and resources continue to guide the development of new treatment standards for ovarian cancer, particularly in front-line therapy. As such, three major approaches are being evaluated: intraperitoneal chemotherapy, dose dense chemotherapy and incorporation of biological therapies. Each of these topics has resulted from previous phase III investigation showing an advantage on relevant endpoints; the latest being ICON-7 and GOG-218, which demonstrated significant reductions in the hazard of recurrence to those women receiving chemotherapy in combination with bevacizumab, continuing the bevacizumab through a maintenance program. IP chemotherapy and dose-dense paclitaxel combination chemotherapy have also demonstrated positive effects on overall survival. Additional trials have focused on unique regimens targeting less common cell types (such as clear cell and mucinous carcinoma) and the potential impact of PARP inhibitors. Clinical investigation in the recurrence setting includes maintenance therapy, surgery, therapy directed at the platinum-resistance/sensitive phenotype, and new targeted agents. However, lack of patient and funding resources sharply challenges the number and type of questions that can be addressed and represents a clear unmet need in ovarian cancer.

RESEARCH AREAS

A. Origins of Ovarian Cancer
B. Tumor Microenvironment and Metabolic Circuits in Ovarian Carcinoma
C. Directed Clinical Trial Design / Development
D. Drug Sensitivity and Resistance
E. Defining the Complete Molecular Spectrum of Ovarian Cancer: Prevention, Early Detection, Surveillance

A. Origins of Ovarian Cancer

Ovarian cancer is treatable if diagnosed at an early stage. Focusing research efforts on the origins of ovarian cancer is likely to result in a significant reduction of mortality from this disease. It is increasingly becoming apparent that ovarian cancer is not a single disease, but rather a very heterogeneous group of tumors. Based on their histology, epithelial ovarian carcinomas are classified into serous, endometrioid, mucinous, clear cell, and undifferentiated subtypes. Based on their malignant behavior, ovarian carcinomas are divided into indolent (type I) and aggressive (type II). It is unclear if the remarkable histological and behavioral diversity of ovarian carcinomas is determined by a distinct "tissue of origin", distinct pluripotential state of the "cell of origin" and/or distinct "transformative events". Uncertainty about the exact origin of ovarian carcinoma impedes the development of strategies for preventive intervention, early detection, and treatment.

Tissue of Origin: The ovarian cancer tissue of origin is difficult to determine because the majority of ovarian cancer patients present with advanced disease, which is characterized by extensive tumor spread and engulfment of the ovaries, fallopian tubes, and other intraperitoneal organs. Pathological examination of early ovarian cancer lesions points to the fallopian tube, ovarian surface and secondary Müllerian system as possible precursor tissues for ovarian carcinoma, but there are no conclusive experimental data demonstrating which epithelium is the true tissue of origin (Figure 2).[15-18] In order to address these questions, future studies will need to focus on early ovarian cancer lesions.

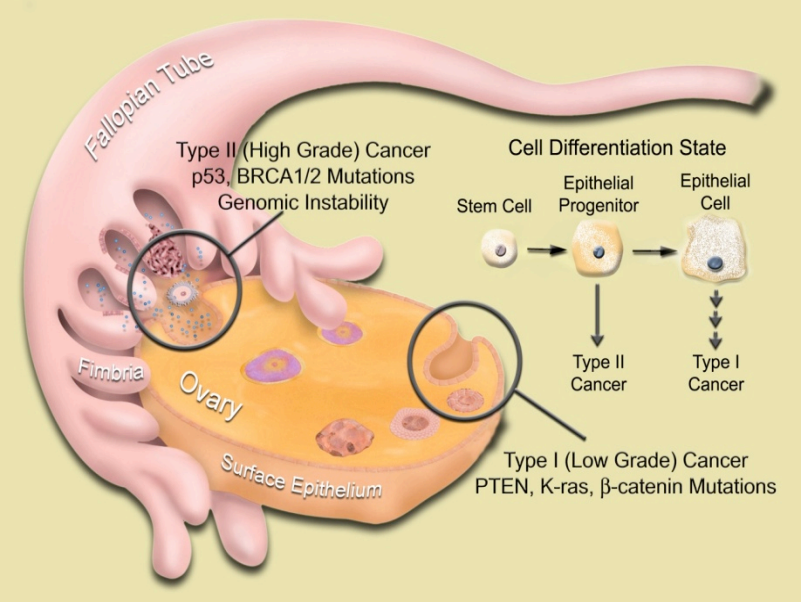

Figure 2: Origin of Ovarian Cancer. Modified from Levanon K, et al., JCO, 2008; 26 (32): 5284-5293 (used with permission).

Cell of origin: It is possible that the phenotypic heterogeneity of ovarian cancers is a reflection of the pluripotential state of the cell of origin. Thus, precursor cells to ovarian carcinoma will need to be defined by developing models in which specific cell lineages can be transformed and tracked during tumor development. Such studies should also address fundamental biological questions about the susceptibility of distinct cell types to specific initiating events, tumor clonality, intratumoral heterogeneity, and the role of tumor-initiating cells in ovarian tumors.

Initiating transformative events: It is uncertain whether ovarian carcinomas of different phenotypes develop via distinct molecular pathways. Findings that TP53 and BRCA1 mutations are more prevalent in serous tumors, while PTEN and CTNNB1 (β-catenin) mutations are more prevalent in endometrioid tumors, indicate that the underlying genetic alterations may be the foundation of tumor heterogeneity.[19-21] However, recent ovarian TCGA data revealed that tumors which share a similar phenotype may have extremely different genetic and epigenetic alterations ranging from mutations in a few genes to a genomically unstable phenotype characterized by multiple losses and gains of focal genomic regions and whole chromosome arms. Delineating pathways that are required for tumor initiation and progression are the key to successful targeted therapies.

Requests for Action:

A1. Develop multi-site consortia organized around precursor lesions of ovarian cancer to:
- obtain sufficient amounts of tumor material, and
- develop uniform methods for molecular characterization.

A2. Develop mouse models in which specific tissues can be targeted.

A3. Request RFA to study ovarian cancer initiating cells in both mouse models and human samples to emphasize:
- metabolic requirements,
- differentiation state, and
- chromatin structure.

A4. Develop strategies to detect micrometastases and circulating cancer cells.

A5. Request funding for studies addressing:
- mechanisms by which specific initiating genetic and epigenetic events, collaborate to induce cell transformation in distinct cell types, and
- identification of ways to effectively interfere with these events.

B. Tumor Microenvironment and Metabolic Circuits in Ovarian Carcinoma

Neoplasms are no longer considered as isolated clusters of transformed epithelial cells invading unsuspecting tissue. There is growing recognition of the role of aberrant cancer microenvironment in facilitating, through reciprocal communication, cancer cell perpetuation. The highly diverse extracellular matrix (ECM) in solid tumors is populated with fibroblasts, immune cells, endothelial cells, mesenchymal and hematopoietic precursors. Collectively, this microenvironment maintains a pro-tumorigenic, anti-immunogenic niche that provides a selective growth advantage. This process is strikingly similar to both a healing wound, and to some processes within embryogenesis. However, in contrast to wound healing and embryogenesis, the signals limiting repair or development are absent in cancers. The notion that the immune system may identify and destroy tumors is longstanding. In ovarian cancer, the five-year overall survival has been related to the presence or absence of tumor infiltrating lymphocytes (TIL), or to the increased frequency of intraepithelial CD8+ T cells.[22] In contrast, patients with increased number of immune suppressive CD4+CD25+ regulatory T cells (Tregs) have reduced survival. To date, the majority of immune directed studies in ovarian cancer have consisted of a variety of targeted approaches designed to generate a specific effector. Multiple tumor associated antigens with a predilection for expression on ovarian cancer have been identified. A variety of approaches have been evaluated largely in phase I trials to include antigens of a variety of types given alone or with an adjuvant; modified or unmodified tumor cell lysates (autologous or allogeneic); dendritic cells primed with a variety of agents; tumor hybrids with antigen presenting cells; or DNA alone or in a recombinant fashion. Adoptive cellular approaches with ex vivo modification of T cells have also been studied. An improved understanding of the complexities of tumor microenvironment holds promise for new and more effective biomarkers and therapeutic approaches.

Cancer Metabolomics: The metabolic needs of cancer cells are distinct from normal cells including hematopoietic progenitors. Tumor cells meet their demand for higher energy by aerobic glycolysis (Warburg's effect). Aerobic break down of glucose provides adequate supply of energy and the necessary building blocks to synthesize nucleotides, lipids and membrane components to sustain cell proliferation. When the availability of glucose is limited, tumor cells resort to alternate sources of energy such as glutamine. Normal tissues on the other hand lower their use of glutamine under similar conditions and generate energy through recycling macromolecules and organelles (macroautophagy). Furthermore, cancer cells maximize energy production by using genetic variants of enzymes that are highly efficient in breaking down substrates. While improving efficiency of energy production, cancer cells also conserve energy by segregating essential mRNAs for survival into P-bodies during treatment with chemotherapy and retrieve them later for reuse. Investigating these dynamic adaptive changes in cancer cells is critical for development of novel therapeutics.

Metabolomics determines the final product, metabolites, of genetic and epigenetic changes in tumor tissues leading to alterations in the transcriptome and translatome (proteomics). There are about 5,000 distinctive metabolites which can be detected in cancer tissues by nuclear magnetic resonance (NMR) and Gas chromatography-mass spectrometry (GC-MS) methods. Instead of studying the entire repertoire of metabolites (Metabolome), a subset of pathway specific intermediaries can be investigated in tumor tissues (Metabolomic 'finger printing'). Tumor tissues (surgical specimens) and body fluids including urine and saliva are analyzed for metabolites. Recent advances in non-invasive imaging methods have provided an unprecedented opportunity to study the temporal changes in tumor tissues during treatment. Adaptive changes in cancer cells extend beyond the Warburg's effect and energy balance. Parallel investigations in animal models can systematically integrate metabolome with transcriptome, proteome and non-coding RNAs. Lipid derivatives function as chemo attractants and regulate tumor/stroma remodeling, provide a sanctuary for tumor initiating stem cells and contribute to chemoresistance. Peritoneal lipid metabolites modulate the microenvironment and facilitate tumor growth. There are about 200 known lipid derivatives that can regulate tumor associated macrophages and maintain an immunosuppressive milieu.

Requests for Action:

B1. Develop a mechanistic understanding of various cell types in the tumor microenvironment:
- evading immune recognition, and
- promoting tumor growth.

B2. Request RFA to study the interactions of tumor stem cells (or progenitor cells) with the stem cell niche in tumor dormancy.

B3. Define gradients and flow of soluble factors for identification of new biomarkers:
- tumor initiation,
- migration,
- inflammation, and
- angiogenesis.

B4. Develop new technologies:
- ovarian specific 3D matrix reconstitution, and
- organotypic models.

B5. Evaluate the immunogenicity and clinical relevance of new targets for immunological approaches against ovarian cancer.

B6. Identify alterations in basal and chemotherapy-induced changes in lipid metabolites to assist development of novel molecular pathways for drug targeting.

C. Directed Clinical Trial Design / Development

A coordinated and focused clinical trials program for patients with ovarian cancer is essential to find the way forward among an ever increasing number of novel therapeutics. Most of these agents target specific proteins believed to be important to the malignant phenotype (proliferation, invasion, metastasis, angiogenesis, etc.) and as such, do not necessarily fall into traditional paradigms of assessing appropriate dose (lack of dose-response pharmacokinetics), toxicity (both on- and off-target effects which may only be recognized with chronic dosing), and efficacy (may only produce cytostatic effects). Considering the limited patient resources through which to evaluate new compounds, efficiency in trial design, exploration and validation of biomarkers, and innovative integrated pharmacodynamics are vital considerations to meet this challenge.

Critical Pathway Discovery: An initial and recurrent step in new therapy development is the discovery and exploitation of the functional role(s) cell biological processes contribute to sustain and drive malignancy. While the highest precision of information can be gathered through proximal direct tissue acquisition (such as biopsy or surgical resection), these can only be practically repeated a limited number of times. However, some clinical scenarios, such as neoadjuvant therapy, provide a reasonable tool for assessment

that resides within a standard of care. Nevertheless, sustained development will ultimately become predicated from the recognition, measurement and validation of surrogate biomarkers from readily available resources, such as peripheral tissue and blood.

TCGA has recently completed and published a comprehensive overview of the genomic landscape of ovarian cancer using multiple microarray and sequencing platforms. Though TCGA has identified TP53 mutations in more than 95 percent of tumors and few other recurrently mutated genes besides BRCA1 and BRCA2, focal copy number abnormalities appear widespread. In addition, canonical pathways (such as RB and RAS/PI3K signaling) are activated mostly through copy number alteration rather than mutation. In contrast, members of the homologous recombination pathway are abnormal in approximately 50 percent of all tumors, which is thought to be associated with increased sensitivity to PARP inhibition. It is critical to study in vitro mechanisms of sensitivity to novel drug targets altered by copy number rather than mutation. Some of the most promising new agents in clinical trials today target canonical pathways altered by mutation, such as the RAS/PI3K pathway. However it is unclear whether these agents will also be active in tumors altered primarily by copy number alterations. Response to PARP inhibition has been demonstrated in women with germline mutations in BRCA1 and BRCA2.[23-25] However, it remains uncertain if other mechanisms of homologous recombination (HR) deficiency, such as BRCA1 methylation or copy number alteration in other HR pathway members, will result in similar sensitivity to PARP inhibition.

Novel Trial Design: Patient resources are greatly outpaced by the number of clinical questions to address in prospective studies. Several prior reports have convincingly shown that alternative trial designs can greatly enhance the operating characteristics of clinical studies. These include efficiency at determining effective dosing, limiting unnecessary toxicity exposure and increasing data to inform existing and developing hypotheses. In addition, certain novel therapeutics may need to convincingly demonstrate alteration of the processes (e.g. signaling, gene expression, protein production) to which they have been primarily developed, particularly if these targets have been deemed primary drivers of the malignant phenotype. Importantly, these endpoints may be reached well below established parameters of unacceptable toxicity. Further, it is likely that biomarkers may be discovered and properly validated within the same trial, which itself may be primarily asking a clinical efficacy question.

Clinical Scenarios: Investigation of treatment outcomes in ovarian cancer patients has identified several unique and independently associated prognostic factors for survival. It is increasingly recognized that certain ovarian cancer histological subtypes share molecular aberrations with similar subtypes of other organs, or activate similar pathways of growth biology. The ability to separate these factors prospectively and in real-time in a clinical study, provides more directed and hypothesis-driven investigation. Nevertheless, there are important considerations to address before embarking on molecularly targeted studies. The need to document the presence or absence of targetable aberrations prior to inclusion criteria in clinical investigation is unknown. Large numbers of compounds must be screened for efficacy in this patient population to select those with most promise for success in phase III trials (Figure 3). It is clear that future cancer therapy will require development, examination and validation of currently known and yet discovered mediators of response. Ultimately, individualized therapy will begin its definition as the exploration of these key research questions initiate (Figure 4).

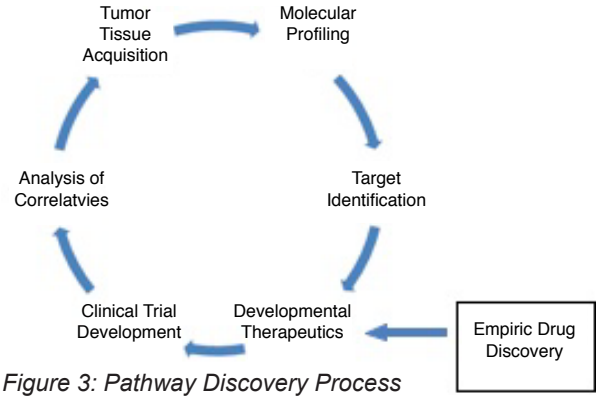

Figure 3: Pathway Discovery Process

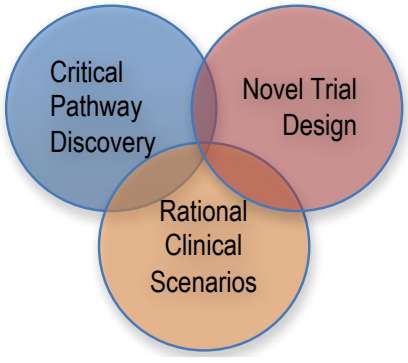

Figure 4: Clinical Development Interactions

Requests for Action:

C1. Evaluate paired primary and metastatic tumors and associated biospecimens, to correlate with clinical trial outcomes to determine which aberrant processes are driving tumor biology.
C2. Develop rational approaches to synthetic lethality considering new knowledge surrounding the complex genomic landscape of ovarian carcinoma.
C3. Improve the phase III trial performance of phase II agents through the use of novel trial designs with combined biologic and clinical endpoints of novel agents that definitively hit their alleged target.
C4. Identify clinically relevant endpoints and associated biomarkers of response for trials in the recurrent disease setting.

D. Drug Sensitivity and Resistance

Advanced serous ovarian tumors will respond to platinum and taxane-based combination chemotherapy in nearly 80 percent of cases, making ovarian cancer one of the most chemo-sensitive common solid tumors. A substantial fraction, however, will develop primary platinum resistance and progress while receiving initial chemotherapy or shortly thereafter. This is in contrast to most patients who will develop acquired resistance to platinum and ultimately succumb to their disease. Acquired platinum resistance may occur early or late in the course of treatment after one or many lines of platinum-based therapy. Since platinum-based therapy became the standard of care for treating ovarian cancer nearly three decades ago, substantial efforts have been directed toward understanding the mechanisms of resistance. Commonly hypothesized mechanisms include reduced drug uptake, increased drug efflux or metabolism, poor delivery due to tumor specific factors, or enhanced DNA repair.[26,27] The greatest challenge to overcoming platinum resistance is the presence of multifactorial mechanisms of resistance. In the modern era of cancer genomics and technologic advances, widespread concerted efforts should once again be directed toward understanding and overcoming platinum resistance. Overcoming resistance to platinum therapy would be one of the greatest advances that could benefit patients with ovarian cancer, but similar approaches can be applied to study resistance to other agents such as taxanes and molecularly targeted therapies.

Drug Delivery: The identification of genetic predisposition to disease and new molecular targets involved in cancer pathogenesis offers opportunities for highly specific and targeted treatments. New classes of pharmaceuticals and biologics (e.g., peptides, proteins, nucleotide-based therapeutics, and small molecule inhibitors) pose unique challenges that require rapid evolution of drug delivery technology. Many of these drugs cannot be effectively delivered by conventional means. Additionally, for many conventional pharmaceutical therapies, the efficacy may be improved and the side effects reduced if the therapy could be administered in a more selective and more frequent manner rather than through conventional burst release techniques. Many solid tumors, including ovarian cancer, present unique barriers to drug delivery (e.g., high interstitial fluid pressure, fibrosis, impaired or dysfunctional vascularity, hypoxia, necrosis) that must be overcome to enhance therapeutic efficacy and reduce side effects. The expanding arena of emerging drugs combined with increased sensitivity to clinical outcomes and healthcare costs are driving the need for alternative drug delivery methods and devices.

Requests for Action:

D1. Immediately increase the supply of properly annotated paired biospecimens through the development of robust tissue banks such that in vivo drug-induced changes can be identified pre- and post-treatment samples.
D2. Integrate the development of drugs and delivery systems to optimize the efficacy and cost effectiveness of therapy.

E. Defining the Complete Molecular Spectrum of Ovarian Cancer: Prevention, Early Detection, Surveillance

Screening programs to detect ovarian cancer in asymptomatic women have been notoriously difficult. Given an estimated lifetime risk of one in 70, any screening strategy will require a minimum specificity of 99.6 percent and sensitivity of at least 75 percent to avoid unacceptable levels of false-positives. New insights, technologies and approaches are needed to develop appropriate screening modalities for earlier detection and surveillance following treatment.

Prevention: Understanding the initiating events leading to the development of ovarian cancer will be a key to designing prevention strategies. Family history and inherited risk are the strongest factors for the development of ovarian cancer but they cannot be modified. Obesity is a known risk factor for the development of ovarian and many other cancer types. Protective factors have been described and include the use of oral contraceptives, pregnancy, breastfeeding, tubal ligation, and hysterectomy. Studies to define the mechanisms by which each of these affect the development of ovarian cancer are needed as well as studies to gauge the effect of manipulation of these factors on cancer development and prevention. Based on histopathologic and genetic studies, the distal fimbriated end of the fallopian tube has emerged as a potential site of origin for serous ovarian cancer. The molecular events leading to the development of a "p53 signature" in cells within the distal fallopian tube and whether these changes are necessary and sufficient for the development of ovarian cancer are not known.

Biomarkers: **Early detection.** As per the current NCI Consensus Statement, the "gold standard" strategy of annual pelvic examination, transvaginal ultrasound and serum measurement of CA125, remains relatively ineffective and does not increase survival for women at average risk. One key to effective biomarker design will be to better define high- and low-risk populations. In addition to the identification of genetic risk factors for ovarian cancer, an ongoing challenge is to develop means of translating these findings, which frequently fall within "gene deserts", into an understanding of specific functional dysregulation.[28,29] These studies would therefore have relevance to disease-associated variants in other tumor types. Similarly, defining the natural history of premalignant lesions and the necessary and sufficient genetic events which lead from early- to late-stage tumors will define the so-called lead-time or window of opportunity for diagnostic biomarkers. Within this context, proteomics and transcriptomics are needed to identify novel serum candidates. The presence of circulating tumor cells (CTC's), tumor-derived genomic DNA and microRNA have been identified in the blood of patients with a number of solid tumors. Studies are required to define and understand their value in diagnosis, prognosis and surveillance of ovarian cancer. The metastasis of ovarian cancer is unique amongst other adenocarcinomas as ovarian tumor cells disseminate within the confines of the abdominal cavity with rare hematogenous spread.

Individualized markers for disease surveillance and estimation of tumor burden: The molecular second look. Current approved surveillance strategies consist of combinations of serial gynecologic examinations, serologic and radiologic studies and even second-look surgery (SLS). Each of these methods has one or more drawbacks, including high cost, poor sensitivity and/or specificity, and, most importantly, none have been demonstrated to increase patient survival. Notwithstanding this "detection failure" using current methodologies, monitoring for earlier diagnosis of recurrence is "integral to a philosophy of active management" and critical for decisions regarding participation in trials of novel therapies (www.sgo.org/WorkArea/showcontent.aspx?id=2702). Given TCGA's demonstration of the large number of mutations and alterations present in each ovarian tumor, ovarian cancer represents an intuitive choice for the development and use of "individualized" cancer-specific assays (Figure 5). Next-generation sequencing (NGS) allows for unprecedented characterization of the cancer genome. Not only can these differences define the basis for "genetically informed" treatment (e.g. EGFR status in lung cancer), but they may also be used as highly specific biomarkers for detecting tumor cells, as first demonstrated in patients with colorectal cancer.

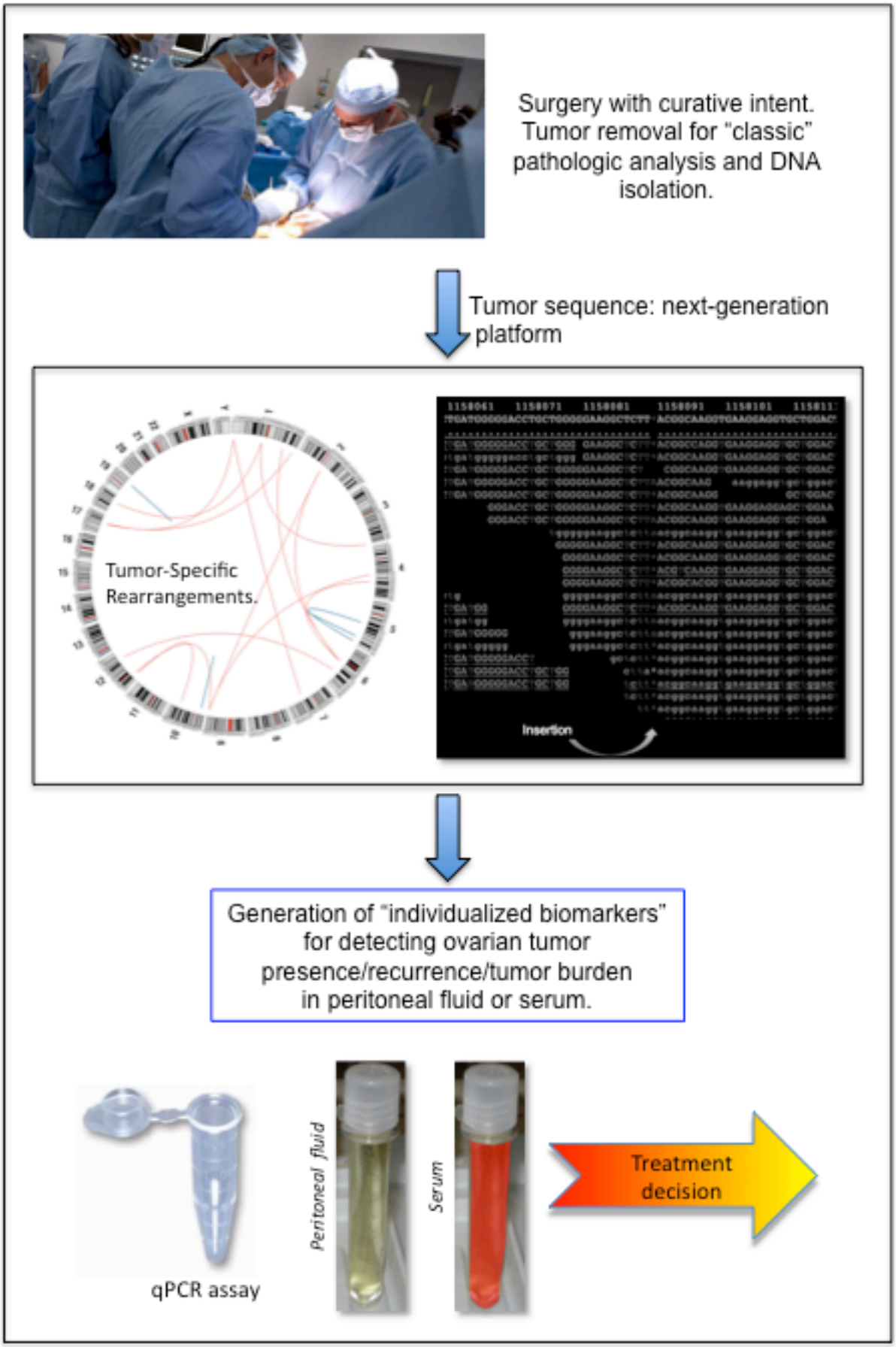

Figure 5: Individualization of Ovarian Cancer Treatment

Requests for Action:

Significant emphasis should be focused on identifying the relevant site(s) of origin for ovarian carcinoma, which will lead to improved strategies for prevention and/or earlier detection (Figure 6).

E1. Apply novel detection strategies to peritoneal fluid, an enriched source of potential bio markers. Proof-of-principle established in ovarian cancer can then be applied to other cancers.

E2. Identify tumor-specific changes not present in the host's normal cells as an approach to biomarker specificity.

- rearrangements,
- insertions/deletions,
- point mutations.

E3. Stratify patient treatment based on pathway directed therapy and genomic sub-typing.

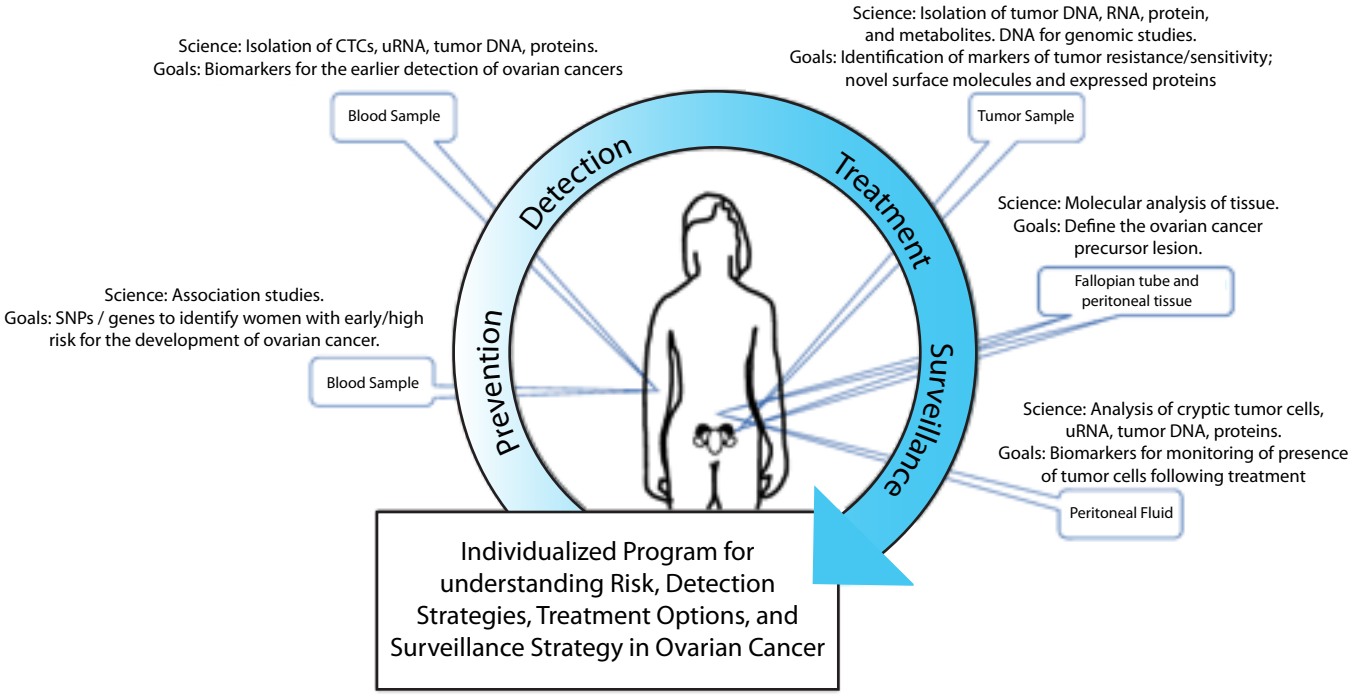

Figure 6: Schema of Prevention, Detection, Treatment and Surveillance in Ovarian Cancer JAM

Table 1-1: Ovarian Cancer Research Priorities

	Short (0-3 years)	Intermediate (4-6 years)	Long (7-10 years)
Low Risk	***1D1)*** Study paired biospecimens to uncover mechanisms of drug resistance.	***1E1, 1B3, 1B6)*** Develop new trial endpoints and biomarkers through imaging and circulating analytes. ***1C1, 1D1)*** Increase biospecimen collection.	***1A1, 1B2)*** Identify the cell of origin and mechanisms of tumor initiation.
Intermediate Risk	***1C3)*** Apply novel clinical trial designs to developing trials.	***1C2)*** Identify biologic factors associated with tumor progression, differentiation, and synthetic lethality.	***1C4)*** Identify new biomarkers of response and therapeutic targets.
High Risk	***1C3, 1C4)*** Identify relevant biomarkers within ongoing clinical trials.	***1A1, 1A3, 1A5, 1B2)*** Define the ovarian cancer initiating stem-like cell.	***1C3,1E3)*** Stratify patient treatment based on pathway directed therapy and genomic subtyping.

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CHAPTER 2: ENDOMETRIAL CARCINOMA

INTRODUCTION AND BACKGROUND

Endometrial cancer is the most common gynecologic cancer and alarmingly, both incidence and mortality are rising (Table I). It is anticipated that the traditional "type I" hormonally-mediated endometrial cancers will continue to increase in part due to growing obesity epidemic. "Type II" endometrial cancers are more aggressive tumors (papillary serous, clear cell, grade 3 endometrioid) and account for less than 25 percent of the cases but for more than half of the deaths. (Table II)

Table I. Endometrial Cancer: Annual Incidence and Mortality

Year	Cases	Deaths
1987	35,000	2,900
2008	40,100	7,170*

**250% Increase; American Cancer Society, 2008.*

Table II. Ratio of Endometrial Cases to Death Per Year

		Cases	Deaths per year
Overall		40,000+	7000+
All Endometrioid		34,000	3710
	Grade 1-2	28,800	1820
	Grade 3	5,200	1890
Papillary Serous		4,000	2,800
Clear Cell		1,200	560
Sarcoma/Carcinosarcoma		800	400

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RESEARCH AREAS

Targets and topics are being investigated in order to decrease incidence, morbidity, and mortality of endometrial cancer include:

A. Obesity
B. Predicting risk of metastatic disease
C. Targeting therapy based on risk factors and molecular characteristics of the disease
D. Addressing racial disparities with respect to incidence and survival
E. Cost effective care

Each of these areas will be discussed below with identification of strategic research goals and requests for action.

A. Obesity and Endometrial Cancer

Obesity has become an epidemic in this country. While the link between increasing body mass index with heart disease and diabetes is well known, the association of obesity with cancer has received less attention. Among all cancers, obesity is most strongly associated with endometrial cancer (Table III) A woman with a body mass index of greater than 30 kg/m2 has a two to four fold increased risk of developing endometrial cancer.

Table III: Obesity Related Cancers

Type of Cancer	Relative Risk-BMI 20-30kg/m²	Relative Risk-BMI ≥30kg/m²	PAF (%) for US Population	PAF (%) for EU Population
Endometrial	2.0	3.5	56.8	45.2
Female Breast (Post menopausal)	1.3	1.5	22.6	16.7
Colorectal (Women)	1.2	1.5	20.8	14.2
Colorectal (Men)	1.5	2.0	35.4	27.5
Kidney (Renal-Cell)	1.5	2.5	42.5	31.1
Pancreatic	1.3	1.7	26.9	19.3
Liver	ND	1.5-4.0	ND	ND
Gallbladder	1.5	2.0	35.5	27.1
Esophageal (adenocarcinoma)	2.0	3.0	52.4	42.7
Gastric cardia (adenocarcinoma)	1.5	2.0	35.5	27.1

Adapted from Calle, E. Nature Reviews Cancer, 4:579, 2004. PAF Population Attributable Fraction; EU European Union; US United States; BMI Body Mass Index.

Endometrial cancer mortality is also adversely impacted by obesity. A prospective study of over 495,000 women followed for 16 years found a significantly increased risk of death in obese and morbidly obese women with endometrial cancer.[2] With targeted use of resources, we believe that scientists can rapidly advance to:

- Define the etiology of obesity-related cancers, including the contribution of insulin resistance and adipokines, (Figure 1)
- Identify novel strategies for the prevention of obesity-related cancers,
  - Bariatric surgery has become an important intervention to lower BMI, with effects on endometrial cancer [3]
- Develop important diet, exercise and lifestyle changes for improved health for the obese cancer survivor.
  - A recent survey indicated that up to 58 percent of women were not aware that obesity increased endometrial cancer risk. A modest investment in education and public awareness is likely to have a substantial benefit.[4]

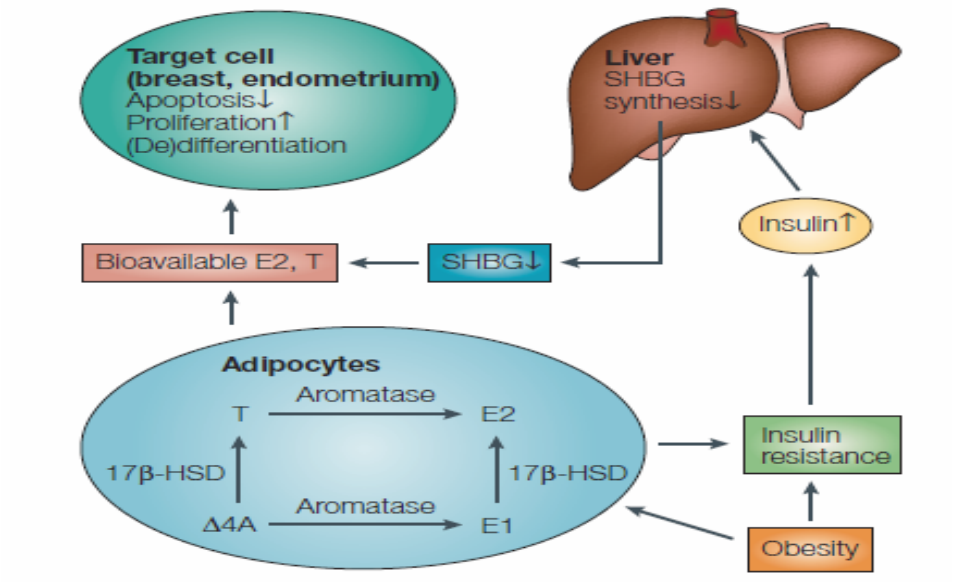

Figure 1: Effects of Obesity on Hormone Production. Mechanisms and Pathways Calle, E. Nature Reviews Cancer 4:579, 2004 (used by permission).

Requests for Action:

A1. Partner with the Transdisciplinary Research in Energetics and Cancer (TREC) Centers (NCI) to conduct research on endometrial cancer and obesity.
A2. RFA from NIDDK, or NCI to define the specific causes of obesity-related endometrial cancer, including the role of insulin resistance and adipokines.
A3. Leverage genome wide association studies (GWAS) of obesity, diabetes, and the metabolic syndrome to determine if SNPs related to these diseases also contribute to endometrial cancer risk.
A4. Perform outcomes research on bariatric surgery that may have both metabolic and cancer prevention benefits, especially in endometrial cancer.
A5. Partner with survivors groups to identify what modalities of weight loss and physical activity will be effective for this patient population.
A6. Partner with CDC to include endometrial cancer in obesity reduction campaigns.

B. Predictors of Risk for Metastatic Disease and predictors of benefit from therapy

Fortunately, 70 percent of endometrial cancers present with early stage disease (stage I) and have an excellent prognosis. Today, surgical staging with inspection of the peritoneal cavity, collection of peritoneal fluid for cytologic evaluation, hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy provide the most sensitive means to identifying extra-uterine spread. Over the past 20 years, a series of seminal studies [5-9] using operatively determined features have determined that use FIGO stage, age, cell type, grade, depth of myometrial invasion, presence of lymphovascular invasion are predictors of subsequent recurrence or death.

Novel predictors for metastatic disease and recurrence are necessary to identify patients with apparent low risk feature disease who will recur. One particular resource that may be leveraged to rapidly and dramatically increase our knowledge in biomarker evaluation and discovery is the GOG study GOG 210: A Molecular Staging Study of Endometrial Carcinoma. Patients enrolled have undergone a standardized surgical procedure (including pelvic and para-aortic lymphadenectomy) with collection of tissue and blood (at diagnosis and at recurrence), and completion of a patient reported epidemiologic questionnaire. In addition to biomarker development, clinic-pathologic studies of conventional prognostic features will be linked to epidemiologic analyses. This includes TMA's, gene expression, and proteomic studies that identify both pathways of disease progression and potential targets of therapy. The GOG 210 study has created a large clinically annotated biorepository of cases. To date 5,412 eligible patients have been enrolled, and 36,200 specimens have been banked. Translational research projects must be independently funded, as such only 20 projects have been developed. Additional support for this important resource is warranted.

- Low risk patients may have up to a five percent chance of having positive nodes.[5]
- Molecular markers could help identify this group of patients and decrease morbidity by reducing the need for extensive surgery.
- Comparisons of gene and protein expression with cases sorted by histology and cell type may yield information about genes associated with invasion and metastasis.
- Molecular diagnostics need to be developed for endometrial cancer that may alone or in combination with clinical-pathologic data, predict recurrence and death as well as benefit from established therapies. Breast cancer profiling may serve as a model for endometrial cancer; Oncotype DX gene expression may be an example.[10]

Requests for Action:

In order to accomplish our goals, we advocate for support in the form of additional research funding and RFA's to develop biomarkers in endometrial cancer.

B1. Characterize and validate biomarkers associated with extra-uterine disease spread.
B2. Characterize and predict response to targeted therapies.
B3. Develop molecular imaging core facilities which may develop and pilot new applications.
B4. Assess circulating tumor cells which may define disease spread in its earliest form.
B5. Partner with a commercial entity for development of proteomics for rapid and accurate testing of patients to define risk of spread.
B6. Request NCI RFA focusing on discriminators of low and high risk metastatic pathways in endometrioid and high risk cell types.
B7. Request NCI national funding to leverage the GOG 210 study biospecimen repository to develop predictive biomarkers of metastasis and recurrence.
B8. Develop novel imaging biomarkers which can discriminate lymph node metastasis on pre-operative imaging, thereby decreasing the morbidity associated with extensive surgical lymphadenectomy.

C. Targeted Therapy for advanced and recurrent endometrial cancer

New treatment and creative trial design are crucial in order to decrease mortality from endometrial cancer. In patients with advanced or recurrent disease, chemotherapy has emerged as the treatment of choice for many patients. GOG 122 was the first randomized study to demonstrate a survival benefit to chemotherapy over radiation in advanced endometrial cancer.[11] Unfortunately, no identified pathologic criteria are associated with prediction of response, and to date, there are no relevant biomarkers that define response to therapy in endometrial cancer.

The prognostic information derived from clinical and pathologic information has withstood the test of time and has proven itself to be clinically useful and relevant, but has marked limitations. While much is known about the mutational events leading to endometrial cancer our treatments don't take advantage of this knowledge. There are potential targeted therapies for the currently identified molecular abnormalities listed below:

- PTEN is mutated in 30-54 percent of endometrial cancers. Inactivating PTEN can increase phosphatidylinositol 3,4,5-triphosphate (PIP3). This in turn can activate AKT. Hence, this may be a good candidate for targeted therapy.
- KRAS is an early mutational event that occurs in 10-30 percent of cancers.
- FGFR2 is mutated in 16 percent of endometrial cancers and targeted therapy is being investigated in GOG trials.
- HER-2/neu is a proto-oncogene which shares some homology with the epidermal growth factor receptor. It is normally expressed at low levels in the cycling endometrium. Gene amplification or overexpression occurs in about 20–40 percent of endometrial carcinomas. Overexpression of HER-2/neu protein has been associated with advanced stage, decreased differentiation, aggressive cell types.
- Mismatch repair abnormalities exist in 30 percent of endometrial cancers.
- p53 mutations are found in 90 percent of serous cancers.

Because the numbers of recurrences are relatively low, national cooperative groups like the GOG have been essential in completing phase II and randomized phase III of therapies for this disease. There is an urgent need to identify new effective treatment strategies. With the exception of localized disease that can generally be cured by surgery and radiation, the current treatment of metastatic and recurrent disease by hormonal therapy or chemotherapy usually produce only short duration partial responses.

Requests for Action :

C1. Request a NCI RFA to delineate common mechanisms of steroid hormone resistance in breast and endometrial cancers with the goal of designing more specific anti-hormone therapies.

C2. Request NCI pathway centered conferences between endometrial and other solid tumors groups such as:

- Colorectal and endometrial: mismatch repair defects,
- Breast and endometrial: HER2 amplification.

C3. Perform systematic analysis of information already available from the TCGA sequencing of endometrial cancers:

- Devise molecular classifications of endometrial cancers from TGCA data and current pathologic prognostic classifications,
- Stratify treatment trials for predictive markers of benefit from:
  - radiation therapy,
  - hormonal therapy,
  - newer targeted agents, including anti-angiogenic agents,
  - cytotoxic chemotherapy.

D. Racial Disparities in Endometrial Cancer

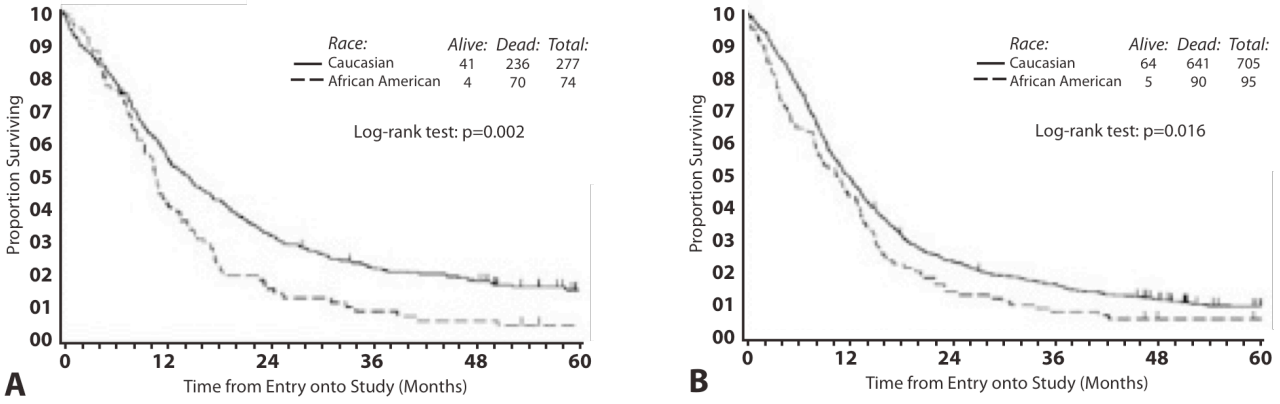

Figure 2: Overall Survival by Race and Endometrial Cancer Histology. These charts illustrate (A) overall survival by race for women who had advanced/recurrent endometrial cancer with endometrioid histology and (B) overall survival by race for women who had advanced/recurrent endometrial cancer with serous histology.[12]

According to the Surveillance, Epidemiology and End Results (SEER) Program, the mortality among African Americans with endometrial cancer is 80 percent higher than in Caucasians resulting in almost 1,000 deaths annually.[13] Interestingly, the incidence of endometrial cancer among African Americans is 33 percent lower than in Caucasians.[14] Although only seven percent of newly diagnosed patients are African American, approximately 14 percent of deaths related to endometrial cancer will occur in this group of patients.[2] African American patients with newly diagnosed endometrial cancer often present with advanced stage, poorly differentiated, non-endometrioid tumors, suggesting that tumors that develop in African Americans are more aggressive than in Caucasians.[15] Population-based investigations verify this:[16]

Although barriers to care and inequalities in treatment may contribute to worse outcome for African American women with endometrial cancer, data from the GOG suggests that African Americans with advanced stage disease have worse survival than Caucasians despite receiving similar treatment while participating in a randomized cooperative group clinical trial setting Multivariate regression revealed a 26 percent greater chance of dying among African Americans compared to Caucasians even when

controlling for co-morbidities, stage, histology, tumor grade, performance status and BMI.[15,16] These findings do not negate the importance of these variables in contributing to the racial disparity in outcome among patients with endometrial cancer. However, the data suggest that other factors may play a role in the disparity in outcome observed in patients with endometrial cancer. Collectively, these data from early and advanced stage endometrial cancer trials suggest that differences in tumor biology between African Americans and Caucasians may in part contribute to racial disparities in outcome.

Data suggests that African American patients may respond differently to surgery and chemotherapy. A meta-analysis performed by the Gynecologic Oncology Group (GOG) reported a lower response rate for African American patients with advanced stage and recurrent endometrial cancer that received chemotherapy on one of four randomized controlled trials. In this analysis, African American women had an overall response rate of 34.9 percent compared to 43.2 percent for Caucasians.[15,16]

- Although there were no racial differences in the number of cycles received, relative dose, relative time, or relative dose intensity, African American patients were more likely to experience grades three to four anemia and genitourinary toxicity, and less likely to experience severe gastrointestinal toxicity.[17]
- A separate GOG trial investigating the effects of estrogen replacement therapy on early stage endometrial cancer recurrence revealed higher recurrence rates among African Americans on hormones even when adjusting for age, BMI and tumor grade.[17]

Molecular analysis of endometrial cancers from African Americans and Caucasians has been performed in an effort to evaluate potential genetic and epigenetic etiologies for differences in observed tumor behavior.

- More frequent mutations in the TP53 tumor suppressor gene and HER-2 oncogene as well as fewer alterations in the PTEN tumor suppressor gene have been reported in endometrial cancers from African Americans compared to Caucasians.[18,19,20] Although these molecular analyses suggest a potential biological etiology for racial differences in outcome, the studies have been limited in terms of being able to show associations between molecular alterations and outcome while controlling for other prognostic factors.
- Methylation of a gene's promoter region may be one epigenetic mechanism by which non-mutational changes in gene expression can contribute to the development and prognosis of endometrial cancer. Investigations of potential epigenetic influences on racial disparity have evaluated methylation of ribosomal DNA and found that endometrial cancers from Caucasians demonstrate significantly more ribosomal DNA methylation than tumors from non-Caucasians.[21] Epigenetic modulation of gene expression within a given tumor may be determined by the culturally and socially defining characteristics of a particular racial group, leading to a unique tumor phenotype determined by environmental exposure.[22]

According to the U.S. Census, the African American population in the United Sates is expected to nearly double its present size to 61 million by the year 2050. Identification of biological origins for racial disparities in endometrial cancer is critically important to enable individualized treatment of endometrial cancer.

Requests for Action:

D1. Perform large scale molecular analyses to identify genetic alterations associated with poor outcome among African Americans with endometrial cancer

- genomic sequencing,
- SNP analysis,
- mass spectrometry based methods,
- proteomic analysis of frozen and paraffin tissue lysates.

D2. Request RFA for epidemiologic assessment of environmental factors in Blacks associated with changes epigenetic mechanisms.
- behaviors,
- dietary consumables,
- occupational hazards,
- psychologic stress.

D3. Create a national endometrial cancer tissue repository that reflects the population of the United States by race and ethnic group and contains additional factors such as:
- clinical data,
- information on barriers to care,
- socioeconomic status.

D4. Seek additional funding for pharmacogenomic and metabolomic analysis of differential response to chemotherapy and hormone therapy observed in clinical trials performed by the GOG.

D5. Perform genomic, proteomic and metabolomic analysis of endometrial cancer specimens and sera from African Americans and Caucasian patients with endometrial cancer aimed at identification of polymorphisms and germ-line molecular alterations as well as environmentally associated epigenetic changes that are correlated with racial disparities in poor outcome.

E. Cost Effective Care Surgery and Lymphadenectomy Performed by a Gynecologic Oncologist

The surgical approach to endometrial carcinoma varies by surgeon, institution, country, and continent. It ranges from total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH/BSO) alone for all patients, TAH/BSO with lymphadenectomy based on the surgeon's criteria for risk of nodal metastasis as determined by preoperative grading and/or intraoperative assessments, to TAH/BSO with full pelvic and para-aortic lymphadenectomy for all patients. However, initial surgical intervention by a trained gynecologic oncologist has been shown to decrease the use of adjuvant therapies, such as radiation, resulting in a cost-savings.[23]

Appropriate Use of Radiation as Adjuvant Therapy: The most common adjuvant therapeutic modality considered for endometrial carcinoma has been radiation therapy. Four randomized trials[24-27] showed that despite improving local control, the use of adjuvant whole pelvic external beam radiotherapy did not improve disease-specific or overall survival in patients with stage I or II endometrial. The reason for this is that patients who have not previously been radiated are likely to be salvaged if they develop a recurrence.

The Post Operative Radiation Therapy in Endometrial Cancer (PORTEC)-2 trial demonstrated that vaginal brachytherapy (IVRT) was equivalent to whole pelvic radiotherapy (WPRT) in achieving locoregional control and resulted in equivalent disease-specific and overall survival in patients with high-intermediate risk endometrial cancers.[24] PORTEC-2 did not require lymphadenectomy, so these findings apply to patients who have not undergone a comprehensive surgical staging procedure. IVRT led to significantly fewer gastrointestinal toxic effects as well as a better QOL.[28] Therefore, IVRT should be the adjuvant treatment of choice over WPRT. The true benefit of radiation therapy in the adjuvant setting for patients with early-stage endometrial carcinoma is debatable.

In GOG 99, a subgroup analysis identified a group of patients at higher risk of recurrence based on age, tumor grade, presence of lymphovascular invasion, and depth of myometrial invasion. This has led many to consider the use of chemotherapy in these high-intermediate risk patients despite the lack of any randomized data to support this practice. There have been two randomized trials comparing adjuvant chemotherapy to WPRT in "intermediate" and "high" risk endometrial carcinomas. These trials did not find an improvement in survival with chemotherapy compared to WPRT. The GOG is currently accruing patients meeting GOG 99 high-intermediate risk criteria to WPRT or chemotherapy with IVRT.

Minimization of Long-Term Treatment Effects: Lymphedema: Lymphedema is a chronic, progressive condition in which there is an accumulation of protein-rich fluid in the superficial tissues of the body. Lymphedema can be characterized as being either primary or secondary in nature and can be categorized into three stages. In stage I disease, edema is mild; fluid accumulates throughout the day but resolves overnight. In stage II disease, the lymphedema is always present but varies in its severity. Stage III disease is characterized by persistent, moderate-to-severe edema of the involved limb(s). Surgical removal of pelvic lymph nodes and radiation therapy are risk factors for the development of lower extremity lymphedema in endometrial cancer. The specific incidences of lower extremity lymphedema following treatment for gynecologic cancer as well as risk factors for development of lymphedema are not well documented in the literature.

A comprehensive study of 487 women with a history of gynecologic cancer found an incidence of symptomatic lymphedema to be as high as 36 percent, with the highest rates occurring in women treated for vulvar cancer.[29] Recent findings from a retrospective study demonstrate that women treated with radical hysterectomy for treatment of cervical cancer were at an eight-fold increase risk of developing lymphedema. Others have found a 41 percent incidence of lymphedema in women treated for cervical cancer (n=54) with severity enough to cause 22 percent of this group to be symptomatic.[30] The incidence of lymphedema in patients undergoing lymphadenectomy for endometrial cancer has been reported in the 5-10 percent range, although prospective data are sparse. The extent of nodal sampling has also been documented as a factor in the development of symptomatic lymphedema. Surgical staging procedures for endometrial cancer involving the removal of greater than 10 or more regional nodes have been found to increase risk for lymphedema. Despite the findings of a few studies investigating this area of research, many unanswered questions remain. For example, we do not know how the presence of lymph node metastasis, the number of lymph nodes removed, or the level of physical activity during and after treatment impact on the development of chronic lymphedema. These risks factors have not been studied in a prospective manner. Comprehending the magnitude of the problem and its associated risks will aid in the development of interventions to reduce the risk of developing lymphedema.

Requests for Action:

E1. RFA for prospective trials to determine:

- if the benefits of learning lymph node status justifies the additional side effects associated with lymphadenectomy,
- if a reduction in side effects is associated with the decreased use of post-operative radiation therapy.

E2. Quality outcomes measures to determine if initial surgery by a gynecologic oncologist provides the most cost-efficient use of Medicare dollars.

E3. Develop prospective trials to further determine the appropriate role of radiation therapy and chemotherapy in high-risk early stage as well as advanced disease.

E4. Quality of Life/survivorship study to document the prevalence of lower extremity lymphedema following surgical staging and adjuvant therapy for gynecologic malignancy. The GOG is poised to launch a 1300 patient prospective study to address this significant health care issue but cannot open the trial without funding.

Table 2-4: Endometrial Cancer Research Priorities

	Short Term (0-3 years)	Intermediate Term (4-6 years)	Long Term (7-10 years)
Low Risk	***2E4)*** QOL/Survivorship Lymphedema Study. ***2A6)*** CDC Educational Campaign EC and Obesity.	***2C2)*** NCI pathway conferences EC and solid tumors.	***2D2)*** Development of EC biorepository reflecting US population.
Intermediate Risk	***2B7)*** National funding for use of GOG 210 biorepository. ***2C3)*** Systematic analysis of TCGA data on EC.	***2E2)*** Quality Outcomes of First Surgery by Gynecologic Oncologist. ***2A1)*** Partner with TREC Centers Obesity/EC connection.	***2A3)*** Outcomes research on bariatric surgery/EC risk.
High Risk	***2E4)*** Prevalence/QOL trial of lymphedema in EC.	***2D1)*** RFA for molecular analysis of racial disparities in EC.	***2A2)*** RFA for EC adipo-kine research. ***2B6)*** RFA for metastasis predictors in EC.

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CHAPTER 3: CERVICAL CARCINOMA

INTRODUCTION AND BACKGROUND

Importance and future impact of continued study of Human Papillomavirus (HPV) prevention, screening and therapy in the era of HPV vaccines: HPV is the most common sexually transmitted infection worldwide, with a cumulative incidence in young women approaching 60 percent[1,2] and a cross-sectional prevalence of 27 percent in young to middle-aged US women.[3] The highest prevalence is among females aged 14 – 24 years (33.8 percent), corresponding to 7.5 million infected young women.[3] Notably, HPV prevalence is nearly as high in males.[4,5] HPV is widely accepted to be the central etiologic agent in cervical tumorigenesis.[6,7,8] Nearly all cervical cancers contain HPV DNA, as do the vast majority of precancerous cervical neoplasms.

With two effective prophylactic HPV vaccines approved by the Food and Drug Administration (FDA), it is clear that there will be a change in the landscape of cervical cancer research. These vaccines were developed as the first cancer prevention vaccines and hold the promise of greatly impacting on cervical cancer incidence in the future. According to the federal Advisory Committee on Immunization Practices (ACIP), the HPV vaccine is targeted for adolescents before the onset of sexual activity with 'catch-up' to age 26.[9] Additionally, recent intention to treat (ITT) efficacy data for the quadrivalent vaccine in the FUTURE trials[10,11] and the bivalent vaccine in the Guanacaste cohort suggest limited, if any, efficacy in women with prior established HPV 16 and 18 exposure. Until cost issues and potential mandates for HPV vaccination in the US are addressed, widespread HPV vaccination is not likely to be achieved in the near future and we will not witness a reduction in cervical cancer and cervical intraepithelial neoplasia (CIN) incidence for decades. However unlike the United States (US), many single payer systems in developed regions have mandated widespread HPV vaccination programs. In these systems, over 80 percent coverage of young women has been achieved. The public health benefits of primary prevention of cervical precancerous lesions will be appreciated much sooner in these systems than in the US.

It is well recognized that cervical cancer continues to be the leading cause of death among women in developing countries (killing >200,000 women/year) and unfortunately from an international perspective, which carries the burden of cervical cancer morbidity and mortality, adoption of HPV vaccines is still in its infancy. This is largely due to the high cost of HPV vaccines, the requirement to refrigerate the vaccine until use, and the need for parenteral injection; all of which are currently very difficult for low-resource regions. Furthermore, the vaccines will reduce, but not eliminate cervical cancer or HPV infection, since many HPV types are not included in the current vaccines and cross-protection is limited. Although HPV types 16 & 18 are associated with 70 percent of cervical cancer cases, they were found to have a prevalence of only 1.5 percent and 0.8 percent, respectively, among US women and did not rank within the 10 most prevalent types.[3] Based on these data, current vaccines will likely not have a major effect on overall rates of HPV infection for many years in the US; and most definitely will have no impact until we see at least 80 percent vaccination rates in vaccine-eligible females for which routine vaccination is recommended by the ACIP. Thus, the development of other additional prevention strategies for HPV infection and cervical cancer has significant clinical implications.

Knowledge of a woman's HPV status is becoming more commonplace. There is increasing use of testing the cervical-vaginal tract for HPV DNA as an adjunct to Pap testing (in women ≥30) or reflex HPV testing for triage of minimally abnormal Pap tests such as atypical squamous cells of undetermined significance (ASCUS) in the US. Additionally, in the US there is now an approved HPV 16/18 genotyping test with more on the way. Knowledge of one's HPV 16/18 infection status, particularly in women over 30 with high risk (HR) HPV as suggested by the American Society for Colposcopy and Cervical Pathology (ASCCP)[12], will most likely soon be commonplace. Also, clinical trends are now shifting toward HPV testing at the top of the cervical cancer screening algorithm. This change, in itself, will minimize the number of procedures due to the extremely high sensitivity of HPV DNA testing, more so than an HPV vaccine[13,14], as it will enrich the population of women undergoing procedures to only those women at highest risk; triaging those at low or no risk to conservative follow-up.

Cervical cancer research, particularly in the arena of prevention and screening, continues to be an important research priority, particularly in the global area where it is anticipated that the majority of women in world in the next 40 years will reside in developing countries, where the preponderance of cervical cancer exists. However, with an ever-growing menu of options for cervical cancer prevention, we have tools to drastically reduce morbidity from cervical cancer globally, if only we can get it to the patients who need this testing and prevention the most.

Cervical cancer continues to be the one malignancy that is entirely preventable with the combination of primary prevention with vaccination and secondary prevention with appropriate screening. However, given the passive and permissive nature of vaccination in the US and certain limitations and shortcomings of current screening regimens, its incumbent that we continue to fund research initiatives in the area of therapeutics as well as outcome research and HPV based screening programs. Most importantly, cervical cancer is a global problem, thus the presence of FDA approved vaccines is simply not enough. Significant reductions in cervical cancer mortality are within our reach but not without a significant research investment in improving clinical trials, current vaccines, delivery mechanisms and future investigation in the area of implementation and dissemination (Figure 1).

RESEARCH AREAS

Specific, immediate research priorities in this area include:

A. Global Health Initiatives
B. HPV Vaccination Outcomes
C. Future Screening Based Research
D. Familial Risk
E. Translational Studies of HPV Biology

A. Global Health Initiatives

Based on recent data from the World Health Organization(WHO)/GLOBOCAN 2008, the world incidence of invasive cervical cancer is 530,232 and the expected mortality is 275,008. Cervical cancer continues to be the second most common malignancy worldwide (second to breast cancer) and third highest cancer-specific cause of mortality. It is anticipated that at least 75 percent of all cases of invasive cervical cancer will occur in developing nations and in regards to population prospects over the next 40 years, it is anticipated that the ratio between women in developed versus developing regions will be 1:10.[15] Screening and prevention continues to be key objectives globally to reduce the incidence and mortality of invasive cervical cancer.

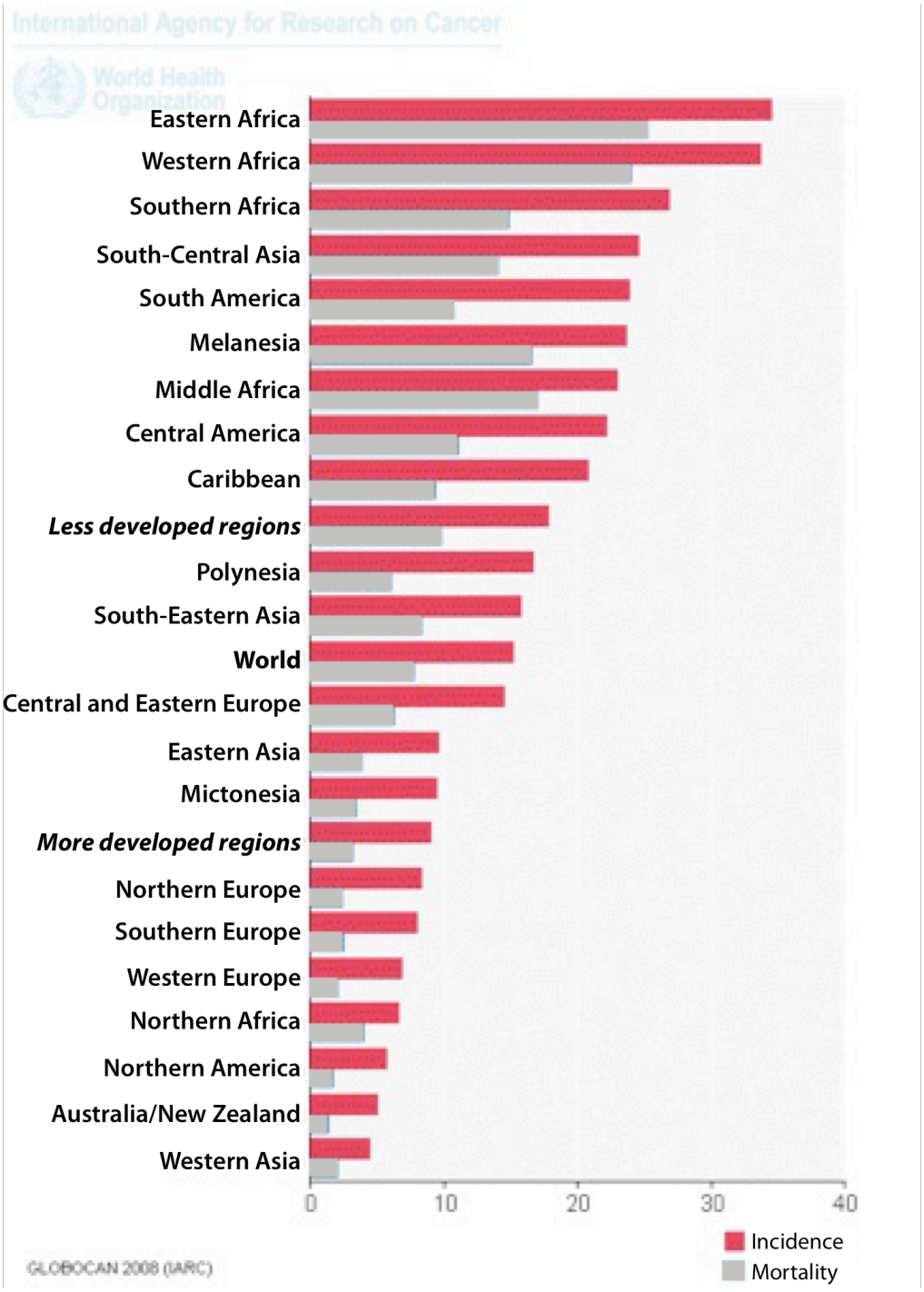

Figure 1: Cervical Cancer Incidence and Mortality Worldwide, 2008 (WHO/IARC) Ferlay J, et al., GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet].Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr

Requests for Action:

A1. Development of novel prophylactic vaccines that focus on broadening the coverage of oncogenic HPV types in addition to HPV types 16 and 18.
A2. Future investigation of alternate modes of administration, doses and dosing schedule Mechanisms.
A3. Partnership with vaccine manufacturers to develop vaccines that bypass cold chain supply/storage and optimize dissemination of HPV vaccines.
A4. Strategic consultation with the pediatrics community for consideration of conjugating HPV vaccine with other vaccines.
A5. Alternative prevention strategies should be sought.
A6. Mechanisms of funding to decrease per dose cost of HPV vaccine, possibly through public-private partnership.

B. HPV Vaccination Outcomes

Despite specific recommendations from the CDC and the ACIP regarding HPV vaccination, this type of prevention continues to be largely 'permissive' in nature and there are no specific mandates for HPV vaccination. In addition, the US does not have specific mechanisms and tools to track the impact of HPV vaccination on the incidence of cervical cancer as well as the rates of abnormal cytology, incidence of HPV and changes in the prevalence and genotypic distribution of HPV.

As stated previously, it will be decades before we will witness a reduction in cervical cancer morbidity and mortality. As such, research should focus on alternate measurements of vaccine dissemination and impact in the US. The development of a specific registry is important as it will also track other HPV related cancers including vulvar, vaginal, anal/rectal and head and neck malignancies and non-malignant conditions including genital warts.

Continued support of the Population-based Research Optimizing Screening Through Personalized Regimens (PROSPR) initiative and similar programs. Since not all pegs fit in all holes, having a menu of prevention strategies that can be adopted to fit a specific community/population need has clear clinical implications. For example, what works in an urban community in the US might not be adaptable in an urban community in sub-Saharan Africa.

Requests for Action:

B1. Development of a mechanism to link vaccination and outcomes to Electronic Medical Records and SNOMED-CT codes to track real time reduction and impact on pre-invasive disease rates.
B2. Funding to perform HPV genotyping to identify the potential for breakthrough lesions in vaccinated women.
B3. Continued support of the Population-based Research Optimizing Screening Through Personalized Regimens (PROSPR) initiative and similar programs.

C. Future Screening Based Research

Evidence from several large randomized clinical trials[16-22] clearly indicates that oncogenic HPV testing is more sensitive than Pap testing. Multiple arguments can be made that primary screening with HPV is cost-effective and triage to cytology may in fact be the best approach for cervical cancer screening.[23,24]

As successive cohorts of women are vaccinated, there will be a reduction in the prevalence of cytologic abnormalities. In the short term, and in settings where there is organized or opportunistic Pap testing, it is plausible to expect a reduction in the cases of atypical squamous cells of undetermined significance

(ASCUS), low-grade squamous intraepithelial lesions (LSIL), and high-grade intraepithelial lesions (HSIL), as well as the number of referrals for colposcopy.[14] Plausible estimates from meta-analyses of etiologic fraction studies suggest a reduction in LSILs by as much as 40% for those vaccinated against HPV types 16/18, and 50 percent for those protected against HPV types 6/11 & 16/18.[25] These proportions are likely to further increase once the next generation of multivalent HPV vaccines is adopted in clinical practice. As an increasing proportion of the population is vaccinated against an increasing number of HPV types, the prevalence of cervical abnormalities will inevitably continue to decrease, which will adversely affect the positive predictive value (PPV) (a major driver of screening costs) of any screening test for cervical cancer. However, as an objective assay not prone to the vagaries of subjective interpretation, HPV testing is likely to suffer less from this effect than Pap cytology.

Under this scenario, a more sensible strategy to screen for cervical cancer is to use a highly sensitive HPV DNA test as a first line screen and to take advantage of the well known high specificity of the Pap test as a second line triage in women who test HPV DNA positive; in essence a HPV followed by Pap triage schema. Despite its potential for much greater accuracy and efficiency in detecting existing high grade cervical lesions, the HPV/Pap triage paradigm has not yet been adopted for primary screening because of lack of long-term follow-up studies on the safety of extended screening intervals.

An additional rationale for using HPV testing as the primary screening test is the benefit it will bring in "enriching" the cytology case load with smears that have a high probability of containing relevant abnormalities. If instead of Pap cytology we assume that HPV DNA testing will serve as a primary screen, we may expect that in any group of HPV positive cases the prevalence of cytological abnormalities will be considerably greater, exceeding 20 percent or more. It has been shown in modeling studies.[26,27] that cytology will have its highest PPV and thus greatest clinical utility if lesion prevalence can be maintained at a high level.

Another major advantage of using HPV testing as the primary screen is the opportunity for extended screening intervals compared with a cytology-centered screening program, which inevitably will help with cost-containment. The safety afforded by a negative HPV test result after even up to four years is equivalent to that of a negative Pap test result after one year, in terms of the cumulative risk of high grade lesions.[28]

Requests for Action:

Research priorities in the arena include:

C1. Support from the National Institute of Health (NIH) and/or CDC for a primary HPV screening trial to establish its utility specifically in the US with emphasis on cost-effectiveness.
C2. Funding of demonstration projects to test the feasibility of school based HPV vaccination programs.
C3. Continued funding in the area of health disparities in cancer prevention. In cervical cancer prevention, identify barriers to screening and vaccination.
C4. Further research in the role and utility of HPV self-collection and testing.
C5. Further research of promising biomarkers that address screening with cost-equipoise.

D. Familial Risk

Although not fully understood and appreciated, there may be familial relationships related to cervical cancer risk of mothers, daughters and sisters that extend beyond known environmental risks and sexual behavior.[29] Cervical cancer continues to be a marker for poverty in the United States, and incidence and mortality is known to be higher in minority women.[30] It has been documented that the mortality rates of cervical cancer is higher in African-American women in the South, Hispanic women along the Texas-Mexico border, American Indians of the Northern Plains and Alaskan natives.[31] Of note, African American women

do participate in cervical cancer screening at a very high rate yet they continue to have the highest rates of cervical cancer mortality.[31] This may due to lack of appropriate follow up after screening or possible differences in management strategies.[32]

Research needs to continue to focus on barriers to HPV vaccination in minorities in the US as well as specific approaches to enhance HPV vaccines uptake. Current concerns reflect the possible reality that groups that may benefit from vaccination the most will in fact, have the lowest rates of vaccination.

Requests for Action:

D1. RFA for studies of high risk HPV families.
D2. Optimization of screening and surveillance strategies for women in high risk families.
D3. Development of risk reduction strategies to include vaccination prior to sexual debut.
D4. Utilizing available data from the NCI-sponsored TCGAP to identify genetic and epigenetic susceptibility genes for cancers related to HPV infection, including uterine cervix and oropharyngeal tonsilar cancers.
D5. Further investigation in enhancing HPV vaccine uptake and barriers to vaccination in minorities and high risk populations.

E. Translational Studies of HPV Biology

Requests for Action:

E1. RFA for study of the mechanisms of invasion of HPV-related squamous cell carcinomas of the head and neck and uterine cervix.
E2. Cooperation between RTOG and GOG to investigate novel radiation techniques and collect specimens for study of radiation resistance mechanisms.
E3. Development of chemotherapies and novel targeted agents for advanced stage, recurrent and radiation resistant cervical cancer.

Table 3-1: Cervical Carcinoma Research Priorities

	Short (0-3 years)	Intermediate (4-6 years)	Long (7-10 years)
Low Risk	***3B1)*** HPV Vaccine Registry Research (linkage to EMR). ***3C1)*** Cost-effectiveness research (screening/vaccination).	***3C1)*** US based Primary HPV Screening Trial.	***3B3)*** Continued support of PROSPR and similar programs.
Intermediate Risk	***3C2)*** School based demonstration projects. ***3D5)*** Health disparities. ***3D4)*** Genetic and Epigenetic susceptibility genes (TCGA).	***3A1)*** Next Generation vaccines. ***3A2)*** Alternate Vaccine Dosing Schedules. ***3C4)*** HPV self-collection/ testing.	***3A2)*** Novel HPV vaccine modes of administration. ***3A3)*** Dissemination/ Storage of HPV vaccines.
High Risk	***3E1)*** Progression of CIN3->SCC (Biology of Invasion).	***3C5)*** Novel screening/ triage biomarker research. ***3E2)*** Novel radiation techniques and mechanisms of resistance.	***3A4)*** Conjugation of HPV Vaccine with other vaccines. ***3E3)*** Targeted chemotherapies and novel agents.

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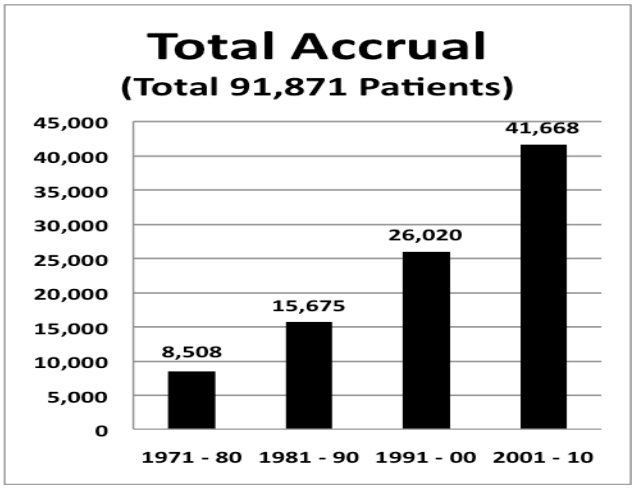
CHAPTER 4: CLINICAL TRIALS

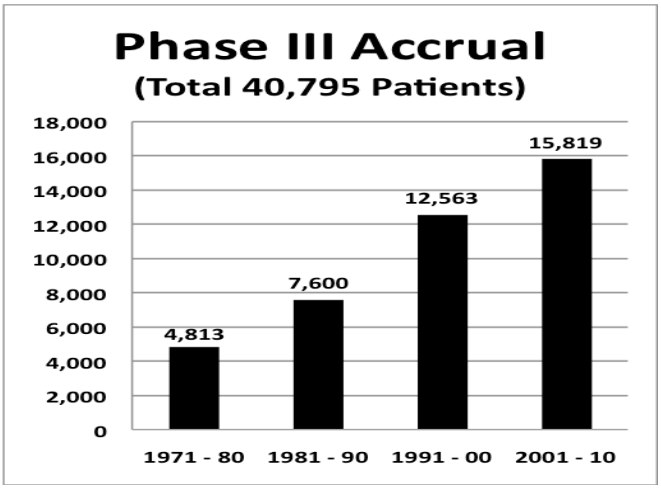
INTRODUCTION AND BACKGROUND

The modern era in the study of gynecologic cancers marks its advent in the decade of the 1970s. Several key events that led to the current circumstances took place leading up to and in that decade. Interest in large, collaborative studies as a means of evolving the standard of care appeared in the preceding 10 to 20 years in the form of cooperative study groups such as the National Surgical Adjuvant Breast Project (NSABP), the Eastern Cooperative Oncology Group (ECOG), and the Southwest Oncology Group (SWOG). These groups, formed primarily by internists interested in cancer (later to be known as medical oncologists), early on focused primarily on hematologic malignancies such as acute leukemia and the lymphomas. Following this example, a group of gynecologic surgeons interested primarily in cancer (gynecologic oncologists) adopted the collaborative study approach to evaluate the use of adjuvant progestational therapy in patients with early-stage endometrial carcinoma. The gynecologic oncologists took bold steps to establish training programs with specific requirements for gynecologists interested in cancer and succeeded in gaining recognition of boards in gynecologic oncology. This marked the first formal boards in a surgical subspecialty focused on cancer and cemented the leading role of gynecologic oncologists in the management of these types of cancers. As women began to seek obstetrician/gynecologists as their primary care physicians; the logical referral pattern of gynecologist to gynecologic oncologist for cases of gynecologic cancer followed naturally. This meant that the gynecologic oncologists essentially determined the management of the vast majority of patients with gynecologic cancers. Efforts by internist-controlled cooperative groups such as the ECOG and the SOG to conduct collaborative trials in gynecologic cancers have not been successful. Without the participation of the gynecologic oncologists, these groups could not accrue sufficient patients to complete large trials. Fortunately, the gynecologic oncologists who collaborated to perform the study of progestins as adjuvant therapy in endometrial carcinoma proposed to the NCI the formation of the GOG in 1970. The GOG thus became an early part of the NCI-sponsored cooperative clinical trials groups.

The approach by the GOG to the study of gynecologic cancers is unique in several important ways. The GOG is truly multidisciplinary with the involvement of gynecologic oncologists, medical oncologists, radiation oncologists, pathologists, nurses and basic and translational researchers. Although the GOG by its bylaws has a gynecologic oncologist as the Group Chair, the disciplines have an important place in the leadership of the group. One of the two Group Vice Chairs is a medical oncologist and the composition of the GOG Board of Directors must include representatives of all disciplines. These are but a few examples of the multidisciplinary nature of the GOG. The GOG in 1988 evolved a method of funding which is based on accrual to studies and has, as a result, been able to tap the resources of over 400 institutions rather than the 50 or so possible under the previous institutional grant system. This strategy greatly enhanced the capture of patients for study (see Figures 1 and 2 as illustrations of the growth of accrual to studies). The 41,668 patients accrued to study during the decade from 2001-2010 is a substantially higher percentage of potentially eligible patients than is seen in other adult solid tumors. The gynecologic oncology community has essentially taken ownership of GOG as its own; and this has resulted in an esprit de corps, which helps to enhance further study participation and the credibility of the GOG research product. The exact value of this esprit de corps is hard to determine objectively; but an approximation of the immensity of this value is found in the fact that the GOG has succeeded where others have failed and that most of the current standards of care for the common and, in some instances, uncommon gynecologic malignancies have all been established by GOG studies.

Despite this outstanding track record of results, clinical trials in gynecologic cancer face significant challenges as we enter the second decade of the 21st century. The goals of this report are to propose strategies to meet these challenges so that continued progress in the prevention and management of gynecologic cancers can be realized.





Figures 1 & 2: "The GOG White Paper, 03/04/2011" accessioned at gog.org on 7/5/11

RECENT DEVELOPMENTS

There are two major issues driving change in the way clinical trials in gynecologic oncology are conducted. These include the move toward more pathway driven clinical research and the recent Institute of Medicine (IOM) report on enhancing clinical trial infrastructure. With respect to the move toward more pathway driven clinical research, NCI Director Harold Varmus made several comments at the Dec. 7, 2010 meeting of the National Cancer Advisory Board. Specifically, he stated,

> *"Most important from my perspective, in this era of molecularly informed therapeutics, the trials are hopefully going to be more amenable to a strong science base." In addition he commented, "the genomic data and ancillary data on gene expression are becoming increasingly important in the design of clinical trials and even in the choice of therapies. The nation's confidence in this development I think is strong, based on the performance of Gleevec and a number of other new drugs being used in the treatment of diseases. But there is also a dark side of this, which is that we haven't yet fully figured out how to credential molecular findings to allow assignment of patients to arms of clinical trials of therapeutic strategies. I do want to recognize that the design of clinical trials, the kind of science that employs genomic methodologies, will be heavily used, and we need to feel confident that those methodologies are telling us important things before we assign patients to the arms of trials of therapeutic regimens."*

It appears, however, that successful use of molecular targets may be modified by organ of origin. Trials conducted by the GOG in HER2neu positive endometrial cancer using targeted therapy (Herceptin) failed to show the expected results based on breast cancer data.[1] Establishing valid predictive and prognostic biomarkers for gynecologic malignancies will require an intensive effort of the whole spectrum of researchers in gynecologic oncology including a robust gynecologic oncology specific clinical trials network.

In addition, the recent report by the Institute of Medicine (IOM), entitled "A National Clinical Trials System for the 21st Century – Reinvigorating the NCI Cooperative Group Program,"[2] has called for reorganizing the nation's clinical trials system. According to "A Cancer Letter"[3], the NCI's reaction to the IOM report was to conclude that there should be four adult cooperative groups and one pediatric cooperative group, which represents significant reduction from the current number of 10 cooperative groups. The way the NCI intends to accomplish this is to issue a new RFA for the cooperative group program, to which any group that wishes to apply could apply, but only four would be funded. It will ultimately be up to the current cooperative groups to decide in what configuration they wish to apply for the new RFA.

"This proposal represents a major conceptual change for the NCI's Cooperative Group Program, moving from a fragmented collection of groups working mostly independently, to an integrated clinical trials network," said James Doroshow, Director of the NCI Division of Cancer Treatment and Diagnosis, in presenting the plan. The reconfigured program, to be called the National Clinical Trials Network, would serve as the institute's primary platform for large phase II and phase III trials. The NCI-designated cancer centers and the Specialized Programs of Research Excellence would be encouraged to work with the groups to move ideas into cooperative group trials. The two primary goals for increased integration of the groups, as presented by Dr. Doroshow, was to promote scientific collaboration between laboratory and clinical investigators for the purpose of translating the science of cancer biology into improved therapeutic outcomes for patients and to improve efficiency by integrating operational support for the groups, including protocol development, statistics and data management, and bio-banking.

RESEARCH GOALS:

The drivers of change in the way clinical trials in gynecologic oncology will be conducted include the move towards more pathway driven clinical research and the IOM report/NCI initiative to enhance the cooperative group clinical trial infrastructure.

Given this background information and recent developments, the Clinical Trials SGO Research Summit Task Force recommends the following goals:

A. Maintain an infrastructure that ensures the viability of gynecologic cancer translational and clinical research.
B. Provide a mechanism for interaction with other cancer disease sites in order to facilitate pathway driven research in gynecologic oncology.
C. Develop a process by which both CTEP and industry resources are utilized in a synergistic manner to conduct clinical trials of high scientific priority.
D. Incorporate innovative phase II clinical trial designs in selected settings that would be able to expand into phase III trials.
E. Enhance time to activation of gynecologic cancer clinical trials.
F. Enhance gynecologic tissue bank resources and improve mechanisms that allow access to specimens for high priority translational trials.
G. Address barriers for all stakeholders that limit participation in gynecologic oncology clinical trials.

A. Maintain an infrastructure that ensures the viability of gynecologic cancer translational and clinical research.

SGO strongly endorses the maintenance of an infrastructure such as that within the GOG that focuses on gynecologic cancers. As has been previously demonstrated, the GOG's infrastructure has been extraordinarily successful in accrual of patients to clinical trials that in large part have defined the current standards of care and have led to improved outcomes in patients affected by gynecologic cancer. No other cooperative group has been as successful in this regard.

Two key attributes have led to the success of GOG's infrastructure and every effort should be made to maintain these in any future restructuring of the current clinical trials cooperative group system. First and foremost, access to patients has been a key attribute that has led to the success of clinical trial research success in gynecologic oncology. This access to patients has been facilitated by the direct involvement of gynecologic oncologists, who should continue to be an integral part of any redesigned gynecologic cancer clinical trials infrastructure. With the exception of epithelial ovarian carcinoma, accrual to large studies of gynecologic cancers comes through the gynecologic oncologist. Even in the case of epithelial ovarian cancers, accrual without the active participation of the gynecologic oncologist is at best extremely difficult, and collection of tissue in sufficient quantity needed to do current and future high priority translational studies would be impossible. Almost all gynecologic oncologists in the US have participated as active members within the GOG and have great pride in what they regard as their

cooperative group. Should any redesigned clinical trials infrastructure interested in the study of gynecologic cancers not fully integrate gynecologic oncologists, access to gynecologic cancer patients would be severely limited. In such a scenario, the study of ovarian cancer would be severely compromised, and the study of other gynecologic malignancies in large clinical trials would essentially cease.

Although gynecologic oncologists should be a critical component of any clinical trials infrastructure with an interest in gynecologic cancer, it will also be essential that a multidisciplinary team of basic, translational, and clinical investigators from many disciplines be engaged in the development and execution of future clinical trials in gynecologic cancer. The infrastructure presently within the GOG has been highly collaborative and has involved a multidisciplinary team of GOG investigators and other external scientific partners, such as gynecologic cancer SPORE and R01 funded investigators. The multidisciplinary translational research effort within the GOG has led to the creation of the single largest tissue bank of gynecologic cancers in the world. This centralized tissue bank, recognized as a model for proper handling and storage of biospecimens, has not only been critical to evaluating translational research aims within GOG clinical trials but has also enabled the GOG to be the only cooperative group to provide specimens to external scientific initiatives such as TCGA project. Any restructuring of the clinical trials cooperative group system should seek to build upon the foundation of multidisciplinary investigative team currently engaged within the infrastructure of the GOG.

Request for Action:

A1. Maintain a gynecologic cancer clinical trials infrastructure that ensures access to patients via gynecologic oncologists and incorporates a multidisciplinary approach to clinical and translational research.

B. Provide a mechanism for interaction with other cancer disease sites in order to facilitate pathway driven research in gynecologic oncology

Several structures that currently exist to facilitate interaction with among various cancer sites should be strengthened. For example, the NCI's Investigational Drug Steering Committee (IDSC) tracks new drug development and makes recommendations to the NCI as to which new drugs should be evaluated in early phase clinical trials. Participation by clinical and translational scientists familiar with gynecologic cancers in the deliberations of the IDSC should be enhanced so that pathway driven therapeutics (not cancer specific) could be investigated in the appropriate gynecologic cancer context. In addition, collaboration between SPORE researchers in different cancer sites should also be fostered. For example, investigators in the only NCI funded cervical cancer SPORE have developed a close collaboration with the Harvard skin SPORE. Strengthening such SPORE-SPORE interactions would also facilitate pathway-driven research. Another proposed mechanism to facilitate collaboration between gynecologic and other select cancers would be to conduct scientific meetings focused on pathway-driven research pertinent to multiple cancer types. HPV meetings, for example, permit researchers with interest in cervical cancer, head and neck cancer, and anal cancer to interact with one another. Similarly, meetings and workshops focused on hereditary cancers would facilitate dialogue between breast and ovarian cancer researchers, as well as between colon and endometrial cancer researchers.

Request for Action:

B1. Expand opportunities to facilitate interaction across cancer sites through the NCI's Investigational Drug Steering Committee, the NCI's SPORE programs, and scientific research meetings, such as those convened by American Association for Cancer Research (AACR) and NCI.

C. Develop a process by which both CTEP and industry resources are utilized in a synergistic manner to conduct clinical trials of high scientific priority.

With the advent of high-throughput molecular biology, the research community is fortunate to have a large number of high-priority molecular targets and a diverse array of therapeutic agents to consider evaluating in various gynecologic cancers. These include antisense oligonucleotides, small interfering RNA constructs, small-molecule inhibitors of tyrosine kinases, antibodies, synthetic binding sites, cytotoxic analogues, natural products with novel cytotoxic mechanisms, and alternative drug formulations. At the same time, investigators are struggling with limited financial resources to support increasingly complex clinical trials that require multiple levels of scientific and technical review. Traditional "low-throughput" incremental approach for the development of phase III trials is not cost-efficient and has proven inadequate to meet current scientific and clinical demands.

In addition, while the CTEP has access to many interesting agents, not all pharmaceutical sponsors have negotiated Cooperative Research And Development Agreements (CRADA) with NCI, and it is imperative that investigators have access to the even larger collection of agents through industry-based scientific and clinical collaborations. As such, SGO recommends that there be developed a dynamic partnership that incorporates the pharmaceutical industry, NCI-CTEP, a cooperative group such as the GOG, and clinical investigators, while maintaining communication with international cooperative groups through the Gynecologic Cancer InterGroup (GCIG). This partnershipmust extend to the NCI Gynecologic Cancer Steering Committee (GCSC), which is charged with reviewing of all large phase II and phase III trials. In particular, in this era of extreme fiscal restraint, it is important to leverage financial resources from all partners in an open and transparent manner. GCSC should continue to review and approve studies based on scientific merit and priority, but it should also have a mechanism to approve studies that receive partial support from the pharmaceutical industry and can be conducted in collaboration with NCI-sponsored national cooperative groups. This collaborative approach will benefit gynecologic cancer patients and investigators as they strive to improve treatment for women with gynecologic cancers.

Requests for Action:

C1. Clinical evaluation of the large number of potential targets and diverse array of agents identified by high-throughput molecular biology, in conjunction with private pharmaceutical industry.

C2. Develop NCI-GCSC recognized collaborative partnerships among NCI-CTEP, the pharmaceutical industry, and a cooperative group infrastructure such as that within the GOG.

D. Incorporate innovative phase II clinical trial designs in selected settings that would be able to expand into phase III trials.

The study populations for gynecologic oncology trials conducted over the past 50 years have been typically defined by the primary cancer site and stage of disease. These trials have attempted to identify treatments that are effective in broadly defined patient populations. Recent advances in molecular biology have provided a rationale for a taking different approach to conducting clinical trials. Recent studies have evaluated genomic or proteomic biomarkers in order to identify either functional (or dysfunctional) cellular pathways that might be exploited by targeted therapies. Results from some of these studies have provided credence to this approach. This shift in the research paradigm can be characterized as a shift from simply identifying widely effective interventions to a search for targeted treatments and their corresponding predictive biomarkers. It necessitates a commensurate shift in study designs in order to promote efficiency, speed drug development and reduce the cost of clinical trials involving targeted agents.

The SGO urges consideration of innovative phase II and phase III trial designs to address the shift in clinical trial research to one that is more pathway driven. A single-arm biomarker-based enrichment design is effective when a validated biomarker is already available for determining whether a treatment's targeted

pathway is functional. In the setting where the probability of responding to a therapeutic in a subpopulation of biomarker eligible patients has not been quantified, a randomized phase II version of the biomarker-based enrichment design should be considered. A phase II randomized discontinuation design can be considered for enriching the study sample with patients who may benefit from treatment when no reliably predictive biomarker is available.

When a validated biomarker is known to accurately indicate whether a particular cellular pathway is functional and a trial is designed to determine whether the study treatment is effective for biomarker-determined subgroup of patients, then a biomarker-targeted randomized phase III trial design is reasonable. When there is uncertainty about the validity of the biomarker or whether the study treatment affects only the targeted pathway, then a biomarker-stratified randomized trial should be considered.

Request for Action:

D1. Prioritize adaptive phase II and III designs for studies involving targeted therapies in gynecologic cancer.

E. Enhance time to activation of gynecologic cancer clinical trials.

The Dilts publication[4] reported on the complex processes and lengthy duration between approval of a clinical trial concept and activation of the trial in the cooperative group setting. The GOG had the shortest duration between concept approval and activation of a clinical trial. That said, there is clearly a need to improve upon the median of 435 days from concept approval and protocol activation even within an infrastructure such as the GOG.

The NCI, which provides the majority of funding (in addition to that from the pharmaceutical industry) for the conduct of clinical trials in gynecologic malignancies, established the Gynecologic Steering Committee in 2009 to provide additional expertise to the development of phase III and selective phase II clinical trial concepts submitted by the GOG, other cooperative groups and Cancer Centers. This mechanism is intended to foster rapid development of trial concepts based upon primarily scientific merit and feasibility. It is important therefore that steps be taken to further enhance the collaborative relationship between the task forces/steering committee and those who are developing phase III and major phase II clinical trials. Currently, delays in concept approval occur because concepts arrive at the task forces for initial discussion, which often suggests modifications/improvements to the concept and resubmission of the concept for further discussion at a later date. Since it cannot be expected that expertise external to the proposers of concepts can attend and participate in concept development meetings, it would seem useful to shorten this delay in development by having the task forces regularly provide both generic and specific advice and dialogue on research directions to investigators. Envisioned would be using one of the task force conference calls every six months, or when necessary, to discuss directions of research and consider possibly specific ideas for various patient groups. These discussions could then form the basis of concept proposals that would likely be more mature, need fewer changes and be approved faster. The discussions could be documented in minutes which could be distributed to investigators involved in protocol development for the various gynecologic malignancies.

A further barrier to timely clinical trials development has been the changes in the fiscal climate of the US government and available research funding. This has resulted in changing expectations and restrictions by the NCI on cooperative group productivity and the ease with which trials have been approved. In the past, success of the co-operative groups has been measured and awarded particularly for the conduct and completion of phase III clinical trials (in addition to phase I and II trials). In this era there appears to be a drive to perform cost effective trials, economic of patient accrual with a strong and specific focus on the scientific basis of clinical trials and with the probability that results will have a high clinical impact (i.e., making a difference for patient outcomes and changing clinical practice). In this era of fiscal constraint, it would appear that such clinical trials can and should only be conducted if there is a pressing and

important clinical question to answer through the phase III structure and if the clinical trial is important enough to justify the incumbent expense. It would be important for the NCI to be transparent about the degree to which fiscal constraint influences decisions for trial acceptance. Funds available for clinical trials are limited with all cancer sites competing (without transparency) for those funds. It is important that priority scores be given to various trials from cooperative group and other investigators as not all scientifically valid proposals can be conducted. This requires that better communication on cross cancer site funding and fiscal constraint needs to be established between the NCI, the cooperative group chairs and the GCSC that functions between the two.

Requests for Action:

E1. Enhance participation of the various disease site task forces and the GCSC in discussions setting research directions that should enable the development of concepts likely to be accepted more rapidly through the GCSC and NCI.

E2. Recommend that the GCSC develop criteria by which investigators are provided evaluations regarding their proposals based upon both scientific validity and constraints that may limit CTEP support.

F. Enhance gynecologic tissue bank resources and improve mechanisms that allow access to specimens for high priority translational trials.

Over the last decade, the gynecologic cancer research community has recognized the increasing importance of translational research in interpreting and designing clinically relevant trials. These studies enable scientists to identify subsets of patients based upon response to therapy (predictive biomarkers), and overall prognosis (prognostic biomarkers). The predictive biomarkers are increasingly critical for the interpretation of effectiveness of targeted agents and the development of personalized medicine. Increasing resources have been dedicated to this effort including the systematic development of clinical trials with embedded biomarkers and the establishment of a first-rate tissue-banking infrastructure. The GOG has been the leader in championing this approach with multiple phase III and tissue collection trials. Translational research has evolved from investigator initiated projects to programmatic translational research in areas of extraordinary opportunities including angiogenesis, “omics” and developmental therapeutics across disease sites. The translational research objectives embedded into recent clinical trials include exploratory evaluations, proof-of-principle initiatives, studies with discovery (training) and test (validation) sets as well as definitive assessments of scientifically-sound and feasible hypotheses.

In order to continue to expand the translational science efforts in gynecologic cancers, several specific goals need to be met. First, continued funding and expansion of tissue banking focused on gynecologic cancers with annotated clinical information needs to be a priority. The GOG tissue bank, located in Columbus, Ohio, serves as the model infrastructure for the proper handling and storage of biospecimens. This tissue bank has banked over 650,000 specimens and distributed over 65,000 specimens over the last decade. This bank has achieved its success through the concerted efforts of gynecologic oncologists and a team of other investigators. In fact, this biorepository effort enabled the GOG to be the only cooperative group to provide specimens to the TCGA which has been given top priority for completion by the NCI.

Resources must be allocated to develop highly collaborative teams of basic, translational and clinical researchers that can rapidly access and utilize bio-repository specimens. This type of collaborative effort yields a product far greater than the sum of its parts. Collaborative efforts can address broad and important translational and clinical questions such as patient stratification and mechanisms of chemoresponse. Furthermore, this team approach will allow for the successful application for NIH and DoD funding including R01, R21, SPORE and U01s.

Requests for Action:

F1. Ongoing investment in tissue banking of gynecologic cancers with clinical annotation.
F2. Establish collaborative teams of investigators that can utilize gynecologic cancer banked specimens to address the critical research questions in the next decade.

G. Address barriers for all stakeholders that limit participation in gynecologic oncology clinical trials.

Various obstacles limit participation in clinical trials for all gynecologic cancer stakeholders. Limited funding, burdensome regulatory processes, complex and cumbersome trial designs, and inconsistent coverage of clinical costs by insurers are examples of the issues that hinder the implementation and widespread accrual to clinical trials. Efforts to reduce the complexity of clinical trials and to ensure insurance coverage of standard clinical costs of federally registered clinical trials should be the highest priority for gynecologic relevant clinical trials.

Request for Action:

G1. Reduce the complexity of clinical trials.
G2. Promote legislation and regulations at both the state and federal level to ensure that health insurers cover standard clinical costs associated with patient participation in a clinical trial.

Table 4-2: Clinical Trials Research Priorities

	Short Term (0-3 years)	Intermediate Term (4-6 years)	Long Term (7-10 years)
Low Risk	***4A1)*** Maintain infrastructure for clinical trials in gynecologic oncology. ***4E2)*** Development of transparent GCSC scoring criteria evaluating science and feasibility in proposed trials. ***4F1)*** Ongoing investment in tissue banking of gynecological cancers.	***4E1)*** Enhance participation of disease site task forces and GCSC in discussions facilitating rapid concept development.	***4F2)*** Establish collaborative teams of investigators to utilize banked specimens for gynecologic malignancies research.
Intermediate Risk	***4)*** Prioritize adaptive phase II and III designs for targeted therapies studies.	***4B1)*** Facilitate interactions across cancer sites. ***4C2)*** Develop NCI-GCSC recognized collaborations with NCI-CTEP, industry, gynecologic clinical trials cooperative group. ***4G1)*** Reduce the complexity of clinical trials.	
High Risk	***4C1)*** Clinical evaluation of high through put potential targets with industry.	***4G2)*** Ensure successful implementation of regulations at state and federal level for insurance cost coverage of clinical trial costs.	

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CHAPTER 5: SURVIVORSHIP IN GYNECOLOGIC MALIGNANCIES

INTRODUCTION AND BACKGROUND

Advances in cancer treatment continue to turn this once uniformly fatal illness into a curable disease for some and a chronic illness for many. Of the patients diagnosed with cancer in 2001, 68 percent survived cancer for at least five years.[1] In 2006, nearly 11.4 million Americans were alive after having been diagnosed with invasive cancer.[1] Age remains the greatest risk factor for cancer and the US Census Bureau projects that the population aged 65 years and older will increase from 40 million in 2009 to 70 million in 2030.[2] The stage is therefore set for a large increase in the number of people in the US who will be living with a cancer diagnosis. From 2010 to 2030, there will be an increase of almost 50 percent in the number of people diagnosed with cancer, from approximately 1.6 million to 2.3 million.[3] Of these, an estimated 45 percent will be women, approximately 10 percent of who will be diagnosed with a gynecologic malignancy.[3] While many survivorship issues are common to all who are diagnosed with cancer, some are gender-, age-, and disease-specific. We are challenged to meet the needs of all cancer survivors and their caregivers.

Cancer survivorship broadly defined entails the maintenance of physical, social, spiritual, sexual and economic well-being by addressing short- and long-term effects of cancer and its treatment. Cancer survivorship research was initially modeled along the linear cancer control continuum, beginning with prevention, early detection, moving through treatment and survivorship, and concluding with end of life care. However this schema provides a narrow view of the issues and does not take into consideration evidence that survivorship research can result in improved care, thereby positively affecting both the quality and QOL.[4] This realization challenges us to develop a new concept of survivorship research and care, such as the model illustrated in Figure 1 below. This model is more of a circular dynamic including prevention, detection, diagnosis, treatment, surveillance and end of life, realizing that many of these areas overlap.

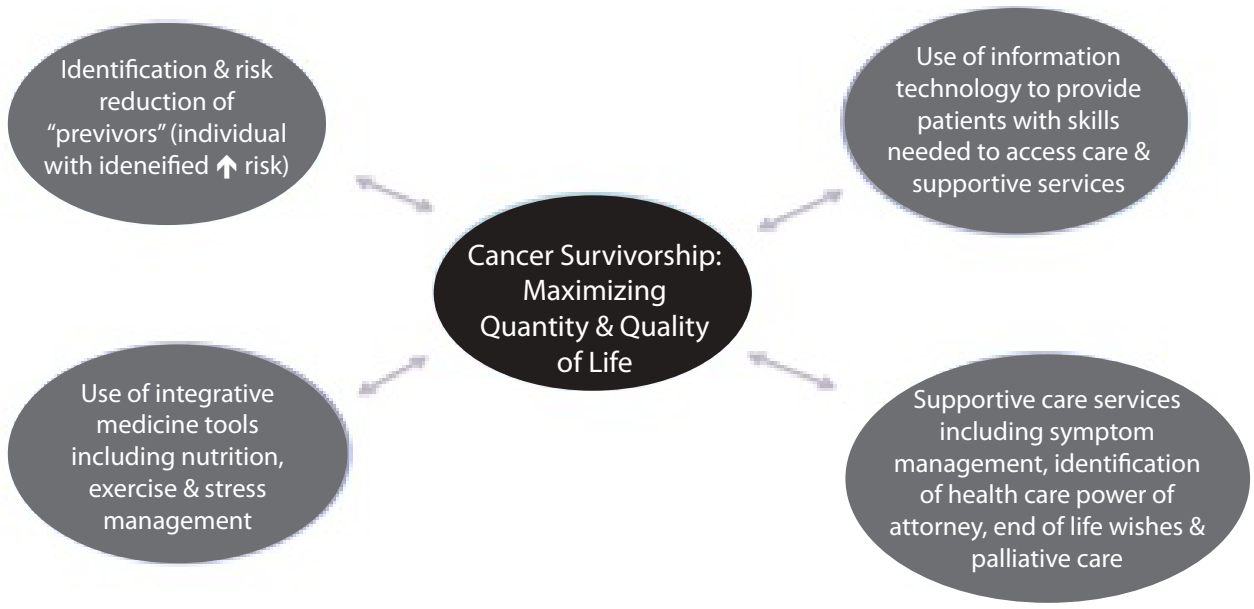

Figure 1. Cancer Survivorship: Maximizing Quantity and Quality of Life

Novel classes of agents and treatment strategies based upon molecular markers are beginning to have significant impact on survival. Substantial research has been conducted in gynecologic oncology, which encompasses cancers of varying prognoses and multiple treatment options. Thus, women present with gynecologic cancer that is often curable (early stage endometrial cancer), and cancer with a high fatality rate (late stage ovarian cancer). The research goals identified in this paper provide examples from gynecologic cancer given the wide range in treatments and prognoses in this area; however, the identified goals are those that will affect all survivors.

The majority of current treatment protocols have as their primary aims overall- and progression-free survival. Additional considerations to address cancer recurrence will become increasingly well-defined as information on the molecular nature of cancers and their response to treatment is understood. These treatment paradigms provide a unique opportunity to develop innovative approaches to survivorship care. Survivors who have undergone curative treatment, or are in long-term remission, often face significant hurdles from late effects of treatment and co-morbidities that may threaten their survival, and will almost certainly threaten their quality of life. Determination of which treatments are given in the recurrent setting will continue to foster significant discussion, offering the opportunity to qualify and quantify the desired goals of treatment. This new world will result in significant challenges to design and implement survivorship care that is in step with biochemical and medical advances.

RECENT RESEARCH ADVANCES

Significant progress has been made in describing survivorship and the trajectories of gynecologic malignancies. This includes the impact on physical, functional, emotional, social, sexual and economic conditions of patients and their caregivers. Outcomes research has recently evolved to include QOL. Due to this development, this type of research is now being described as patient-reported outcomes (PROs).

Along with survival, QOL has emerged as an important endpoint when evaluating cancer treatments. A key concept that has emerged is that QOL is a prognostic indicator of survival.[5,6] Thus, identification of impairments in QOL and interventions which improve QOL may impact both quality and quantity of survival. Great progress has been made in quantifying aspects of QOL. Differences in domains of patients' lives have emerged; often social and emotional well-being is maintained, even in the face of impairments in physical and functional well-being. Realization that cancer and treatment for cancer affects multiple aspects of patients' lives has widened the scope of factors assessed. Cancer and treatment for cancer affects families and caregivers, has an economic impact, changes body image and sexual functioning, brings forth spiritual concerns, and makes daily living more difficult.[7]

These overarching effects of cancer and treatment for cancer may not affect all members of society equally.[(8)] Socially disadvantaged survivors may be less well equipped to deal with the impact of cancer, and may suffer disproportionately from a decrease in QOL. Assessment of QOL has been refined and tools enable us to quickly and reliably identify which aspects of a person's life are affecting QOL. For example, the Patient-Reported Outcomes Measurement Information System (PROMIS) is an NIH Roadmap initiative designed to develop, validate and standardize patient-reported outcome tools for clinical research and practice.[9,10,11] Goals of PROMIS include developing and testing item banks in five broad domains: fatigue, pain, physical function, emotional distress and social health. These item banks enable computerized adaptive testing (CAT) to derive valid, efficient and tailored patient-reported outcome assessments that are more precise than those developed using classical approaches and less burdensome to both patients and staff. These state-of-the-art self-report measures have been tailored for use in oncology.[12] Identification of impairments is crucial if meaningful interventions are to be designed and outcomes improved.

Interventions will need to span all aspects of life. Novel, integrative approaches dealing with the whole person will be important in prolonging life, but also in maintaining a high QOL for long-term survivors, and supporting those at the end of life. As treatments continue to improve, the number of people living a life touched by cancer will increase. Evidenced-based and cost-effective methods of providing care for survivors need to be developed.

Finally, rapid advances of science in oncology will increasingly identify survivors who are likely to respond well to treatment, but also those whose prognosis is less favorable. Ensuring that health care providers are rapidly informed of these advances and are able to counsel patients concerning treatment options will become increasingly important. Transparent communication on the part of physicians and patients regarding the outcome of treatments in the recurrent setting is very important. Working with patients to navigate the courses of remission and long-term survivorship, or recurrences and end of life, will become critical as the prevalence of people diagnosed with cancer increases and the knowledge base concerning their likely trajectory becomes more complex.

RESEARCH GOALS

The overarching purpose of a robust survivorship research agenda is to implement effective interventions that will positively affect the trajectory of the cancer process, maximizing survival and QOL, and minimizing morbidity. The needs of cancer survivors, identified and quantified by researchers, as well as by survivors themselves, dictate the proposed research goals.

Interventions should begin at diagnosis to provide needed information that will improve the potential for survival, reduce morbidity and increase short- and long-term QOL. These interventions should encompass novel, and integrative, agents once they are demonstrated to be effective. The rapid advances in cancer treatment options, and likely prognoses, will need to be rapidly and efficiently transmitted to health care providers – survivors need access to the best treatment options, and need to understand the likely onsequences of treatment. This information will require communication between the health care system and survivors – treatment should be tailored to the individual to provide care that is state of the art, yet cost- effective. This care should be available and accessible to all members of our community. As these interventions are implemented, the number of survivors will continue to increase – and mechanisms to meet general health care needs, as well as health care needs specific to cancer and treatment for cancer will need to be refined. Finally, difficult decisions concerning the end of life need to balance compassionate, evidence-based, yet cost-effective options.

The following goals will be explored:

A. To ensure patients have access to, and understand, the essential interventions required at diagnosis and/or recurrence to maximize quantity and QOL.
B. To optimize the use of integrative oncology to positively impact survivorship.
C. To transmit our ever-evolving understanding of the treatment of cancer to healthcare providers, patients, and caregivers in an expedited fashion.
D. To describe how patient- and disease-specific factors affect survivorship issues, and develop interventions to best address these issues.
E. To engage population science in order to identify and address the unequal burden of cancer faced by diverse survivors.
F. To comprehensively describe and address end of life issues in an effort to balance QOL and cost.
G. Integrative steps to achieve research goals.

A. To ensure patients have access to, and understand, the essential interventions required at diagnosis and/or recurrence to maximize quantity and QOL.

The diagnosis of cancer requires that people become almost instantaneously knowledgeable about their disease, their treatment options, possible toxicities, and likely outcome. This disease, and the treatment it requires, will have a major impact on their home life, their caretakers, their economic situation and their overall QOL, and within this context, decisions need to be made.[13]

These decisions need to be made immediately, for example, data from women with ovarian cancer demonstrate that undergoing treatment by sub-specialists improves outcome.[14,15] Subsequent treatment decisions based on the tumor biology will need to be made[16], but this requires that health care providers, and the patient, are aware of this information, and understand it. During treatment, patients will face multiple toxicities. Their ability to tolerate these toxicities will determine, in part, their receiving optimal treatment. For example, a recent study of intraperitoneal therapy found that only 42 percent of patients received all cycles of the assigned therapy.[17]

Options for obtaining information range from their physicians and other members of the health care team, to families, friends, books, magazines, publications and the internet. Obtaining and using this information to make decisions about initial treatment is only the first step; subsequent decisions that affect survivorship are complex, involve multiple providers, and range from receiving flu shots to making decisions about maintenance chemotherapy.[4] QOL includes physical, functional, emotional, social well-being, as well as sexual health and function, psychosocial health, and economic impact.[17] Long-term effects of treatment can include fatigue, cognitive problems, neuropathic pain syndromes, sexual dysfunction, body image issues, osteoporosis, second malignancies, and complications due to radiation.[4] Valid instruments have been developed that allow for the identification of survivors with impairments in specific domains, and these instruments can also be used to objectively determine treatment effectiveness. Treatments and supportive care are available to manage many of these potential issues, but they have to be effectively used by those who need them.

Recurrence is a devastating development requiring more treatment decisions.[17,18] Often, first line treatment options are better defined than those available in the recurrent setting. Again, characteristics of the patient, including information about their tumor biology, should be considered when making a treatment plan.

These research goals are considered low-risk, relatively rapidly attainable goals as much of this information is already known. Extensive research has been conducted in this field and mechanisms to provide care that is currently optimal have been identified. Too much of this research, however, is scattered and unfocused, so that patients walking into doctors' offices will receive very different levels of information, education, and options. For example, a recent study of hospital discharge data from 6,854 women with ovarian cancer from five states found that only 67 percent received appropriate surgery (recommended by the NIH Ovarian Cancer Consensus Guidelines).[19]

Lack of information and knowledge, as well as lack of understanding and awareness of, effective treatments and interventions to treat cancer, reduce symptom burden, minimize morbidity and increase QOL are barriers that can be overcome. Research to develop effective methods to disseminate the appropriate information to survivors in an understandable and usable format so that they may begin to navigate their journey as informed and involved participants is key. Development of these methods will be of increasingly value as more information becomes available and will ensure the provision of appropriate, current, evidence based, compassionate and cost-effective care.

Requests for Action:

A1. Identify the essential interventions all cancer survivors require at diagnosis and/or recurrence to maximize quantity and QOL.
A2. Define and address survivorship needs in order to improve all the domains of QOL.

B. To optimize the use of integrative oncology to positively impact survivorship.

Advances in cancer care have been characterized by a simultaneous movement toward a more holistic view of patients and their health as well as a desire to individualize care to their unique personal and tumor characteristics. The principles of integrative oncology are perfectly suited to these advances and to the goals of optimizing cancer survivorship. Practitioners describe integrative oncology as both a science and a philosophy that focuses on the complexity of the well-being of cancer patients and proposes a multitude of approaches to accompany conventional therapies to facilitate health as illustrated in Figure 2.[20]

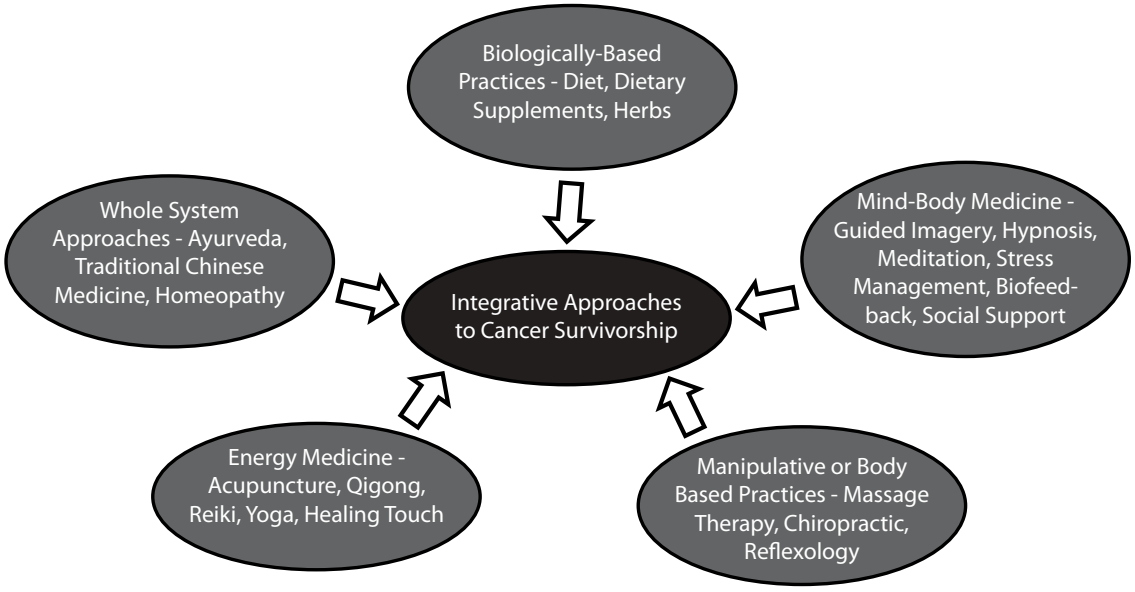

Figure 2: Model of Integrative Approaches for Survivorship

In addition integrative oncologists strive to support the innate healing abilities of the individual, utilizing techniques for self-empowerment, individual responsibility and lifestyle changes that could potentially reduce both cancer recurrence and second primary tumors.[20]

Most oncology patients use some form of complementary or alternative medicine (CAM). In 2008 the National Center for Health Statistics indicated that 38 percent of all Americans use some form of CAM. A 2005 IOM report detailed this trend and reported that Americans were spending at least $27 billion out of pocket for CAM products and services.[21] Use of CAM is particularly common among people with cancer. Studies indicate that up to 80 percent of all cancer patients use some form of CAM most commonly including acupuncture, massage, yoga, energy healing, Traditional Chinese medicine, Ayurveda, mind-body interventions and a wide variety of vitamins, mineral supplements, antioxidants and herbs.[22] However, not all modalities have been evaluated for safety, efficacy or, ideally, both.

It is clear that multiple modifiable aspects of lifestyle impact cancer risk and prognosis including stress, social support, physical activity and nutrition. In vivo, in vitro and clinical studies show that stress related process can impact cancer progression through pathways involved in immunoregulation angiogenesis and invasion.[23] Researchers postulate that stress-induced immunosuppression or dysregulation may

contribute to the development and progression of malignancy.[24] For example, in ovarian cancer patients, depressed and anxious mood is associated with a greater impairment of the cellular immune response and an increase in tumor progression.[25,26] Stress can be a co-factor for the initiation and progression of cancer. The catecholamine stress hormone, norepinephrine may influence tumor progression by modulating the expression of factors implicated in angiogenesis, apoptosis and metastasis such as matrix metalloproteinases.[24-28] Rigorous, well-designed studies of cancer outcomes are needed to demonstrate the connection between these exciting laboratory findings and the utility of strategies to address stress including relaxation training, meditation, graded exercise, yoga, tai chi, and other mind-body interventions that induce the relaxation response.[20-22]

Small studies focusing on individual methods such as the use of herbs and mind body approaches for symptom management have shown promise. In addition, longitudinal studies have suggested that specific dietary components may have preventive benefits as well as impact on prognosis in cancer patients. For example, in a longitudinal study of over 300 women with ovarian cancer, longer survival was associated with yellow and cruciferous vegetables intake.[30] In a population-based cohort of over 600 women with epithelial ovarian cancer followed for up to five years, death was reduced in women who reported higher intake of vegetables and cruciferous vegetables.[29,30] Inverse associations were seen between protein, red meat and white meat and survival. A study examining ovarian cancer survivors who were on and off active treatment found that those meeting public health guidelines for physical activity had lower self-reported levels of fatigue, and better scores for peripheral neuropathy, depression, anxiety and sleep quality than women not meeting guidelines.[31] An additional study of women undergoing gynecologic surgery found that baseline characteristics such as physical and mental health, age and body weight affect QOL scores.[32] Therefore, regular physical activity may enhance survival by increasing QOL and improving ability to tolerate surgery and chemotherapy.

Operationalizing these findings demand both short- and long-term research investments. Targeted interventions based on laboratory work such as the use of stress management techniques in patients identified to be at increased risk based on established biomarkers are needed. In addition, large randomized trials of multi-modal life style interventions that include use of patient-specific nutritional approaches, physical activity and stress management techniques to improve cancer prognosis and prevent secondary malignancies must be conducted.

Request for Action:

B1. Utilize integrative oncology to positively impact survivorship.

C. To transmit our ever-evolving understanding of the treatment of cancer to healthcare providers, patients, and caregivers in an expedited fashion.

Our understanding of molecular mechanisms of cancer continues to grow exponentially. In an environment of transparency, seamless and immediate transmission of new knowledge to healthcare providers, patients, and their caregivers is needed to optimize cancer care. New methods to communicate this information in “real time” are essential, particularly to those in most need of such knowledge.

As health care reform moves forward, so will electronic medical records. As hospitals and health systems improve their efficiency, personal health records and patient portals utilization will become normative. And as the number of cancer survivors increases, so will the need for efficient access to each individual’s health information. We argue that cancer patients and their families must have timely access to accurate, disease-specific and detailed information. Present websites are generalized (Institute of Medicine Survivorship Report and American Cancer Society), while others do not permit patient access (NCCN).

Our challenge is to develop a system with appropriate infrastructure to cope with this surge of information and translate it into an easily accessible and understandable format. Furthermore, web-based templates should also include side effect profiles and cost analyses in order to improve patient and caregiver comprehension of treatment-related issues and the costs of medical interventions.

Request for Action:

C1. Provide accurate information about our rapidly-advancing progress in cancer care efficiently in order to effectively address survivorship needs.

D. To describe how patient- and disease-specific factors affect survivorship issues, and develop interventions to best address these issues.

Basic research in oncology continues to define characteristics of cancers that are likely to affect response to treatment thus allowing for the identification of effective, and cost-effective, treatment options. However, patients also bring to the treatment process other characteristics that are likely to influence outcome. Obesity in endometrial cancer patients, for example, is associated with higher mortality from causes other than the cancer – they are less able to tolerate treatment.[33] Smokers with locally advanced cervical cancer treated with chemoradiation have worse survival rates than non-smokers.[34] Women with ovarian cancer and poor QOL have decreased survival rates.[5] Age, educational level, body mass index, physical and emotional health are some of the variables that can affect QOL.[32]

The significance of this line of research is that knowledge gained has the potential to alter prognoses based on the biology of the cancer, potential outcomes resulting from treatment, and perhaps treatment decisions. Patient characteristics such as obesity, level of education, smoking status, and poverty will interact with treatments to affect outcome from this disease. Increased morbidity resulting from treatment in some populations has significant cost-effectiveness implications in addition to the effectiveness implications resulting from decreased survival. The extent to which these characteristics can be addressed is unknown; therefore, this line of research is considered intermediate risk. The increased uncertainty inherent in treating patients with these negative health characteristics will be balanced by the reduced uncertainty resulting from knowledge about tumor biology and response to treatment. Designing and implementing cost-effective interventions that will maximize the ability of patients to tolerate treatment will be necessary if the advances in the science of treating cancer are to be realized. It would be a great sadness if the spectacular advances in science became obscured by declines in patient controlled health behaviors.

Research in proteomics, pharmacogenomics, cellular physiology, and the myriad of new possibilities will be for naught if the patient dies during treatment because she is too overweight, smokes, and has been physically inactive her whole life.

Request for Action:

D1. Define how patient- and disease-specific factors change survivorship issues and how we will meet these needs.

E. To engage population science in order to identify and address the unequal burden of cancer faced by diverse survivors.

The inequitable delivery of health care leads to differences in health outcomes. A recent study found that patterns of care for endometrial cancer surgery in Arizona differed as a function of insurance coverage, race, surgeon and hospital.[35] Differences in care afforded minority groups were initially understood purely in racial terms; however, disparity is now known as having its genesis in poverty and the lack of social and medical infrastructure to address the needs of affected patient groups. A study of care provided to patients with ovarian cancer in New York City public hospitals found these women were less likely to

have gynecologic oncologists as surgeons.[36] The authors point out that given the low overall number of ovarian cancer patients within the public health system, an appropriate referral model could remove the inequity in care – in other words, this is a problem that can be addressed. In an ideal world, all socio-economic and racial disparities would be removed. However, in the short term, research goals to specifically identify and overcome inequities in the provision of evidence based, life and death determining, effective treatments to all members of society should be a major focus.

Efforts are required to broaden the understanding of health disparities faced by underserved and understudied populations. Potential reasons for health care disparities are presented in Figure 3. Quality of care and disparity are integrally related concepts that benefit from the coordination of interventions, through information technology, and to address the structural and process-based deficits in the health care delivery system.

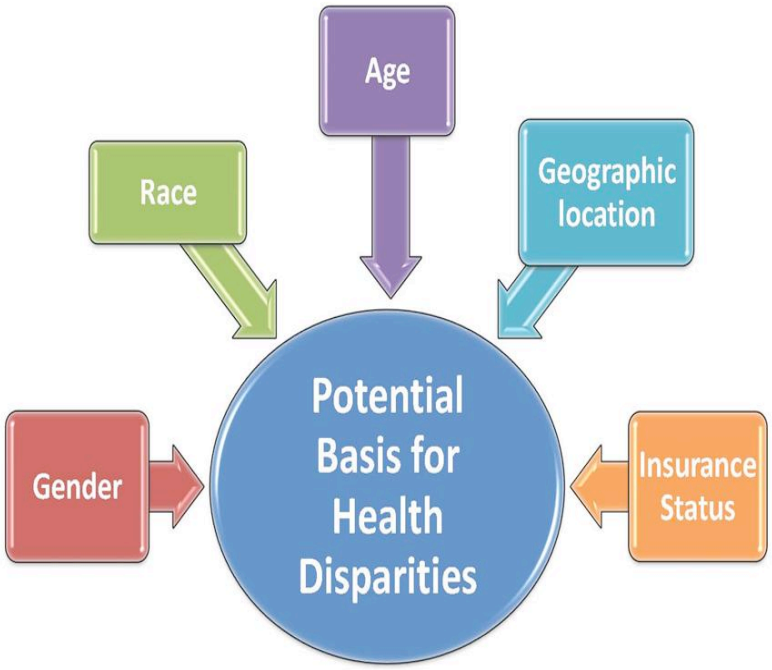

Figure 3: Model of Potential Basis for Health Disparities

Requests for Action:

E1. Design prognosis-specific, cost effective models of survivorship care using information technology to best address the needs of cancer survivors and their caregivers.
E2. Define and address survivorship needs in order to improve all the domains of QOL.

F. To comprehensively describe and address end of life issues in an effort to balance QOL and cost.

Approximately 32 percent of total Medicare spending goes to provide care for patients in the last two years of their lives, with a substantial portion spent on repeated hospitalizations. Research in this area is critical, both to delineate concerns of survivors and their health care and familial providers, as well as to optimize QOL in a cost-effective manner. While women with cancer may have similar needs at the end of life, such as pain relief and social requisites, patients with different cancer primaries have different palliative needs. For example, women dying of ovarian cancer commonly have repetitive admissions for gastrointestinal issues while women dying with lung cancer have shortness of breath. It would be anticipated that predictors of death with earlier hospice interventions would be different based on specific end of life symptoms.

A growing body of literature suggests that cancer survivors can enjoy improved QOL at the end of life through tailored utilization of palliative care services. In a study of patients with metastatic non-small-cell lung cancer, participants were randomized to palliative care versus standard oncologic care alone. Both groups were treated with the same chemotherapy regimen. General guidelines for the palliative care visits in the ambulatory setting were adapted from the National Consensus Project for Quality Palliative Care and included monthly visits with a board-certified palliative care physician and advanced-practice nurse monthly. Patients in the intervention group had significant improvements in QOL, mood, less aggressive care and increased median survival.[37] However, hypothesized benefits have not undergone rigorous study nor have they been applied to other cancer patient groups.

Finally, most oncology patients use some form of complementary or alternative medicine and it is not clear how these potential therapeutic agent may enhance palliative care. Again, further study is needed.

Request for Action:

F1. Define the trajectory of disease in cancer patients so as to improve end of life care while balancing cost and QOL.

G. Integrated Steps to Achieve Research Goals.

Advances in survivorship care depend upon accurate and timely information-sharing, use of appropriate models, and a comprehensive, multidisciplinary approach. Lack of information and knowledge, as well as lack of awareness and understanding of effective treatments and interventions to treat cancer, remain prevalent. By first identifying gaps in essential information required by survivors and their caretakers, we can then develop appropriate and meaningful interventions required to meet their needs. Using ancillary services such as supportive care consultations at the time of diagnosis, providing clear information about clinical trials, and developing ways to help patients and their caretakers "navigate the system" are a critical part of the foundation that needs to be laid. Use of information technology resources, such as web-based assessment templates, must be further studied and validated in an effort to best address the needs of survivors and their caregivers. Furthermore, new methods of information-sharing should be utilized to communicate ever-evolving discoveries, treatment recommendations, and other important topics to healthcare providers, patients, and their caregivers. We must develop the appropriate infrastructure to seamlessly and immediately transmit new knowledge to all who will benefit from this information.

We recognize that cancer outcomes are significantly influenced by patient- and disease- specific factors. To this end, our model for survivorship care must include, but not be limited to, such factors as ethnic and socioeconomic disparities and personal risk factors. These needs must be further identified and addressed if we are to level the playing field for all cancer survivors. Our models for survivorship care must be constructed in such a manner that they will be not only prognosis-specific, but also cost-effective. Again, the importance of information technology use remains critical. It is also imperative that we study and evaluate the trajectory of disease in order to improve end of life care. Further information must be obtained to build models to help balance cost and QOL during this part of the cancer journey.

Finally, we are of the opinion that multidisciplinary care should be provided to cancer survivors. Opportunities abound in the field of integrative oncology, such as further studying the association of QOL and patient outcomes with mind/body meditation. The potential benefits of integrative approaches such as mind-body medicine, energy medicine, and biologically-based practices need to be evaluated further. Survivorship research has already shown that interventions can improve specific domains in patients' QOL. Additional clinical trials are required to investigate ways to make improvements in the physical domain of ovarian cancer survivors and functional domain in endometrial cancer survivors, again throughout the trajectory of their disease. Clearly we must focus on appropriate biomarker and genetic identifiers to optimize remission and cure by targeting specific interventions. An example of this is the ability of tumor norepinephrine to identify patients who will benefit from stress management approaches.

The ultimate goal of this robust research agenda is to develop, clinically and economically evaluate, and institute multidisciplinary interventions to positively impact the overall trajectory of disease for cancer survivors. The needs of cancer survivors, identified and quantified by researchers, dictate these aggressive research goals.

Requests for Action:

G1. Utilize multidisciplinary interventions to modify the overall trajectory of disease and evaluate their economic impact.

G2. Target interventions based upon biomarker and genetic identifiers to optimize remission and cure.

Table 5-1 : Cancer Survivorship Research Priorities

	Short Term (0-3 years)	Intermediate Term (4-6 years)	Long Term (7-10 years)
Low Risk	***5A1)*** Identify the essential interventions all cancer survivors require at diagnosis and/or recurrence to maximize quantity and QOL.	***5B1)*** Utilize integrative oncology to positively impact survivorship.	***5C1)*** Provide accurate information about our rapidly-advancing progress in cancer care efficiently in order to effectively address survivorship needs.
Intermediate Risk	***5D1)*** Define how patient- and disease-specific factors change survivorship issues and how we will meet these needs.	***5A2)*** Define and address survivorship needs in order to improve all the domains of QOL.	***5F1)*** Define the trajectory of disease in cancer patients so as to improve end of life care while balancing cost and QOL.
High Risk	***5E1)*** Design prognosis-specific, cost effective models of survivorship care using information technology to best address the needs of cancer survivors and their caregivers.	***5G2)*** Target interventions based upon biomarker and genetic identifiers to optimize remission and cure.	***5G1)*** Utilize multidisciplinary interventions to modify the overall trajectory of disease and evaluate their economic impact.

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CHAPTER 6: TRAINING THE NEXT GENERATION OF WOMEN'S CANCER RESEARCHERS

INTRODUCTION AND BACKGROUND

In 1974 Gynecologic Oncology was established by the American Board of Obstetrics and Gynecology (ABOG) as a formal subspecialty with required fellowship training and Board certification. The subspecialty was conceived, and continues to this day, to provide multidisciplinary cancer care for women's reproductive cancers, including surgery and chemotherapy, as well as palliative care. In 1996, ABOG's Division of Gynecologic Oncology established a requirement that all accredited Gynecologic Oncology fellowship programs provide trainees with a mentored protected research year, resulting in a publishable thesis with a formal defense, in addition to an additional two to three years of clinical training. Recognizing that appropriate research training is fundamental to the infrastructure of scientific inquire, this requirement has positioned our field to be on the cutting-edge of research training for Gynecologic Oncology fellows and has allowed Gynecologic Oncology to evolve into a highly academic discipline, particularly in comparison to other cancer specialties. According to SGO survey data, in 2010 65 percent of US. Gynecologic Oncologists were in full-time academic practice, with an additional 18 percent in private practice with academic affiliations. As a result, academic output is high in quality, especially considering that there are only approximately 1,000 practicing Gynecologic oncologists in the US.

Developing and enriching the academic/research training of gynecologic oncologists is an imperative component of our mission, at both the Fellow and Junior Faculty levels. Not only will this markedly enhance the care of women with gynecologic malignancies, but it will allow us to recruit the best medical students, residents, and PhD/post-doctoral fellows into our field. The complexity in "growing" our research training program, at both the Fellow and Junior Faculty levels, is significant. Creative programs are needed to provide sustained opportunity for those committed to a research career in gynecologic oncology. These programs need to be developed at multiple levels, including departmental, institutional, regional and national, with recognition of priorities at every level. Identification of individuals with the talent and drive to pursue a research career is vital, so that resource utilization is maximized.

To further develop and implement the most effective training for the next generation of women's cancer researchers in science and medicine, addressing issues of discovery/innovation, as well as access to health care/clinical trials. To achieve these goals as discussed below, we will have to develop new programs, develop new partnerships and innovative opportunities for: Fellow Training, Junior Faculty, and Role of the Society of Gynecologic Oncology.

FELLOW TRAINING

A. Develop new opportunities for fellow training in research.

The one to two year research training period during a gynecologic oncology fellowship does provide trainees with the opportunity to gain exposure and learn the basics for science inquiry. In addition, having a clinical fellow in a basic research laboratory also helps to educate the basic scientist in the clinical relevance of his/her research activities. However, it is clear that this relatively short research training period is insufficient for most individuals to lay the groundwork for a successful research career. Undoubtedly, additional dedicated training beyond the fellowship is required for most individuals to establish a career and obtain extramural funding in basic science or translational research (see below).

Beyond additional training, other opportunities must be developed and implemented for Fellows to not only launch their research/academic careers, but to prepare them for implementation of tomorrow's novel therapies based on today's rapidly advancing basic and translational investigations. Assistance in helping Fellows identify their academic "road map" based on their specific research interests. In that, the goal is a lifelong contribution to the academic mission, it is absolutely imperative that individuals identify their own passion in the research arena. To facilitate this, the Fellowship Programs should continue to provide a broad exposure to the different types of research opportunities present in gynecologic oncology.

Request for Action:

A1. Develop New Research Opportunities:

- Additional Basic Science/Translational Research Training.
- Comparative Outcomes, Quality of Life, Educational, Cost Effectiveness.

B. Expansion of clinical trials training for Fellows.

Clinical Trial Training is a particularly important area. ABOG's Division of Gynecologic Oncology requires a minimum of two postgraduate level courses to be taken during the Fellowship, one of which is biostatistics. The biostatistics course lays the foundation for training in clinical trials. Additionally, a majority of Fellowship training programs are members of the GOG, which provides a vital framework by which Fellows extend their educational experience and increase their fund of knowledge in clinical trials. However it is imperative that we look beyond these traditional approaches given the rapidly changing of clinical investigation due to the increasing availability of biological and targeted agents. This changing landscape of cancer therapeutics has been recognized by NCI and NIH and is the subject of a 2010 IOM consensus report.

Individual institutions should play a major role in the development of new clinical trials training program. For instance, a **Masters of Science Degree in Clinical Investigation** is already available in many institutions. Such programs should specifically address progressive approaches beyond the traditional phase I and II trials, and be aimed to develop clinical trial investigations designed to meet the challenges of increasing numbers of biological therapeutics.

Another institutional program that would prepare fellows to pursue careers in clinical investigation is the **Institutional Certificate in Type 2 Translational Research**. The certificate in type 2 translational research addresses a well documented gap in what should be a continuum between basic health and medical research discoveries and the application of those discoveries in clinical and public health practice. To bridge this gap new discoveries must move beyond efficacy studies (type I translational research) to research that tests effectiveness in real world settings.

Finally, **extramural clinical research electives** are available for additional training opportunities. The NIH offers a variety of short-term clinical rotations and research elective opportunities, as well as specialized "year out" programs designed to provide advanced training in basic science, translational research, or clinical research, to highly qualified medical and dental students. The American Association for Cancer Research (AACR) also offers an intensive week-long workshop for fellows and junior faculty devoted to the development of a clinical trial protocol to be implemented at the participant's institution.

Requests for Action:

B1. Develop Institutional Graduate Programs in Clinical Investigation
- Masters in Science, Clinical Investigation,
- Develop Institutional Certificate in Type 2 Translational Research.

B2. Develop Fellow Interest in Extramural Clinical/ Research Electives
- NIH
- AACR

C. Develop a pathway of lifelong mentoring for Fellows.

Mentors play a critical role in the development of a Fellow into a successful gynecologic oncologist, both clinically and in research. While a natural affinity will exist between the faculty in the fellowship training program and the fellow locally, mentorship should not be limited to local faculty. Fellows should be encouraged to meet and discuss clinical and research interests with other gynecologic oncologists in the region and nationally. Faculty should encourage such interactions by facilitating introductions to the appropriate person(s) outside their institution.

Request for Action:

C1. Develop mentoring programs for lifelong professional development that begin in fellowship training.

D. Expand opportunities for fellow interaction and collaboration in related academic areas.

Fellows have more opportunities than ever to explore research in new venues important to the academic enterprise. While it was often assumed that a good clinician would be a great teacher that is not necessarily the case. Teaching is a skill that can be taught with great effect and mastered by fellows. Not all institutions have courses specifically designed to “teach the teacher” but these could be developed. In addition, research in educational methods and outcomes has risen to the forefront of planning in both residency and fellowship training. Exploration of teaching and training trials should be encouraged by fellows. Finally, interactions between faculty in the **Academy of Distinguished Educators** and fellows interested in becoming master educators should be facilitated.

In this new era of cost-cutting and cost-effectiveness, **Comparative Outcomes Research** plays a critical role in insuring that patients receive the most appropriate care, not just the cheapest. Consideration of cost in relation to care should be incorporated into the training program. Gynecologic oncology fellows with an interest in outcomes research should be introduced to mentors experienced in the field.

Gynecologic oncologists have a long history of providing end-of-life care for our patients. The expertise of gynecologic oncologists in **Palliative Care** has been recognized by the American Board of Hospice and Palliative Medicine, where gynecologic oncologists may become double boarded. As demonstrated in Chapter 5, research in end-of-life issues and palliative care will be an important component of the careers of fellows in training. Fellows should be invited to the Palliative Care Network within the SGO.

Finally, as cancer patients survive longer, especially pediatric cancer patients, **Survivorship** will become a major research arena. Research questions regarding Survivorship are discussed in Chapter 5, and fellows should be aware of these opportunities.

Request for Action:

D1. Expand fellow research training opportunities to include:

- Education
- Comparative Effectiveness Research
- Palliative Care
- Survivorship

JUNIOR FACULTY

There is a critical window of opportunity for appropriate career development and acquisition of the necessary skills for those individuals interested in gynecologic oncology research. Programmatically approaching the immediate post Fellowship years is vital in laying the ground work for a successful research career. Identification of those individuals most likely to successfully develop a robust research career must have the institutional resources aligned to insure their success.

E. Facilitate the successful application for mentored career development awards.

Mentored career development awards allow individuals to conduct the research at their own institution. NIH Career Development Awards include: Standardized Awards for K01 (Mentored Research Scientist, Development Awards), K08 (Mentored Clinical Scientist, Development Awards), K12 (Mentored Clinical Scientist Development Program Awards), K23 (Mentored Patient-Oriented Research Career Development Awards. The NIH salary cap varies by Institute and may be supplemented by clinical departments.

In addition to awards funded through the NIH, specific organizations, either alone or in conjunction with the NIH, provide financial support for junior faculty embarking on a research career. For example, the American College of Surgeons (ACS) together with a specialty society provides competitive matching awards (e.g., total award $150,000) for individuals who successfully apply for or who have previously have received either a K08 or a K23 Award. This same organization provides supplemental support for recipients of NIH K08 or K23 awards (Mentored Clinical Scientist Development Award or Mentored Patient-Oriented Research Career Development Awards, respectively).

Requests for Action:

E1. Assist junior faculty to compete for established NIH Career Development Awards.

- K01, K08, K12, K23, Other

E2. Encourage junior faculty to compete for Non-NIH Career Development Awards.

- American College of Surgeons

F. Facilitate NIH Loan Repayment Program.

Specifically five loan repayments programs are available: Clinical Research, Pediatric Research, Health Disparities, Clinical Researchers for Disadvantaged Backgrounds, and Contraception and infertility Research. In exchange for a two-year commitment to a clinical research career, the NIH will repay up to $35,000 per year of qualified education debt, pay an additional 39 percent of the repayments to cover Federal taxes, and may reimburse state taxes that result from these payments. Eligibility applies to “All Doctoral-level researchers with domestic nonprofit or US government (Federal, state or local) funding”. To participate, one must conduct clinical research for 50 percent or more of the total level of effort for an average of at least 20 hours per week during each quarterly service period.

Request for Action:

F1. Facilitate eligible junior faculty application to the five loan repayment programs.

G. Facilitate Participation in Novel Course Work.

Course work that supports the Junior Faculty's Research should be encouraged. The ACS has available the following courses: Outcomes Research Course, Clinical Trials Methods Course and Surgical Investigators Conference. The NIH has developed the following courses: **(1) Principles of Clinical Pharmacology:** This course covers the fundamentals of clinical pharmacology as a translational scientific discipline focused on rational drug development and utilization in therapeutics. The course is taught by faculty members from the National Institutes of Health (NIH) and guest faculty from the Food and Drug Administration (FDA), the pharmaceutical industry, and several academic institutions from across the United States. **(2) Introduction to the Principles and Practice of Clinical Research:** The Introduction to the Principles and Practice of Clinical Research (IPPCR) course is based on a curriculum on how to effectively conduct clinical research. Many academic medical centers lack a formal course in training for clinical research, and investigators have relied on mentors to learn how to conduct clinical trials. This course formalizes that instruction **(3) Bioethics:** The Ethical and Regulatory Aspects of Clinical Research course is offered to anyone interested or involved in clinical research involving human subjects. Other organizations, such as ACOG and the home institution also provide specific courses of interest.

Request for Action:

G1. Facilitate access to and enrollment in novel and related coursework.

- Principles of Clinical Pharmacology,
- Introduction to the Principles and Practice of Clinical Research,
- Bioethics.

H. Facilitate successful application of junior faculty for training grants.

Training grants, non-specific to gynecologic oncology, are available and should be considered: **BIRCWH (Building Interdisciplinary Research Careers in Women's Health) Awards** promote interdisciplinary research careers in women's health with an innovative effort to foster career development in women's health research. The emphasis is on innovative interdisciplinary mentoring across a variety of disciplines.

WRHR (Women's Reproductive Health Research Career Development Program): The WRHR Program was initiated by the NICHD in 1998, through the Reproductive Sciences Branch in response to concerns about the need for greater numbers of obstetrician-gynecologist physician scientists performing research on women's health. Investigators with established research programs covering a broad range of basic and applied biomedical and biobehavioral science, in obstetrics and gynecology departments and collaborating departments, form an intellectual and technical research base for mentoring WRHR Scholars. The emphasis is on research relevant to obstetrics and gynecology and/or its subspecialties: maternal-fetal medicine, gynecologic oncology, and reproductive endocrinology and infertility.

RSDP (The Reproductive Scientist Development Program): The RSDP was established in 1988 to train obstetrician-gynecologists committed to academic investigative careers in fundamental biomedical science. The program is supported by Eunice Kennedy Shriver the National Institute of Child Health and Human Development (NICHD) of the NIH in collaboration with private agencies, professional societies, foundations, and private industry. The candidates for the two-year award are selected by a distinguished Selection Committee following a national competition. To apply, candidates must first obtain a commitment of a faculty position by a sponsoring department with a minimum of seventy-five percent protected time for research for the first three faculty years following training.

Institutional Training Grants, such as T32 – Institutional Training Grants For Advanced Pre- and Post-Doctoral Fellows, should be considered, such as the Health Disparities Research Scholars Program. Finally, the **NIH Career Development Awards** (K Series) can provide real opportunity (see above).

A training grant specifically for gynecologic oncologists, should be developed and implemented, such as a Young Investigator award modeled after the WRHR, BIRCWH, RSDP (multidisciplinary approach). This would be the most relevant, and promising option for young faculty interested in clinical, basic, and translational research in gynecologic oncology. Because gynecological oncologists are involved in both surgical and chemotherapeutic aspects of their patient's care, they are uniquely positioned to lead clinical and translational research aimed at increasing understanding and development of novel therapeutics for gynecologic cancers. The structure of the grant would allow graduating fellows to identify research mentors in their putative institutions and develop a joint application similar to current K-awards. Applications would be reviewed by a study section comprised of members of SGO/GCF/NCI. An important potential advantage would be that the evaluation process would include experts from the field of gynecologic oncology thus ensuring a more relevant and accurate evaluation of merit, potential impact, and significance compared to current "generic" K awards. Applicants will be expected to identify at least one mentor outside of their putative institution. Progress reports would be reviewed on an annual basis by the study section.

Requests for Action:

H1. Facilitate application for Grants Non-Specific to Gynecologic Oncology.
- BIRCWH; WRHR; RSDP; Institutional (T32); NIH Career Development Awards

H2. Develop and Implement a Training Grant Specific to Gynecologic Oncology.
- Modeled after BIRCWH, WRHR, and RSDP

I. Develop the Women's Cancer Bridge Program (WCBP).

Develop the WCBP designed to sustain research projects that have lost extramural funding. This program could provide one-time support to eligible Principal Investigators (PI) within eight years of their first appointment to assist with re-establishing external funding. A PI will be eligible for the WCBP, provided him/her: (1) Has lost, or will lose most of his/her extramural funding within six months of the Bridge application deadline; (2) Received continuous extramural funding from peer-reviewed sources during the five years preceding the request; (3) Has made substantial efforts to re-establish funding, and in the opinion of the Chair is likely to be funded again. Awards will be granted for a maximum of two years or until the grantee re-establishes funding from other sources, whichever comes first. Consideration will be given to need, and the strength of the overall research program. Individual grants will be for a maximum of $50,000 - $100,000, or the average annual direct costs received by the PI from peer-reviewed extramural grants during the previous five years, whichever is less. In calculating previous grant support, only funds from federal or other funding agencies with rigorous peer review will be considered. Requests that provide evidence of a cost-sharing commitment by the PI's home Institution will receive a higher priority for funding. When extramural funding is re-established, all unspent funds will be returned to the Bridge Program to assist other investigators.

Request for Action:

I1. SGO and the Foundation for Women's Cancer should develop a bridge program to sustain investigators in gynecologic malignancies who have lost extramural funding.

J. Increase junior faculty completion of advanced degrees in addition to the doctorate of medicine.

Diversity in faculty training is essential to maintain economic viability of clinical and research enterprises, both in academia and private practice. Some junior faculty may have the aptitude and interest to pursue additional advanced degrees after obtaining the M.D. Examples of such additional degrees are: Masters in Epidemiology, Masters in Health Studies/Certificate in Health Studies, Masters in Public Health, Masters in Business Administration, Masters in Health Policy, and Masters in Translational Clinical Trial Design.

Junior faculty pursuing advanced degrees should be offered protected time for coursework. Reimbursement, stipends or tuition waivers would facilitate completion of the additional degree.

Request for Action

J1. Facilitate the obtainment of advanced degrees by junior faculty.

ROLE OF THE SOCIETY OF GYNECOLOGIC ONCOLOGY

As the premier organization representing women's cancer specialists, the SGO should obtain funding to develop and maintain a web site containing a current listing of research funding and training opportunities for both fellows and junior faculty members, with appropriate links to further information and applications. This web site should also contain information regarding loan-repayment programs for which junior faculty may be eligible. The ability to have this relevant up to date information in a single site would be of great value to SGO's members as they attempt to navigate the opportunities for obtaining research funding.

SUMMARY

Gynecologic Oncologists, as multidisciplinary women's cancer specialists, have a long legacy of research training and a substantial record of research accomplishments of which to be proud. In order to maintain and increase the pace of discovery, a continued program of systematic effort and support is required.

The key elements of this are as follows:

- ***Identify*** individuals, early in their training, with the ability and commitment to develop a productive career in women's cancer research, both translational and clinical.
- ***Train and mentor*** these individuals over the entire course of their career.
- ***Fund*** specific programs to support research in women's cancers.
- ***Retain*** productive researchers in academic departments where they have the resources and support to continue their mission.

Table 6-1: Training The Next Generation Of Women's Cancer Researchers' Goals

	Short Term (0-3 years)	Intermediate Term (4-6 years)	Long Term (7-10 years)
Low Risk	***6E1)*** Focus on Established NIH Career Development Awards.	***6F1)*** Facilitate application to the five loan repayment programs.	***6H1)*** Facilitate application for Grants Non-Specific to Gynecologic Oncology.
Intermediate Risk	***6B1)*** Develop Institutional Certificate in Type 2 Translational Research.	***6B1)*** Develop Institutional Graduate Programs in Clinical Investigation.	***6J1)*** Facilitate the obtainment of advanced degrees.
High Risk		***6H2)*** Develop and Implement a Training Grant Specific to Gynecologic Oncology.	***6I1)*** Develop a bridge program to sustain investigators who have lost extramural funding.

ABBREVIATIONS

ABOG	American Board of Obstetrics and Gynecology
ACOG	American Congress of Obstetricians and Gynecologists
ACIP	Advisory Committee on Immunization Practices
ACS	American College of Surgeons
ASCCP	American Society for Colposcopy and Cervical Pathology
ASCUS	Atypical Squamous Cells of Uncertain Significance
BIRCWH	Building Interdisciplinary Research Women's Health
BMI	Body Mass Index
BRCA	Breast Cancer Genes 1 and 2
CAM	Complementary or Alternative Medicine
CAT	Computerized Adaptive Testing
CDC	Centers for Disease Control
CIN	Cervical Intraepithelial Neoplasia
CRADA	Cooperative Research And Development Agreements
CTC	Circulating Tumor Cells
CTEP	Cancer Therapy Evaluation Program
DNA	Deoxyribonucleic Acid
EC	Endometrial Cancer
ECM	Extracellular Matrix
FDA	Food and Drug Administration
FIGO	Federation International Gynecology and Obstetrics
GCF	Gynecologic Cancer Foundation, now known as the Foundation for Women's Cancer
GCIG	Gynecologic Cancer InterGroup
GC-MS	Gas Chromatography-mass Spectrometry
GCSC	Gynecologic Cancer Steering Committee
GOG	Gynecologic Oncology Group
HPV	Human Papilloma Virus
HR	Homologous Recombination
HSIL	High Grade Squamous Intraepithelial Lesion
IARC	International Agency for Research on Cancer
IDSC	Investigational Drug Steering Committee
IOM	Institute of Medicine
IP	Intraperitoneal
IPPCR	Introduction to the Principles and Practice of Clinical Research
ITT	Intention to Treat
IVRT	Intravaginal Radiotherapy
LSIL	Low Grade Intraepithelial Lesion
mRNA	Messenger Ribonucleic Acid

NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NMR	Nuclear Magnetic Resonance
PAP	Papanicolaou Test
PARP	Poly ADP Ribose Polymerase
PORTEC	Post Operative Radiation Therapy in Endometrial Cancer
PPV	Positive Predictive Value
PRO	Patient-reported Outcomes
PROMIS	Patient-reported Outcomes Measurement Information System
PROSPR	Population-based Research Optimizing Screening Through Personalized Regimens
QOL	Quality of Life
RFA	Request for Applications
RNA	Ribonucleic Acid
RSDP	Reproductive Scientist Development Program
RTOG	Radiation Therapy Oncology Group
SCC	Squamous Cell Carcinoma
SGO	Society of Gynecologic Oncology
SEER	Surveillance, Epidemiology and End Results
SNOMED-CT	Systematized Nomenclature of Medicine--Clinical Terms
SPORE	Specialized Program of Research Excellence
TCGA	The Cancer Genome Atlas
TIL	Tumor Infiltrating Lymphocytes
TMA	Tissue Microarray
WCBP	Women’s Cancer Bridge Program
WHO	World Health Organization
WPRT	Whole Pelvis Radiotherapy
WRHR	Women’s Reproductive Health Research

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