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## Gynecologic Oncology Group Survival

In 2010, the Institute of Medicine (IOM) produced a report recommending wide-ranging changes in the Cooperative Group program and, in response the National Cancer Institute (NCI) has proposed a reorganization of the nation's cancer Clinical Trials program that would significantly change the program's current structure. Of interest is the fact that the IOM committee responsible for the report had minimal representation from current Cooperative Group members. Among the changes proposed is the consolidation of the current nine Groups studying adult cancers into four multi-disciplinary, multi-disease site Groups, including the consolidation of the operations and data management centers. In addition, there would be a consolidation from nine grants for human tissue banks to three grants. The existing Children's Oncology Group (COG) would remain unchanged as a single Pediatrics Cooperative Group. COG was formed ten years ago in a voluntary consolidation of four different small Pediatric Cooperative Groups. Dr. James Doroshow, Director of the NCI Division of Cancer Treatment and Diagnosis, has stated, "We are interested in supporting a system that would rapidly complete large randomized multi-site Phase II and Phase III clinical trials of high scientific priority." No one would disagree with that statement but some would argue that this has been happening in gynecologic malignancies due to the effort of the Gynecologic Oncology Group (GOG).

There have been several reports over the last twenty years recommending a change in the Cooperative Group Program. None of these reports have suggested eliminating the Clinical Trials program within the Cooperative Group effort. The reports have however recommended various modifications. The IOM report has been interpreted as recommending consolidation of the Groups in an effort to improve efficiency. It is unclear how said consolidations would achieve the goal of improved outcomes but nonetheless a change appears imminent. The question is why the recommendation calls for the consolidation from nine to four adult cooperative groups, and further, does this suggest the merger of Groups with similar disease site portfolios? The purpose of this "White Paper" is to address the impact of the IOM Report on the GOG. First and foremost, it is important to note that the GOG is the only NCI-funded cooperative group in the United States currently conducting trials in gynecologic cancer. There is a clear reason for this. 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 is impossible. Almost all gynecologic oncologists in the United States participate as active members of the GOG and have great pride in what they regard as their cooperative group.

As a result, the GOG has been able to accrue successfully not only to trials of epithelial ovarian cancer but also to studies of other gynecologic malignancies such as carcinomas of the uterine cervix and, most impressively, to studies of endometrial carcinomas. Study results in recurrent and locally advanced endometrial cancer have, over the last ten years, established for the first time a role for systemic therapy and have improved outcomes in patients with these very difficult circumstances. Studies of concurrent chemoradiation in carcinomas of the cervix have led to a new standard of care documented in a clinical alert of the NCI. As stated above, the GOG is the only cooperative group in the United States that has been able to conduct such practice-changing studies in gynecologic cancer on a consistent basis over the last 40 years and the only group currently able to conduct such studies independently. The study of gynecologic cancers has been attempted by Groups other than the GOG. In point of fact, SWOG has attempted to accomplish this on two occasions without success, and ECOG's attempt in this area also was unsuccessful.

Historically, the idea for the GOG began as a multi-institutional cooperative study of endometrial carcinoma in the 1960's. This study led to the establishment of the GOG in 1970. Over the last 40 years, the GOG has prospered with increasing productivity despite less than optimal federal funding. It is recognized that the NCI provides about 150 million dollars a year for the Cooperative Group program. Multiple prior reports including the recently completed IOM recommendations have documented the insufficient level of funding provided by the NCI for the Cooperative Group studies. In order to conduct quality research, the Groups need to receive substantial resources through philanthropy, industry contracts, and, most important, a great deal of volunteer time from their members and their member institutions. In the field of gynecologic cancers, this volunteerism is spearheaded by the gynecologic oncologist, whose specialty is unique in adult cancer therapy in that it incorporates surgery, radiation therapy, and chemotherapy as part of the training and certification. The GOG is led by gynecologic oncologists, but its membership includes multiple disciplines, such as medical oncology, pathology, radiation oncology, basic scientists, quality of life experts, and patient advocates. There is an "esprit de corps" among the investigators which has kept the GOG productive and efficient despite attractive alternative funding in the community from competing industrial protocols. This commitment, particularly among the gynecologic oncologists, is a key to studying malignancies of the genital tract and it will be in jeopardy with the proposed reorganization.

To date, the proposal for the reorganization of the Cooperative Group program with the goal of consolidating nine adult Groups into four adult Groups has been the following: two existing large, primarily Medical Oncology Groups, ECOG and SWOG, would be two of the four adult Groups. A third adult Group would be centered on a merger of CALBG and NCCTG and possibly ACOSOG. All of the above except ACOSOG are primarily Medical Oncology Groups. These three groups (ECOG, SWOG, and the new merged entity) are essentially involved in similar research with much overlap of purpose and in fact with many studies in which all of the groups participate in common. This leaves four Groups in the "outfield". One of these, NSABP, conducts trials in breast cancer and colorectal cancer.

In the specific case of the GOG, "esprit de corps" has been the mainstay and the adhesive leading to the productivity of the GOG. The GOG is the only group studying gynecologic malignancies. It is important to emphasize this fact and analyze the reason for failure of prior attempts to delegate gynecologic cancers to a subcommittee of a large multiple disease site group. Should the spirit and integrity of the GOG be disrupted by attaching portions to various large medical oncology groups, the outcome will be repeated failure. Among the malignancies studied by the GOG is ovarian cancer, which is a critical disease for both clinical and basic science research. The availability of tissue for ovarian cancer research is primarily in the hands of the gynecologic oncologists who perform the surgery. Should the GOG dissipate or disband, the study of this important malignancy would be severely compromised in the United States, and the study of other gynecologic malignancies in large clinical trials would essentially cease. The

productivity of the GOG to date is summarized in Table 1 and Figures 1, 2 and 3, in the Appendix attached to this letter.

In the last ten years, there has been a considerable effort in developing translational research (bench-to-bedside) projects in conjunction with Phase II and Phase III studies within the GOG. All of this translational research (TR) has been supported by outside funding. Over the last decade, GOG has recognized the increasing importance of translational research in interpreting and designing clinically relevant trials. Thus, the GOG has progressively identified and dedicated additional resources to this effort. Translational research in the GOG has transitioned from investigator initiated projects to programmatic TR in areas of extraordinary opportunities including angiogenesis, “omics” and developmental therapeutics across disease sites since 2003. The TR objectives embedded into GOG 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.

The TR effort with GOG has been highly collaborative involving “teams” of GOG investigators and more importantly many additional outside groups and scientific partners. This collaborative effort has yielded a product far greater than the sum of its parts. The TR endpoints embedded within GOG has led to the creation of the single largest tissue bank of gynecologic cancers in the world. This bank has been recognized as a model for proper handling and storage of biospecimens and this has been achieved only by the concerted efforts by a team of investigators (surgeons, nurses, medical oncologists, administrators, and bank personnel) all dedicated to improving the lives of women with these cancers. In fact, the centralization of GOG clinical trial tissue specimens enabled GOG to be the only cooperative group to provide specimens to The Cancer Genome Atlas project. Further, TR efforts within GOG has allowed for the successful application for NIH and DOD funding including RO1, R21, SPORE and UO1. Only through coordinated efforts involving basic and translational scientist in conjunction with clinicians and the tissue bank has this been successful. These grants are an example of the value added the GOG TR efforts bring to the research portfolio conducted by cooperative groups.

A few examples of GOG TR efforts which exemplify the above features include GOG protocols 199, 210 and 218. For example, *GOG-0199* is a prospective, international, two-cohort, non-randomized study by Dr. Mark Greene and the GOG, Clinical Genetics Branch, Division of Epidemiology and Genetics (an NCI Intramural Research Program), and Cancer Genetics Network of women at genetic risk of ovarian cancer, who chose either to undergo risk-reducing salpingo-oophorectomy (RRSO) or screening, at study enrollment to quantify and compare ovarian and breast cancer incidence in the two study groups, assess the feasibility and performance characteristics of a novel ovarian cancer screening strategy (the Risk of Ovarian Cancer Algorithm), evaluate various aspects of quality of life and non-oncologic morbidity related to various interventions in at-risk women, and create a biospecimen repository for subsequent translational research. This protocol is providing invaluable prospectively-collected observational data, normal blood DNA, serial serum and plasma and some tissue specimens from women at high familial ovarian cancer risk, including substantial numbers of women carrying *BRCA1* or *BRCA2* mutations. Specimen collection was directly built into *GOG-0199* for TR which has yielded more than 52,000 specimens including 2,351 whole blood specimens for extraction of normal DNA, over a 1,000 paired frozen samples from left and right ovaries as well as fallopian tubes, 1,050 peritoneal washings, 22,175 serial serum specimens and 22,095 serial plasma specimens. Thus far, the GOG has contributed normal DNA and resources from *GOG-0199* to the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) to examine the associations between single nucleotide polymorphisms (SNPs) and the risk of developing breast and/or ovarian cancer. This has led multiple major publications and will continue to move the field of molecular epidemiology forward.

*GOG-0210* is a molecular staging study of endometrial cancer and uterine carcinosarcomas. (Currently, these are the most common gynecologic malignancies in the United States.) All patients undergo surgical staging and follow up for post-operative cancer treatment, recurrence, disease progression, survival and epidemiologic factors including demographics, body mass, smoking history, menstruation, menopause, contraceptive and hormone use, medical history, family cancer history and use of other drugs and medications. Specimen banking was directly embedded into *GOG-0210*, which has yielded more than 35,000 well-annotated specimens including fixed and embedded tissues (4,606 primary tumors, 421 metastatic tumors, 60 recurrent tumors and 4,993 normal tissues), frozen tissues (4,473 primary tumors, 401 metastatic tumors, 30 recurrent tumors and 4,841 normal tissues), serial sera (5,086 pre-op, 4,434 post-op, 1,629 3-year follow up and 197 at recurrence), and 5,029 urine specimens. Current studies connected with *GOG-0210* supported by various types of funding including P50, R01, R21, CTSA, U10, U24, Intramural and Department of Defense. Promising findings from *GOG-0210* and The Cancer Genome Atlas project in endometrial cancer will be validated with independent specimens and resources from *GOG-0210*, as well as the well-annotated specimens banked with the current randomized phase III protocols in endometrial cancer, *GOG-0249* and *GOG-0258*.

*GOG-0218* was a CTEP- and Genentech-sponsored, three-arm, randomized, double-blinded, placebo-controlled phase III trial by Burger and colleagues in women with previously-untreated epithelial ovarian, peritoneal or tubal cancer who underwent adequate surgical staging and cytoreduction with FIGO stage III disease with any gross or palpable residual disease or FIGO stage IV disease. Specimen banking and TR were directly embedded into *GOG-0218*, which have yielded 1,737 archival FFPE tumor, 1365 pre-treatment serum, 1,191 pre-treatment plasma, 169 frozen tumor and 1,007 normal DNA specimens from whole blood. Thus far, the TR connected with *GOG-0218* focuses on validating predictive genomic profiles associated with outcome and resistance, predictive genetic variations in genes associated with essential hypertension including *WNK lysine deficient protein kinase 1 (WNK1)*, *G protein-coupled receptor kinase 4 (GRK4)* and *kallikrein B (KLKB1)* associated with bevacizumab-induced hypertension, prognostic common polymorphisms in *ERCC1*, *BRCA1* and *ABC* genes, promising findings from The Cancer Genome Atlas project in ovarian cancer as well as the clinical utility of cell-free DNA from plasma, and serum markers including soluble EGFR. *GOG-0218* specimens and resources are also targeted for use for GWAS studies, common polymorphisms associated with bevacizumab, and genes associated with resistance to anti-angiogenic therapies, and to contribute in collaborative, consortium-type pharmacogenomics and pharmacogenomics studies.

Over the last forty years, the GOG has progressed to its current state where it produces well organized and high quality scientific research. It has progressed dramatically, from checking earlier reported therapeutic outcomes to developing means of rapid and dependable processing of studies, especially in the field of translational research. It has been very successful in adjusting to the changing presentations of scientific progress in oncologic research. A central contribution to the methodology of clinical trial research was the fact that from its initial discussion and beginnings the GOG was one of the first Groups to strongly emphasize the role of various specialties working together to care for patients who have or may develop a cancer of the female reproductive tract. The GOG continues to function as a multi-disciplinary, multi-modality clinical trial research group integrating modern diagnostic, therapeutic and surveillance techniques to meet the needs of patients presenting with cancer as well as those at increase risk for developing cancer. The products of GOG research have led to the following: modern staging of gynecologic cancers, state of the art therapies for these cancers utilized throughout the world, and a broad foundation of tissue and data for future basic research into the ideology and treatment of these devastating illnesses.

In summary, the dismantling of the current structure of the GOG will produce a dramatic down-turn in the scientific study of gynecologic cancers. The make up and function of the GOG is unique (as is the Children's Group), and it will not merge easily with other Groups. The structure in any reorganization must preserve its current operational integrity. If in fact the purpose of the reorganization is to improve operational efficiency, it makes far more sense to retain the GOG as one of the adult groups because of its unique features, its ability to conduct trials that have not been successfully conducted in settings such as the broad medical oncology groups, and the fact that, of all the cooperative groups, GOG was the most efficient at trial development in the Dilts study. To do otherwise is to risk having no active effort to study effectively gynecologic cancers that affect substantial numbers of women in the United States and elsewhere.

Sincerely,

A handwritten signature in black ink, appearing to read "P. DiSaia, M.D.", with a stylized, cursive script.

Philip J. DiSaia, M.D.  
Chair, Gynecologic Oncology Group  
Professor, Department of Obstetrics and Gynecology  
University of California, Irvine

cc: Dr. Harold Varmus  
Dr. James Doroshow  
Dr. Jeffrey Abrams  
Dr. Margaret Mooney  
Dr. Edward Trimble

## Appendix

Table 1

**GOG Protocol Activity**

<b>Protocol Type</b>	<b>Completed</b>	<b>Currently Active</b>
Phase III	82	12
Phase II	311	24
Phase I/Pilot	52	7
Staging	9	1
Special Studies	23	6
<b>Total</b>	<b>477</b>	<b>50</b>

Figure 1

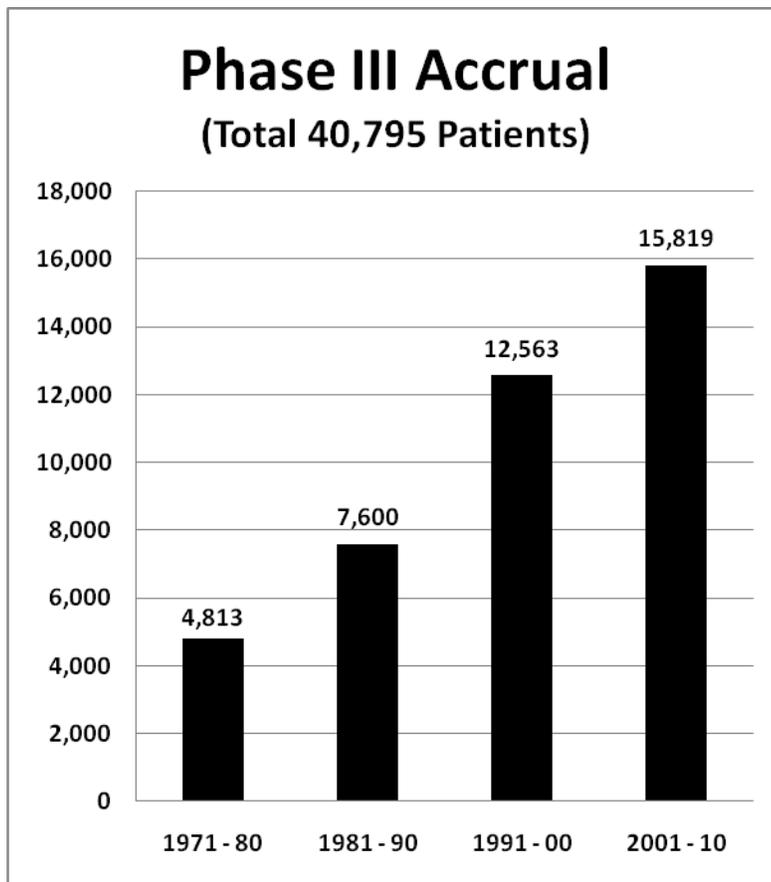


Figure 2

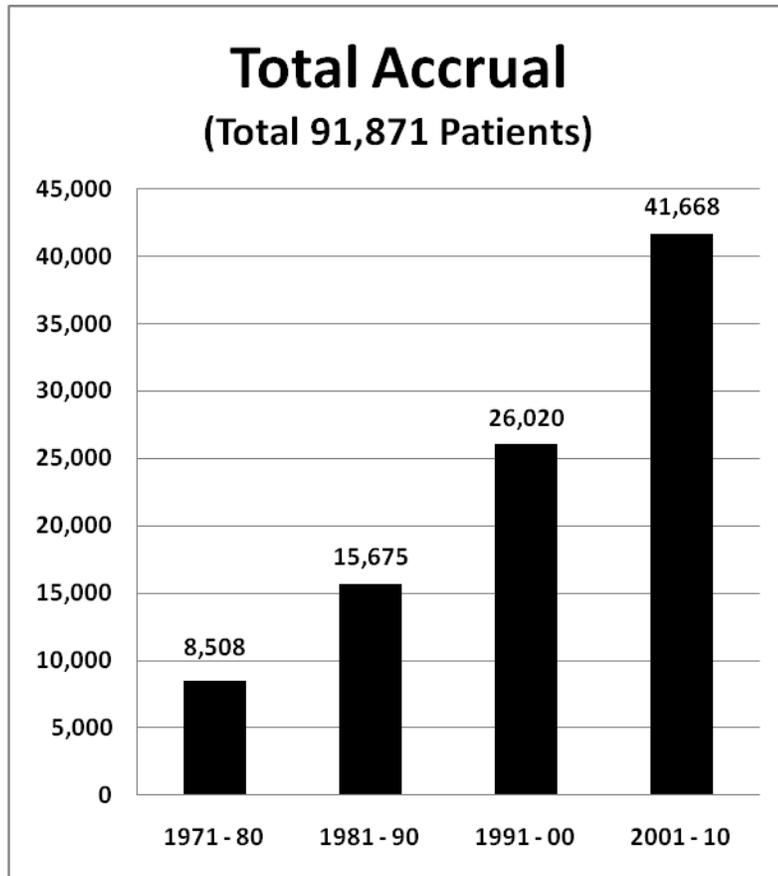


Figure 3

