University of Minnesota Grand Challenges Research Initiative

Phase 1 Final Report

Development Of A Clinical Precision Medicine Program In Ovarian Cancer As A Paradigm For 21st Century Tailored-Health Care Solution

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b. Michael Anglesio, PhD, University of British Columbia
c. Stefan Kommoss, MD, Department of Women's Health, Tübingen University Hospital, Tübingen, Germany.
d. Florian Heitz, MD, Kliniken Essen-Mitte, Gynäkologie und Gynäkologische Onkologie, Germany

Part One: Project Information and Outcomes

1A: Accomplishments

The University of Minnesota Ovarian Cancer Precision Medicine Initiative (UMN-OCPMI) was launched with the following objectives:

- **Primary Objective 1**: Achieve short term progress on the development of more accurate, clinically-deployable diagnostic (Precision Medicine) tests for identification of ovarian cancer subtypes with different therapeutic responses.
    - **Secondary Objective 1**: Provide benefit to the development and deployment of current clinical molecular testing and gain benefit (in terms of improved data acquisition) from implemented tests.
- **Primary Objectives 2 and 3**: **Establish (PO2)** an institutional, multi-disciplinary science platform for Precision Medicine (PM) that will drive patient engagement, biospecimen collection and banking, cutting-edge multi-"omic" analyses, computational modeling, and outcomes-driven research. This PM platform in ovarian cancer will drive future project proposals and national/international collaborations to fight ovarian cancer *and* create a reproducible infrastructure that can be translated to other disease areas. Demonstrating excellence with this integration of patients, specimens, analyses, and outcomes will **enable (PO3)** participation in national and international consortia for Precision Medicine.
- **Primary Objective 4**: Provide educational and research opportunities to trainees of various levels across disciplines within the context of the UMN-OCPMI.
- **Primary Objective 5**: Develop intellectual property which will drive academic-industry partnerships that bring benefits of the PM program to a broader medical market and drive further innovation at the University of Minnesota.

Accomplishments to date

1. We have obtained all regulatory, clinical and scientific approvals for this study in order to actively enroll patients diagnosed and treated with ovarian cancer at the University of Minnesota. Consent forms and procedures have been created to engage patients into the research process and customize their level of participation and receipt of results.
2. We have completed enrollment of 30 patients into the study as proposed. All biomaterials have been collected at the time of enrollment and primary debulking surgery. In addition, we have extended the IRB-approved protocol to continue prospective enrollment of patients into the program; to date 7 additional patients have been fully enrolled. These patients are receiving oncology and genetic counseling care through the standard channels of the UMN-OCPMI; their biospecimens have been banked for future analysis pending acquisition of additional funding.
3. Genetic counseling has been completed for 27 of 30 patients by the program genetic counselor Whiwon Lee, MS, LGC and her Genetic Counseling program trainees; the GC process occurs after patients have received their primary surgical and adjuvant chemotherapy treatments. 16 of 30 patients have completed primary germline sequencing with clinical return of results; 10 of 30 have received the expanded germline genetic results. To highlight the importance of this testing, a hereditary mutation was found in the expanded, medically relevant testing for one patient that changed her subsequent surgical management in respect to anesthesia management. The remainder of the cohort is scheduled for GC care and completion of testing in the coming months.
4. A regulatory and data-security compliant REDcap database has been established for clinicopathologic data; this information has been collected for all enrolled patients. A centralized, secure and regulatory compliant clinical data repository (CDR, hosted by the Institute for Health Informatics) for raw and processed genomic data has been developed, and data transfer into the warehouse is continuously ongoing. A University of Minnesota-hosted local instance of the cBioPortal for Cancer Genomics biomedical database (originally developed by Dr. Nik Schultz, Memorial Sloan Kettering Cancer Center) has been implemented. As data is populated into the UMN-cBioPortal, researchers and

clinicians across the campus will have interactive access to all genomic and non-identifying clinical information in a HIPPA-compliant, secure manner.

5. A pharmacogenomics discovery bioinformatics pipeline has been developed by Dr. Zach Rivers and Dr. Sarah Munro; 16 of 30 patients (for whom germline Medical Exome sequencing has been completed) have been processed for primary analysis. Secondary analyses by Dr. Rivers are ongoing as part of his PhD training.
6. Tumor samples from the 30 patient cohort were batched from the biospecimen bank for processing at the University of Minnesota Genomics Core (UMGC). 32 total samples were submitted for analysis, including a matched primary and recurrence sample for one patient. Tumor samples have been prepared for DNA Whole Exome somatic sequencing and RNA transcriptome sequencing in a single batch; this strategy was the most cost effective avenue and will provide the highest quality research data (minimizing batch effects) for downstream computation analysis, which is on-going.
7. RNA from all 30 patients is undergoing Nanostring gene expression analysis in collaboration with Drs. Michael Anglesio and David Huntsman (University of British Columbia) using a proprietary molecular classifier gene set developed to categorize intrinsic molecular subtypes of ovarian cancer.
8. The first project manuscript: Winterhoff et al. "Developing a Clinico-Molecular Test for Individualized Treatment of Ovarian Cancer: The interplay of Precision Medicine Informatics with Clinical and Health Economics Dimensions" has been prepared for submission (please see confidential appendix).
9. A patent application entitled "Methods for predicting a response to bevacizumab or platinum-based chemotherapy or both in patients with ovarian cancer" has been submitted (please see confidential appendix).
10. Seven abstracts have been submitted for the Society of Gynecologic Oncology 2019 meeting, including contributions from 7 trainees (clinical residents and fellows) in the department of OB-GYN (see Public Events section below). This is in addition to 9 abstracts previously presented at various local and national scientific meetings.
11. Additional external funds were awarded to Dr. Winterhoff ($450k direct costs; see External Funding section below) to initiate a parallel study for single cell sequencing of ovarian cancer leveraged on the infrastructure created by the UMN-OCPMI. Our group has completed single cell sequencing of 18 patients also enrolled in the UMN-OCPMI, and samples/data from 8 additional patients are in process. These patients represent a unique, rich data set which combines single cell gene expression and mutation analysis, bulk tumor gene expression and mutation analysis, and germline (normal) medical exome sequencing.
12. Genetic counseling and germline analysis has been completed for all 30 patients of the Phase 1 pilot project. All clinical and research return of results for primary and secondary genetic data have been returned to the patients. Full germline genetic information has been processed for downstream research utilization in pharmacogenomic and cancer genetic applications. Updated results were presented at the 2019 annual ACMG national meeting, and a manuscript is in preparation (see below).
13. Work has continued for genetic and clinical health information in the University of Minnesota local instance of the cBioPortal Cancer Genomics biomedical database. The team is still actively collaborating across Gynecologic Oncology, Laboratory Medicine & Pathology, the Masonic Cancer Center, the Institute for Health Informatics, and the Minnesota Supercomputer Institute to optimize this critical resource for the broader UMN research community. Importantly, this has aligned with work on the Phase 3 Single Cell Analysis of Ovarian Cancer Grand Challenges Research project. We are scoping the integration of a database tool from the Broad Institute that is capable of archiving and displaying single cell sequencing (scSeq) data being generated in that project. The scSeq database will interface in parallel with the UMN-cBioPortal database. This will create the first-of-kind integrated research tool bringing together germline, bulk somatic, and single cell genomic information with clinical-pathologic data on a patient-by-patient basis.
14. Bulk DNA exome sequencing was completed and has undergone primary analysis. This data has also been used for on-going clinical validation and implementation of focused genomic diagnostic tools in the Molecular Diagnostic Laboratory.

15. Bulk RNA sequencing analysis was completed following optimization of sample handling and library preparation procedures. This data has also undergone primary analysis. Secondary analysis by Dr. Jinhua Wang and his team is ongoing to apply clinically relevant predictive algorithms for predicting response to bevacizumab and platinum-based chemotherapy.
16. The first project manuscript was accepted and published in this extension period. "Developing a Clinico-Molecular Test for Individualized Treatment of Ovarian Cancer: The interplay of Precision Medicine Informatics with Clinical and Health Economics Dimensions." AMIA Annu Symp Proc. 2018 Dec 5;2018:1093-1102. eCollection 2018.
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1B: Budget summary

The proposal award was for a total of $60,000.

1C: External funding

Dr. Winterhoff was awarded the Ovarian Cancer Research Fund Alliance Liz Tilberis Early Career Award for his proposal "Precision Medicine in Ovarian Cancer: Using Single Cell Analysis". This provided Dr. Winterhoff with $450,000 in direct cost to start a comprehensive single cell sequencing and mice Avatar program in ovarian cancer. Our group has been the first group that has successfully performed single cell sequencing on viable ovarian cancer cells from the operating room. Dr. Winterhoff is co-enrolling patients from the UMN-OCPMI into the single cell study, making this the *most comprehensive molecularly-characterized ovarian cancer patient cohort to date*.

In addition, two NIH-R01 proposals leveraging the UMN-OCPMI were submitted in 2017 and 2018, but not funded. Revisions are on-going for resubmission. The first proposal submitted by Drs. Starr and Winterhoff was entitled "Single cell analysis of ovarian cancer chemotherapy resistance." The central hypothesis for this proposal is: platinum-resistant cells can be detected in primary ovarian cancer samples by analyzing gene expression patterns at the single cell level. The second proposal submitted by Drs. Winterhoff, Nelson, Aliferis, and Starr was entitled "Molecular stratification for bevacizumab and platinum based chemotherapy response in ovarian cancer." The central hypothesis for this proposal is: response to platinum-based chemotherapy and anti-angiogenic treatment with bevacizumab can be predicted using clinical and molecular tumor characteristics in patients with ovarian cancer. This predictive capability can lead to the creation of a clinico-molecular test to guide improved treatment strategies. Revisions are on-going for resubmission and will be substantially improved by the preliminary data we are continuing to generate out of the UMN-OCPMI Grand Challenges project.

We received additional funding through the Ovarian Cancer Research Alliance (PI: Dr. Winterhoff) for $200,000 for 2 years. This grant will for the first time attempt single cell sequencing from fresh frozen samples tumor obtained from an immune based clinical trial (TRIO026) in recurrent ovarian cancer. This work will help to identify patients most likely to benefit from immune based treatments and is only possible because of support from the GC phase 1 and 3.

1D: Student involvement

The success of the project to date has benefited tremendously from trainees participating on the research team. The following individuals have made key contributions:

1. Locke Uppendahl, MD, Clinical Fellow worked extensively with Aaron Grad, BS, Clinical Research Coordinator, Whiwon Lee, MS, LGC, Genetic Counselor and the co-PI team to obtain IRB/regulatory approvals, write study consent materials, and organize the patient enrollment and tissue collection protocols.

2. Zenas Chang, MD, Clinical Fellow continued work with patient enrollment and specimen collection, including optimization of collection procedures for single cell analysis. He has participated in single cell data analysis and trained additional Gyn-Onc clinical fellows and OB-GYN residents in aspects of the research project.
3. Zach Rivers, PharmD, Oncology Pharmacist, PhD Student in Social and Administrative Pharmacy (SAPh) developed the germline pharmacogenomics project approach and has worked collaboratively to develop bioinformatics pipelines for this research.
4. Shobhana Talukdur, MD Clinical Fellow continued work with patient enrollment and specimen collection for single cell and bulk analysis.
5. Sabrina Bedell, MD, 3rd year OB/Gyn resident helped with data collection and analysis as well as manuscript writing.
6. Anneliese Wilhite, MD, 3rd year OB/Gyn resident helped with data collection and analysis as well as manuscript writing.
7. Ryan Campbell, undergraduate (camp0746@umn.edu) has worked on secondary germline analysis under the supervision of Whiwon Lee, MS, LGC.
8. Lauren Thomaier MD, Clinical Fellow in Gynecologic Oncology, and Jennifer Hagen, MD, Resident in Ob/Gyn have joined the research team, contributing to a genomics research abstract to be presented at the upcoming 2020 Society of Gynecologic Oncology meeting (see below).

In addition, approximately 12 additional residents in both Obstetrics-Gynecology and Laboratory Medicine & Pathology as well as medical students rotating on these services have participated in care and analysis of patients enrolled in the UMN-OCPMI. Also, genetic counseling students have seen UMN-OCPMI patients with Whiwon Lee, MS, LGC during her clinic appointments. These residents and students have learned about the process of prospective, translational research in Precision Medicine through these experiences.

1E: External partners

Four significant academic external collaborators have contributed to scholarship produced from the UMN-OCPMI. Drs. Konecny, Kommoss, and Heitz were part of the ICON7 and GOG 218 clinical trial groups that contributed data and insight to the development of computational approaches detailed in the Winterhoff et al. manuscript (see Appendix). Dr. Anglesio is collaborating on focused gene expression analysis of the cohort using a proprietary, focused signature for ovarian cancer classification.

Academic External Partners

1. Gottfried E. Konecny, MD, University of Califronia Los Angeles
2. Stefan Kommoss, MD, Department of Women's Health, Tübingen University Hospital, Tübingen, Germany.
3. Florian Heitz, MD, Kliniken Essen-Mitte, Gynäkologie und Gynäkologische Onkologie, Germany
4. Michael Anglesio, PhD, University of British Columbia
5. A new partnership with Sage BioNetworks (SBN) has been established based on the value of the integrated bulk RNAseq data produced during the Phase 1 GCR funding linked with the scRNAseq data produced first through Dr. Winterhoff's OCRF support and now through Phase 3 of the GCR. SBN is a non-profit research entity that promotes community-based research and facilitates multi-institutional collaboration with a key focus on benchmarking computational methods in biomedical research. They currently our sponsoring a crowd-sourced Dream Challenge to identify best practices for cell-type deconvolution of bulk tissue RNAseq data. We will provide ground-truth data for this Challenge through the integration of our histopathology, bulk RNAseq, and single cell RNAseq methods. This will provide authorship for team members of our group on the forthcoming Dream Challenge publication plus valuable analysis for our goal to understand the heterogeneity of the ovarian cancer microenvironment to improve patient stratification and personalized therapy.

Three key industry external partners have been recruited to expand the potential future impact of the UMN-OCPMI. These individuals and the companies they represent are similarly trying to expand the possibilities of future therapies for ovarian cancer and develop novel strategies to tailor those therapies to each individual patient. We have initiated discussions with these companies to identify synergies for translating new approaches for ovarian cancer patient assessment and care into the clinic.

Biotechnology External Partners

1. Paul Haluska MD, PhD, Global Director of Scientific Affairs, Oncology, Merck Research Laboratories
2. Patricia L. Judson, MD, Senior Medical Director, Women's Oncology & Prostate Oncology, US Medical Affairs, AstraZeneca
3. Timothy Lu, MD, PhD, CEO and Co-founder, Senti Biosciences

1E: Public events and outreach activities.

Information and research results related to data acquired and/or methods developed in the UMN-OCPMI have been disseminated through a number of abstract presentations at local, national, and international symposia:

1. Society of Gynecologic Oncology, New Orleans, LA. March 2018. "Single cell sequencing: A descriptive subgroup analysis of individual tumor cells from 4 patients with ovarian cancer"
2. Society of Gynecologic Oncology, New Orleans, LA. March 2018. "Single cell sequencing identifies distinct immune cell profiles in primary ovarian cancer"
3. Society of Gynecologic Oncology, New Orleans, LA. March 2018. "Single cell exome sequencing reveals somatic BRCA1 heterogeneity in a patient with BRCA1 germline mutation"
4. University of Minnesota Masonic Cancer Center, 8th Annual Research Symposium. March 29, 2018. "Implementation of a Precision Medicine Initiative in Ovarian Cancer at the University of Minnesota"
5. University of Minnesota Grand Challenges Research Expo. April 18, 2018. "Development of a Clinical Precision Medicine Program in Ovarian Cancer as a Paradigm for 21st Century Tailored-Health Care Solution"
6. ASCO Annual Conference, Chicago, IL. June 1-5, 2018. "Significant overall survival improvement in proliferative subtype ovarian cancer patients receiving bevacizumab"
7. ASCO Annual Conference, Chicago, IL. June 1-5, 2018. "Prediction of post-operative resideual disease in advanced-stage ovarian cancer (AOC) using whole transcriptome expression: An exploratory analysis of the AGO-OVAR 11 (ICON 7) trial"
8. 13th Annual Women's Health Research Conference, Minneapolis, MN. October 1, 2018. "A descriptive subgroup analysis of individual tumor cells from 4 patients with ovarian cancer"
9. University of Minnesota Molecular Pathology and Genomics Symposium. October 11, 2018. "Development of a Clinical Precision Medicine Program in Ovarian Cancer as a Paradigm for 21st Century Tailored-Health Care Solution"
10. Society of Gyneologic Oncology. Honolulu, HI, March 16-19, 2019 (submitted). "Single cell RNA-sequencing identified unique immune cell profiles across metastatic sites in a case of primary ovarian cancer"
11. Society of Gyneologic Oncology. Honolulu, HI, March 16-19, 2019 (submitted). "Comparison of single cell analysis with histology and TIL score
12. Society of Gyneologic Oncology. Honolulu, HI, March 16-19, 2019 (submitted). "Comprehensive single cell sequencing of an individual's primary, recurrent, and xenograft tumor"
13. Society of Gyneologic Oncology. Honolulu, HI, March 16-19, 2019 (submitted). "Single cell exome analysis of hereditary breast and gynecologic cancer loci"
14. Society of Gyneologic Oncology. Honolulu, HI, March 16-19, 2019 (submitted). "Development and implementation of a multidisciplinary precision medicine program in ovarian cancer: A new paradigm"
15. Society of Gyneologic Oncology. Honolulu, HI, March 16-19, 2019 (submitted). "Single cell sequencing provides a novel inside intra-tumor heterogeneity between multiple metastatic sites of a single ovarian cancer"

16. Society of Gyneologic Oncology. Honolulu, HI, March 16-19, 2019 (submitted). "Gene expression of programmed cell death (PD-1) and its ligand, PD-L1, in primary epithelial ovarian and fallopian tube tumor cells: Possible use of PD-1/PD-L1 targeted therapy"
17. American College of Medical Genomics, Seattle, WA, April 2019. "Development of the University of Minnesota Ovarian Cancer Precision Medicine Initiative: Clinical and Molecular Findings from Pilot-Phase Patient."
18. Society of Gynecologic Oncology, Toronto, ON, March 2020. "Identification of clinically relevant genomic alterations in ovarian cancer: A comparison of a focused cancer next generation sequencing (NGS) assay and whole exome sequencing."
19. Society of Gynecologic Oncology, Toronto, ON, March 2020. "Development of predictive signatures for immune therapy in ovarian cancer: Whom to treat and whom not to treat?"

1F: International contributions.

The team has been expanded to include Dr. Anglesio from the University of British Columbia in Vancouver. He and his team are performing the TCGA molecular subtyping using the NanoString platform and have developed the Gold Standard assay for ovarian cancer. In addition we have partnered with Drs. Kommoss and Heitz from the German AGO Cooperative Trial Group using obtaining gene expression data from patients ovarian cancer tumor samples enrolled in a the phase III frontline trial ICON7.

Part Two: Reflections on Interdisciplinary Scholarship

2A: Interdisciplinary team integration

Integration of the UMN-OCPMI interdisciplinary team was perhaps the most significant achievement of the Phase 1 initiative. We have aligned a diverse spectrum of expertise in: gynecologic oncology/surgery, anatomic and molecular pathology, genetic counseling, basic biologic sciences, computational science, health informatics, and genomic technology. This team created the infrastructure to engage patients, collect and store biospecimens, aggregate routine clinical data and laboratory testing, and integrate research data in a manner that is sustainable and scalable. These approaches are broadly transferable to other areas of disease research, are regulatory compliant, and data secure. Key opinion leaders from these disciplines were necessary to accurately assess needs, identify new approaches, means-test proposed solutions, and translate the Grand Challenge of an institutional, multi-disciplinary science platform for Precision Medicine into reality. By creating the infrastructure of the UMN-Ovarian Cancer Precision Medicine Initiative, we have successfully attained our Primary Objective 2 and furthermore Drs. Jinhua Wang and Doug Yee are leading the Masonic Cancer Center's work to engage with national and international consortia including the AACR Genie Project and Caris Centers of Excellence (Primary Objective 3). The integrated, multidisciplinary team assembled by this UMN Grand Challenges Project is well-positioned to continue the University of Minnesota's leadership in Precision Medicine research and clinical implementation into the future.

2B: Interdisciplinary scholarship

Interdisciplinary scholarship is crucial because the combination of perspectives and expertise areas will bring different insights into complex problems facing our society. In the realm of medicine, interdisciplinary scholarship connects clinicians who struggle daily with the limitations of current clinical practice to basic scientists who have an extraordinary understanding of biologic mechanism; this provides synergy to connect new, clinically-relevant observations with novel, innovative approaches for diagnosis and therapy. Similarly, the connection between health informatics, computational sciences, and clinicians drives interconnection of clinical data and multi-dimensional analyses that identify associations which would not be uncovered by human observation of patterns in the clinic alone. As an example, we recently have completed the first manuscript from the UMN-OCPMI which describes a clinically actionable classifier (i.e., assay and interpretative computing) for optimal treatment selection in ovarian cancer and are in the process with the OTC for IP protection and other legal groundwork toward market deployment (meeting Primary Objectives 1 and 5;

see appendix). The estimated health economic impact of deploying this personalized precision medicine (PPM) test across the health system –treating all patients with bevacizumab compared to treating only the group predicted to strongly benefit amounts to $30 Billion savings over a 10 year horizon.

Meeting the goal of Secondary Objective 1, the interdisciplinary scholarship of the project has enabled Dr. Nelson and colleagues to optimize clinical testing in the UMMC Molecular Diagnostics Laboratory (MDL). The team of Ms. Lee MS-LGC, Dr. Henzler, and Dr. Nelson have utilized research testing performed through the UMN-OCPMI to improve the accuracy of germline testing in challenging genomic regions (i.e. PMS2 vs. PMS2-CL sequencing). The pharmacogenomics project of the UMN-OCPMI (run by Drs. Rivers, Munro, Jacobson, and Nelson) has been utilized to drive validation of the MDL's clinical pharmacogenomics assay slated to go-live in early 2019. In these examples, interdisciplinary scholarship has been an important contributor to current clinical molecular tests.

2C: Engagement

The engagement of patients with the UMN-OCPMI project has been astounding. Nearly 98% of patients who were approached and informed of the project chose to participate. These courageous women, faced with the immense personal challenge of ovarian cancer, found value and strength in the process of engaging with their academic care team to push forward our understanding and treatment of this aggressive disease. We are inspired by the resolve of our patients, humbled to be part of their care, and deeply grateful for their willingness to help us change outcomes for future ovarian cancer patients.

Importantly, the academic care team included a number of medical trainees in obstetrics-gynecology, pathology, and genetic counseling. These trainees see first-hand how this disease affects patients and how the efforts to personalize care resonates with them. As listed above (section 1D), several fellows and students made significant contributions to the success of building and implementing the infrastructure for the UMN-OCPMI; their work was invaluable. Time limitation is the most significant barrier to academic scholarship in the Academic Health Center clinical disciplines; this is true both for faculty and trainees. A challenge to embracing students into the Project was identifying time to familiarize and train them into their roles and for them to complete those roles on top of other course and/or clinical work they were responsible for. We were successful in the engagement of our trainees (Primary Objective 4) and learned invaluable lessons for ways to continue this process as we move forward with the UMN-OCPMI both through our pending UMN Grand Challenges Phase 3 proposal as well as external funding mechanisms.

2D: Unanticipated outcomes

Fortunately our team did not experience any significant adverse unanticipated outcomes. One positive unanticipated result came for one of the first 10 patients for whom all secondary germline research results were completed. We identified a clinically actionable mutation in the gene *RYR1*, which predisposes to a potentially life-threatening condition known as malignant hypothermia during anesthesia. This condition was unknown to the patient prior to enrollment in the UMN-OCPMI, including at the time of initial surgery. The patient was counseled on this result, which were documented in the medical record as part of our protocols. Her clinical care team, newly aware of this predisposition, appropriately modified her subsequent surgical procedures to minimize risks associated with this condition. Although anecdotal, this experience almost immediately cemented the importance of a comprehensive, personalized approach to patient care for the entire interdisciplinary team early on in the project.