

## Example #1

### **Finding Support: Accessing Resources Among Burn Survivors in Iowa**

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#### **Problem**

Support services are a key factor in recovering quality of life after a serious burn. Recent analysis by Grieve et al. has shown that participation in support groups is linked to better outcomes in a variety of areas. This includes better satisfaction in relationships, work, and even a stronger sense of purpose [1].

Despite these demonstrable benefits, 53% of burn survivors in the Midwest have never participated in a support group [2]. While University of Iowa's Burn Treatment Center provides several support programs, they may not be reaching all those who could benefit from them. There is scant research about how survivors learn about these programs and why some choose to participate while others do not. It is important to understand what barriers if any exist to participation to ensure the best possible outcomes for burn survivors.

#### **Hypothesis**

The barriers to participation in support services for burn survivors in Iowa can be identified and enumerated.

#### **Aims**

The aims of this study are to understand the barriers that exist to participation in support services in Iowa. These barriers may be financial, social, or based on physical distance from support services. Overall awareness of support services and their perception among burn survivors will be another area of interest. Additionally, the study will address how well these services are meeting the psychosocial needs of burn patients in Iowa.

#### **Background Information**

Burns result in 500,000 hospital visits and 40,000 hospitalizations annually in the United States [3]. In addition to the immediate physical concerns and the trauma of the burn itself, survivors face a variety of psychosocial challenges during recovery. Symptoms from the burn, disfigurement, and emotional distress following trauma can make re-entry to family life, society, and work incredibly difficult.

While the majority of scholarship on burn recovery is focused on physical recovery, researchers and physicians have increasingly acknowledged the importance of psychosocial factors in successful long-term recovery. Recently there has been an increase in patient focused research identifying factors that contribute to a return to high quality of life. One major advance in this area has been the development of the 196 question Life Impact Burn Recovery Evaluation Questionnaire (LIBRE-192), which focuses on the social aspects of burn recovery to aid caregivers in identifying areas in need of improvement [4]. Burn survivors face a variety of psychosocial challenges in recovering from their burns. Scarring, loss of facial features, and deformities of limbs can lead to social deprivation, negative public reactions, difficulties returning to work, and unemployment [5]. The goal of LIBRE is to determine norms that can be used to benchmark recovery from a burn injury.

One important finding of research done to date has been the importance of peer support in addressing the psychosocial needs of burn survivors. This type of support has several advantages over other forms of psychological support. It tends to be traditional individualized counseling.

Studies to date on burn survivor peer support, while scant, have demonstrated a strong sense of social support and promotion of feelings of belonging that are vital to successful rehabilitation [6]. Sproul noted that peer support was instrumental in providing hope to survivors [7]. More recently, Grieve demonstrated with the LIBRE data that survivors attending a support group showed significant improvement over peers who did not attend support groups in 5 or 8 life domains [1]. A final study by Badger used interviews conducted at the World Burn Congress, a burn survivor conference, to identify the importance of peer support. All interviewed had strong positive views on the value and benefit from peer support. The participants expressed that peer mentors provided hope and a glimpse at what recovery looked like. Ninety percent of participants would recommend support groups to others alongside treatment [8].

Despite these benefits, the Midwest region has the lowest participation rate in peer support groups at 47% [2]. The University of Iowa Hospital and Clinics attempt to address the psychosocial needs of the patients through several programs. Initiatives include in hospital visits from SOAR (Survivors Offering Assistance in Recovery) certified volunteers, monthly peer support groups, mobile clinics and support groups throughout Iowa, promotion of the Phoenix Society for burn survivors, and the annual summer Miracle Burn Camp of Iowa for children affected by burns.

## **Methods**

This study has two components. The first component will consist of a mailed survey sent to a representative sample of burn survivors in Iowa. This sample will comprise of patients who were treated as inpatients at University of Iowa Hospital burn unit over the past 10 years. At this hospital there are approximately 250 inpatient admissions for burns annually. We approximate a 60% response rate [9]. The survey will include basic demographics, treatment history, and questions concerning their participation in and awareness of support services. We will also include a sample of questions from the LIBRE-192 study or similar evaluation method to identify overall trends in psychosocial recovery among burn survivors in Iowa and identify subjects for future research. The survey will be available online, but we will make written surveys available upon request to accommodate the largest possible number of respondents.

The second part of the study will be a set of 10 interviews with burn survivors who were treated in the University of Iowa burn unit. Patients returning questionnaires will be solicited as well as more recent patients who are returning to clinic for routine follow-up. These patients will be asked to participate in a 30-60 minute in-depth interviews. This smaller sample will include a mix of those who have and have not participated in a support group. In addition to the mailed survey items, the participants will be questioned about their knowledge and experiences with survivor support services. We are interested in ways that they learned of the services, how they have helped and also areas in which they have unmet needs. We are also interested in comparing the experiences of survivors who have received support services and those who have not. These answers will be transcribed and coded for topics and themes to help us better interpret the survey results. This will help us to better connect burn survivors to support services.

## Significance of Research

Results from this study will help ensure that hospital and social service agencies have the information to ensure that burn survivor support groups are easily accessible to those who stand to benefit from them. If Iowa conforms to the regional average, the majority of burn survivors in Iowa have not taken advantage of the programs available. If this study can identify the reasons for this lack of participation the results have the potential to improve outcomes for burn survivors in the state of Iowa and beyond.

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## Example #2

### **Establishing reference intervals in laboratory testing for transgender patients**

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#### **Introduction/Background**

Clinical laboratory testing is an integral part of modern medicine, with test results influencing diagnosis, prognosis, and management of disease.<sup>[1,2]</sup> In order to provide a context to results of laboratory testing, reference intervals are regularly included with laboratory test results.<sup>[3]</sup> A reference value is defined as the value for an analyte obtained by measurement of individuals (reference individuals) precisely selected using defined criteria, for example, sex, age, state of health or other relevant characteristics.<sup>[4]</sup>

However, as access to transgender healthcare becomes more readily available in the United States, interpreting laboratory results is difficult within the male/female gender binary reference intervals. Interpretation of laboratory results for transgender patients remains a challenge. Previous research studied interpretation of laboratory results in transgender women (transfemales) but did not tackle the reference interval issue.<sup>[5]</sup> Currently, no reference intervals specific to transgender men and women are provided when laboratory results are added to the patient chart.

Research on the health status of sexual and gender minorities presents many unknowns, challenges, and barriers.<sup>[6,7]</sup> Past Institute of Medicine (IOM) reports recommended advancing knowledge and understanding of Lesbian, Gay, Bisexual, and Transgender (LGBT) health, collecting data on sexual orientation and gender identity in the electronic health record, and the development and standardization of sexual orientation and gender identity measures.<sup>[7]</sup>

The University of Iowa is uniquely situated to address the laboratory testing reference interval issue for transgender patients. In 2012, University of Iowa Health Care opened an LGBTQ clinic at its Iowa River Landing (IRL) outpatient facility to treat the health concerns of the LGBTQ community. This represented the first coordinated effort to offer transgender healthcare at University of Iowa Health Care. The clinic has received national recognition from the Human Rights Campaign as a Healthcare Equality Index Leader.<sup>[8]</sup> The LGBTQ clinic is directed by Katie Imborek, MD and Nicole Nisly, MD.

#### **Hypothesis**

We predict unique patterns for both transgender male/female test results compared to the cisgender male/female reference intervals. In addition, we suspect greater deviation from established reference ranges in individuals receiving relatively higher rates of hormonal therapy.

#### **Specific Aims of Study**

1. Review and analyze laboratory test results for transgender patients in the UIHC pathology laboratories.
2. Determine how hormone therapy affects the value of commonly ordered laboratory tests.

3. Determine whether new recommendations for laboratory test reference ranges are indicated in order to improve clinical care of transgender patients.

## Methods

The study will involve retrospective data collection by chart review from October 2012 to May 2016. Sources of data include UIHC records/specimens, specifically the electronic medical record (Epic). This study is in the process of receiving approval from the Institutional Review Board. The research mentor has extensive experience with data mining tools in Epic. Patients will be identified by Epic report using ICD-9/ICD-10 codes for 'gender dysphoria' or 'endocrine disorder, unspecified' with Drs. Imborek or Nisly as the provider. Transgender status of the identified patients will be verified by Drs. Imborek or Nisly with the LGBTQ clinic list. For the purposes of our study, we will only review the charts of individuals who were at least 18 years old at time of laboratory testing and receiving hormone therapy for at least 6 months. Privacy of identified patients will be protected by designation of a 'participant number' and storage of extracted data on protected University of Iowa Health Care servers (already set up by Department of Pathology informatics). Variables to be considered include:

1. MRN #
2. Date of birth
3. Gender (in Epic)
4. Ethnicity
5. Medications/dosing information
6. Gender confirmation procedures
7. Vitals data (BMI, height, weight, blood pressure)
8. Other chronic conditions/health issues
9. Laboratory testing
  - a. Liver function tests
  - b. Hematology tests (*e.g., hematocrit, hemoglobin*)
  - c. Blood lipid levels
  - d. Hemoglobin A1C
  - e. Sex hormone levels (*testosterone or estrogen, depending on direction of gender transition*)

Data analysis will involve basic statistics including calculation of frequencies and statistics that assess the impact of hormone therapy on laboratory test values. In addition, we will perform detailed reference range analysis using EP Evaluator software (specialized software available in the Department of Pathology for analysis of clinical laboratory data). Our early estimates predict a patient population much larger than previous studies. A larger sample size increases applicability of the study and limits the possibility that analysis will yield non-generalizable results. To date, no reference ranges are provided specific to transgender patients. To our knowledge, there has been no investigation concerning transgender males with respect to laboratory testing in the literature.

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### Example #3

## **Updating Tumor Grade in the University of Iowa Hospitals and Clinics Neuroendocrine Tumor Registry and Correlation with Patient Survival**

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### **Introduction**

Gastroenteropancreatic neuroendocrine tumors (GEP NETs) are tumors that arise from enterochromaffin cells of the gut and islet cells of the pancreas.<sup>1</sup> They are relatively rare but their incidence has been increasing.<sup>2</sup> Two of the most common areas for this malignancy to develop are the small bowel (SBNETs) and pancreas (PNETs). Over 50% of patients with SBNETs and PNETs present with metastases in the liver or lymph nodes.<sup>3</sup> Effective treatment relies on knowledge of the primary tumor's location. Surgical resection and debulking of metastatic sites is the preferred treatment. However, SBNET resections tend to have better outcomes than PNET resections. Targeted therapeutics, such as the mTOR inhibitor everolimus and the multikinase inhibitor sunitinib, are approved for PNET patients, but have limited effectiveness in SBNET patients. GEP NET patients tend to have a better prognosis stage-for-stage compared to similar site adenocarcinomas. Poor prognostic indicators include advanced age, carcinoid heart disease, elevated 5-hydroxyindoleacetic acid (5-HIAA), elevated chromogranin A (CgA), plasma neurokinin A (NKA) levels greater than 50 pg/ml, incomplete surgical resection, tumor spread, and high grade or poorly-differentiated histology. The median survival of NET patients with localized, well-differentiated GEP NETs is approximately 10 years. Median survival decreases in NET patients with metastatic disease to 4.8 years.<sup>2</sup>

The University of Iowa Hospitals and Clinics (UIHC) has one of the largest collections of NET patients seen at a single clinic nationally. The UIHC NET registry includes patient demographics, clinical factors, pathologic factors, and tumor grade. This tumor registry is a very useful tool for performing clinical studies in patients with NETs, and currently contains data from nearly 1600 patients. One difficulty with performing studies using this registry is that of incomplete information. Most of the patients evaluated at the UIHC NET clinic are from outside of Iowa, and clinical records often come from a variety of institutions. Updating the tumor registry has been very labor intensive and an ongoing project for two research assistants.

Pathologic information from each patient is the cornerstone of any clinical study using the tumor registry. Identifying the primary tumor site is critical, as are its size, nodal, and metastatic status. One of the most important factors for determining prognosis is tumor grade, but for most patients, the tumor grade was determined in a subjective manner which varied depending on the pathologist. The World Health Organization (WHO) released a more reliable and standardized classification system for GEP NETs in 2010, based on mitotic index and Ki-67, a maker of proliferation.<sup>4</sup> Of the two, Ki-67 is considered more accurate. Studies have established the relationship between Ki-67 grading and prognosis, but have been limited by small sample size.<sup>5,6</sup> The UIHC tumor registry, with its large number of patients, is a potentially valuable resource for confirming the relationship of NET tumor grade with prognosis, but we are currently limited by not having standardized grading criteria for most patients. Fortunately, we have unstained slides from tumor blocks in a large number of our patients available for Ki-67 staining. Determining tumor grade in our patients will allow for correlative studies of tumor grade with patient survival in GEP NETs.

## **Hypothesis**

Pathologic information in the UIHC NET registry needs to be updated to reflect the 2010 WHO standard classification system. GEP NET WHO grade can be objectively determined by Ki-67 staining, and will show significant differences in progression-free survival and overall survival in patients with grade I, II, and III GEP NETs.

## **Specific Aims of the Study**

- A. Determine the grade of archived tumors based on Ki-67 immunostaining and the WHO standard classification system.
- B. Update the UIHC NET registry with standardized WHO tumor grades.
- C. Determine differences in progression-free and overall survival in patients with grades I, II, and III GEP NETs.

## **Background**

The Howe lab and University of Iowa Specialized Programs of Research Excellence (SPORE) have expended significant effort to construct, update, and maintain an NET surgical database and tumor registry containing patient demographics, clinical symptoms, tumor markers, imaging results, and pathology data. The database is an ongoing project that is constantly being updated with new patient information. The tumor grades for specimens in the surgical database were completely updated by the applicant last year based on the WHO standard classification system, which included 232 primary tumor specimens from 151 patients and 335 metastases derived from 117 patients. Tissue specimens from primary tumors, liver metastases, and lymph node metastases were obtained during surgery under an institutional review board approved protocol. Data analysis for this group of tumors showed that there was a significant difference in progression-free survival for patients with different tumor grades in their primary tumors versus their metastases. Once standard tumor grades have been determined for archived tumors and entered into the UIHC NET registry, the relationship between tumor grade and survival can be tested in this even larger collection of patients.

## **Proposed Methods**

### **A. *Reading Ki-67 immunostained slides***

Ki-67 and hematoxylin and eosin (H&E) slides will be stained in the UIHC Department of Pathology research laboratory. The H&E slides will be used as a reference to identify areas of tumor. This is especially helpful for samples that lack a lot of tissue or where the tumor is spread diffusely throughout the tissue. Extremely difficult cases will be referred to our pathologist (Dr. Andrew Bellizzi), who will identify the specific area of tumors. These areas of highest tumor density will be marked on the Ki-67 slide with a Sharpie based on their location on the H&E stain. Ki-67 slides will be observed under a light microscope connected to a digital camera and computer. Slides will be initially observed at 50x magnification to focus the view, then at 100x to identify hotspots. Ki-67 hotspots are areas of the slide that contain a high number of Ki-67 stained cells. In slides with multiple hotspots, an area will be selected to maximize the total number of tumor cells while avoiding stroma, blood vessels, and other non-tumor areas. Further magnification to 200x and 400x will be used to refine the view. At least 500 tumor cells will be counted in a hotspot. Some slides may have less than 500 tumor cells due to extremely small, widespread pockets of tumor cells. These cases will be noted, and the view that maximizes the total number of tumor cells will be selected. Once a suitable view is found, an image will be



taken using a digital camera and Celsense software. To take a clear image, the view will be refocused for the camera, the microscope light will be set to maximum brightness, ISO set to 200, and brightness compensation at 1/3. The image will be saved as a 4080x3072 JPEG file. The image will be opened in Microsoft Paint to manually count tumor cells. Counted cells will be marked with the marker function to avoid recounting. The number of negative cells and positive cells will be counted separately and recorded in an Excel spreadsheet. The Ki-67 index will be calculated as total # positive cells/(total # negative cells + total # positive cells). Tumor cells will be identified by their distinct “salt and pepper” appearance, roundness, size, and their tendency to group into pockets.

### **B. Updating the database**

The data obtained from the Ki-67 slide readings will be recorded in the Howe lab database and the UIHC NET registry. The FileMaker Pro program is used to maintain and update the Howe database and RedCap in the tumor registry. New entries will be created for each new patient, and demographics and tumor grade will be entered, as well as the images taken during Ki-67 slide reading and used for calculating Ki-67 index.

### **C. Data Analysis**

Dates of surgery, disease progression, last follow-up, and death will be compiled from the Howe lab database and UIHC NET registry. All event times will be defined from the date of diagnosis and/or surgery. Median event times will be estimated using the Kaplan-Meier method and P values calculated using the Log-Rank test. Follow-up times will be estimated by the reverse Kaplan-Meier method. For values showing significant association with outcomes on univariate analysis ( $p < 0.05$ ), multivariate Cox regression models to further explore the independence of these associations. Patient characteristics will be compared using Fisher Exact or Wilcoxon Rank-Sum test, and all analyses will use R v.3.0.1 (Vienna, Austria).

## **Summary**

GEP NETs are rare tumors with increasing incidence that frequently present with liver and/or lymph node metastases. The two most likely sites of NET primaries are from the pancreas and the small bowel, and treatment depends on the site of the primary tumor. Surgical resection of PNETs can be complex and is associated with high morbidity, while SBNETs are commonly multifocal and not identified on preoperative imaging. Post-treatment progression-free survival depends on many factors, such as tumor grade. The WHO released a standard tumor grade classification system for NETs in 2010 that used Ki-67 or mitotic index to objectively assign tumor grade. The University of Iowa has one of the largest NET databases in the nation and updating the tumor grade based on the WHO classification system will provide a large amount of objective data that can be used to further study the relationship between tumor characteristics and patient prognosis. Facilitating this type of research will improve understanding of NETs and pave the way for improved treatment and medical management for patients.

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