Oregon Health & Science University
School of Medicine

Scholarly Projects Final Report

Title *(Must match poster title; include key words in the title to improve electronic search capabilities.)*

Genetic Outreach for Multiple Endocrine Neoplasia (MEN2A) in a Mexican Immigrant Cohort

Student Investigator's Name

Matt Jorizzo

Date of Submission *(mm/dd/yyyy)*

03/09/2023

Graduation Year

2023

Project Course *(Indicate whether the project was conducted in the Scholarly Projects Curriculum; Physician Scientist Experience; Combined Degree Program [MD/MPH, MD/PhD]; or other course.)*

Scholarly Project Curriculum

Co-Investigators *(Names, departments; institution if not OHSU)*

Ryan Li MD MBA, Lourdes Quintanilla-Dieck MD

Mentor's Name

Ryan Li MD MBA

Scholarly Project Final Report

Mentor's Department

OHSU Department of Otolaryngology Head & Neck Surgery

Concentration Lead's Name

Lisa Silbert MD, MCR

Project/Research Question

Can individuals from Michoacan, Mexico living in Prineville, Oregon at risk for MEN2A be identified using chart review and genetic interviews of patients treated for MEN2A or medullary thyroid cancer?

Type of Project *(Best description of your project; e.g., research study, quality improvement project, engineering project, etc.)*

Research and Outreach Study

Key words *(4-10 words describing key aspects of your project)*

Multiple Endocrine Neoplasia, MEN2A, medullary thyroid cancer, genetic testing, cultural outreach, Hispanic and Latino immigrant population

Meeting Presentations

If your project was presented at a meeting besides the OHSU Capstone, please provide the meeting(s) name, location, date, and presentation format below (poster vs. podium presentation or other).

Presented at the OHSU Capstone meeting 3/10/2023

Publications *(Abstract, article, other)*

If your project was published, please provide reference(s) below in JAMA style.

This research has not been published.

Scholarly Project Final Report

Submission to Archive

Final reports will be archived in a central library to benefit other students and colleagues. Describe any restrictions below (e.g., hold until publication of article on a specific date).

No restrictions.

Next Steps

What are possible next steps that would build upon the results of this project? Could any data or tools resulting from the project have the potential to be used to answer new research questions by future medical students?

The data collected in this project can be used to pursue genetic testing of individuals at risk for MEN2A and may give insight to future outreach programs to further expand the reach of testing.

Please follow the link below and complete the archival process for your Project in addition to submitting your final report.

https://ohsu.ca1.qualtrics.com/jfe/form/SV_3ls2z8V0goKiHZP

Student's Signature/Date *(Electronic signatures on this form are acceptable.)*
This report describes work that I conducted in the Scholarly Projects Curriculum or alternative academic program at the OHSU School of Medicine. By typing my signature below, I attest to its authenticity and originality and agree to submit it to the Archive.

X _____

Student's full name

Mentor's Approval *(Signature/date)*

X _____

Mentor Name

Scholarly Project Final Report

Report*: Information in the report should be consistent with the poster, but could include additional material. Insert text in the following sections targeting 1500-3000 words overall; include key figures and tables. Use Calibri 11-point font, single spaced and 1-inch margin; follow JAMA style conventions as detailed in the full instructions.*

Introduction *(≥250 words)*

Multiple endocrine neoplasia (MEN) is a rare genetic condition that predisposes patients to developing endocrine tumors. The condition is autosomal dominant and is associated with several germline RET mutations including Cys618Ser [Moline et al, 2019]. Virtually all patients with the untreated 2A variant of this condition (MEN2A) will develop medullary thyroid carcinoma (MTC), a malignancy with an estimated 5-year survival of 68-80% [Safioleas et al, 2006]. The peak incidence of MTC in this population is in the third decade of life, which is why current guidelines from the American Thyroid Association recommend prophylactic thyroidectomy at a young age [Wells et al, 2015]. In patients with the Cys618Ser mutation, 1223% were found to have pheochromocytomas, and 2-12% developed hyperparathyroidism during their lifetime. For this reason, it is suggested that these patients begin screening for these conditions beginning at age 20 [Moline et al, 2019].

Through treatment of MTC and subsequent genetic testing, several patients from a Mexican immigrant population in Prineville Oregon were found to have the Cys618Ser mutation. The population mainly immigrated from the region of Michoacan, and it was determined that this population likely had a significantly increased instance of MEN2A. While some efforts had been made to create a genetic history to identify susceptible family members, cultural and linguistic barriers were limiting factors in offering testing to at-risk individuals. With the consequences of malignancy in untreated persons at a young age, further work to construct a more extensive pedigree would help to identify individuals who could benefit from genetic testing and subsequent prophylactic treatment.

Methods *(≥250 words)*

This study focuses on identifying existing patients with MEN2A and MTC via chart review to determine if they have the Cys618Ser mutation. The chart review was conducted using search functions in electronic health records system to find patients who had the diagnosis of multiple endocrine neoplasia or MTC. The results of these reports were then reviewed for either documentation of genetic testing. Additional charts were identified using the information on familial relationships listed in the patient contact portions of the health records.

In addition to health records, the initial start of the genetic pedigree was assisted from a series of smaller notes and pedigrees (many handwritten) that had been gathered from visits with other providers. While these pedigrees only included at most three generations identifying immediate family members, these documents alluded to several other relatives that may also be at risk.

Once patients with the Cys618Ser mutation were identified and the initial pedigrees organized, a list of at-risk individuals was created. The criteria for determining at-risk relatives was created, with the necessary data collected from chart review and phone interview with patients and family members. Criteria for being considered "at-risk" required the untested relative to have a parent or sibling with at least one of the following attributes: confirmed Cys618Ser mutation via genetic testing, known medullary thyroid cancer or other endocrine tumor, death from unknown malignancy, or have a parent or sibling who was also determined to be at-risk. After being determined as at-risk, further research was done to determine if the individual had been tested, and whether the results of the test were positive or negative Untested individuals

in the at-risk group were identified separately, and excluded from if they were found to have a parent or grandparent from the at-risk lineage who was confirmed negative for the Cys618Ser mutation via genetic testing. The resulting data was compiled into a master pedigree linking together all at-risk individuals.

Results *(≥500 words)*

Using the combination of chart review and patient or family genetic interviews discussed above, 125 family members were included for further analysis. These individuals came from three large families and were traced back across four generations. These three families were linked together by common cousins in the first generation. Breaking the at-risk persons down by generation, 10 (8.0%) were from the first generation, 32 (25.6%) were from the second generation, 77 (61.6%) were from the third generation, and 6 (4.8%) were from the fourth generation. 11 (8.8%) of these individuals were identified via chart review, while the remaining 114 (91.2%) were discovered via genetic interviews with family members.

Of the at-risk family members identified, 70 (56.0%) were untested. 33 (26.4%) of the total at-risk group were found to be positive for MEN2A either by genetic testing or because one of their offspring tested positive for inheriting the Cys618Ser mutation, and 18 (14.4%) tested negative for the mutation. 7 (5.6%) were determined to have malignancy-related deaths; however, it was unclear how many of them were due to medullary thyroid cancer given that most of them occurred in the first and second generation where testing was minimal. Nearly half of those with confirmed MEN2A (16, 48.5%) were also diagnosed with medullary thyroid carcinoma.

The construction of the pedigree also allowed for each generation to be evaluated separately. In the first generation, 6 (60.0%) of the relatives were confirmed as positive for MEN2A, 0 tested negative, and 4 (40.0%) were untested. Within this group, there was 1 cancer related death, however it was unclear what the malignancy was.

Within the second generation, 14 (43.8%) of relatives were confirmed positive for MEN2A, while 5 (15.6%) tested negative and 11(34.4%) were untested. Within this generation, there were 4 cases of medullary thyroid cancer.

In the third generation, 14 (18.2%) of relatives were positive for MEN2A, 13 (16.9%) tested negative and 51(66.2%) were untested. There were 9 documented cases of medullary thyroid cancer in the third generation.

In the fourth generation, the 2 tested relatives were positive for MEN2A (33.3%) and 4 (66.7%) remain untested. There have not been any confirmed negative cases in this generation.

The majority of the interview data was collected from a limited number of individuals (about 5 family members). This was because most of the people who were contacted either did not answer their phone or declined to participate in the genetic interview. While this data reflects the known at-risk individuals identified by the outreach program, each individual interviewed acknowledged that there were likely several other relatives that they had either lost contact with or had never met who was also likely at risk. Outreach to clinics and public health networks in the Prineville area were contacted to see if more persons could be identified, however given that most of the data collection was performed during the COVID19 pandemic, the institutions did not have the resources available to provide further assistance. Moreover, interviews were limited to phone conversations to limit person-to-person contact during this time.

Scholarly Project Final Report

Discussion *(≥500 words)*

The autosomal dominant nature of Multiple Endocrine Neoplasia Type 2A makes genetic interviewing important for identifying familial cases. Statistically, half of the individuals born to a parent with MEN2A have a 50% chance of inheriting the same mutation. Based on the data collected during this study, there are almost certainly many individuals with undiagnosed MEN2A in the at-risk untested group. Over half of the total persons included in this study have not been tested, ands with the total number of confirmed positive cases in this group at 26.4%, it can be estimated that only about half of the mutations within the identified at-risk group have been found. Given that virtually all individuals with MEN2A go on to develop medullary thyroid cancer if untreated, this represents a significant number of malignancies that can be prevented.

Looking further into the dataset, the majority of untested individuals reside in the third and fourth generations. This in large part is because most of the family members who participated in interviews were from these generations. Based on these interviews, it is estimated that the majority of persons in the second generation are over the age of 40 and that most of the third generation are in their 20s and 30s. With the highest prevalence of MTC discovered in the third decade of life, the third generation is at especially high risk for developing this malignancy if prophylactic treatment is not initiated.

There are several challenging factors that make outreach to the at-risk population more difficult. While this study primarily focused on families living in Prineville, several of their relatives were noted to be living elsewhere. Of the untested individuals, 26 of them are currently residing in Mexico, 6 are in California, 4 are in Texas, and 2 are in other regions of Oregon. There are also 23 untested relatives that the interviewees were not in contact with and could not provide a location. Another difficulty is the high rates of distrust of the United States healthcare system. The majority of the relatives who were reached by phone declined to participate in an interview, with several hanging up abruptly when asked. Almost all of the individuals who were interviewed acknowledged this distrust, as they had repeatedly tried to convince several of the untested individuals to pursue genetic testing. The limitations of only conducting phone interviews during the COVID19 pandemic further exacerbated these concerns and made it very difficult to develop rapport with many individuals.

While the current genetic pedigree provides many starting points for initiating further outreach, it is by no means comprehensive. There are several gaps of information that could not be filled by interviewees, and the limited number of participants and records returned by the chart review made it difficult to verify the testing status of several individuals. While the large number of people in need of testing may seem daunting at first, taking a top-down approach to genetic testing can significantly reduce the amount of total testing needed. If a parent is determined to not have the Cys618Ser mutation, that would remove all subsequent relatives from the at-risk pool.

Conclusions *(2-3 summary sentences)*

In conducting chart review and family interviews, 125 individuals were identified as having a parent or sibling with multiple endocrine neoplasia type 2A. Within this group, 77 were untested and susceptible to MEN2A related conditions including medullary thyroid carcinoma. While there were several cultural and logistical barriers to constructing a comprehensive pedigree of individuals requiring MEN2A testing, the data collected presents many opportunities for future initiatives to offer genetic testing of at-risk individuals in the Prineville immigrant population and several others from Michoacan, Mexico.

Scholarly Project Final Report

References *(JAMA style format)*

1. Moline J, Eng C. Multiple endocrine neoplasia type 2: an overview. *Genet Med*. 2011;13(9):755-764.
2. Safioleas M, Stamatakos M, Karampali E, Rompoti N, Mouzopoulos G, Lygidakis N. Diagnostic and therapeutic aspects in medullary thyroid carcinoma. *Chirurgia (Bucur)*. 2006;101(2):121-126.
3. Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid*. 2015;25(6):567-610.