FUNDING YOUR RESEARCH: K AND EARLY CAREER GRANTS

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AAS Early Career Development Course

San Francisco, CA

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AAS
Association for Academic Surgery

CONFLICT OF INTEREST

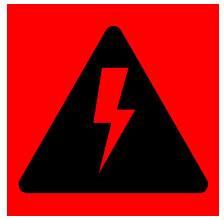
No disclosures

MY STORY….

K07 first submission

	Reviewers		
Candidate	2	1	1
Career Development	1	2	3
Research Plan	4	7	4
Mentors	3	2	2
Institution	1	1	1

TRIAGE



K07 Resubmission

	Reviewers		
Candidate	1	1	2
Career Development	3	2	1
Research Plan	4	3	4
Mentors	2	2	3
Institution	1	1	1

Two years

Five years

1.

DO THE GROUND WORK

PLAN AHEAD

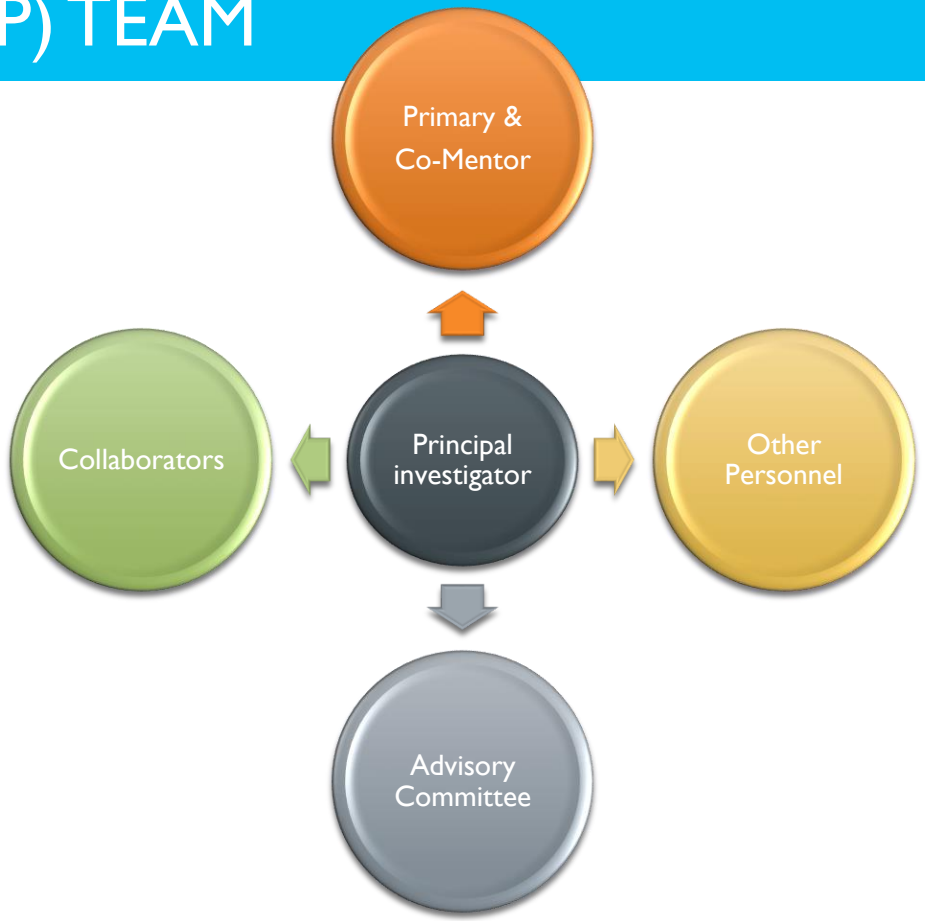
- Make sure you have institutional support
- Take your time
  - Schedule (a lot) of protected time
  - Plan on at least three months for a K
- Ask for help early and often
  - Seek out mock grant review
  - People NOT in your field of expertise (the reviewers won't be)

WRITING IS A SPORT

- Schedule practice time
- If you aren’t writing a paper, you should be writing a grant
- If you are waiting for grant to be scored, write another
- Writing is a skill that needs to be practiced

BUILD A STRONG (MENTORSHIP) TEAM

- Senior, but relevant
- Know your weaknesses and fill in gaps
- Specify meeting times
- Involve them in grant writing process from start



DO….

- Read successful grants
- Listen to failures
- Ask for feedback
- Volunteer to give a talk on the topic
- AAS/SOC/SUS work in progress sessions

2.

BELIEVE IN IT

PICK A TOPIC YOU* ARE PASSIONATE ABOUT

- Time and funds are precious
- If you don’t believe in your work, no one will
- This is the foundation for your research program
- Reviewers want to know how you will advance the science

** And others*

IF YOU DON'T KNOW….

- Read guidelines in your field for areas for future research
- NIH Reporter
- Meet with anyone you can
- Read high impact journals outside of surgery
- Consider new methodology

3.

SELL THE WORK

KNOW YOUR AUDIENCE

- Look up your study section's meeting roster
- Most reviewers will NOT be familiar with your area of clinical expertise
- Be in contact with your program officer – they are your advocate
- Read NIH news releases

READ (AND FOLLOW) INSTRUCTIONS

- Think like a reviewer
  - Make it the grant you choose to read first
  - White space, pictures (1/pg), large font, simple
- Use formatting for clarity
  - Be simple and clear – tell a story
  - State why the project is important (critical need), how you are going to do it, and then restate the impact

SPEND MOST OF YOUR TIME ON THE SPEC AIMS

- This is the only page most of the reviewers will read
- It is never finished
- 75% of time
- Make is easy to read
  - “My overarching goal is…”.
  - “I will test these hypothesis by completing the following specific aims…”

BODY

- Overall goal
- Background
- Unmet need
  - Preliminary data
- General approach
- Hypotheses
- Deliverables

AIMS

- Broad and clear aims (usually 3)
- +/- Subaims (not methods)
- Corresponding specific hypothesis

IMPACT

- State why the research is a critical need
- Tell them you have the team and resources to do it

Thyroid Nodule Treatment Optimization: A Personalized Approach

Specific Aims

The goal of this research is to optimize the care of patients with thyroid nodules and reduce thyroid cancer morbidity (TC). Specifically, we will develop and use a microsimulation model to examine the potential impact of emerging diagnostic technologies and personalized surveillance strategies on meaningful patient outcomes, and to identify patient management approaches that improve clinical outcomes, reduce costs, or both.

The incidence of TC has increased more than 300% over the past four decades, and US prevalence exceeds 700,000 patients.[5] Related healthcare costs are projected to double to over $3 billion in the next decade.[6] The majority of newer cancers are small, indolent papillary thyroid carcinomas (PTC) that are not associated with significant effects on patient survival.[7,8] The concern for over-treatment has led to less aggressive management approaches including active surveillance in patients with papillary microcarcinomas (PTmC).[9-11] However, recent evidence shows that there is also an increasing incidence and mortality of advanced TC.[12] There is thus a critical need to identify personalized approaches, which harness emerging molecular technologies and risk-stratified surveillance strategies, in order to optimally treat patients with aggressive disease while minimizing harm and costs associated with overtreatment of those with indolent disease.

Previous research studying PTC from national databases does not consider co-existing benign thyroid nodular disease (6-8x more common than cancer) and other thyroid cancer subtypes when evaluating appropriateness of care, outcomes, and cost. Moreover, conducting clinical trials in this population is prohibitively time-consuming and costly. A mathematical disease simulation model of benign and malignant thyroid nodules that incorporates tumor subtypes and other patient factors can provide a comprehensive framework to evaluate the management of both indolent and aggressive tumor subtypes and inform changes in clinical paradigms.

The proposal will address the following critical issues: 1) there is minimal reported risk in observing a PTmC, yet missing small aggressive medullary thyroid cancers by increasing biopsy size thresholds may delay identification of localized disease and may thus impact survival in this population;[13] 2) while widely used, the impact and utility of costly molecular diagnostic tests on long-term outcomes are unknown; 3) the effects on patient outcomes of performing lobectomy versus total thyroidectomy of PTC up to 4 cm and what constitutes appropriate frequency and duration of surveillance are unknown;[11] and 4) the use of predictive biomarkers such as *BRAF* to guide extent of treatment and frequency of surveillance may be a cost-effective approach.[14,15]

Dr. Lubitz is an early stage investigator (ESI) and leader of a multidisciplinary research team that is comprised of decision scientists, statisticians, and clinical experts who care for patients with thyroid disease. The proposed research plan will build upon prior work by her research team, including: the development of a mathematical model that simulates the pre-clinical course of both benign thyroid nodules and PTC[16], a prospective study of the health-related quality of life (HRQoL) in patients undergoing surgery for PTC[17], and an evaluation of the true prevalence and costs associated with benign nodules compared to cancers using claims data. Our overarching hypothesis is that personalized strategies that incorporate individual patient risk-stratification will improve outcomes while minimizing the mortality and morbidity of missed aggressive disease and overtreatment of indolent disease. We will test this hypothesis with the following **specific aims**:

Aim 1: Create a natural history simulation model of benign and malignant thyroid nodules
- 1.1 Utilize SEER cancer registry data and medical claims data to refine model inputs
- 1.2 Calibrate the model to incidence and survival targets in *all* thyroid cancer subtypes

Aim 2: Use the model to assess diagnostic technologies to improve risk stratification
- 2.1 Assess the impact of screening all patients with serum calcitonin levels to identify medullary TC
- 2.2 Evaluate effectiveness of molecular diagnostics versus conventional fine-needle aspiration alone
- 2.3 Evaluate risk-stratified surgical approaches using predictive biomarkers (e.g. *BRAF*)

Aim 3: Determine optimal surveillance strategies for the management of thyroid nodules
- 3.1 Compare cost-effectiveness of revised surveillance strategies to prior guidelines
- 3.2 Determine the impact of varying utility (HRQoL) and risk-stratified surveillance strategies
- 3.3 Estimate the value of additional research to resolve uncertainty in current data

Successful completion of this proposal will identify optimal risk-stratified clinical approaches that are tailored to individual patients, prioritize areas for further research, and, ultimately, improve quality of care. An interactive on-line version of the model will allow stakeholders to visualize the implementation of the model.

MAKE YOUR GOALS REASONABLE

- Reviewers have all been there – you need to convince them you will do what you say you will
- Make sure timeline and budget make sense

Specific Aims		Year 1		Year 2		Year 3		Year 4		Year 5	
Aim 1	**Develop natural history model of PTC**										
1.1	Model construction										
1.2	Model calibration										
Aim 2	**Conduct studies to inform key model parameters**										
2.1	Develop and validate a prediction algorithm for recurrence of PTC										
2.2	Assess the HRQoL of patients										
Aim 3	**Compare effects of standard versus alternate management strategies**										
3.1	Evaluate the impact of standard treatment on natural history of PTC										
3.2	Assess magnitude of over-diagnosis and over-treatment										
3.3	Investigate the value of risk-tailored approaches.										
	Manuscript preparation										
	R01 preparation and submission										

PROVE YOUR SUPPORT

- Submit biosketches and/or letters of support for all members of team (unless explicitly told not to)
- Use letters from collaborators to verify access to datasets/support
- Institutional support and personal productivity vary

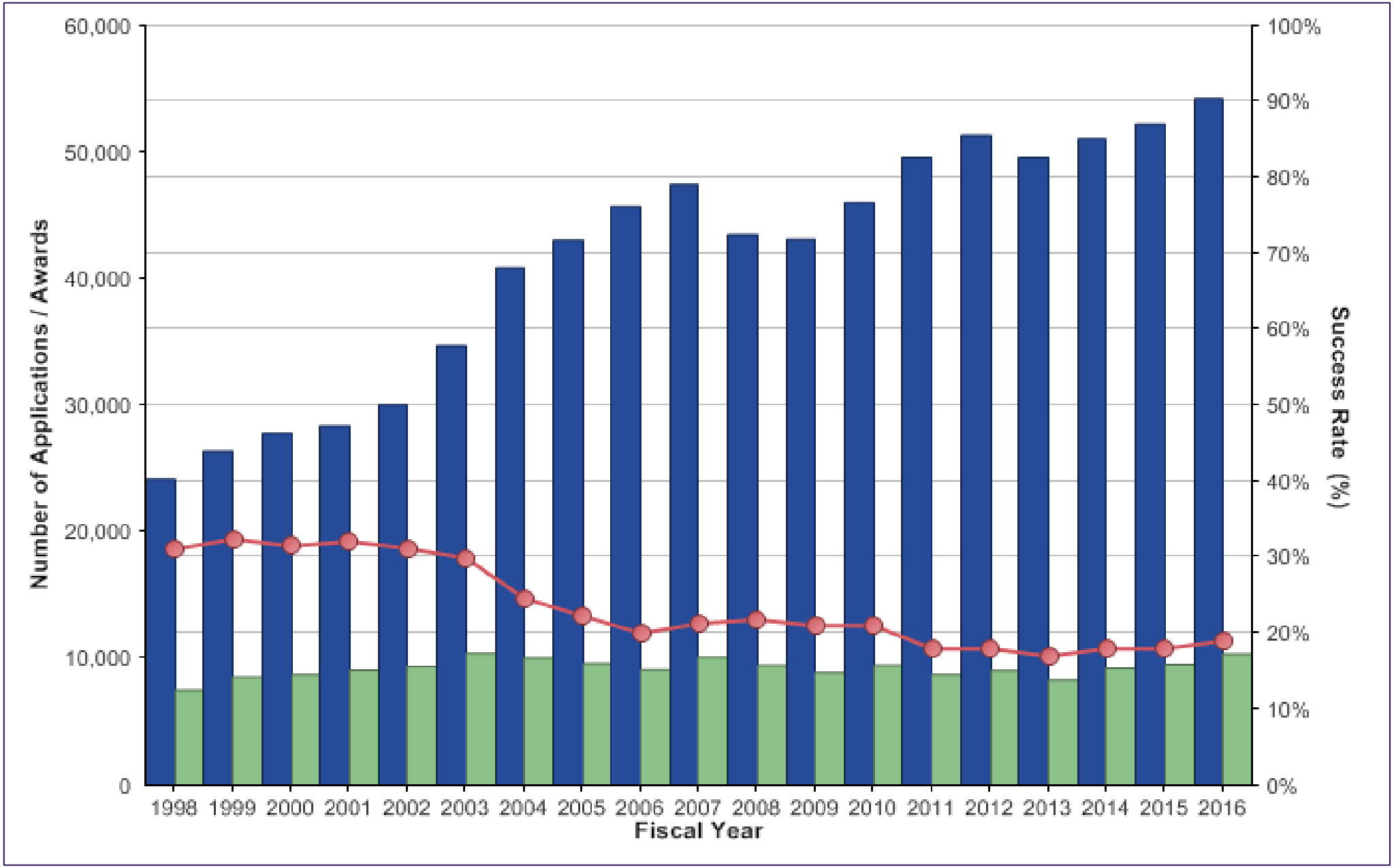
CAREER DEVELOPMENT SECTION

- Prove to the reviewers that you have the time and support
- Specific coursework, conferences, % clinical activities, teaching

Table 2. Planned didactic courses to be completed during K07 award period				
Harvard School of Public Health/Harvard University	***Complementary Aims***	***Expected Date***	***Audit/Credit***	***Credit hours***
RDS285 - Decision Analysis Methods - Focuses on Markov modeling and microsimulation approaches	1,3	Year 1	Credit	2.5
HPM299 - Research with Large Databases	1,3	Year 1	Audit	2.5
BIO226 - Applied Longitudinal Analysis - Includes analysis of repeated measures & incomplete data	1-3	Year 2	Credit	2.5
BIO234 - Meta-Analysis in Public Health and Medicine	1,3	Year 2	Credit	2.5
EPI289 - Models for Causal Inference - Methods for estimating causal effects and biases	1-3	Year 3	Audit	2.5
HPM530 - Measuring Health Outcomes - Concepts & methods in HRQoL for CER	2	Year 3	Audit	2.5
Harvard Catalyst / MGH Clinical Research Program				
REDCAP Advance Programming Training	2	Year 2	N/A	–
Using MGH Clinical Care Data for Clinical Effectiveness Research	1,3	Year 3	N/A	–
Grant Review and Support Program (GRASP)	K07→R01	Years 1-5	N/A	–
Total				**15**

4.

DON’T GIVE UP



https://nexus.od.nih.gov/all/2017/02/03/fy2016-by-the-numbers/

Ambition is the path to success.
Persistence is the vehicle you arrive in.

-- Bill Bradley

Nothing in this world can take the place of persistence. Talent will not. Nothing is more common than unsuccessful [wo]men with talent. Genius will not. Unrewarded genius is almost a proverb. Education will not. The world is full of educated derelicts. Persistence and determination alone are omnipotent.

-- Calvin Coolidge

READ (AND FOLLOW) INSTRUCTIONS

- Resubmissions - answer each and every criticism

RESUME AND SUMMARY OF DISCUSSION: This revised application for a K07 Career Development Award from Dr. Carrie Lubitz, Assistant Professor at Massachusetts General Hospital/Harvard Medical School, focused on papillary thyroid cancer. Dr. Lubitz is an outstanding candidate and she seeks this award to support additional training in decision science, Markov modeling, and data analysis and to develop a natural history model of papillary thyroid cancer. Her mentoring team is very strong as is the environment and institutional commitment. The career development plan is clearly written and integrated with the study aims. The proposed research fills an important knowledge gap and the analytic plan is improved from the previous submission. However, several issues raised in the prior review have not been fully clarified and there are still numerous weaknesses in the research plan.

Introduction to the Revised Application

Based on the summary of the discussion of our proposal "Thyroid Nodule Treatment Optimization: A Personalized Approach", the reviewers noted several areas of strength including a "strong investigative team" and that the research and approach had significant potential to impact clinical practice. The reviewers also noted several ways to improve our proposal: broadening the team's effort and expertise; opportunities to improve innovation; assure quality of data sources; and a need to enhance our dissemination strategy. In response, we have made substantial revisions that have significantly strengthened the current proposal. We have marked changes in the proposal with a vertical line in the left margin and summarized by theme below.

Increased team effort and principal Investigator experience: Two reviewers recommended increased effort and depth of expertise to the team. Since the last submission, the PI published a second microsimulation project.[1] Efforts of several co-investigators have been increased (Research Plan (C1) and Budget Justification): Co-I J. Chhatwal, PhD will now commit 20% effort to the project. He has extensive microsimulation experience and specific expertise in model efficiency and value of information (VOI) analysis. Co-I G.S. Gazelle, MD, MPH, PhD will increase his effort to 10%. He has extensive experience developing cancer screening models and disseminating the findings to inform policy. Dr. Mercaldo (Biostatistician) will commit 5% effort and provide guidance on joint distributions, valid aggregation of data sources, and adjustment for verification bias for input data and calibration targets, as well as providing overall statistical support for the project.

Enhanced innovation and model dissemination: The reviewers cited the use of established modeling approaches and opportunities to incorporate innovative methodology. We have strengthened the proposal by adding additional data sources (see below) and including more aggressive thyroid cancer subtypes (e.g. medullary thyroid carcinoma). We added value of information analysis (new Aim 3.3), used by AHRQ, NIH, PCORI and others to establish research priorities, to systematically prioritize which specific areas of model input uncertainty would benefit from future research. While we propose to use established (and state of the art) methods for model development and calibration, we believe that we are among the first groups to apply this approach to key questions in the treatment of this large population of patients with thyroid nodular disease. The time and cost of clinical trials in this population would be prohibitive. Lastly, in the revised dissemination plan, we will build an interactive publicly available on-line version of the model that will allow stakeholders to visualize the implementation of the model in real-time.

Added contemporaneous patient-level datasets: In the current proposal, we added SEER-Medicare and MarketScan claims data sources. These datasets will provide real-world cost, utilization, and outcomes data from a nationally representative population of patients. In addition to improving the sample size (and therefore precision), these datasets will provide granular data that can be utilized to generate joint distributions for calibration targets. Given that the most common form of thyroid cancer may take many years to recur and data are missing and/or incomplete from national databases, long-term observational studies are additional critical datasets for specific calibration targets missing from registry data (i.e. tumor recurrence) in this population. As recommended, results of a primary validation of the text pattern recognition methodology used for RPDR clinical reports are now included (Aim 1, Limitation and Solutions).

Assess and adjust for verification bias: Regarding the accuracy of molecular diagnostic testing (Aim 2), we use only studies that have surgical pathologic verification as these data provide accurate assessments of false-positive rates (i.e. those patients that are called "suspicious" on molecular testing but prove to have benign tumors). True false-negative results, however, are not ascertainable (i.e. would be unethical in the context of a "benign" molecular test and no other indication for surgery), and thus there is the potential for verification bias. We have added a systematic analysis using established statistical methods to adjust for this bias.[2-4] We will assess the uncertainty around the false-negative rate of the molecular platforms with sensitivity analyses and VOI as above. We agree with the reviewers that quantifying the consequences of misdiagnoses including surgical complications and health-related quality of life are critical to this analysis and will be included.

Obtained primary data for health-related quality life inputs: Reviewer 2 noted the importance of direct measurement of utilities in this population. We will use emerging short and long-term employable primary survey data (Short Form-12v2 and SF-36v2®) from patients undergoing treatment and/or surveillance for thyroid cancer from multiple collaborators (Drs. Lundgren, Roman, and Sippel, see Letters of Support) in addition to our primary data (Preliminary Data). Development of a thyroid-specific index is the subject of related project development.

DIVERSIFY

- Apply to different grant mechanisms
  - Federal: VA/NIH alphabet soup (R, K, U, P)
  - Society awards
  - Institutional/departmental awards
  - Industry
- Diversify the aims
- Think outside the box
- Grants beget grants

RESOURCES

The best-kept secrets to winning grants

With competition for research funding approaching an all-time high, experts reveal their top tips and tricks.

BY KENDALL POWELL

An aesthesiologist and clinical researcher Peter Nagele started his first independent position in good shape. It was 2007 and he had already earned two early career grants for his laboratory at Washington University in St Louis, Missouri. But when he applied for his first major research grants from the US National Institutes of Health (NIH) he got two crushing rejections.

Nagele had made some rookie mistakes: one proposal, for a 10,000-patient clinical trial, was too large in scope to be eligible, and the other was not a priority research area for the agency. "Those projects never saw the light of day," he says, "and rightfully so."

By his third attempt he had learnt some invaluable tips and tricks. He got feedback from colleagues on his draft proposal, he talked to a grants programme officer at the NIH to work out the best strategy, and he added experienced co-investigators to his proposal.

In 2015, his homework paid off. His application for a smaller clinical trial to look at the use of beta-blockers to prevent post-surgery heart problems was funded for roughly US$500,000 a year. The difference between between failure and success, in his

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https://projectreporter.nih.gov/reporter.cfm

https://www.youtube.com/watch?v=fBDxI6l4dOA&feature=youtu.be (Mock study-section)

https://nexus.od.nih.gov/all/2017/02/03/fy2016-by-the-numbers/

Powell, Nature, May 2017

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