GIANT CELL ARTERITIS:

DIAGNOSTIC PREDICTION MODELS,

TEMPORAL ARTERY BIOPSY AND EPIDEMIOLOGY

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GLOSSARY OF ABBREVIATIONS AND SYMBOLS

ACR – American College of Rheumatology

BPGCA – biopsy-proven giant cell arteritis

BSR – British Society of Rheumatology

c-statistic – concordance statistic, or area under receiver operating characteristic curve

CCA – complete case analysis

CD4 – cluster of differentiation 4; a glycoprotein on the surface of T helper cells

CI – confidence interval

CRP – C-reactive protein

CRP/ULN – C-reactive protein divided by its upper limit of normal

CT – computerized tomography (imaging)

DC – doctoral candidate (thesis author)

DCA – decision curve analysis

DCT – dynamic contour tonometry

ESR – erythrocyte sedimentation rate (Westergren)

EULAR – European League Against Rheumatism

e^ - base of the natural logarithm, Euler's number =2.718281828

FDR – false discovery rate

FNR – False-negative rate

GCA – giant cell arteritis

Headache_new – new onset headache

HLA-DRB1 – Human Leukocyte Antigen – DR isotype class II beta chain

H–L*p* - probability of Hosmer– Lemeshow test

HZ – herpes zoster

ICD – International Classification of Diseases

IL-6 – interleukin 6

IR_{GCA} – incidence rate of giant cell arteritis

IR_{HZ} – incidence rate of herpes zoster

IVHet - fixed-effect inverse variance heterogeneity model

JC – jaw claudication

ln – natural logarithm

log - also refers to the natural logarithm in this thesis (exception: logworth is $\log_{10}$)

LR – logistic regression

MCR – misclassification rate

MDA – missing data analysis

MRI – magnetic resonance imaging

n – number of subjects

NLR – negative likelihood ratio

NN – neural network(s)

NN-LR – Neural Network and Logistic Regression model (n=1,201)

NPV – negative predictive value

O&N – ophthalmologist and neurologist survey respondents

OPA – ocular pulse amplitude

O.R. – odds ratio

PD-1 – programmed cell death protein 1

PD-L1 – programmed death-ligand 1

PLR – positive likelihood ratio

PM(s) – prediction model(s)

PPV- positive predictive value

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

pROC = open-source package to compare ROC curves for R and S+

P*t* – threshold probability

Q1, Q2, Q3 – quarter of the journals with the highest, 2nd highest and 3rd highest rankings respectively (SCImago Journal Rank)

R^2 – McFaddens pseudo-R squared for logistic regression

REB – research ethics board

Risk – the probability of an event or outcome

ROC – receiver operating characteristic

SJR – SCImago Journal Rank (higher SJR score indicates greater journal prestige)

P-LR – Primary Logistic Regression model (n=530)

SVM – support vector machines

TA – temporal artery

TAabn – temporal artery abnormality (pulselessness or tenderness)

TABUL – Temporal Artery Biopsy versus ULtrasound study for GCA

TABx – temporal artery biopsy

TanH – hyperbolic tangent function

T-cell – white blood cell (lymphocyte) that originates in the bone marrow and matures in the thymus gland.

Th – T-helper cell or CD4+ cells

TLRs – toll-like receptors

TRIPOD – Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (EQUATOR Network)

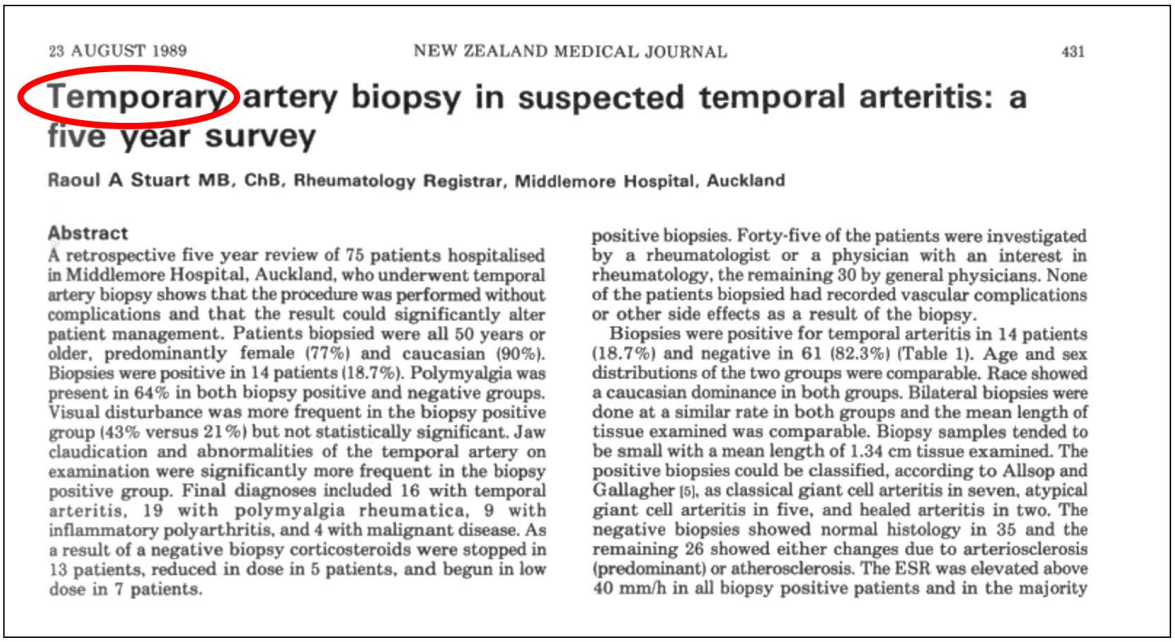
US – ultrasound (Doppler)

VL – vision loss attributable to ischemia

Z815A – billing code for temporal artery biopsy in Ontario, Canada

PREFACE

Figure 1. "Temporary" artery biopsy malapropism



23 AUGUST 1989 NEW ZEALAND MEDICAL JOURNAL 431

Temporary artery biopsy in suspected temporal arteritis: a five year survey

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Abstract

A retrospective five year review of 75 patients hospitalised in Middlemore Hospital, Auckland, who underwent temporal artery biopsy shows that the procedure was performed without complications and that the result could significantly alter patient management. Patients biopsied were all 50 years or older, predominantly female (77%) and caucasian (90%). Biopsies were positive in 14 patients (18.7%). Polymyalgia was present in 64% in both biopsy positive and negative groups. Visual disturbance was more frequent in the biopsy positive group (43% versus 21%) but not statistically significant. Jaw claudication and abnormalities of the temporal artery on examination were significantly more frequent in the biopsy positive group. Final diagnoses included 16 with temporal arteritis, 19 with polymyalgia rheumatica, 9 with inflammatory polyarthritis, and 4 with malignant disease. As a result of a negative biopsy corticosteroids were stopped in 13 patients, reduced in dose in 5 patients, and begun in low dose in 7 patients.

positive biopsies. Forty-five of the patients were investigated by a rheumatologist or a physician with an interest in rheumatology, the remaining 30 by general physicians. None of the patients biopsied had recorded vascular complications or other side effects as a result of the biopsy.

Biopsies were positive for temporal arteritis in 14 patients (18.7%) and negative in 61 (82.3%) (Table 1). Age and sex distributions of the two groups were comparable. Race showed a caucasian dominance in both groups. Bilateral biopsies were done at a similar rate in both groups and the mean length of tissue examined was comparable. Biopsy samples tended to be small with a mean length of 1.34 cm tissue examined. The positive biopsies could be classified, according to Allsop and Gallagher [5], as classical giant cell arteritis in seven, atypical giant cell arteritis in five, and healed arteritis in two. The negative biopsies showed normal histology in 35 and the remaining 26 showed either changes due to arteriosclerosis (predominant) or atherosclerosis. The ESR was elevated above 40 mm/h in all biopsy positive patients and in the majority

The title of this 1989 study from New Zealand (Stuart, 1989) *has a malapropism encircled in red. Instead of "temporal" the title lists "temporary". Paradoxically the malapropism appropriately conveys the desire of patients and clinicians to have a non-invasive but accurate method to confirm the pathologic diagnosis of giant cell arteritis, without leaving a permanent scar.*

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I much appreciate the clinical perspectives of my Canadian rheumatology colleagues Dr Christian Pagnoux and Dr Philip Baer. I acknowledge the invaluable expertise of my statistician colleagues Dr Wanhua Su, Dr Matthias Schonlau and Dr Samuel Wong. I thank Dr James Farmer and Dr Anita Godra for their clinical pathology insight.

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ABSTRACT

Giant cell arteritis (GCA) is the most common primary vasculitis in the elderly and can cause irreversible blindness, aortitis, and stroke. Diagnostic confirmation of GCA usually entails temporal artery biopsy (TABx) – a time-consuming and invasive test, or ultrasound. The primary treatment of GCA is with high dose glucocorticoids that have numerous potential side effects. Glucocorticoids are initiated prior to the TABx result, due to the risk of interim blindness. By 2050 the cost of blindness from GCA in the United States is estimated at $76 billion with an additional $6 billion from glucocorticoid-induced fractures.

This thesis examines knowledge gaps in the **diagnosis and epidemiology of GCA**. Needed refinements in the **diagnosis of GCA** included: i) the optimization of diagnostic prediction models (PMs) and ii) clarification of the contemporary utilization parameters of TABx. With regards to i) previous PMs are usually based on limited sample size, do not leverage sufficient clinical predictors, or include continuous variables, and not compliant with the transparent reporting guidelines for diagnostic PMs (TRIPOD). Using multicentre data of consecutive patients undergoing TABx, the largest (n=1,201) and most comprehensive logistic regression and, neural network PMs for GCA were formulated. Age, platelet level, jaw claudication and vision loss eventuated as the key predictor variables. An online risk calculator was developed from the PM and could decrease both the number of TABx performed on low-risk patients, and the morbidity from unneeded glucocorticoids. Regarding ii) although TABx has long been acknowledged as the gold standard test for GCA the current preference for TABx versus ultrasound amongst neuro-ophthalmologists and the utility rate of TABx are unknown. The thesis survey revealed that 91% of neuro-ophthalmologists preferred TABx over ultrasound as the confirmatory test for GCA. The first systematic review for the utility rate of TABx disclosed a median positive yield of 25% and provides a benchmark for institutions performing this procedure.

Knowledge gaps in the **epidemiology of GCA** important for public health planning included the incidence of GCA in Ontario, Canada, and the controversial role of herpes zoster in the development of GCA given the advent of zoster vaccines. Pathology audit and an assay of billing data revealed the incidence of biopsy-proven GCA in Ontario to be 4.9 per 100,000 individuals 50 years of age or older. On ecologic analysis, the inverse relationship

of the incidence rates of herpes zoster versus GCA per country suggested zoster is not a major immunopathogenic trigger for GCA.

In summary, this thesis advances the diagnosis and epidemiology of GCA, most notably in the area of clinical prediction models that aid in the triage of patients with suspected GCA.

Chapter 1. INTRODUCTION

Giant cell arteritis (GCA) is the most common primary vasculitis in adults. This autoimmune inflammation of the arteries can cause ischemia from luminal stenosis, with the potential for irreversible blindness, aortitis, myocardial infarction, stroke and occasionally death. It is a disease of immunosenescence that almost always occurs after the age of 50 years. GCA is a prime emergency in ophthalmology (Torun and Ing, 2008; Danesh-Meyer, 2012; Waldman, Waldman and Waldman, 2013) and by the year 2050, the projected cost of GCA from visual impairment in the United States alone is estimated to be US$76 billion, with an additional $US6 billion from glucocorticoid-induced fractures (De Smit, Palmer and Hewitt, 2015).

The thesis publications focus on the diagnosis and epidemiology of GCA. Knowledge gaps in the diagnosis of GCA were suboptimal diagnostic prediction models (PMs) and the contemporary utilization parameters of temporal artery biopsy (TABx) - the traditional "gold standard" confirmatory test for GCA. Prior PMs were undersized, did not leverage 10 clinical predictors or include continuous variables, (Cumberland *et al.*, 2014), and were noncompliant with the rigour of guidelines for the transparent reporting of multivariable prediction models for individual diagnosis (TRIPOD) (Collins *et al.*, 2015). Although TABx has long been acknowledged as the reference standard confirmatory test for GCA, the positive yield of TABx in pathology series and the current work-up preference of TABx versus Doppler ultrasound amongst neuro-ophthalmologists were unknown. GCA can be difficult to identify, and two conditions that mimic or overlap with GCA are also briefly discussed in the diagnosis section.

Salient topics in the epidemiology of GCA important for public health planning, were the incidence of GCA in Ontario, Canada, and the contentious role of herpes zoster in the development of GCA. The province of Ontario houses one-third of Canada's population, but the incidence of GCA in this locale had not been previously researched. To determine if there was a biologic gradient between herpes zoster and GCA, a novel ecologic analysis was performed comparing the published incidence rates of zoster versus GCA from different countries. The relationship between zoster and GCA is important to clarify especially given the advent of the zoster vaccines. The coherence of the publications on the diagnosis and epidemiology of GCA is illustrated in Figure 3.

1.1 The Immunology and Pathology of GCA

This thesis does not investigate the complex immunopathology of GCA, but the same is reviewed to provide context on this critical field of study. Immune checkpoints are molecules on immune cells that need to be activated or inactivated to start an immune response. Inefficiency of the PD-1 / PD-L1 (programmed cell death protein 1 / programmed death-ligand 1) immune checkpoint has been recently described in GCA, and implicated in other eye diseases including uveal melanoma and uveitis (Wang *et al.*, 2019). Programmed cell death protein 1 (PD-1) is a co-inhibitory receptor expressed on T-cells and delivers negative signals when engaged by its immunoinhibitory ligand PD-L1 which is located in the vascular dendritic cell. After binding with PD-L1, PD-1 normally acts like an "off-switch" and restrains T-cells from attacking. With GCA the vascular dendritic cells have a low expression of PD-L1 and the tissue-invading T-cells are unrestrained.

Vascular dendritic cells are the immune sentinels of the blood vessel and reside at the junction of the outer and middle layer of the blood vessel (adventitia-media border). In GCA, the dendritic cells become activated by an unknown trigger(s) possibly via toll-like receptors[1] (transmembrane pattern-recognition receptors on the dendritic cell that sense pathogens or signals of endogenous damage) resulting in the production of cytokines and chemokines (signalling proteins that attract white blood cells) (Weyand, Liao and Goronzy, 2012; Terrades-Garcia and Cid, 2018). Failure of the activated vascular dendritic cells to express the immunoinhibitory ligand PD-L1 within an aged arterial wall leaves the PD-1 positive CD4 T-cells insufficiently suppressed that in turn contribute to macrophage activation and further excessive production of pro-inflammatory cytokines. The latter polarize the CD4 T cells toward T-helper 1 (Th1) and T-helper 17 (Th17) differentiation. Th1 cells produce interferon-gamma, a potent activator of macrophages that can damage the vessel wall. The interleukin 6 (IL-6) cytokine is a pivotal driver for the polarization of CD4 T cells toward the Th17 phenotype that in turn produce interleukin-17 which is involved in the development of the systemic inflammatory symptoms of GCA. Glucocorticoids and tocilizumab can decrease the activation of Th17 cells, and thereby the production of IL17, but do not alter the Th1 pathway. (Mohan *et al.*, 2011; Weyand, Berry and Goronzy, 2018)

[1] Toll-like receptors (TLRs) are a key player in the innate immune system. The designation TLRs is due its resemblance to a protein from the *Drosophila* toll gene.

Histologic specimens to test for the diagnosis of GCA usually are obtained from the temporal artery. The pathology of GCA characteristically shows granulomatous inflammation in the arterial wall with histiocytes (activated macrophages), epithelioid cells (epithelioid histiocytes) and/or abnormally large multinucleated epithelioid cells with the appellation of "giant cells". Although atherosclerosis may also show intimal thickening, typical GCA displays active mural inflammation.[2]

1.2 GCA: Clinical Background

The diagnosis of GCA can be difficult and often is delayed because GCA can present in a protean fashion, with non-specific symptoms, (Prior *et al.*, 2017) and has no highly-specific serologic biomarker (De Smit *et al.*, 2016). There are three main subtypes of GCA that can phenotypically overlap: 1) cranial arteritis with propensity for vision loss and cerebral ischemia; 2) large vessel vasculitis (aortic arch syndrome, aortitis); and 3) polymyalgia rheumatica. (Dejaco *et al.*, 2017) The symptoms and signs of GCA can mimic other diseases such as infection, malignancy, amyloidosis (Ing *et al.*, 1997), or other vasculitides (Ong Tone, Godra and Ing, 2013), sinusitis, idiopathic orbital inflammatory syndrome (Islam *et al.*, 2003), dental or temporo-mandibular conditions, non-arteritic ischemic optic neuropathy, and atherosclerotic disease.

Medical students and physicians are taught universally to suspect GCA in any older patient who develops headache, vision loss or diplopia. Notwithstanding, some GCA patients still develop vision loss from undiagnosed ocular ischemia, especially if the disease presents in an occult (Hayreh, Podhajsky and Zimmerman, 1998)(Husain *et al.*, 2008) or atypical manner. Occasionally, despite the expedient diagnosis and immediate treatment with maximal intravenous steroids patients with cranial GCA may succumb to progressive, *irreversible* ischemic blindness from GCA that can sequentially *involve both eyes*, or rarely be bilateral (Loddenkemper *et al.*, 2007).

At the start of the period during which this thesis was undertaken, the main guidance to assist in the identification of GCA was the 1990 American College of Rheumatology (ACR)

[2] See section 4.1.1 page 55 for a discussion on the pathology of healed arteritis.

classification criteria.[3] (Hunder *et al.*, 1990) However, the ACR classification criteria were developed for research purposes to differentiate GCA from patients with other forms of vasculitis, rather than for the diagnosis of individual patients who might have other non-vasculitic diseases that mimic the presentation of GCA (Hunder, 1998). The ACR criteria misidentify many ophthalmic cases of GCA with 26% false negatives and 28% false positives. (Murchison *et al.*, 2012).

According to the Swedish Society of Rheumatology 2018 guidelines (Turesson *et al.*, 2019) and other authorities,(Danesh-Meyer, 2012; Ness *et al.*, 2013; Banerjee, Petrou and Plant, 2014; Weyand and Goronzy, 2014; Frohman *et al.*, 2016; Koster and Warrington, 2017) temporal artery biopsy (TABx) remains the "gold" standard confirmatory test for GCA. However, TABx is an invasive, somewhat time-consuming test that can be difficult to obtain in a prompt fashion at some centres. Complications of TABx are uncommon, but include hematoma, wound dehiscence, scarring, infection and rarely facial nerve palsy, scalp necrosis, and very rarely cerebral ischemia if the temporal artery is a critical collateral to the brain circulation. The sensitivity of TABx is between 77% (Rubenstein *et al.*, 2019) and 87%, (Niederkohr and Levin, 2007) but there may be false negatives when the vasculitis is segmental and the specimen does not sample an affected area. The permanent section pathology result from TABx usually requires days or even a week to obtain. Given the above, the European League Against Rheumatism guidelines (Dejaco *et al.*, 2018) suggest ultrasound and high-resolution MRI as an alternative to TABx at centres with sufficient expertise in conducting these studies.

Unfortunately, there is no consensus on the sensitivity of ultrasound for GCA. One meta-analysis of ultrasound for clinically diagnosed GCA suggests a sensitivity of 77% (95% CI: 62%-87%) (Duftner *et al.*, 2018), but a larger meta-analysis from the same time period found the sensitivity was 68% (95% CI: 57%-78%) (Rinagel *et al.*, 2019). The sensitivity of MRI for GCA may be 73% (95% CI: 57-85%) (Duftner *et al.*, 2018). In comparison the sensitivity of TABx for GCA varies from 77% (95% CI: 72%-82%) on meta-analysis (Rubenstein *et al.*, 2019) to 87% (95% CI: 82%-92%) on Bayesian analysis (Niederkohr and Levin, 2007).

The mainstay treatment for GCA is prolonged glucocorticoids which have many potential side effects including glucocorticoid-induced fractures, bone loss, diabetes mellitus,

[3] The 1990 ACR classification criteria for GCA are: age >=50 years of age, new onset localized headache, temporal artery tenderness to palpation or decreased pulsation, erythrocyte sedimentation rate >=50 mm/hour, and positive temporal artery biopsy.

pneumonia, cataract, glaucoma, (Broder *et al.,* 2016) hypertension and peptic ulcers. Due to the risk of vision loss, if GCA is suspected, steroids are initiated prophylactically prior to TABx. Adjunctive treatment with the IL-6 receptor inhibitor, tocilizumab is a recent development. (Stone *et al.*, 2017) (Sadun and Gordon, 2020)

Due to the potential for irreversible vision loss, and the side-effects of glucocorticoids, GCA is a high stakes diagnosis. My motivation for pursuing research in GCA is that it is one of the most-anxiety provoking diseases in my ophthalmology practice. Over the last 30 years, I have encountered many apprehensive, elderly patients with clinical or bloodwork abnormalities suspicious for GCA, who cannot decide whether to undergo TABx, start glucocorticoids, or continue on their prescribed glucocorticoids without a tissue diagnosis. Both patients and physicians wish that TABx could be less invasive, (See Figure 1) and avoided if patients can be determined to be at low risk. To clarify, "risk" in this thesis refers to the probability of occurrence of an event or outcome (Ranganathan, Aggarwal and Pramesh, 2015).

Artificial intelligence and actuarial models are usually superior to clinical intuition for medical diagnosis (Meehl, 1954; Ayres, 2007; The Medical Futurist, 2016; Mukherjee, 2017). The diagnosis of GCA by clinical intuition alone is prone to bias because humans in comparison with statistical models cannot objectively or accurately weigh the multiple risk factors for GCA, especially those with a non-linear profile (See

Figure **8**). Actuarial classification algorithms can provide an objective risk assessment that aids medical decision-making, and potentially allow physicians to deliver better care (Bower, 2018; Parikh, 2018). Furthermore, a risk calculator for GCA may help avoid TABx in patients deemed at low risk for GCA.

This thesis also explored the epidemiology of GCA with respect to the incidence of GCA in Ontario, Canada, and the role of herpes zoster in GCA. Although Ontario is the most populous province in Canada, no prior incidence study had been performed. To examine the relationship between herpes zoster and GCA, we published the first ecologic analysis comparing the incidence rates of both conditions in different countries.

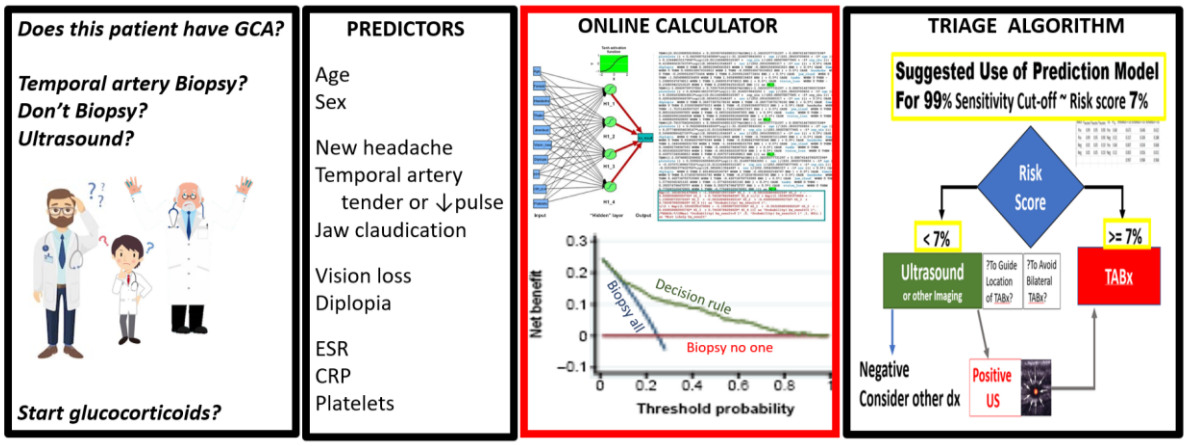
In summary, my thesis addresses challenges in the epidemiology and diagnosis of GCA. Knowledge gaps in the epidemiology of GCA important for public health planning included

the incidence of GCA in Ontario, Canada, and the controversial role of herpes zoster in the development of GCA given the advent of the zoster vaccines.

Needed refinements in the diagnosis of GCA included the clarification of the contemporary utilization parameters of temporal artery biopsy (TABx), and optimization of diagnostic prediction models (PMs).

The most significant, original contribution of the publications in this thesis are the PMs that stratify a patient's risk of GCA prior to TABx. PMs with more than one predictor variable i.e. multivariable PMs were developed using three different classification algorithms: logistic regression, support vector machine and neural networks. Logistic regression is one of the most used classification algorithms in medicine and was chosen over linear regression / polynomial (quadratic) regression because the outcome of our PMs is binary i.e. negative TABx versus positive TABx. (see the Methodology Section 4.1) Each algorithm was examined to determine if misclassification errors particularly false-negative errors could be minimized as a missed opportunity to prevent potential blindness is one the costliest errors in GCA. The PMs are intended to allay patient angst, support patient-doctor collaborative decision-making, and provide a pretest probability for GCA that allows clinicians to adjudicate better between observation versus investigative options, and to determine if glucocorticoid treatment or other treatment is appropriate.

Figure 2. Précis of the major contribution of this thesis

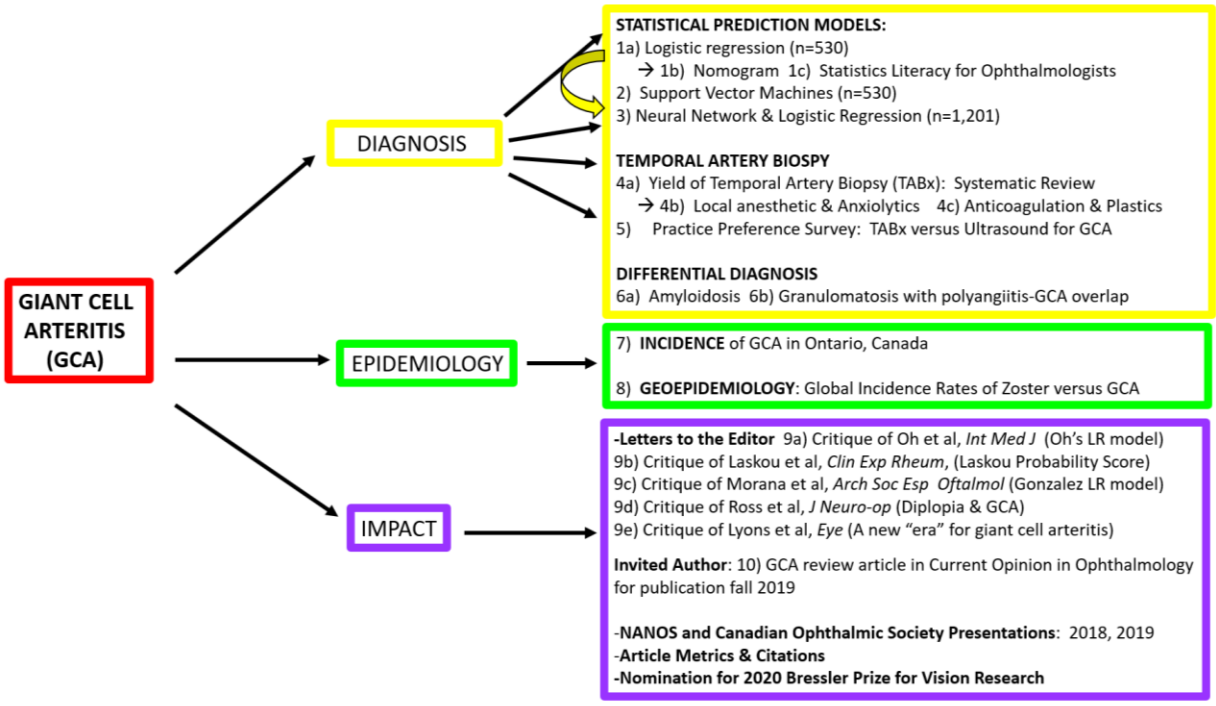


The multivariable diagnostic prediction models in this thesis risk stratify patients with suspected giant cell arteritis (GCA) prior to temporal artery biopsy. Increasing age and

platelet levels, and the presence of jaw claudication, and vision loss were found to be the strongest predictors of GCA.

Chapter 2. THESIS PUBLICATIONS

Figure 3. Pictorial Summary of Thesis Publications



DIAGNOSIS: Statistical Prediction Models

1. a) Multivariable prediction model for suspected giant cell arteritis: development and validation. **Ing EB**, Lahaie Luna G, Toren A, Ing R, Chen JJ, Arora N, Torun N, Jakpor OA, Fraser JA, Tyndel FJ, Sundaram AN, Liu X, Lam CT, Patel V, Weis E, Jordan D, Gilberg S, Pagnoux C, Ten Hove M. Clin Ophthalmol. 2017 Nov 22;11:2031-2042.

1. b) The Use of a Nomogram to Visually Interpret a Logistic Regression Prediction Model for Giant Cell Arteritis. **Ing EB**, Ing R. Neuroophthalmology. 2018 Feb 5;42(5):284-286.

1. c) Aids to statistics literacy for ophthalmologists. **Ing E**. Can J Ophthalmol. 2016 Oct;51(5):e142-e143.

2. Support Vector Machines and logistic regression to predict temporal artery biopsy outcomes. **Ing E**, Su W, Schonlau M, Torun N. Can J Ophthalmol. 2019 Feb;54(1):116-118.

3. Neural network and logistic regression diagnostic prediction models for giant cell arteritis: development and validation. **Ing EB,** Miller NR, Nguyen A, Su W, Bursztyn LLCD, Poole M, Kansal V, Toren A, Albreki D, Mouhanna JG, Muladzanov A, Bernier M, Gans M, Lee D, Wendel C, Sheldon C, Shields M, Bellan L, Lee-Wing M, Mohadjer Y, Nijhawan N, Tyndel

F, Sundaram ANE, Ten Hove MW, Chen JJ, Rodriguez AR, Hu A, Khalidi N, Ing R, Wong SWK, Torun N. Clin Ophthalmol. 2019 Feb 21;13:421-430.

DIAGNOSIS: Temporal Artery Biopsy: Utility rate, Technique, Practice Preferences

4. a) Systematic Review of the Yield of Temporal Artery Biopsy for Suspected Giant Cell Arteritis. **Ing EB**, Wang DN, Kirubarajan A, Benard-Seguin E, Ma J, Farmer JP, Belliveau MJ, Sholohov G, Torun N. Neuroophthalmology. 2018 Jun 19;43(1):18-25.

4. b) Local anaesthesia and anxiolytic techniques for oculoplastic surgery. **Ing EB**, Philteos J, Sholohov G, Kim DT, Nijhawan N, Mark PW, Gilbert J. Clin Ophthalmol. 2019 Jan 10;13:153-160.

4. c) New oral anticoagulants and oculoplastic surgery. **Ing E**, Douketis J. Can J Ophthalmol. 2014 Apr;49(2):123-7.

5. Practice Preferences: Temporal Artery Biopsy versus Doppler Ultrasound in the Work-up of Giant Cell Arteritis. **Ing E**, Xu Q, Chuo J, Kherani F, Landau K. Accepted by Neuro-Ophthalmology, Aug 13, 2019.

DIAGNOSIS: Differential Diagnosis:

6. a) Polyangiitis overlap syndrome with granulomatosis with polyangiitis (Wegener's) and giant cell arteritis. Ong Tone S, Godra A, **Ing E**. Can J Ophthalmol. 2013 Feb;48(1):e6-8.

6. b) Systemic amyloidosis with temporal artery involvement mimicking temporal arteritis. **Ing EB**, Woolf IZ, Younge BR, Bjornsson J, Leavitt JA. Ophthalmic Surg Lasers. 1997 Apr;28(4):328-31.

Epidemiology:

7. The incidence of giant cell arteritis in Ontario, Canada. **Ing EB**, Lahaie Luna G, Pagnoux C, Baer PA, Wang D, Benard-Seguin E, Godra I, Godra A, Munoz DG, McReelis K, Ten Hove M. Can J Ophthalmol. 2019 Feb;54(1):119-124.

8. Does herpes zoster predispose to giant cell arteritis: a geo-epidemiologic study. **Ing EB**, Ing R, Liu X, Zhang A, Torun N, Sey M, Pagnoux C. Clin Ophthalmol. 2018 Jan 11;12:113-118.

Impact: Critiques of GCA Literature

9. a) Bloodwork statistical prediction model for giant cell arteritis. **Ing E**. Intern Med J. 2018 May;48(5):607-608. (Comments on: Full blood count as an ancillary test to support the diagnosis of giant cell arteritis. [Intern Med J. 2018])

9. b) Comments on the giant cell arteritis probability score (Laskou's model). Ing E, Sambhi G, Torun N, Pagnoux C. Clin Exp Rheumatol. 2019 Mar-Apr;37 Suppl 117(2):150. Epub 2019 May 8. Clin Exp Rheumatol (Comment on: Laskou F et al. A probability score to aid the diagnosis of suspected giant cell arteritis. Clin Exp Rheumatol. 2019 37 Suppl 117(2): 104-108.)

9. c) Ing E. Letter to the Editor. Neural network and logistic regression predictive calculator for giant cell arteritis. Arch Soc Esp Oftalmol. 2019 Sep 5. pii: S0365-6691(19)30235-7. doi: 10.1016/j.oftal.2019.07.011. [Epub ahead of print] English, Spanish. (Comments on Moraña MN, Sevillano C, Martínez S, Carral ML. Giant cell arteritis and usefulness of a predictive calculator.)

9. d) Ing E, Miller N, ten Hove M, Torun N. Letter to the Editor. Diplopia and giant cell arteritis: Response. J Neuroophthalmol. 2019 Sep 5. doi: 10.1097/WNO.0000000000000847. [Epub ahead of print] (Comments on Ross, Ahmara G.; Jivraj, Imran; Rodriguez, Geoffrey; More et al. Retrospective, Multicenter Comparison of the Clinical Presentation of Patients Presenting with Diplopia from Giant Cell Arteritis vs Other Causes. J Neuro-Ophthalmology. 39(1):8-13, March 2019.

9. e) Ing E. Comment on: "A new era for giant cell arteritis", Eye, (Lond), online ahead of print Nov 25, 2019. (Comments on Lyons HS, Quick V, Sinclair AJ, Nagaraju S, Mollan SP. A new era for giant cell arteritis'. Eye (Lond). 2019 Oct 3, online ahead of print)

10. Ing E, Pagnoux C, Torun N. Advances in the diagnosis of giant cell arteritis.. Curr Opin Ophthalmol, 2019 Sep 9. doi: 10.1097/ICU.0000000000000616. [Epub ahead of print]

Cross-Cutting Publications:

Ing E. Neuro-ophthalmic History, Ophthalmology emedicine chapter, peer-reviewed, annually updated Nov 2018, accessed Nov 26, 2018. https://emedicine.medscape.com/article/1832674-overview#showall

Ing E. Neuro-ophthalmic Physical examination, Ophthalmology emedicine chapter, peer reviewed, updated Jul 2019, accessed Jul 1, 2019. https://emedicine.medscape.com/article/1820707-overview#showall

The next section of the thesis will present the research undertaken, providing a summary of each study and key findings. The first nine papers focus on the diagnosis of GCA, followed by two studies on the epidemiology of GCA.

2.1 Diagnosis of GCA and Prediction Models

2.1.1 Multivariable logistic regression prediction model for suspected GCA: development and validation. Clinical Ophthalmology, 2017

Based on clinical experience, a review of the literature, and a pilot study of ocular pulse amplitude in patients undergoing TABx (Ing, Pagnoux, *et al.*, 2018) I *a priori* selected for the logistic regression model the predictors: age, gender, new-onset headache, temporal artery tenderness or pulselessness, jaw claudication, vision loss, diplopia, Westergren erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and platelet level.[4] All these variables, including platelets (Price and Clearkin, 1994) are information commonly collected from patients with suspected GCA. Chart review by myself and collaborators at multiple centres was performed on consecutive patients who underwent a TABx for suspected GCA. Patients using systemic glucocorticoids for more than 2 weeks were excluded from the study, because glucocorticoids can obscure the pathologic findings of GCA.

On multivariable logistic regression (LR) with external validation, this primary model (n=530) found that the platelet level, age, jaw claudication, vision loss, log CRP, new-onset headache and, temporal artery abnormality were statistically significant predictors of GCA, but the log ESR, gender, and diplopia were not.

In comparison with other LR models in the literature listed in Table 1, (Gabriel *et al.*, 1995; Rodriguez-Valverde *et al.*, 1997; Rieck *et al.*, 2011; González-López *et al.*, 2013; De Lott and Burke, 2015; El-Dairi *et al.*, 2015; Grossman *et al.*, 2016; Weis *et al.*, 2017; Oh, Wong, Andrici, *et al.*, 2018) the prediction models described in this thesis are the largest in the literature, had sufficient GCA events to support the 10 *a priori* predictors, increased statistical power by maintaining age and bloodwork predictors as continuous variables, one of the few rules to consider CRP, and are the only models with external validation and compliance with the rigorous transparent guidelines for the reporting of prediction models (TRIPOD) from the EQUATOR network (Collins *et al.*, 2015). Unlike some other models, (De Lott and Burke, 2015; Weis *et al.*, 2017; Oh, Wong, Andrici, *et al.*, 2018) the thesis models utilize symptoms and signs as well as bloodwork values. Only one other model has an associated spreadsheet risk calculator, (González-López *et al.*, 2014) but it is not useful for a pre-biopsy risk calculation as it requires input of the length of the TABx (Ing, 2019b; Moraña *et al.*, 2019).

[4] Polymyalgia rheumatica was *not* chosen as a predictor variable for the four reasons listed on page 56, section 4.1.1.

Also, the Gonzalez-Lopez calculator is not publicly available, and must be requested from the author.

Table 1. Review of the Logistic Regression Prediction Models for GCA in the Literature

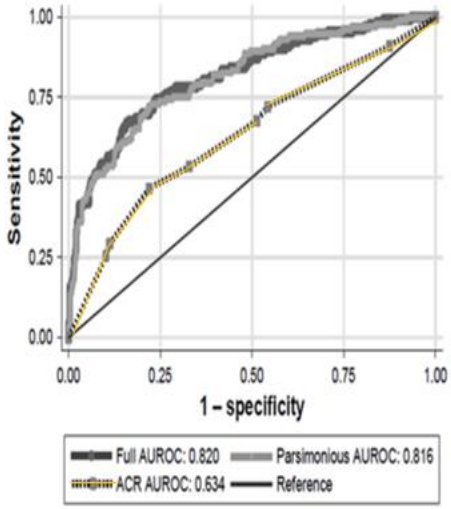
Author (Year)	N [complete case analysis] (positive biopsy events)	Statistically Significant Predictors	Odds Ratio
Gabriel (1995)	525 (172)	All claudication Synovitis TAabn Highest ESR	4.55 0.31 2.55 1.01
Rodriguez-Valverde, (1997)	227 (90)	New headache TAabn Jaw claudication Raised liver enzymes < 70 years old at disease onset	13.6 4.2 4.8 2.9 0.11
Rieck (2011)	82 (22)	Jaw claudication Weight loss	4.50 3.76
Gonzalez-Lopez (2013)	335 (81)	Jaw claudication New headache TAabn Pain and stiffness in neck and shoulders Unintentional weight loss Age Biopsy Length ESR	4.6 4.4 2.8 2.3 1.33 1.085 1.079 1.042
De Lott (2015)	239 (?90)	Age Platelets	1.06 1.01
El-Dairi (2015)	213 (61)	Age > 65 years White Jaw claudication CRP > 0.5 mg/dL Platelets > 400K/µL	4.28 6.59 3.45 2.6 3.2
Grossman (2016)	224 (57) [25 biopsy negative GCA cases were included]	New headache Jaw claudication ESR Platelets	6.0 4.5 1.5 1.74
Weis (2017)	119 (29)	ESR Platelets (Jaw claudication)	1.03 1.01 (4.81)

Ing (2017)	530 (133)	Age Jaw Claudication Vision Loss Platelets LogCRP	1.04 4.0 2.7 1.005 1.35
Oh (2018)	347 (79)	Platelets ESR	3.187 2.005
Ing (2019)	1,201* (300)	Age Headache TAabn Jaw claudication Vision loss LogESR LogCRP Platelets	1.060 1.540 1.466 3.398 2.611 1.200 1.370 1.005

GCA = giant cell arteritis; TAabn = temporal artery abnormality on physical exam
*In this series which is discussed extensively later in the thesis a total of 1,833 subjects underwent TABx; 1, 201 had complete information for logistic regression analysis.

The primary logistic regression (P-LR) model (n=530) had a good area under the receiving operating characteristic (AUROC) of 0.81 on bootstrap cross validation, which was sustained on serial geographic external validation with AUROC 0.75-0.85. The P-LR model handily outperformed the 1990 American College of Rheumatology (ACR) classification criteria for GCA (Hunder *et al.*, 1990). Although the ACR *classification* criteria were never meant for the diagnosis of individual patients with GCA, (Hunder, 1998) numerous articles have attempted to repurpose them (Davies and May, 2011; Quinn *et al.*, 2012; Pieri *et al.*, 2013; Cristaudo, Mizumoto and Hendahewa, 2016; Hussain *et al.*, 2016). The P-LR model was a better discriminator for the diagnosis of GCA than the 1990 ACR classification criteria.

Figure 4. Discrimination of the Full and Parsimonious Primary Logistic Regression Model (published in 2017; n=530; upper, gray and black ROC curves) versus the 1990 American College of Rheumatology clinical classification criteria (lower, yellow ROC curve)



ROC curves for full, parsimonious and ACR models.

Notes: Full model (n=530) $p_{Hosmer-Lemeshow}$ =0.549. Parsimonious model (n=530) $p_{Hosmer-Lemeshow}$ =0.812. ACR model = (n=525). $p_{Hosmer-Lemeshow}$ =0.0223 (Five patients under the age of 50 years were excluded from logistic regression.).

Abbreviations: ROC, receiver operator characteristics; ACR, American College of Rheumatology Classification non-histologic Criteria.

Diagnosis of GCA

2.1.2 The Use of a Nomogram to Visually Interpret Logistic Regression Prediction Model for Giant Cell Arteritis. Neuroophthalmology 2018

Statistics literacy is essential for the interpretation of the medical literature and life-long learning (Ing, 2016). Logistic regression with its odds ratios is one of the most used classification algorithms in medicine. Odds are the ratio of the probability of an event occurring over the probability of the event not occurring. In the context of our logistic regression prediction models, the odds ratios (O.R.) represent the constant effect of the predictor variable on the "likelihood" that the patient has GCA. If the O.R. is unity, then the predictor variable does not affect the outcome of GCA. If the O.R. is less than one, and the p-value is statistically significant (confidence interval does not cross one) the predictor variable decreases the odds of having biopsy-proven GCA. If the O.R. is greater than one, and the p-value is statistically significant, the predictor variable increases the odds of having biopsy-proven GCA. Many clinicians may not realize that just examining the magnitude of the O.R. and its p-value when interpreting O.R. may not reveal which predictor contributes the most to the final risk score - it is also important to know if the predictor is a binary versus continuous variable.

From the logistic regression table shown in Figure 5, one might wrongly conclude that platelets with O.R. of 1.005 or age with an O.R. of 1.046 would not contribute much to the final risk score compared to jaw claudication (O.R. 3.656) and vision loss (O.R. 2.803). However, in the P-LR, jaw claudication and vision loss are binary variables, whereas platelets and age are continuous variables with a wide range. The O.R. represents the increase in odds of GCA per unit increase in the predictor variable, and as such even small statistically significant O.R. of continuous variables can contribute much to the final risk score. In the P-LR model (n=530) the platelet level has an O.R. of 1.005082 which was rounded to 1.005 in Figure 5; as the confidence interval for platelets does not cross unity it is statistically significant. The corresponding beta coefficient for platelets is ln (1.005082) = 0.0050691. Although a 1-unit change in the platelet value only results in a marginal increase in the odds, a 10-unit increase in platelets has the effect of $e^{\wedge(\beta platelets \times 10)} = e^{\wedge(0.0050691 \times 10)} = 1.05\times$ increase in the odds. A 50-unit increase in platelets results in a $e^{\wedge(0.005691 \times 50)} = 1.29\times$ increase in the odds.

A nomogram is a graph of scaled variables that facilitates the approximate computation of a mathematical function via intersecting lines, and lucidly illustrates the relative importance of predictor variables in a multivariable logistic regression. There were no previous applications of nomograms for GCA. Although some feel nomograms are "outmoded medical relics", (Grimes, 2008) the nomogram for the P-LR model clearly shows non-statisticians that the small O.R. of continuous variables may actually contribute more to risk than the seemingly larger O.R. of binary variables. Although logit functions may be difficult for some clinicians to recall, the length and location of the lines associated with each predictor are a graphical representation of the variable's corresponding O.R. and p-value (Zlotnik and Santos, 2013).

Figure 5. The relationship between odds ratios (top) versus the Kattan nomogram risk score (bottom) for binary versus continuous variables on a logistic regression model (n=530) for GCA.

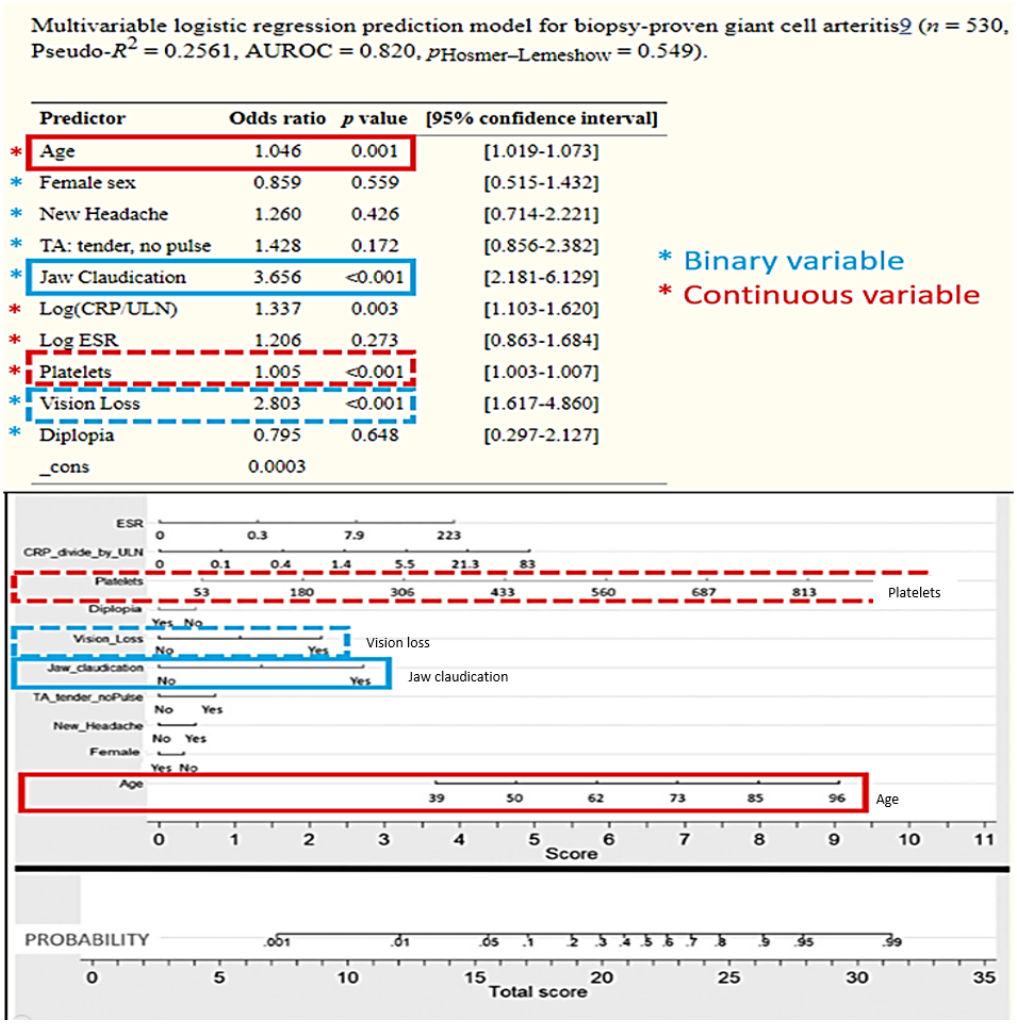


Figure 5 Legend.

TA = temporal artery, Log = natural logarithm., CRP/ULN = C-reactive protein divided by its upper limit of normal, ESR = Westergren erythrocyte sedimentation rate. Vision loss = ischemic optic neuropathy, central retinal artery occlusion, or other presumed ischemic vision loss. _cons = constant., ESR = erythrocyte sedimentation rate; CRP_divide_by_ULN = C-reactive protein divided by its upper limit of normal; TA_tender_noPulse = Clinical temporal artery abnormality (tenderness and/or decreased or absent pulse); New-Headache = new-onset headache

Kattan-style nomograms are used for binary LR predictive models. To use the Kattan nomogram, a vertical line is drawn from the value of the predictor variable down to the score scale. For example, a platelet level of 433 contributes about 4.5 points. The sum of the scores for all the predictor provides a total score, which can be converted to a risk probability for GCA.

2.1.3 Support Vector Machines and Logistic Regression to predict temporal artery biopsy outcomes. Can J Ophthalmol. 2019

Although the P-LR model (n=530) was serviceable, we sought to decrease its 18% misclassification rate, and explored an alternative classification algorithm. Machine learning techniques such as support vector machines (SVM) are being increasingly recognized in medicine and ophthalmology (Lee *et al.*, 2017). In a 2014 abstract Lee et al. reported that a SVM algorithm had 100% classification accuracy in their test set of 40 patients, out of a total dataset of 182 TABx patients (Lee *et al.*, 2014). SVM is a supervised machine learning algorithm that identifies the hyperplane (decision boundary function) that best partitions and classifies a set of data. Support vectors are the data points at the edge of each class closest to the hyperplane that if removed, would alter the position of the hyperplane partition. The optimum hyperplane provides the widest margin between the hyperplane and the data points in the two separate classes. SVM is often combined with kernelling, a method of pattern analysis that can map data into a higher dimensional space so that even non-linear hyperplanes can be determined.

We used the patient data from the P-LR set and applied it to a SVM model (Ing, Su, *et al.*, 2019). The SVM model was optimally tuned with gamma= 0.01267 and cost = 26.466, with 133 support vectors. The AUROC/misclassification rate/false- negative rate for the P-LR versus SVM respectively were 0.827/0.184/0.524 and 0.825/0.168/0.571. On DeLong's test,

there was no statistically significant difference between the AUROC of the two models. As the discrimination of the two models was almost identical, the extra complexity of the SVM algorithm was not warranted. SVM does not provide direct probability estimates, which require calculation using cross-validation. SVM had a slightly larger-than-average precision and a slightly smaller misclassification rate but also had a higher false-negative rate compared with logistic regression. In the management of GCA, the greatest penalty is with false-negative errors, as untreated GCA may result in irreversible blindness or rarely death. As such, SVM was not advantageous to logistic regression for the classification of GCA in our dataset of 530 TABx subjects with 10 covariates.

2.1.4 Neural network and logistic regression diagnostic prediction models for GCA: development and validation**.** Clinical Ophthalmology, 2019

As the SVM prediction model did not decrease the false-negative rate of TABx we turned to a neural network (NN) model. NNs are akin to putting many layers of logistic regression functions together. Compared to the lucid odds ratios of LR, that can suggest the relative contribution of predictor variables to risk, NNs are a "black box". (See Figure 6) However, unlike LR, NN can determine non-linear relationships without the specification of polynomial terms. NNs are data-intensive and as such, my colleagues and I recruited a second wave of patients from different North American medical centres to increase our dataset. The same predictor variables were used.

Figure 6. Diagram of the neural network model.

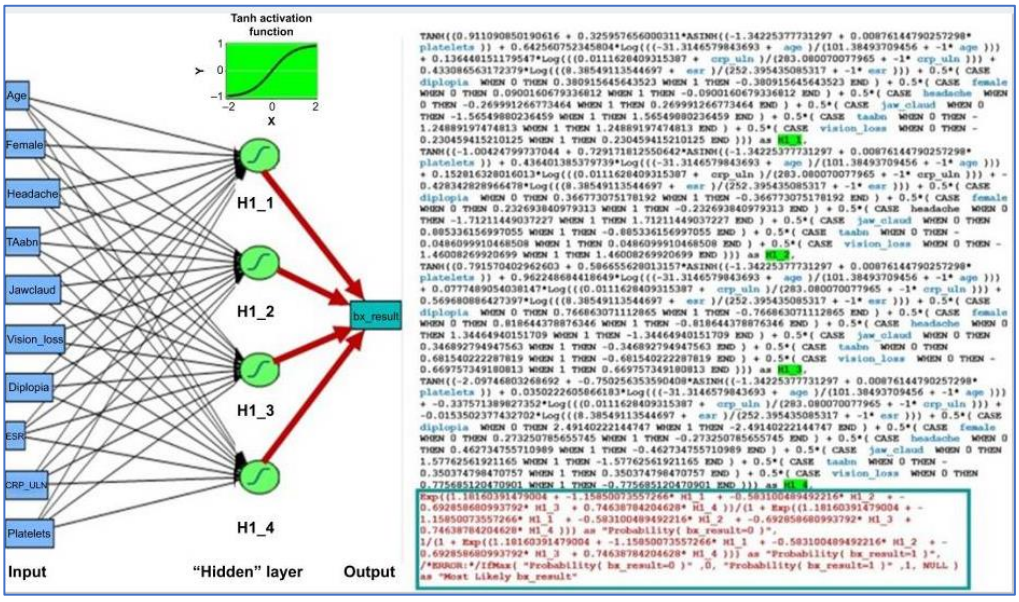


Figure 6 Legend. The neural network has 10 input predictor variables, 4 hidden nodes in a single hidden layer, and 1 output which codes for the diagnosis of GCA. Each of the 10 inputs connects to a hidden node and is associated with a unique weight (the black numbers at the right of the rectangle). The hyperbolic tangent activation function varies from -1 to +1.[5] *The sum from each of four weighted hidden node values (red numbers) contributes to the final output.*

Only one other NN model has been described in the GCA literature (Astion *et al.*, 1994). It was developed from a database of 807 vasculitis patients, of whom 214 had the diagnosis of GCA. Astion et al's NN was intended for the *classification* of vasculitis, rather than the diagnosis of GCA in individual patients. Their NN also required the result of the TABx; did not consider vision loss (one of the most feared complications of GCA), C-reactive protein or platelets; had no external validation; and assigned missing data a value of zero.

Of the 1,833 patients who underwent chart review for the NN-LR model, we had complete information on 1,201 (66%) of them. Three hundred patients had biopsy-proven GCA (BPGCA) and complete information. The patients with positive TABx had statistically significant greater age, temporal artery pulselessness or tenderness, jaw claudication, vision loss, and acute phase reactant bloodwork values than the negative biopsy group. (Table 2)

Table 2. Characteristics of subjects with positive versus negative temporal artery biopsy.

Factor	Negative biopsy	Positive biopsy	*P*-value	Value range
n	1,368	465		
Age, years, μ (SD)	72.8 (10.4)	77.2 (8.2)	<0.001	38, 98
Female	933 (68.7%)	329 (71.2%)	0.31	
Headache, new onset	957 (73.3%)	313 (74.5%)	0.61	
TAabn	441 (34.3%)	193 (46.6%)	<0.001	
Jaw claudication	257 (19.9%)	215 (49.8%)	<0.001	
Vision loss	235 (18.1%)	126 (29.5%)	<0.001	
Diplopia	105 (8.1%)	47 (11.0%)	0.071	
ESR, μ (SD)	41.2 (30.1)	55.2 (30.1)	<0.001	0.01, 224
CRP, μ (SD)	5.7 (12.1)	11.6 (14.4)	<0.001	0.01, 212
Platelets, $\times 10^9$/L, μ (SD)	282.6 (104.9)	371.8 (142.9)	<0.001	27, 1,199
Biopsy length, cm, μ (SD)	2.3 (1.0)	2.3 (.90)	0.24	0.3, 7.5

Abbreviations: CRP, C-reactive protein divided by upper limit of normal for each lab; ESR, erythrocyte sedimentation rate; μ, mean; n, number of subjects; TAabn, tenderness or decreased pulsation of temporal artery.

Jaw claudication is not a common symptom, but prevalent in our patients (see Table2).

[5] The hyperbolic tangent function (TanH) is a sigmoid function. The advantage of the hyperbolic tangent function is that it is not limited to only positive outputs in the hidden layer. TanH is the centred and scaled version of the logistic function and transforms values to be between -1 and +1.

Perhaps jaw claudication was overdiagnosed by some of the clinicians that contributed to the data, and see Chapter 6, page 85 for further comment.

Vision loss is one of the most feared sequelae of GCA and as such, this parameter is specifically reviewed in our large cohort of patients. Of the 1,833 subjects who underwent TABx, there were 361 patients with ischemic vision loss. In 171 (47.3%), further details of fundoscopy and the ophthalmic history were available; 59 had BPGCA and 112 did not. Of the 59/300 (19.7%) patients with BPGCA and vision loss, 49 (83%) had anterior ischemic optic neuropathy (AION) that was bilateral in four (7%) subjects; three subjects (5%) had posterior ischemic optic neuropathy, six subjects (10%) had retinal arteriolar occlusion and one patient (2%) had a central retinal vein occlusion. The average age of the BPGCA patients with vision loss was 77.9 years and 59% were female.

Of the 112 patients with negative TABx and vision loss, 64 (57%) were deemed to have non-arteritic AION (NAION), and there were no cases of bilateral simultaneous AION. The average age of the negative biopsy group with vision loss was 74.1 years, and 61% were female. Twenty-six patients (23%) in the biopsy-negative group had a retinal arterial occlusion, twenty-three central, one hemi-retinal, and two branch.

On multivariable logistic regression (n=1,201), platelets, jaw claudication, vision loss, log C-reactive protein, log erythrocyte sedimentation rate, headache, and clinical temporal artery abnormality were statistically significant predictors of a positive TABx (all $p \leq 0.05$)

Table 3. Multivariable logistic regression for the outcome of biopsy-proven GCA (n=1,201)

Variables	OR	*P*-value	95% CI, OR
Age	1.060	<0.001	1.036, 1.085
Female	0.923	0.686	0.627, 1.359
Headache	1.540	0.035	1.030, 2.301
TAabn	1.466	0.019	1.064, 2.017
Jaw claud	3.398	<0.001	2.314, 4.991
Vision loss	2.611	0.005	1.327, 5.138
Diplopia	1.127	0.606	0.714, 1.780
log(ESR)	1.200	0.043	1.005, 1.433
log(CRP/ULN)	1.370	<0.001	1.246, 1.507
Platelets	1.005	<0.001	1.003, 1.006
Constant	0.000		

Notes: n=1,201; McFaddens R^2=0.243, log pseudolikelihood=510.985.
Abbreviations: CRP/ULN, C-reactive protein divided by upper limit normal of each lab; ESR, erythrocyte sedimentation rate; Jaw Claud, jaw claudication; log, natural logarithm; R^2, pseudo *R* square; TAabn, clinical temporal artery abnormality.

Figure 7. The Effect Summary plots the LogWorth values for the effects in the logistic regression model (n=1,201).

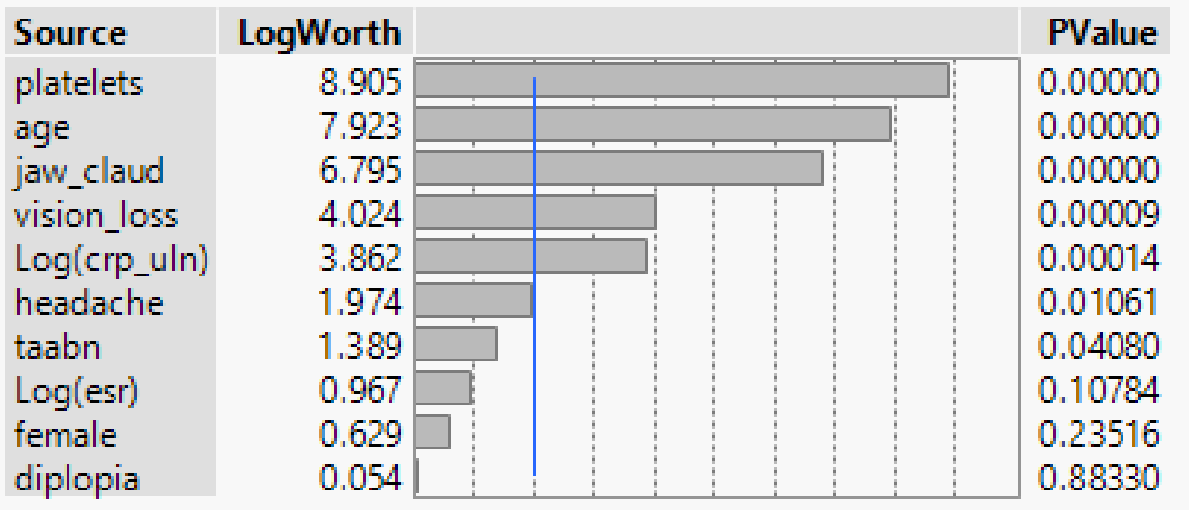


Figure 7. The logworth for each model effect, defined as -log10(p-value). This transformation adjusts p- values to provide an appropriate scale for graphing. A value that exceeds 2 is significant at the 0.01 level, because $-\log_{10}(0.01) = 2$.

Revelations from the final LR model (n=1,201) include:

i) Age, platelets, jaw claudication and vision loss were the most valuable predictors for GCA as shown on the Effect Summary plot (Figure 7). The maintenance of age and acute phase reactant predictors as continuous variables helped to optimize our prediction models. Of the 1,833 subjects who underwent TABx, 1,515 of them had accompanying platelet levels. The mean/median platelet count X 10^9/L was 372/342 in the positive TABx group, and 283/264 in the negative TABx group ($p<0.001$) (Ing, Miller, *et al.*, 2019). Maintaining bloodwork as continuous variables instead of dichotomizing (e.g. platelet level above or below 400 X 10^9/L) rendered platelets a stronger predictor for GCA than ESR or CRP.

ii) Neither female gender nor diplopia were strong predictors of GCA. Although more patients with GCA are women, female sex is not a strong predictor for GCA. The female predominance of GCA is consistent with 2016 Canada census report that of citizens 65 years of age or older, the female: male ratio was 1.2. For the 85 years and older population, there were two women for every man (Statistics Canada, 2017a). "Every country with reliable health statistics reports that women live longer than men." (Harvard Health Publishing and Harvard Medical School, 2010; Ortiz-Ospina and Beltekian, 2018) Diplopia may be a poor

predictor of GCA because patients who lose vision in one or both eyes are usually less likely to experience binocular diplopia.

The area under the receiver operating characteristic curve/Hosmer-Lemeshow *P* for LR was 0.867 (95% CI, 0.794, 0.917)/0.119 vs NN 0.860 (95% CI, 0.786, 0.911)/0.805, with no statistically significant difference between the areas under the curves (*P*=0.316). The NN model had 17% fewer false negatives than the LR model. The misclassification rate/false-negative rate of LR were 20.6%/47.5% versus 18.1%/30.5% for NN, respectively. Missing data analysis did not change the results. Misclassification remains a concern, but the cut-off values for 95% and 99% sensitivities were posted for use with the online calculator (https://goo.gl/THCnuU).

A probability score cut-off of 7% provides approximately 99% sensitivity to detect biopsy-proven GCA. In our study, electing to biopsy only those patients with a risk score of 7% or greater would have resulted in 0.8% false negatives, but the avoidance of 14% of the TABx that eventually were deemed negative. In 2016 the estimated costs of a TABx in Australia and UK were £253 and £514 respectively (Cristaudo, Mizumoto and Hendahewa, 2016; Luqmani *et al.*, 2016).

The LR-NN prediction models are the largest in the literature, and the only models compliant with the rigour of the transparent reporting guidelines for prediction rules (TRIPOD; see Appendix H) (Collins *et al.*, 2015). The prediction models are unique in that they contained data from multiple centres in North America, with both ophthalmology and internal medicine patients, which enhances generalizability, and allowed for geographic external validation. The free, user-friendly online calculator (https://goo.gl/THCnuU) allows clinicians a method to determine objectively the risk score of patients with suspected GCA prior to TABx.

Our NN-LR study did not appear to be compromised by the possible biases of i) biopsy length, ii) unilateral versus bilateral TABx, (Danesh-Meyer *et al.*, 2000) or iii) referral from ophthalmology versus internal medicine sources.

i) In 1,501/1,833 (82%) of subjects, the biopsy length was readily available. The average length was 2.25 cm (±0.95) in the 1,142 subjects with a negative TABx, and 2.32 cm (±0.90) in the 359 with a positive TABx, with no statistically significant difference (*p*=0.24).

ii) Although some clinicians routinely perform bilateral TABx in hopes of decreasing the risk of false-negative biopsy, “routine bilateral biopsies are discouraged” (Weyand and Goronzy,

2014). Of the 1,105/1,833 subjects that had information on unilateral versus bilateral biopsy, 437 (40%) had bilateral TABx. The proportion of BPGCA in the unilateral TABx group was 162/667 (24.3%), and that in the bilateral TABx group was 109/437 (24.9%), which was not a statistically significant difference (p=0.80).

iii) The prediction profile curves for the model re-emphasize the ability of actuarial algorithms to calculate multiple risk factors, especially for continuous non-linear predictors such as age and bloodwork. (See

Figure **8**)

Figure 8. Prediction risk profile curves of the logistic regression model with linear and non-linear responses.

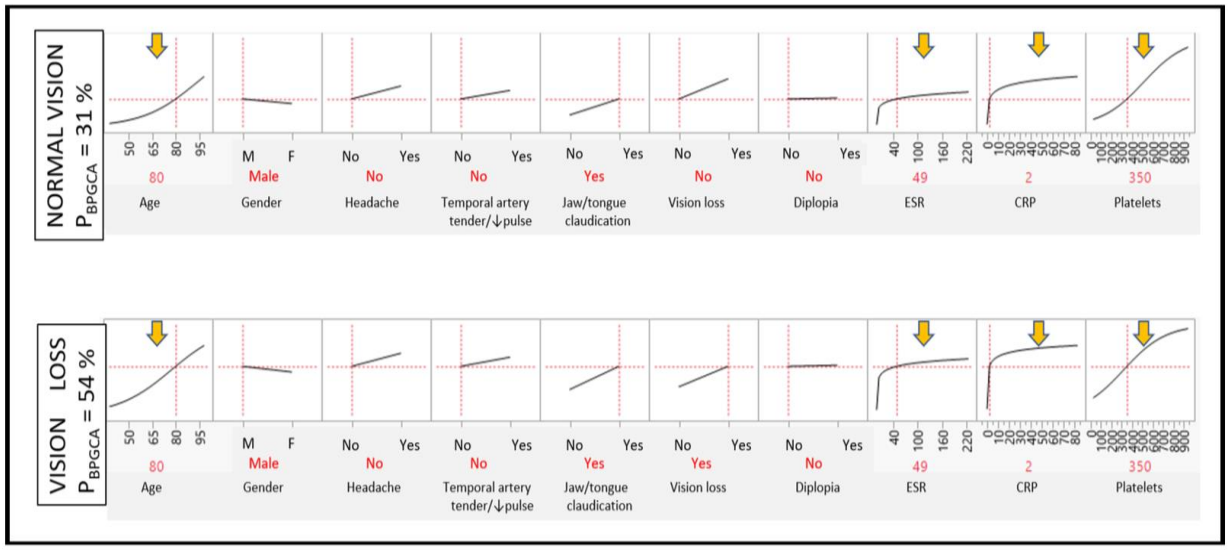


Figure 8. The risk profile curves from the logistic regression model (n=1,201) shows the output for the hypothetical case of an 80-year-old man with jaw claudication, but no new-onset headache, no temporal artery tenderness, and no diplopia. The erythrocyte sedimentation rate (ESR)is 49 mm/hour with C-reactive protein level (CRP) that is twice normal, and a "normal" platelet of 350 x 109/L. In the top readout, the patient retains normal vision and the estimated risk for biopsy-proven GCA (BPGCA) is 31%. In the bottom readout, the patient has vision loss, and the risk of BPGCA increases to 54%. Note the age and bloodwork variables are continuous variables and do not have a linear response (see arrows). Few humans can mentally calculate the risk score from ten predictor variables, especially those with a non-linear response.

Figure 9. Boxplots of the predicted risk scores of the Neural Network and Logistic Regression Models for the positive and negative temporal artery biopsy groups.

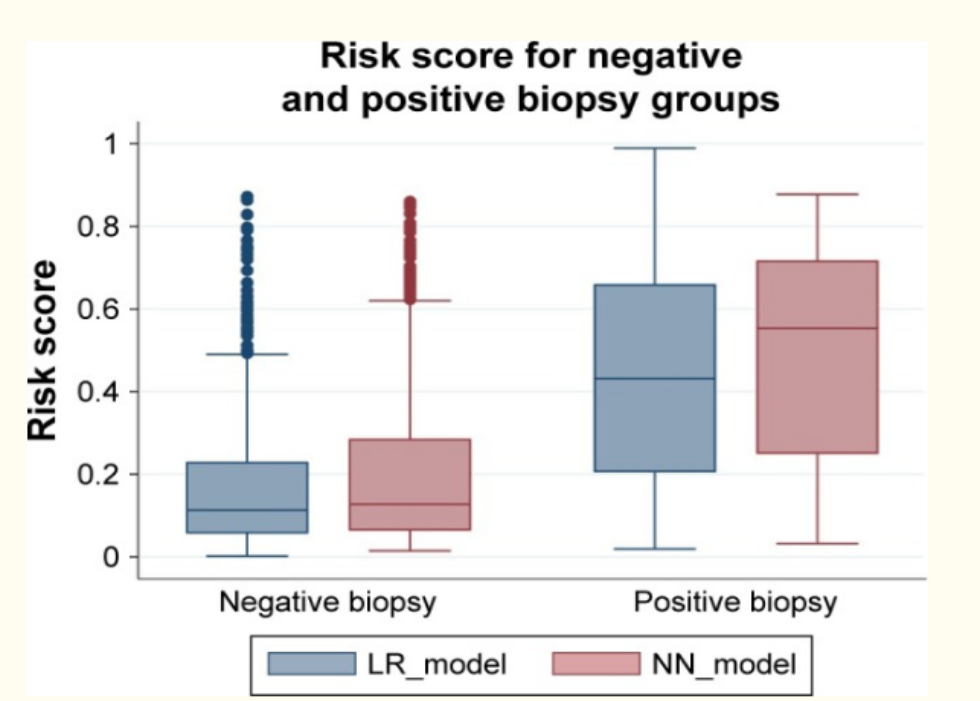


Figure 9 Legend. LR_model= logistic regression; NN_model = neural network model The horizontal line contained within the rectangle of the boxplot is the median value. The lower hinge of the box is the 25th percentile, and the upper hinge the 75th percentile. The dots above the top of the box plot are outliers with high-risk scores in the negative biopsy group.

Unfortunately, prediction models can still fail as infrequently GCA can present in an occult fashion, or more commonly because other diseases can mimic the symptoms, signs and, serology of GCA, as illustrated by the case reports (Section 2.3). The high score outliers in the negative TABx group of Figure 9 represent either false negative TABx or the overlap of symptoms and signs of GCA with other diseases (see Section 2.3 Differential Diagnosis). These outliers are problematic when trying to improve classification algorithms.

Patients with a positive TABx but ESR, CRP and platelets within normal limits (seronegative GCA) are also enigmatic for classification algorithms. Normal serology (the combination of ESR < 50 mm/hour and, CRP and platelets at or below their upper limit of normal) was present in 30 of the 300 subjects with complete information and biopsy-proven

GCA. Six of these "seronegative" GCA patients (6/30=20%) were diagnosed as healed arteritis (See page 55). In 2013 Grzybowski and Justynska summarized 11 publications with GCA and normal serology (Grzybowski and Justynska, 2013). In the Solans-Laque et al series of 418 patients with biopsy-proven GCA, 3.3% of patients had negative ESR and CRP at the time of diagnosis (Solans-Laque *et al.*, 2018). Perhaps patients with seronegative GCA have early stage disease; medications such as non-steroidal anti-inflammatory drugs and statins may reduce ESR or possibly CRP.

In the P-LR and NN-LR study patients with healed arteritis were considered to have a positive TABx if they had a steroid response and were maintained on steroids after the result of TABx returned. In the NN-LR study, 1.7% of all subjects carried the diagnosis of healed arteritis and accounted for 20% of the seronegative GCA patients. If we excluded subjects with healed arteritis from our study, our model would have performed even better; the LR AUROC improves from 0.815 (n=1,201) to 0.832 (n=1,160). However, since healed arteritis is a scenario that can confront clinicians, we maintained these patients in the dataset.

2.2 Temporal Artery Biopsy

2.2.1 Systematic Review of the Yield of TABx for Suspected GCA. Neuroophthalmology, 2018

Temporal artery biopsy (TABx) remains pivotal in the diagnosis of GCA (Danesh-Meyer, 2012) and the reference standard confirmatory test for GCA. As such, the expected positive yield (utility rate) of TABx is important to ascertain. The utility rate of a TABx indicates how many biopsies are positive for GCA out of the total number of TABx performed, and is a different metric than the diagnostic sensitivity of TABx. The utility rate provides a possible benchmark for decisions regarding the under/overutilization of TABx, may assist in decision-making for GCA, and can aid in the evaluation of non-invasive alternatives such as ultrasound and high resolution MRI for the investigation of GCA. There was no systematic review of the literature on this topic prior to our work which was unique to the International Prospective Register of Systematic Reviews (PROSPERO) ID=CRD42017078508. This prototypal review of the last two decades of the TABx literature encompassed 4,344 GCA studies, of which 113 had relevant, unbiased TABx results for meta-analysis (Ing, Wang, *et al.*, 2018). Of the 30,898 TABx, 7379 (23.9%) were positive for GCA. The yield of TABx from the

articles had a right skew distribution with a median yield of 0.25 (95% confidence interval 0.21 to 0.27) and an interquartile range of 0.17 to 0.34. The I^2 statistic of 92% meant that heterogeneity was too large to perform a meta-analysis, but a univariate meta-regression suggested that age was the only statistically significant patient factor associated with TABx yield. The 25% median utility rate of TABx reinforces the conviction that prediction rules for GCA (using pre-biopsy criteria) might increase the yield of TABx by avoiding biopsy of subjects at very low-risk for GCA.

The relevance of the systematic review of TABx in modern medical practice is not anachronistic with the emergence of ultrasound. Although the European League Against Rheumatism (EULAR) guidelines propose that at centres with appropriate equipment and sufficient radiologic expertise modalities such as doppler ultrasound or perhaps MRI may be first-line investigations for suspected GCA (Dejaco *et al.*, 2018), others do not concur (Danesh-Meyer, 2012; Bilyk *et al.*, 2018; González *et al.*, 2018). Due to the myriad of potential side effects with long term glucocorticoid treatment (see Section 1.2 page 14), the British Society of Rheumatology (BSR) Guidelines for GCA (Mackie *et al.*, 2020) strongly recommends that "Patients with suspected GCA should have a confirmatory diagnostic test. This could be either a temporal artery biopsy at least 1cm in length, or an ultrasound of the temporal and axillary arteries, or both." Figure 1 of the BSR guideline is a flow diagram (see Figure 19) with 3 risk categories and 5 possible initial ultrasound investigation pathways, but 3/5 of the ultrasound scenarios eventuate in TABx.

Three- dimensional fat-saturated contrast enhanced vessel-wall MRI at 3 Tesla has recently been suggested to increase diagnostic accuracy for GCA (Poillon *et al.*, 2019). Perineural enhancement of the optic nerve on MRI has been described with GCA but is non-specific (Serrano Alcalá et al., 2019). As of 2020, there are no dedicated fast-track ultrasound facilities for GCA assessment in the Greater Toronto Area which is Canada's most populous metropolitan area. At most medical centres in Toronto, ultrasound of the temporal arteries and cranial MRI for GCA are impractical for GCA work-up because these outpatient studies may require more than three weeks to obtain.[6]

Furthermore, 2019 practice preference survey showed that the vast majority of North American and European neuro-ophthalmologists and Canadian rheumatologists still prefer

[6] CT of the orbit and sinuses are routinely obtained in GCA suspects within 12-24 hours, concurrent with glucocorticoid initiation, to exclude sinusitis.

TABx over ultrasound (Ing, Xu, *et al.*, 2019). A systematic literature review and meta-analysis estimated the sensitivity of TABx at 77% and concluded that TABx is not less sensitive than temporal artery imaging (Rubenstein *et al.*, 2019). A second systematic review of the literature comparing imaging and pathology confirmed that the hypoechoic halo sign on temporal artery doppler ultrasound had 68% (95% CI: 57–78) sensitivity and 81% (95%CI: 75–86) specificity compared with a positive TABx (Rinagel *et al.*, 2019). Conditions such as arteriosclerosis, other forms of vasculitis (ANCA-associated vasculitis) and infections can cause a false-positive halo sign on Doppler ultrasound (De Miguel *et al.*, 2018; Bardi and Diamantopoulos, 2019). Even the EULAR task force conceded that TABx "should be performed in all cases, where GCA cannot be confirmed or excluded based on clinical, laboratory and imaging results." (Moiseev *et al.*, 2019)

Skip lesions (see Section 2.2.3, page 37) aside, adequate length negative TABx have clinical value if they allow glucocorticoids to be stopped (Hedges, III, Gieger and Albert, 1983). TABx also may reveal alternative diagnoses such as syphilis (Smith, Israel and Harner, 1967), sarcoidosis, (Levy and Margo, 1994), renal cell metastases, (Ing *et al.*, 1996) amyloidosis, (Ing *et al.*, 1997) granulomatosis with polyangiitis (Ong Tone, Godra and Ing, 2013) and other antineutrophil cytoplasmic antibody-associated vasculitides, calciphylaxis, Mönckeberg's medial calcific sclerosis and zoster sine herpete which may not be discovered in an expedient fashion without tissue pathology (Ing, Wang, *et al.*, 2018).

TABx are pivotal to the diagnosis of GCA (Danesh-Meyer, 2012) and performed almost exclusively under local anaesthesia as an outpatient procedure. Many patients requiring TABx are on anticoagulation for other age-related ailments, and biopsy of a blood vessel is prone to haemorrhage. As such the supporting articles on perioperative anticoagulant considerations and local anaesthetic technique for TABx are germane.

2.2.2 New oral anticoagulants and oculoplastic surgery. Canadian Journal of Ophthalmology, 2014

During most operations, surgeons strive to avoid blood vessels. TABx requires intentional sampling of an artery with an increased risk of haemorrhage. The potential for bleeding is compounded when an elderly patient referred for TABx is also on anticoagulants for co-morbid conditions such as atrial fibrillation, stroke or myocardial infarction. Hemostasis is

essential in these elderly outpatients who are quickly discharged from the clinic post-procedure. When the new direct oral anticoagulants (non-Vitamin K oral anticoagulants) dabigatran, apixaban, and rivaroxaban emerged circa 2010, oculoplastic surgeons knew little about them, and there were no reversal agents available at that time. The Canadian Society of Oculoplastic & Reconstructive Surgery asked me to review this topic. My co-author was a haemotologist and we scrutinized: i) the pharmacology of the newer anticoagulants, including their duration of action and mechanism of excretion, ii) the herbal and homoeopathic supplements that could cause bleeding and iii) the risks and potential gains of stopping versus continuing anticoagulants prior to periorbital soft tissue procedures such as TABx (Ing and Douketis, 2014).

In patients with suspected GCA who cannot stop their anticoagulation whether it be a direct oral anticoagulant or warfarin, and in whom ultrasound and MRI are deemed inadequate for diagnosis, my recommendation for soft tissue procedures such as TABx are: 1) discontinue over-the-counter medications such as vitamin E (see Appendix A for expansive list), optimize treatment of hypertension, and if possible dispense a lower-dose formulation of the anticoagulant perioperatively. During TABx in the reverse Trendelenburg position, if initial local anaesthetic administration does not result in a large hematoma I continue with the procedure. Occasionally suction and oxidized regenerated cellulose may be helpful. Two permanent ligatures are placed at the proximal end of the vessel and one is secured distally. After the biopsy, a compressive head dressing is placed over the wound for three days to decrease the risk of haemorrhage. I avoid any TABx if the internist suggests the bleeding risk is so high that the need for prothrombin complex concentrate, idarucizamab, adexanet alfa or aripazine should be considered (Ing, 2019c).

2.2.3 Local anaesthesia and anxiolytic techniques for surgery. Clinical Ophthalmology, 2019

The adroit administration of local anaesthetic and anxiolytics is paramount to the success of awake surgeries such as TABx "as it ensures patient cooperation, aids hemostasis, and enhances the patient's surgical experience and perception of good care." (Ing, Philteos, *et al.*, 2019) Lidocaine cream prior to needle injection may decrease patient discomfort. It is critical to map accurately the location of the artery with a marker prior to anaesthetic injection. If ultrasound has been performed, and TABx confirmation still is requested, the vessel segment

corresponding to the hypoechoic halo on the symptomatic side should be preferentially biopsied. In patients with a readily visible or palpable artery, epinephrine can be incorporated with the initial local anaesthetic injection. The epinephrine in local anaesthetic causes vasospasm and diminution in arterial diameter, making it more difficult to identify the artery. Therefore, in patients with indeterminate surface vessel markings and poor arterial pulsation, I refrain from using epinephrine in the local anaesthetic solution until after the vessel is identified subcutaneously. Local anaesthetic is injected approximately 1 centimetre (cm) away from either side of the vessel but not into the vessel. If there is any concern that the vessel markings will be obscured by the prep solution, the vessel location can be scratched with a needle tip prior to the antiseptic scrub. Our local anaesthetic paper is one of the few papers that summarizes the ancillary anxiolytic techniques that can be used during awake procedures such as TABx including sedatives, stress balls and hand massage, breathing exercises, verbal anaesthesia, music relaxation, vibration, and visualization techniques.

It is plausible that the aforementioned anticoagulation and local anaesthetic considerations were neglected in the recent Role of Ultrasound Compared to Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis (TABUL) study. In 7.3% of the TABUL study subjects, instead of a temporal artery specimen, structures such as a vein, fat, muscle or a nerve were harvested. This is an unacceptably high failure rate. Of the temporal artery specimens obtained in the TABUL study, a remarkable 43% were less than 1 cm in length (Luqmani *et al.*, 2016). To avoid skip lesions the BSR guidelines advocate a biopsy of at least 1 cm (Mackie *et al.*, 2020). Oh et al.'s pathology study found that a 1.5 cm biopsy was the optimum length threshold to avoid a false-negative GCA diagnosis on pathology, and that each millimetre increase in TABx length increased the odds of a positive biopsy by 3.4% (p=0.024) (Oh, Wong, Gill, *et al.*, 2018).

2.2.4 Practice Preference Survey: Temporal Artery Biopsy versus Doppler Ultrasound in the Work-up of Giant Cell Arteritis. Journal of Neuro-ophthalmology, October 2019

To review, TABx has long been acknowledged as the "gold standard" confirmatory test in patients with suspected GCA. Of the imaging techniques described for GCA including MRI, MR angiography, computed tomographic angiography and positron emission tomography, in 2018 EULAR recommended Doppler ultrasound (US) of the temporal +/- axillary arteries as

the first imaging modality in patients with suspected predominantly cranial GCA at centres with appropriate equipment and sufficient radiologic expertise (Dejaco *et al.*, 2018). The 2020 British Society of Rheumatology guidelines for GCA (Mackie *et al.*, 2020) suggested the use of a confirmatory test for GCA which can either be, " a temporal artery biopsy at least 1cm in length, or an ultrasound of the temporal and axillary arteries, or both."

Given the above recommendations, my objective was to determine if ophthalmologists and neurologists currently prefer ultrasound or TABx as their test of choice to confirm GCA. There is debate between the merits of these two investigations (Bilyk *et al.*, 2018; González *et al.*, 2018) and a systematic review has questioned the reliability of US in comparison to TABx (Rinagel *et al.*, 2019).

No prior audits have been published regarding practice preferences in the work-up of GCA. Our 2019 online survey canvassed ophthalmologists and neurologists in North America, Europe and, Israel; Canadian rheumatologists were also included. We also solicited EULAR but did not receive any results from European rheumatologists.

In total 406 surveys were completed in a median time of 22 seconds. The estimated survey response rate was 18% (see Appendix D). There were 253 (62.3%) ophthalmology and neurology respondents (O&N) from North America, 82 (20.2%) O&N participants from Europe, and 71 (17.5%) Canadian rheumatologists.

The survey margins of error (x) were determined using the calculator from https://www.surveysystem.com/sscalc.htm and reported as a 95% confidence intervals in the format (+/- x)$^{95\%CI}$ (see Appendix D).

The overall results from the O&N group showed that 303 (90.5 +/-2.9%)$^{95\%CI}$ preferred TABx as their confirmatory test for GCA, whereas 22 (6.6 +/-2.4%)$^{95\%CI}$ favoured Doppler ultrasound. Of the O&N practitioners who preferred TABx, 268 (88.4 +/-3.3%) $^{95\%CI}$ indicated they use TABx exclusively, and 35 (11.6 +/- 3.3%)$^{95\%CI}$ ordered both TABx and US but preferred TABx. Ten of the 335 O&N participants (3.0 +/-1.8%)$^{95\%CI}$ did not order TABx or ultrasound for their GCA suspects; one used MRI head exclusively, one endorsed ultrasound of the central retinal artery, three deferred work-up decisions to their group's neuro-ophthalmologist, and the remaining five respondents did not provide a reason.

On a regional basis, 242/253 (95.7 +/- 2.31%)$^{95\%CI}$ of North American O&N preferred TABx as their confirmatory test, compared with 61/82 (74.4 +/- 7.7%)$^{95\%CI}$ of their European counterparts. Doppler ultrasound was the favoured test in 2/253 (0.8 +/- ~1.13%)$^{95\%CI}$ of North

American O&N versus 20/82 (24.4 +/-7.6%)$^{95\%CI}$ of European physicians. The regional differences were statistically significant as the confidence intervals do not overlap; also, the non-survey-weighted two-sample test of proportions, as well as Pearson chi^2 test, showed $p < 0.001$ (see Appendix D).

Seventy-one Canadian rheumatologists were surveyed, and 64/71 (90.1 +/- 6.0%)$^{95\%CI}$ preferred TABx, 4/71 (5.6+/- 4.6%) $^{95\%CI}$ endorsed Doppler ultrasound, and 3/71 (4.2+/- 3.9%) $^{95\%CI}$ ordered neither. One rheumatologist from the latter group used MRI head as the preferred investigation.

With regards to test preference and clinician speciality, 34/37 (91.9%) neurologists, 269/298 (90.3%) ophthalmologists and 64/71 (90.1%) rheumatologists endorsed TABx as their confirmatory test for GCA, with no statistically significant difference on repeated two-sample test of proportions (all p-values >= 0.75, Appendix D).

In summary, as of July 2019, most O&N clinicians in North America and Europe prefer TABx to ultrasound in the work-up of GCA. The greater proportionate use of US in Europe versus North America may be because of the EULAR guidelines. The advantages of US over TABx include its non-invasive nature and lower cost. US can assess both the temporal and axillary arteries and increase the diagnostic yield (Luqmani *et al.*, 2016), and serial US can help monitor the effect of treatment. Also, if pathology confirmation is desired, ultrasound may help guide the optimal site for TABx. However, US is highly examiner-dependent technique (Landau, Savino and Gruber, 2013). Systematic review of articles comparing imaging and pathology showed that the hypoechoic halo sign on temporal artery Doppler ultrasound had 68% (57%,78%)$^{95\%CI}$ sensitivity and 81% (75%,86%)$^{95\%CI}$ specificity compared with a positive TABx (Rinagel *et al.*, 2019). Conditions such as atherosclerosis can cause false-positive halo signs on Doppler ultrasound (De Miguel *et al.*, 2018). The low 39% sensitivity for TABx compared with ultrasound in the TABUL study is attributable to deficiencies in the performance of TABx (see Section 2.2.3, page 37). Furthermore, the TABUL study used the ACR clinical classification criteria to diagnose GCA, but these were not intended for same. Even the EULAR task force conceded that TABx "should be performed in all cases, where GCA cannot be confirmed or excluded based on clinical, laboratory and imaging results." (Moiseev *et al.*, 2019)

A potential weakness of our survey is the 18% survey response rate, but this may be an underestimate because some members had multiple listings on the same society membership; retired members were still listed on the internet line; members who belonged to both neuro-

ophthalmology and the oculoplastic societies were double-counted; and pediatric subspecialists would be unlikely to encounter patients with GCA. Our report of 95% confidence intervals mitigates bias in the response rates. Furthermore, the direct correlation between response rate and study validity has been questioned (Morton *et al.*, 2012). Some surveys with low response rates, even as low as 20%, may yield more accurate results than studies with response rates of 60% to 70% (Visser *et al.*, 1996). Investigations with low response rates may be only marginally less accurate than those with higher response rates (Holbrook, Krosnick and Pfent, 2007).

The results of this physician survey elucidated geographic and physician speciality trends in the work-up of GCA, and may aid in the assessment of future preferred practice patterns.

2.3 Differential Diagnosis

Case reports can be "valuable resources of unusual information that may lead to new research and advances in clinical practice. Many journals and medical databases recognize the time-honoured importance of case reports as a valuable source of new ideas and information in clinical medicine." (Ortega-Loubon, Culquichicón and Correa, 2017) TABx can occasionally reveal unsuspected diagnoses as illustrated by the following case reports and the other entities (see Section 2.2.1, p 35). The presentation of GCA can especially mimic malignancy or infection or vice versa. We reported two patients whose clinical presentations were confused with isolated GCA.

2.3.1 Systemic amyloidosis with temporal artery involvement mimicking temporal arteritis. Ophthalmic Surgery and Lasers, 1997

The first patient was a 77-year-old man with jaw claudication, arthralgias, myalgias, weight loss and ESR 35 mm/hr, but no vision loss. He was eventually diagnosed with light chain amyloidosis and multiple myeloma after amyloid was noted on the TABx (Ing *et al.*, 1997). As of 2017, there were 14 other case reports of light-chain amyloidosis mimicking GCA (Ghinai *et al.*, 2017). Both GCA and amyloidosis can cause the symptoms of polymyalgia rheumatica or jaw claudication. Also, amyloidosis is purported to cause non-arteritic ischemic optic neuropathy (Neri *et al.*, 2013). Ghinai et al. advocates Congo red staining of TABx specimens and suggests that amyloidosis should be considered in GCA suspects with an atypical response to glucocorticoids.

2.3.2 Polyangiitis overlap syndrome with Granulomatosis with polyangiitis (Wegener's) and giant cell arteritis. Can J Ophthalmology, 2013

The second case report was of a 61-year-old woman who presented with headache, diplopia, possible jaw claudication, elevated ESR 65 mm/hr and thrombocytosis of 435 x 10^3 mm^3 with transmural inflammation on TABx (Ong Tone, Godra and Ing, 2013). In addition, she had abnormally high anti-neutrophil cytoplasmic antibodies directed to proteinase 3 and fibrocellular glomerular crescents on kidney biopsy. The importance of identifying this GCA - granulomatosis with polyangiitis (Wegener's) overlap syndrome is that in addition to systemic glucocorticoids, treatment with cyclophosphamide or rituximab is required. Antineutrophil cytoplasmic antibody-associated vasculitis and GCA are the most common primary systemic vasculitides in adults. As of 2018, 14 other cases of GCA and granulomatosis with polyangiitis have been reported (Hassane *et al.*, 2018).

2.4 Epidemiology of GCA

GCA is a burgeoning public health concern and the second theme of this thesis is the epidemiology of GCA. As our population ages, the incidence of GCA will likely increase. By 2050 in the United States alone, the estimated cost of GCA due to visual impairment and glucocorticoid-related fractures is estimated to be US$76.3 billion and US$6.6 billion respectively (De Smit, Palmer and Hewitt, 2015). The incidence and predispositions for GCA are important to determine for public health planning. Thus, the motivation for the incidence study for GCA which has not been well documented in Canada, and the geoepidemiologic analysis of the incidence of herpes zoster versus the incidence of GCA in different countries. No prior incidence study had been performed in Canada's most populous province, Ontario. Also, no prior ecologic analysis has compared the incidence rates of zoster and GCA.

2.4.1 The incidence of GCA in Ontario, Canada. Canadian Journal of Ophthalmology, 2019

Disease incidence is important to document for epidemiologic reasons and to facilitate the allocation of public health expenditures. The annual incidence of GCA (IR_{GCA}) ranges from 1.6 to 34.3 cases per 100,000 individuals 50 years of age or older and varies according to geographic location. In general, Scandinavia is thought to have the highest incidence, and

Europe has an intermediate incidence. Japan and Asia report few cases of GCA (Lee *et al.*, 2008; Gonzalez-Gay *et al.*, 2010; Weyand, Liao and Goronzy, 2012; Moraña *et al.*, 2019).

Prior to our incidence study (Ing, Lahaie Luna, *et al.*, 2019), the only Canadian report was from Saskatchewan, a province which has only 3% of Canada's population. The 2007 Saskatchewan study did not specify its enumeration method but found the incidence of biopsy-proven GCA (BPGCA) to be 9.4 per 100,000 people over the age of 50 years (Ramstead and Patel, 2007).

Ontario is Canada's most populous province with 38% of the nation's population. Despite a universal health care system, Ontario has no central registry of positive pathology results, and the provincial billing data does not distinguish GCA from other vasculitides. As such we used two methods to determine the incidence of BPGCA in Ontario, Canada: i) a retrospective pathology audit in Kingston, Ontario, a city with a single dominant medical provider, and a well-contained catchment area, and ii) an incidence estimate from provincial billing data of TABx in conjunction with a meta-analyzed expected positive yield for TABx in Ontario.

There were 35 subjects with positive TABx in the Kingston area over the 4-year period, from a population of 179,503 individuals 50 years of age or older (≥50 years) yielding a minimum cumulative annual incidence of BPGCA of 4.9 per 100,000 individuals over the age of 50 years.

Provincial billing data showed that there were 2,404 individual patients from Ontario who underwent 3,022 TABx (billing code Z815A) from July 1, 2015, to June 30, 2017; approximately 20% of GCA suspects in Ontario had bilateral TABx. From the 2016 Canada census, the population of Ontarians 50 years of age or over was 5,143,610 persons (Statistics Canada, 2017b). A literature search revealed five series of TABx with information on positive yield from Ontario, Canada. Random effects meta-analysis of these five series found the positive yield of TABx in Ontario to be 0.21 (95% CI0.18–0.24) with I^2 13.1% (Fig. 2). As such the incidence estimate of BPGCA from provincial billing data is 4.9 (95%CI 4.2–5.6) per 100,000 persons 50 years of age or over which is in complete agreement with the Kingston, Ontario chart review. Perhaps the lower IR_{GCA} in Ontario compared with Saskatchewan is because of the greater ethnic diversity in Ontario. The IR_{GCA} in Ontario, Canada is also comparable to the rates reported in northern Germany, Australia, and Italy which are between

3.2 and 5.8 per 100,000 population 50 years of age or more (see Appendix B). The IR_{GCA} are higher in Finland, Norway, the United Kingdom, the United States, Israel and, France in part because these figures included clinically diagnosed GCA as well as BPGCA (see Appendix B).

Figure 10. Incidence rate calculations from provincial billing data and pathology lab audit.

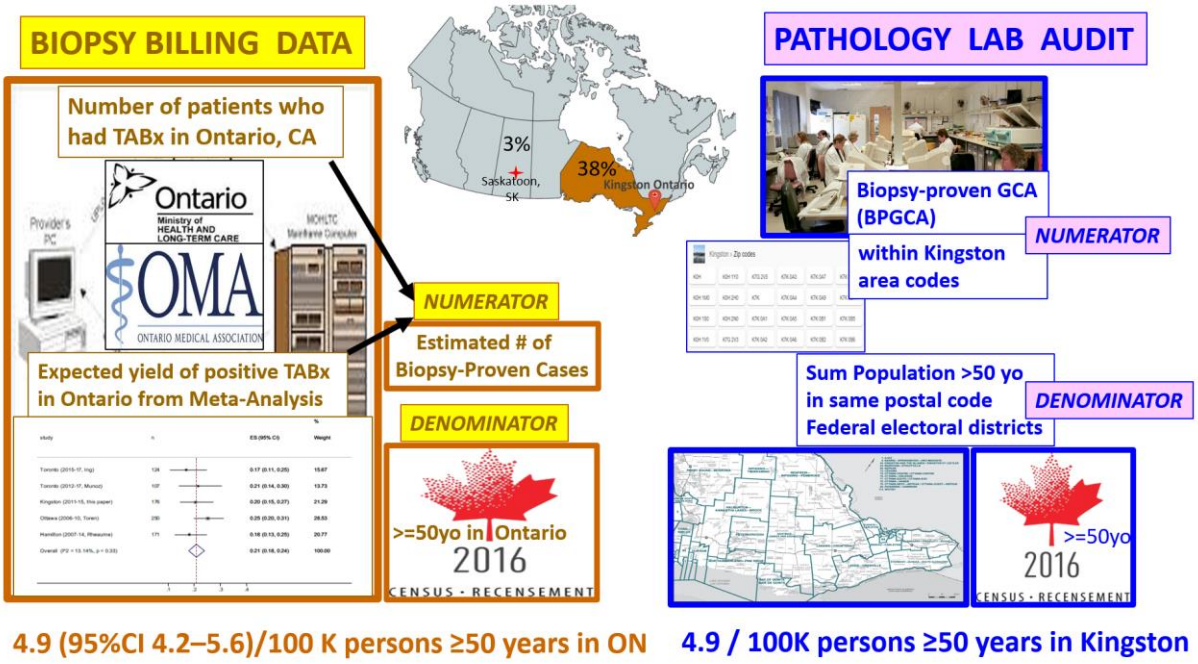


Figure 10. The incidence of GCA in Ontario was estimated from temporal artery biopsy provincial billing data, and the meta-analyzed expected positive yield of TABx in Ontario. Also, the incidence of GCA in Kingston, ON, Canada was enumerated from hospital pathology audit in Kingston, ON noting the postal codes of patients with a positive biopsy. In both methods, the corresponding population denominators were determined from Canada census data for patients 50 years of age and older. Both techniques yielded a GCA incidence of 4.9 per 100,000 patients 50 years of age or older.

2.4.2 Does herpes zoster predispose to GCA: a geoepidemiologic study. Clinical Ophthalmology, 2018

A possible immune trigger for GCA is infection. In particular, there has been much controversy as to whether or not herpes zoster contributes to GCA, heightened by the recent availability of the zoster vaccines. Infections theoretically can predispose to systemic vasculitis through mechanisms such as molecular mimicry, epitope spreading, immune

response to subdominant epitopes normally hidden from T-cell recognition, or bystander activation (Moiseev *et al.*, 2017). Gilden and Nagel found varicella zoster virus (VZV) in the temporal arteries of 73% of patients with BPGCA and proposed VZV as a possible trigger in the immunopathogenesis of GCA (Gilden *et al.*, 2015; Nagel *et al.*, 2015). Although the role of VZV in the development of GCA has not been substantiated by most other investigators and remains controversial, Gilden suggested adjunctive antivirals be considered in the treatment of GCA (Gilden and Nagel, 2016).

As previously mentioned, the incidence rate (IR) of GCA varies widely by country, being the highest in Scandinavian countries and lowest in Asia (De Smit, Palmer and Hewitt, 2015; Mahr *et al.*, 2017).

I hypothesized that if VZV was a strong immune precursor for GCA, the IR for GCA (IR_{GCA}) per country should mirror the local IR for herpes zoster IR (IR_{HZ}). No other publications have tested this original hypothesis. With respect to ecologic studies in epidemiology, the unit of observation is the population. Our geoepidemiologic analysis is the first published ecologic study comparing incidence rates of herpes zoster and GCA.

To test this hypothesis, a literature search was performed and linear regression analysis using the published IR_{GCA} and IR_{HZ} from different countries was plotted. Only countries/regions that had IRs available for both GCA and HZ were used for analysis. Only incidence figures prior to the availability of the zoster vaccines were considered. Paired t-test was used to examine the time difference in year of publication between the GCA and HZ studies for each country.

The IRs for both GCA and HZ were available for 14 countries and are plotted in Figure 11. IR_{GCA} with: IR_{HZ} in 50-year-olds was -0.51 (p=0.07), and IR_{HZ} in 70-year-olds was -0.40 (p=0.16). Linear regression with robust standard errors showed a regression coefficient (β) -2.92 (95% CI -5.41, -0.43; p=0.025) between the IR_{GCA} 50-year-olds, and the IR_{HZ} in 50-year-olds. For the IR_{HZ} in 70-year-olds, no statistically significant linear dependence of the mean IR_{GCA} on IR_{HZ} was detected (β=-1.78, 95% CI -4.10, 0.53; p=0.12). White's test did not suggest heteroscedasticity. A two-sided $p<0.05$ was considered statistically significant.

Figure 11. Incidence of giant cell arteritis versus the incidence of herpes zoster per country.

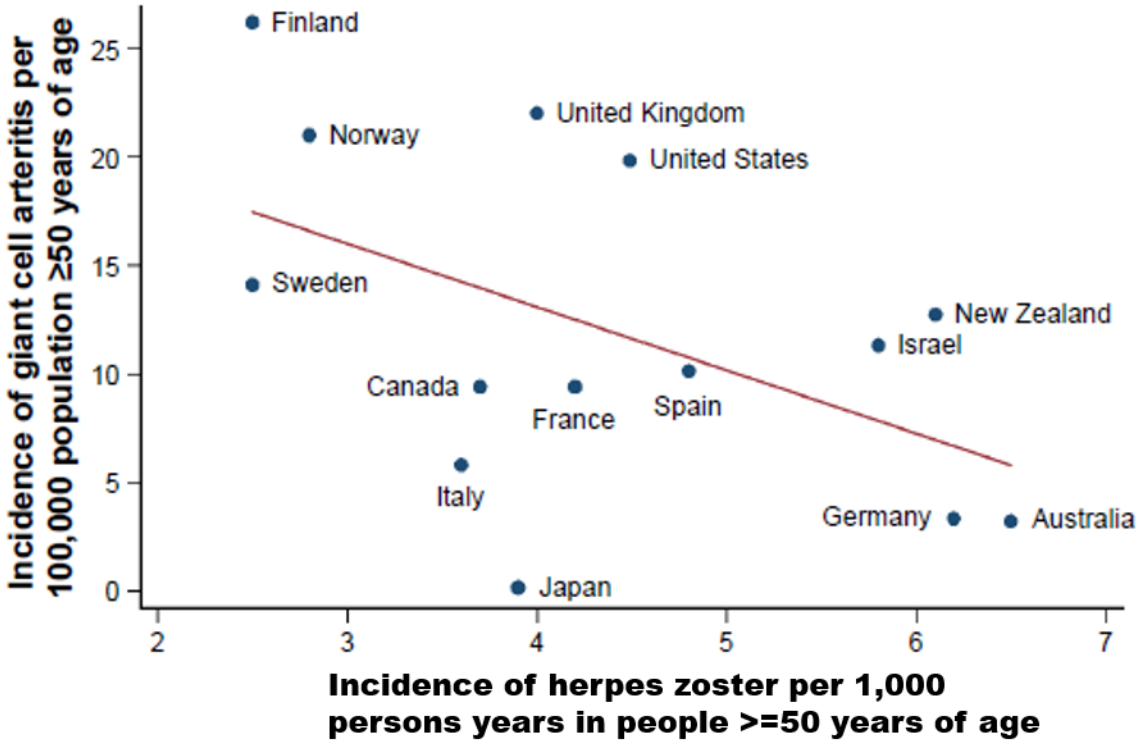


Figure 11. The red line with a negative slope is the line of best linear fit using the least-squares method. The GCA incidence figure for Canada (from Saskatchewan) was the only one available at the time of the original study.

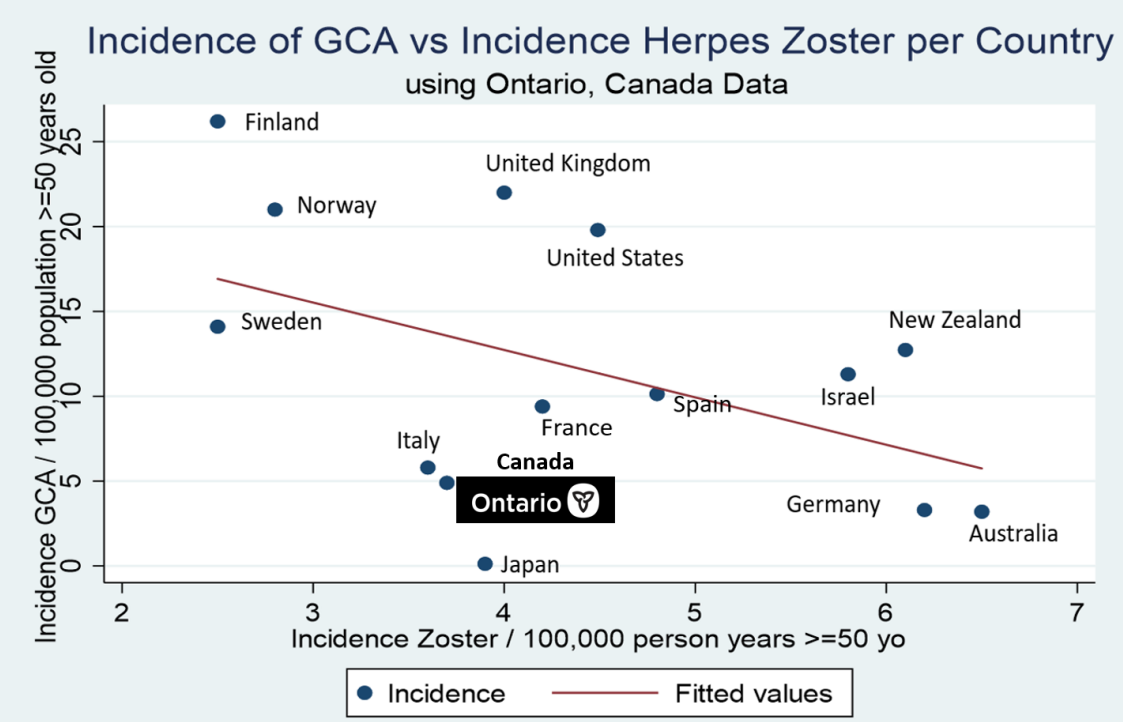
Our ecologic study does not support a positive biologic gradient between the IR_{HZ} and IRG_{CA}. Subgroup regression analyses of the per-country IR_{GCA} and IR_{HZ}, with and without overlapping timeframes were not statistically significant and did not show a positive regression coefficient (see Appendix E).

Our ecologic analysis of the incidence rates of herpes zoster versus GCA is unique in the literature (Ing, Ing, *et al.*, 2018). Although there is potential for aggregation bias with any ecologic analysis, the results of this investigation support the conclusion that *if* there is an association between herpes zoster and GCA, it is not a strong one. A retrospective cohort study found a modest statistical association between VZV and GCA, but given the infrequency of HZ in GCA concluded there are additional immunologic triggers for GCA other than HZ.

Furthermore, antivirals and the zoster vaccines did not consistently mitigate the risk of incident GCA (England *et al.*, 2017).

Our published ecologic analysis was performed when the Saskatchewan study was the only Canadian IR_{GCA} study available. Repeating the analysis using the Ontario, Canada incidence data did not change the result.

Figure 12. Incidence of giant cell arteritis versus the incidence of herpes zoster per country, using Ontario, Canada data.



The red line with a negative slope is the line of best linear fit using the least-squares method. Substituting the incidence of GCA for Ontario, Canada did not change the results.

There is a possible effect of vitamin D on toll-like receptors and GCA, which might render latitude and sunlight in different countries as a confounder. Vitamin D can affect the induction of cell differentiation and immunomodulation. The production of Vitamin D is related to sunlight exposure and therefore latitude. As mentioned earlier the activation of adventitial dendritic cells through TLRs may be the inciting factor in the immunopathology of GCA. Vitamin D supplementation may down-regulate the expression of the TLRs and their

pro-inflammatory effect (Dickie *et al.*, 2010; Adamczak, 2017). Vitamin D has also been shown to boost immunity against herpes zoster (Chao *et al.*, 2014). A possible hypothesis is that vitamin D levels can confound the incidence rates of GCA and zoster such that: i) Subjects using vitamin D supplementation may be less prone to developing zoster or GCA, regardless of their country of origin, latitude or sunlight exposure, and ii) areas with vitamin D deficiency would be expected to have higher rates of both zoster and GCA. These conjectures are difficult to substantiate. Global vitamin D levels are not accurately known, although there appears to be severe hypovitaminosis D in the Middle East and South Asia (Edwards *et al.*, 2012). However, both these regions have a low incidence of GCA.

The contribution to original knowledge from the thesis publications in the context of the existing literature is summarized in Table 4 below.

2.5 Summary of Contributions to Original Knowledge in the Context of Existing Literature

Table 4. Summary of Contributions to Original Knowledge in the Context of Existing Literature

ABBREVIATED ARTICLE TITLE (with clickable link)	**CONTRIBUTION TO ORIGINAL KNOWLEDGE AND THE GIANT CELL ARTERITIS LITERATURE**
DIAGNOSIS OF GCA: STATISTICAL PREDICTION MODELS	
Multivariable prediction model for suspected GCA. 2017	This logistic regression (LR) model with 10 predictors (age, gender, new-onset headache, temporal artery tenderness or pulselessness, jaw claudication, vision loss, diplopia, platelet level, erythrocyte sedimentation rate and C-reactive protein) estimates the risk for GCA prior to TABx. Age and bloodwork were maintained as continuous variables. The LR rule was developed from multi-centre data and was one of the largest series of patients undergoing TABx for suspected GCA to date (n=530 complete cases). It was one of the few/ only prediction models with i) enough cases to support 10 predictors, ii) geographic external validation, iii) compliance with the TRIPOD guidelines for model reporting (including missing data analysis), iv) inclusion of both internal medicine and ophthalmology patients, and v) a user-friendly online risk calculator. Age, jaw claudication, vision loss, platelets, and the log-transformed CRP were statistically significant predictors for GCA.

	This primary LR model handily outperformed the 1990 American College of Rheumatology Classification Criteria for GCA, which many have inappropriately used in the past to diagnose GCA.
Nomogram to Visually Interpret a LR Prediction Model for GCA. Clin Ophthal, 2018	This is the first description of nomograms for the diagnosis of GCA. The length and location of the predictor lines on the Kattan nomogram graphically correlate with the magnitude of the odds ratio and p-value of each predictor in the logistic regression model. The appropriate relative risk contribution of continuous versus binary variables is visually illustrated.
Aids to statistics literacy for ophthalmologists. Can J Ophthal, 2016	Lifelong learning necessitates the ability to independently synthesize the medical and scientific literature especially as machine learning algorithms become increasingly prominent in medicine. This article pools the learning resources available to clinicians who want to learn and interpret statistics and supports the need for visual statistical aids such as nomograms.
Support Vector Machines to predict TABx outcomes. Can J Ophthal, 2019	In a meeting *abstract*, M. Lee et al (Lee *et al.*, 2014) suggested that a GCA statistical model using support vector machines (SVM) had 100% classification accuracy. Using our data (n=530) with proper tuning of the SVM did not show that SVM performed better than logistic regression. This appears to be the only published *article* detailing the application of an SVM model for the prediction of GCA.
Neural network and logistic regression prediction models for GCA. Clin Ophthal, 2019	This multivariable neural network and logistic regression prediction model builds on the framework of the primary 2017 logistic regression (LR) paper, using the same 10 predictors. This even larger multicentre collaboration is the most comprehensive prediction model for GCA in the literature (n=1,201 complete cases). Both internal medicine and ophthalmology patients were biopsied. Missing data analysis and the stipulations of the transparent reporting guidelines (TRIPOD) were upheld. On multivariable LR age, platelets, jaw claudication, vision loss, log C-reactive protein, log erythrocyte sedimentation rate, headache, and clinical temporal artery abnormality were statistically significant predictors for GCA. Platelets were a stronger predictor for GCA than ESR or CRP. The AUROC /Hosmer-Lemeshow p-value for LR was 0.867/0.119 vs NN 0.860/0.805, with no statistically significant difference (p=0.316). The misclassification rate/false-negative rate of LR was 20.6%/47.5% vs 18.1%/30.5% for NN. Decision analysis curves supported the utility of both models. Missing data analysis did not change the results. The neural network model had fewer false negatives than the logistic regression model. Misclassification remains a concern, but the cut-off value for 99% sensitivity is provided (https://goo.gl/THCnuU). The use of the NN-LR calculator may decrease the reliance on TABx for subjects at low risk for GCA. Only one other neural network for GCA has been published, (Astion *et al.*, 1994) but it was developed from classification criteria and a database of known vasculitis patients, and did not include factors such as vision loss, C-reactive protein and platelets.
DIAGNOSIS OF GCA: TEMPORAL ARTERY BIOPSY	

Systematic Review Yield of TABx for Suspected GCA. Neuroophthal, 2018	This is the first systematic review of the utility rate (positive yield) of TABx in the literature and is registered on PROSPERO. From 113 filtered articles, the median yield of 25% with interquartile range (17%-34%) provides a benchmark for decisions regarding the under/overutilization of TABx and aids in the evaluation of non-invasive alternatives for the investigation of GCA such as ultrasound
Local anaesthesia and anxiolytic techniques for oculoplastic surgery. Clin Ophthal, 2019	TABx is performed under local anaesthetic. This article reviews local anaesthetic techniques to facilitate oculoplastics procedures such as TABx. It is one of the few articles that formally outlines anxiolytic techniques that can be used in conjunction with local anaesthesia.
New oral anticoagulants and oculoplastic surgery. Can J Ophthal, 2014	Oculoplastics surgeons are the ophthalmologists who most frequently perform TABx. In 2014, the direct oral anticoagulants (non-Vitamin K oral anticoagulants) were still emerging and had no antidote. Our subspecialty was unsure how to deal with the many patients who were presenting for biopsies and surgery while on these medications. This literature review co-authored with a prominent haemotologist was the first article to summarize the pre-operative considerations and pharmacology of the direct oral anticoagulants from an oculoplastic surgeon's perspective.
Practice Preferences: Temporal artery biopsy versus Doppler ultrasound in the work-up of giant cell arteritis. J Neuro-Ophthalmology, Oct 2019	Although TABx has long been regarded as the gold standard confirmatory test for GCA, the 2018 EULAR guidelines and the 2020 revision from the BSR (drafted in 2019) have suggested Doppler ultrasound (US) of the temporal arteries (+/- axillary arteries) as a possible alternative first-line investigation. The preferred confirmatory test for GCA amongst ophthalmologists and neurologists was unknown. Towards this end, an online survey of ophthalmologists, neurologists in North America, Europe and, Israel was conducted in summer 2019; Canadian rheumatologists were also included. There were 406 survey participants with an estimated survey response rate was 18%. To determine the survey margin of error, 95% confidence intervals were used. Of the North American practitioners, 94.4 +/- 2.4% preferred TABx compared to 74+/-7.7% of their European physicians. Two per cent of North American practitioners preferred doppler ultrasound versus 24% of European physicians. Regional differences were statistically significant ($p < 0.001$). There was no statistically significant difference in the proportion of ophthalmologists versus neurologists versus rheumatologists who preferred TABx ($p > 0.75$). These results may aid in the future evaluation of preferred practice patterns.
DIAGNOSIS: DIFFERENTIAL DIAGNOSIS	
Overlap syndrome: granulomatosis with polyangiitis and GCA, Can J Ophthal, 2013	Patients with both GCA and granulomatosis with polyangiitis require more treatment than just glucocorticoids. This uncommon case appears to be one of only 15 patients in the English literature with this constellation of findings.
Systemic amyloidosis mimicking GCA. Ophthalmic Surg Lasers, 1997	Amyloidosis can present with many features that overlap with GCA including jaw claudication. This uncommon entity has only been reported in fourteen other patients in the English medical literature.
EPIDEMIOLOGY OF GCA	

Incidence of GCA in Ontario, Canada. Can J Ophthal, 2019	At the time of publication this was one of only two GCA incidence papers from Canada, and at the time of publication the sole study considering data from Ontario, which is Canada's most populous province. Dual calculation methods using pathology data from Kingston, Ontario as well as provincial billing data found the same cumulative annual incidence of biopsy-proven GCA at 4.9 per 100,000 individuals aged 50 years or greater.
Herpes zoster and GCA: a geo-epidemiologic study. Clin Ophthal, 2018	The role of herpes zoster in promoting GCA has been questioned. This is the first ecologic analysis to examine the association in incidence rates between zoster and GCA in different countries. The inverse relationship between the incidence rates of these two conditions reaffirms that zoster is unlikely to be the predominant immunopathogenic trigger for GCA.
IMPACT	
Comments on Oh's Bloodwork statistical prediction model for GCA. Int Med J, 2018	This letter to the editor discusses Oh et al's use of the full blood count as an ancillary test to support the diagnosis of GCA (Oh, Wong, Andrici, *et al.*, 2018). Clinical symptoms such as jaw claudication and vision loss were not included. The importance of accurately reporting the number of patients (n=347 complete cases, versus n=537 with missing data) for a multivariable logistic regression model is stressed, as well as testing for multicollinearity testing given the multiple lymphocyte ratio analyses.
Comments on Laskou's GCA probability score. Clin Exp Rheumatol, 2019	This letter to the editor critiques Laskou's et al probability schema for GCA (n=122) (Laskou *et al.*, 2019) with respect to i) overfitting given the small number of patients ii) the inaccurate assignment of arbitrary integer value risk scores to predictors of unequal importance or continuous variables, and iii) the value of an online calculator in contrast to the botheration of adding Laskou's 17 charted risk factors manually.
Comment on Moraña, GCA and usefulness of a predictive calculator, Arch Soc Esp Oftalmol, 2019, accepted July 2019	The authors contend that prediction models may decrease the need for TABx. They suggest the use of the González-López logistic regression prediction model, but this requires the input of the temporal artery biopsy length. Logistic regression requires complete-case analysis without missing data. The NN-LR prediction models that calculate GCA risk prior to the TABx result are presented as a more practical alternative.
Comment on Ross, Diplopia and GCA, J Neuro-Ophthal, 2019	Ross et al published a case-control study on GCA and diplopia (n=27) in the Journal of Neuro-ophthalmology. The data from our NN-LR prediction models provided an even larger cohort of GCA patients with diplopia (n=40). We were able to more accurately contrast the characteristics of diplopia patients with positive versus negative TABx (instead of a case-control group) and emphasized that on multivariable analysis, diplopia is not a statistically significant predictor for GCA.
Comment on Lyons et al, A new era of giant cell arteritis. Eye, 2019. Online ahead of print Nov 25, 2019	Lyons et al suggested that TABx was no longer the gold standard for the diagnosis of GCA. In my correspondence I provided references for a meta-analysis and Bayesian analysis which both showed >=77% sensitivity of TABx. The possibility of false-positive ultrasound, the advantages of tissue diagnosis for diseases that mimic the symptoms and signs of GCA, and the high initial cost of point-of-care ultrasound equipment was also discussed. My comment on the suboptimal TABx from the TABUL study (7% missed

	biopsies, and 43% TABx less than 1 cm) was acknowledged by the authors who responded, "Sadly, this reflects routine care within the normal NHS practice".
Advances in the diagnosis of giant cell arteritis. Current Opinion in Ophthalmology, Nov 2019, Vol 30, Issue 6.	This invited paper to a top quartile ophthalmology journal summarizes some of the notable developments in GCA during the 18 months prior to June 2019. Corneal oedema and proptosis from lacrimal gland ischemia are less common signs of GCA. Drug-induced GCA from cancer treatment with immune checkpoint inhibitor therapy is mentioned. The author's study on decreased ocular pulse amplitude from DCT as an independent, statistically significant predictor for GCA is reviewed. Transdermal optical coherence tomography and photoacoustic imaging are discussed as new imaging modalities for GCA. The thesis prediction models are presented.
CROSS-CUTTING PUBLICATIONS	
Neuro-ophthalmic History, Medscape Ophthalmology chapter, updated Nov 2018	The patient history and physical examination are the cornerstones of medical diagnosis. These review chapters discuss many neuro-ophthalmic entities including giant cell arteritis, an eye disease that should never be missed. These two medical chapters which have been updated biennially for the last two decades are part of the Medscape Ophthalmology library under WebMD. "WebMD's network of websites is used by more unique visitors each month than any other leading private or government healthcare website, and is the leading health publisher in the United States." https://bit.ly/2EFyBO6
Neuro-ophthalmic Exam, Medscape Ophthalmology chapter, updated Jul 2019	The patient history and physical examination are the cornerstones of medical diagnosis. These review chapters discuss many neuro-ophthalmic entities including giant cell arteritis, an eye disease that should never be missed. These two medical chapters which have been updated biennially for the last two decades are part of the Medscape Ophthalmology library under WebMD. "WebMD's network of websites is used by more unique visitors each month than any other leading private or government healthcare website, and is the leading health publisher in the United States." https://bit.ly/2EFyBO6

AAO = American Academy of Ophthalmology; BSR = British Society of Rheumatology; Can = Canadian; Clin = Clinical; EULAR = European League Against Rheumatism; GCA = giant cell arteritis; LR = logistic regression; NCT = non-contact tonometry; Opin = opinion; Ophthal = Ophthalmology; Sur = surgery; TABx = temporal artery biopsy; vs. =versus

Chapter 3. AUTHORSHIP CONTRIBUTION TO PUBLICATIONS

The doctoral candidate (DC):

i) is first author of all the major publications, with estimated percentage contribution of at least 95% (see Table 5).

ii) conceived and designed, acquired, analyzed and interpreted all the data for the publications.
iii) obtained research ethics board (REB) approval for all the articles that required the same.
iv) drafted and critically revised all the articles, and gave final approval of all the articles.
v) is accountable for all aspects of the work and attest to its accuracy and integrity.
vi) performed the primary statistical analysis of all the articles except for the support vector machines (SVM) article, where Dr Wanhua Su had to tune the SVM model using the R statistics package. Royce Ing input the web programming and spreadsheet formulas to place the neural network and logistic regression calculators online.

There is one supporting publication where the DC is the senior responsible author but not the first author. The DC's estimated percentage contribution to the granulomatosis with polyangiitis case report is 60%.

The publications in this thesis have ***not*** been previously submitted for an award at an institute of Higher Education either in the UK or overseas. See Appendix C (Form RD12a)

Table 5. Estimated Contribution of Candidate to Each Publication

ABBREVIATED ARTICLE TITLE (with clickable link)	First Author	Conception and Design	Data Acquisition, Analysis, Interpretation	Draft, Revision, Approval
DIAGNOSIS OF GCA				
Multivariable prediction model for suspected GCA (Ing *et al.*, 2017)	Yes	100%	95%	95%
Nomogram to Visually Interpret a Prediction Model for GCA. Clin Ophthal (Ing and Ing, 2018)	Yes	100%	100%	100%
Support Vector Machines to predict TABx outcomes. Can J Ophthal, (Ing, Su, *et al.*, 2019)	Yes	100%	65%	95%
Neural network and logistic regression prediction models for GCA. Clin Ophthal, (Ing, Miller, *et al.*, 2019)	Yes	100%	95%	95%
Systematic Review Yield of TABx for Suspected GCA. Neuroophthal, (Ing, Wang, *et al.*, 2018)	Yes	100%	95%	95%
Local anaesthesia and anxiolytic techniques for oculoplastic surgery. Clin Ophthal, (Ing, Philteos *et al.*, 2019)	Yes	100%	100%	100%
New oral anticoagulants and oculoplastic surgery. Can J Ophthal, (Ing & Douketis, 2014)	Yes	100%	95%	90%
Practice Preferences: Temporal Artery Biopsy versus Doppler Ultrasound in the Work-up of Giant Cell Arteritis. Neuroophthalmology, (Ing et al, 2019)	Yes	100%	100%	90%
Overlap syndrome: granulomatosis with polyangiitis and GCA, Can J Ophthal, (Ong Tone, Godra and Ing, 2013)	No	100%	95%	60%
Systemic amyloidosis mimicking GCA. Ophthalmic Surg Lasers, (Ing *et al.*, 1997)	Yes	100%	100%	100%
EPIDEMIOLOGY OF GCA				
Incidence of GCA in Ontario, Canada. Can J Ophthal, (Ing, Lahaie Luna, *et al.*, 2019)	Yes	100%	95%	95%
Herpes zoster and GCA: a geo-epidemiologic study. Clin Ophthal, (Ing, Ing, *et al.*, 2018)	Yes	100%	100%	100%
IMPACT: LETTERS TO EDITOR				
Bloodwork statistical prediction model for GCA. Int Med J, (Ing, 2018)	Yes	100%	100%	100%
Comments on (Laskou's) GCA probability score. Clin Exp Rheumatol, (Ing, Sambhi, *et al.*, 2019)	Yes	100%	100%	100%
Comments on Moraña's choice of a predictive calculator. Arch Soc Esp Oftalmol, (Ing, 2019)	Yes	100%	100%	100%

Diplopia and GCA, J Neuro-Ophthal, (Ing et al, 2019)	Yes	100%	100%	100%
Advances in the Diagnosis of GCA. Current Opinion in Ophthalmology, (Ing et al, 2019)	Yes	95%	95%	95%
CROSS-CUTTING AND SUPPORTING ARTICLES				
Neuro-ophthalmic History, emedicine chapter, updated Nov 2018	Yes	100%	100%	100%
Neuro-ophthalmic Examination, emedicine chapter, updated Jul 2019	Yes	100%	100%	100%
Lower OPA with DCT is associated with biopsy-proven GCA. Can J Ophthal, 2018	Yes	100%	95%	100%
DCT vs. NCT in Older Patients with Headache/Vision Loss. Open Ophthal J, (Ing et al, 2018)	Yes	100%	90%	95%
Aids to statistics literacy for ophthalmologists. Can J Ophthal, (Ing et al, 2016)	Yes	100%	100%	100%

AAO = American Academy of Ophthalmology; DCT = dynamic contour tonometry; GCA = giant cell arteritis; LR = logistic regression; NCT = non-contact tonometry; OPA = ocular pulse amplitude; Ophthal = Ophthalmology; TABx = temporal artery biopsy; vs. =versus

Chapter 4. RESEARCH METHODOLOGY

4.1 Overview, Data Collection and Classification (Prediction) Models

The method used to collect data for the prediction models and the pathology audit portion of the incidence study was a multicentre retrospective chart review. The provincial billing data for the incidence study was obtained from the Ontario Medical Association database. The survey data was obtained prospectively using an online format. The articles for the systematic review of temporal artery biopsy were obtained from online database and handsearch. The methods used for data collection further summarized in Table 7. REB approval was obtained for all studies requiring new/unpublished patient information. All work was compliant with the Declaration of Helsinki.

The research was predominantly quantitative. The published works span the evidence hierarchy of editorials, case reports, surveys, cross-sectional studies, cohort studies, systematic reviews and, meta-analyses.

The statistical programs used were Stata versions 14.2 and later 15.1 (StataCorp LP, College Station, TX, USA) and JMP Pro 13.2 (JMP, Marlow, Buckinghamshire, UK). P-values less than alpha 0.05 were regarded as statistically significant. For the logistic regression and neural network prediction models, discrimination with receiver operating characteristic curves and calibration with Hosmer-Lemeshow and missing data analysis was

conducted. Decision curve analysis was also performed for the neural network-logistic regression study.

The basic design of each publication, study size, and statistical analyses where applicable is summarized in Table 7 and further elaborated below. GCA research collaborators were canvassed for at our Canadian national ophthalmic meetings, and with our online neuro-ophthalmology and oculoplastics subspecialty groups.

The cynosures of this thesis are the multivariable diagnostic prediction models which were developed using three different supervised classification algorithms: logistic regression (LR), support vector machine (SVM) and artificial neural networks (NN). Linear regression and polynomial (quadratic) regression were not employed because our outcome variable was binary, i.e. "zero" for negative TABx versus "one" for positive TABx. (Judd, McClelland and Ryan, 2017) Linear regression assumes that the outcome variable is normally distributed, which is not the case with a binary dependent variable. Also, if linear regression was used to model a binary outcome, there may be inappropriate predicted values outside of the range of (0,1) especially since our three bloodwork predictor variables were prone to outliers. Finally, logistic regression allows disproportionate stratified random sampling on the dependent variable without biasing the coefficients (Allison, 2015). In other words, the odds ratios of logistic regression are generalizable and do not depend on the prevalence of GCA in a particular geographic area. Attempts to use quadratic terms in the logistic regression led to overfitting on the prediction response profile curves, and as such were avoided.

A systematic review found that when comparing clinical prediction models with low risk of bias, machine learning techniques such as SVM and NN may not have superior performance over LR with respect to the area under the receiver operating characteristic curve, but many of the articles examined had poor methodology especially with respect to calibration performance and validation procedures (Christodoulou *et al.*, 2019). We specifically examined each classification algorithm to determine if misclassification errors could be minimized especially the false-negative errors because a missed opportunity to prevent blindness is the costliest error in GCA. Also, we applied a rigorous geographic external validation for our LR and NN models.

Binary logistic regression (LR) was utilized because it is the most common classification method used in medicine, (Dreiseitl and Ohno-Machado, 2002) and because the odds ratio can

aid statistical inference. LR is useful for comprehending the influence of independent predictors on a single outcome but is sensitive outliers. The probability for the outcome is estimated by fitting data on the logit function.

SVM was examined because a 2014 GCA study abstract with 182 patients reported 100% classification accuracy with SVM (Lee *et al.*, 2014). SVM represents the training data as points in space separated into categories by a gap (hyperplane) that is as wide as possible. When new cases are presented, they are mapped into the same space and categorized based on which side of the gap they are located. However, SVM does not provide direct probability estimates, which require calculation using cross-validation.

NN was employed to try and decrease the number of false-negative errors from the logistic regression model. NN have building blocks or learning units, akin to neurons organized in layers, and share common roots in statistical pattern recognition with LR. The neurons in a neural network are functions that transform input vectors into some output. After input, the neurons in our model used a non-linear inverse tangent function to output to the next layer. During the training phase weightings are applied to signals passing from one unit to the next, and these weightings are optimized to adapt the neural network to the problem at hand.

We did not pursue random forest decision tree as a prediction model because its false-negative rate was 82% using our data. [7]

4.1.1 Logistic Regression and Neural Network Prediction Models

The 2019 NN and LR prediction model (n=1,201) is an extension of the P-LR (n=530) article. The predictors collected for the NN-LR and P-LR models were the same, and the methodology for the larger LR model differs little from its predecessor. For brevity, I only review the methodology of the NN and LR prediction models once and emphasize the largest and latest study (n=1,201 subjects with complete records out of 1,833 subjects who underwent consecutive TABx). The methodology for the SVM model is discussed separately in a later section.

The GCA prediction model studies were approved by the Michael Garron Hospital REB and by the Institutional REB from each contributing centre. Individual patient consent was not

[7] For comparison, the false negative rate of the logistic regression model was 47.5% and for the neural network model 30.5%. See the Random forest decision tree section in the Supplementary Materials of the NN-LR article. https://docs.google.com/document/d/1kHVMxFmFDE-1UdSGMc65juD_h5Vd7mQCvAGR3s3bPJ4/edit

required as there was no patient randomization, there was no allocation to treatment groups, there were no new treatments, and because the study involved no more than record analysis, which was deidentified. The chart review was not blinded.

A retrospective chart audit of consecutive adult patients who had TABx for suspected GCA was conducted at 14 secondary and tertiary care medical centers in Canada (Toronto, ON; Kingston, ON; London, ON; Ottawa, ON; Hamilton, ON; Montreal, QC; Winnipeg, MB; Vancouver, BC), the United States (Baltimore, MD; Boston, MA; Rochester, MN; Fisherville, VA; and Tampa, FL), and Zurich, Switzerland. The outcome variable for the prediction models was biopsy-proven GCA, i.e., the pathologic diagnosis from TABx was considered the final diagnosis. Indeterminate TABx were regarded as negative TABx. Healed arteritis was considered a positive TABx if glucocorticoid improved the patient's symptoms, and long-term steroid treatment was prescribed. The inclusion of healed arteritis in our group of positive biopsy results requires a caveat. There are no absolute histopathological features that distinguish healed arteritis from changes due to atherosclerosis, arteriosclerosis, or trauma (often referred to as "healed arterial injury"). Indeed, in a study of the interobserver variability in the histopathologic diagnosis of giant cell arteritis, the category of healed arteritis had the greatest interobserver variability (up to 50%) (McDonnell *et al.*, 1986). The interpretation of this result as representing healed arteritis is a clinic-pathologic decision made in conjunction with the clinical response to glucocorticoids and serological features of each individual patient. Most studies do not specify the diagnostic criteria used to qualify a case as healed arteritis, but as this diagnosis results in treatment, this was included as a positive biopsy.

The predictor variables were chosen from clinical judgment, the results of a prior pilot study (Ing, Pagnoux, *et al.*, 2018) and literature including the 1990 ACR classification criteria for GCA (Hunder *et al.*, 1990). The predictor variables were age, gender, new-onset headache (HA), clinical temporal artery abnormality (TAabn), jaw claudication (JC), permanent retinal, optic nerve or visual pathway ischemic vision loss (VL), diplopia, pre-steroid erythrocyte sedimentation rate (ESR), pre-steroid C-reactive protein (CRP) divided by the upper limit of normal (for vasculitis) for each lab, and pre-steroid platelet level. For this study, VL was interpreted as decrement in prior acuity not explained by refractive error or media opacity, fundus abnormality (e.g. nerve fibre layer infarct, disc oedema, CRVO) visual field loss or a relative afferent pupillary defect.

The dose and duration of glucocorticoid treatment prior to TABx was recorded, as was the length of the biopsy. Because our endpoint was biopsy-proven GCA, subjects who did not have TABx within 2 weeks of glucocorticoid initiation were excluded. TABx may remain positive for 2–6 weeks after commencement of treatment (Dasgupta *et al.*, 2010) but the 2-week cut-off was chosen to minimize the chances of false-negative pathology, and because the histologic findings of GCA may begin to alter only after 4 days of glucocorticoid treatment (Font and Prabhakaran, 2007). Bloodwork values that were not obtained prior to glucocorticoid initiation were not used for analysis, but patients were still considered for the missing data analysis (MDA). In patients who had bilateral TABx, the sum of the biopsy lengths was recorded as the biopsy length.

Polymyalgia rheumatica (PMR) was not included as a predictor variable as it can be a nonspecific clinical manifestation, with overlapping age and acute phase response characteristics with GCA. The distinction of PMR from osteoarthritis flare can be difficult; reports of joint X-rays were not uniformly available in this study. Also, rotator cuff injury and fibromyalgia may have overlapping clinical features with PMR. El-Dairi's study did not find that PMR was a statistically significant predictor for a positive TABx (El-Dairi *et al.*, 2015).

Race/ethnicity was excluded as a study variable because it can be difficult to define and is an indeterminate proxy for genetic similarity. Many scholars view racial identity as primarily a social construct and one that can misdirect the categorization of participants in biomedical research. In addition, many of our charts did not identify ethnicity or race. Using the internal biologic effect of an individual study participant's self-reported race/ethnicity is thought to have low potential validity in observational research (Kaufman and Cooper, 2001). Although GCA may be rare in China and Japan, a recent U.S. study found similar rates of GCA in blacks and whites (Gruener *et al.*, 2019).

Our minimum required sample size was 600 patients, to allow for 100 events and 200 non-events in each of the development and validation sets, as recommended for external validation of LR prediction rules (Vergouwe *et al.*, 2005). A formal sample size calculation for an NN is exceedingly difficult to make. Our aim was to acquire at least 1,000 subjects for an NN, to facilitate the development training, validation, and test (holdout) sets. Internal validation and geographic external validation were performed for the neural network and logistic regression models.

The individual patient was the unit of analysis for the statistical models. Statistical evaluations were performed using Stata 14.2 - 15.1 (StataCorp LLC, College Station, TX, USA), JMP Pro13.2 (JMP SAS Institute, Marlow, Buckinghamshire, UK), and R 3.5.0 (R Foundation for Statistical Computing, 2018, Vienna, Austria). An α=0.05 was used for statistical significance.

The continuous variables were graphed. Histogram of the CRP and ESR data showed a right skew distribution, but the distribution of the platelets was approximately normal. A logarithmic transform was used to normalize the CRP and ESR and improve the LR model. For the NN, the "transform covariates" option (Johnson distribution) in JMP Pro was selected for the continuous variables.

Tests for multicollinearity were performed. The LR model had no model misspecification and no multicollinearity, with a mean variance inflation factor 1.17, and the variance inflation factors for ESR, CRP, and platelets were 1.42, 1.54, and 1.18, respectively.

The NN was designed in JMP Pro 13.2 with a single hidden layer and the hyperbolic tangent activation function Figure 7. The number of nodes in the hidden layer was determined from a preliminary analysis of the minimum root mean square error (RMSE) (Duke Fuqua, 2007) of models with one to nine nodes in the hidden layer; four nodes provided the lowest RMSE. To fit the NN, we transformed covariates, used the absolute penalty method, and performed 20 runs. Continuous variables were transformed using the Johnson distribution to minimize the negative effects of outliers or highly skewed distributions. The absolute penalty method further decreased the chance of overfitting and was chosen over the squared penalty method because our previous P-LR analysis had shown that the ten input variables had unequal predictive ability. The 20 runs (designated as tours in JMP Pro) mitigate the issue with local minimums. The NN analysis with one hidden layer, four hidden units, transformed covariates and squared penalty method was run 25 times. The NN with the least number of FNs was chosen as the final model.

Internal validation using tenfold cross-validation was performed. For the LR, the *c*-statistic was averaged for each fold with bootstrapping of the cross-validated area under the curve (Luque-Fernandez, Maringe and Nelson, 2017). Tenfold cross-validation was also performed for the NN using JMP Pro for internal validation with a random seed of zero.

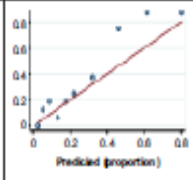
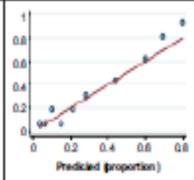
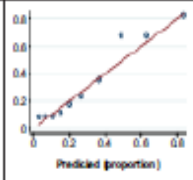
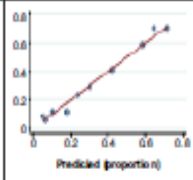
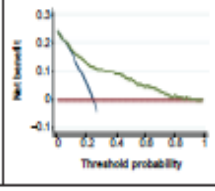
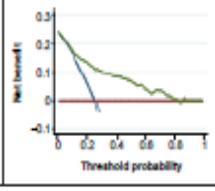
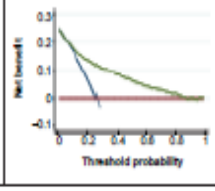
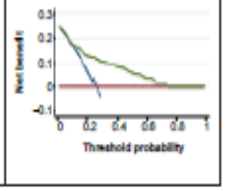
Instead of using a holdout set with the same probability distribution as the training set, external validation by geographic study site was used as a more rigorous evaluation of the generalizability our prediction models. External validation by geographic site simulated the

real-world situation of a prediction model developed in one region, being tested in a new environment. To facilitate geographic external validation, the data from each contributing centre was maintained clustered. The cluster LR was performed with the same training set (n=1,181) data partition as the NN model. For the NN the validation set had 311 subjects and the holdout (test) set had 341 subjects. Subjects in the holdout set were from the geographic centres located the furthest from Toronto, Canada which included British Columbia, Switzerland, or the sites most culturally disparate i.e. Quebec and Switzerland. Model performance was reported for discrimination, calibration, and clinical utility. Receiver operating characteristic curves (ROC) analysis and *c*-statistic was performed in JMP Pro to determine the discrimination of each model. Calibration was performed with the Hosmer–Lemeshow test and calibration plots using Stata. Overall performance measures were reported using the Brier score and generalized R^2. The clinical utility of the models was determined with decision curve analysis (DCA).

DCA uses a net benefit approach that incorporates "benefits" (true positives) and "harms" (false positives) weighting the latter to reflect relative clinical consequences i.e. to determine whether basing clinical decisions on a model would do more good than harm (Vickers and Elkin, 2006). With DCA, the strategy with the highest net benefit (true positive) at a particular threshold probability has the highest clinical value (Vickers and Elkin, 2006). The threshold probability (*Pt*) on the *x*-axis is the probability where the expected benefit of performing TABx is equal to the expected benefit of avoiding TABx i.e. the minimum probability of GCA at which the patient will opt for TABx. For our DCA, we assumed there was no harm in performing a TABx, although it is invasive with risks of facial nerve palsy, infection, and bleeding. TABx is also time-consuming and incurs a moderate expense. DCA showed that both the LR and NN models had clinical utility for a wide range of threshold probabilities (*Pt*). Both models were equivalent or better than a "biopsy-all strategy" for all *Pt*, and superior to a "biopsy none" strategy up to *Pt*,0.81 (See bottom of Table 6).

MDA was performed with the "informative missing" option in JMP Pro for LR and NN using mean imputation for continuous effects. For categorical effects, the missing value was coded as a separate level of the effect. Multiple imputation (MI) with chained equations with 30 imputations was performed using Stata for the LR and R for the NN. Stata does not perform NN analysis. Further methodology details are found in the supplementary materials for the article in the link below.

Table 6. Comparison of Model Performance. Logistic Regression versus Neural Network with complete case analysis and missing data analysis by mean imputation on the test (holdout) set.

Model	Logistic regression (CCA)	Neural network (CCA)	Logistic regression (MDA)	Neural network (MDA)
Sensitivity	0.525	0.695	0.531	0.602
Specificity	0.951	0.891	0.904	0.838
PLR	10.610	6.380	5.500	3.710
NLR	0.500	0.340	0.520	0.480
PPV	0.861	0.789	0.732	0.648
NPV	0.774	0.833	0.794	0.809
Accuracy	0.794	0.819	0.780	0.760
MCR	0.206	0.181	0.220	0.241
FNR	0.475	0.305	0.469	0.398
Calibration H–L *P*	0.119	0.805	0.420	0.987
Calibration plot Observed proportion (blue circle) Predicted proportion (red line)				
Discrimination (c) (95% CI)	0.867 (0.794, 0.917)	0.860 (0.786, 0.911)	0.827 (0.772, 0.870)	0.809 (0.752, 0.855)
Brier score	0.148	0.143	0.153	0.162
Generalized R^2	0.446	0.458	0.373	0.337
Decision curve analysis Net benefit Biopsy all (blue) Biopsy none (red) Prediction rule (green)				

Abbreviations: c, concordance statistic or the area under receiving operating curve; CCA, complete-case analysis; FNR, false-negative rate; H–L *P*, probability of Hosmer–Lemeshow test (calibration is acceptable if $P>0.05$); MCR, misclassification rate; MDA, missing data analysis; n, number of subjects; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value; R^2, square or percent of variance explained by the model; ROC, receiver operating characteristic.

4.1.2 Nomogram

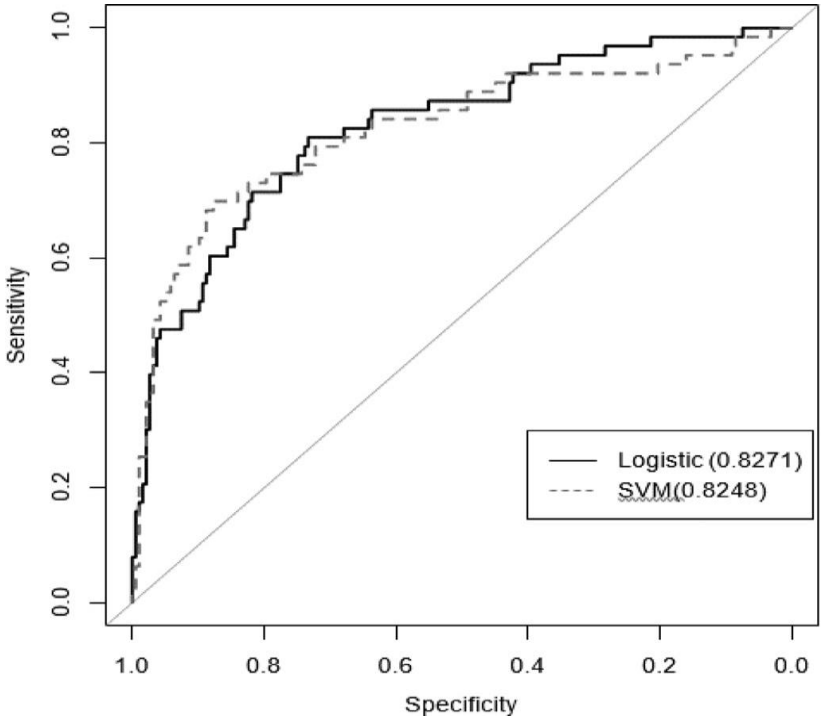
Kattan nomograms for logistic regression equations can be constructed in Stata by entering the command "nomolog" after the logistic regression has run. Nomolog is a Stata plug-in (Zlotnik and Santos, 2013).

4.1.3 Support Vector Machines Model

The methodology for the SVM prediction model (n=530) varied slightly from the LR and NN models, although the model employed the same 10 predictor variables (age, sex, temporal artery tenderness or decreased pulsatility, new-onset headache, vision loss, diplopia, jaw claudication, platelet level, log of the erythrocyte sedimentation rate (ESR), and log of the C-reactive protein (CRP) and outcome (temporal artery biopsy result). Although logistic regression can process skewed data, the logistic regression model was more accurate when the ESR and CRP data were normalized via log transformation. We maintained the log transformation to compare the logistic regression and SVM models. Age and bloodwork were maintained as continuous variables. My statistician co-author Dr Wanhua Su used the R statistics package (version 3.4.2, http://www.R-project.org/) to compare logistic regression and SVM. The dataset of 530 subjects was randomly split into training and test sets. The resulting training set had 210 subjects with negative TABx and 70 subjects with positive TABx. The test set had 187 negative TABx and 63 positive TABx. Models were fit on the training set and their performance compared on the test set. The area under the receiving operating curve (AUC), average precision (AP), misclassification rate (MCR), and false-negative rate (FN) were determined for each model. The SVM model with a radial basis function kernel was further tuned examining both the AUC and MCR with 5-fold cross-validation to determine the optimum ɣ and cost (c) parameters. The logistic regression and SVM receiver operating characteristic (ROC) curves were compared with DeLong's test for 2 correlated ROC curves (DeLong, DeLong and Clarke-Pearson, 1988) and the statistical package (pROC) (Robin *et al.*, 2011).

For our dataset, the SVM model with optimal discrimination had gamma= 0.01267 and cost = 26.466, with 133 support vectors. DeLong's test showed no statistically significant difference between the logistic regression and SVM ROC curves ($z = 0.16621$, $p = 0.868$) with almost overlapping ROC curves (see Figure 13). However, the SVM model had a 5% higher false-negative rate than LR and in GCA false-negative errors are the greatest concern with GCA. Given the increased difficulty in tuning and interpreting SVM results compared to LR, SVM did not offer any distinct advantage over LR in our dataset of 530 TABx subjects.

Figure 13. ROC analysis of logistic regression and optimized support vector machine predictive models.



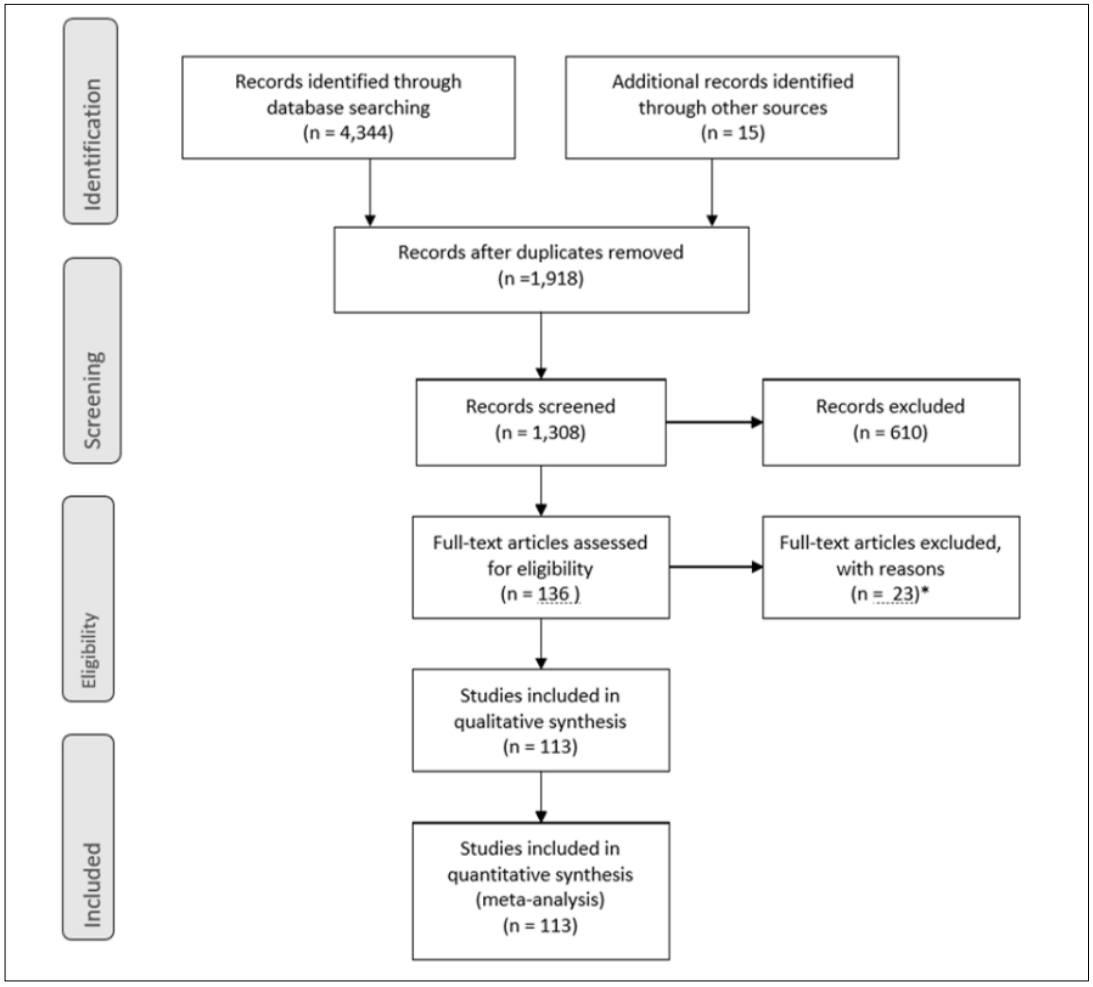
The discrimination of the logistic regression and support vector machine models are almost identical. Logistic = logistic regression; SVM= support vector

4.2 Systematic Review of the Yield of Temporal Artery Biopsy for Suspected GCA

The systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) ID=CRD42017078508.

Relevant articles were sourced from PubMed, Embase, Cochrane Central Register of Controlled Trials, Google Scholar, Open Grey, and hand search from 1 January 1998 to 31 December 2017, using the search terms ("giant cell arteritis OR temporal arteritis") AND "biopsy". Studies were excluded if they reported patients with positive TAB only or patients with negative TAB only, or if only patients with an established clinical diagnosis of GCA were selected. Four thousand three hundred and fifty-nine GCA studies were identified and after review 113 remaining articles were included for meta-analysis. (see Figure 14, PRISMA diagram)

Figure 14. Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Flow Diagram for Meta-analysis of Yield of Temporal Artery Biopsy



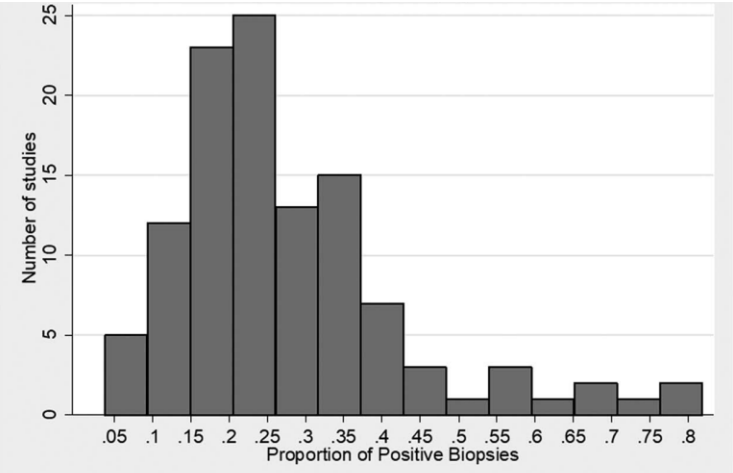
Five authors elected eligible studies and performed the quality analysis (DW, EB, JM, AK, and GS). Disagreements were adjudicated by the principal author (EI). The quality analysis was performed from the perspective of the potential for bias in the TABx results.

The major criteria for selection bias were non-consecutive TABx in the study group and verification bias. Although articles investigating ultrasound/magnetic resonance imaging (MRI) for GCA may have had little bias with respect to the imaging investigation, TABx may not have been obtained in all patients, or the decision to perform TABx may have been influenced by the result of the imaging study, leading to verification bias. In a large TABx series of unilateral and bilateral biopsies, if only results of the bilateral biopsies were reported

this was considered selection bias. If only subjects with high ACR scores underwent TABx, this was considered a possible performance bias. If the pathologist was not blinded to the patient's symptoms, bloodwork results, or ACR score, this was a possible detection bias. Withdrawals from TABx (e.g. patient refusal to undergo TABx, or a vein or nerve specimen rather than the artery) were considered an attrition bias. If the pathology results from all patients that underwent TABx were not listed, this was considered a reporting bias. The main reason for "other bias" was because TABx series from the same city, author, or institution had a partial overlap of patients that we could not eliminate.

The 113 articles encompassed 30,898 TABx, of which 7379 (23.9%) were positive. The yield of TABx from the articles had a right skew distribution with a non-weighted mean 27.7%, and median 25.0% with interquartile range 17% to 34%.

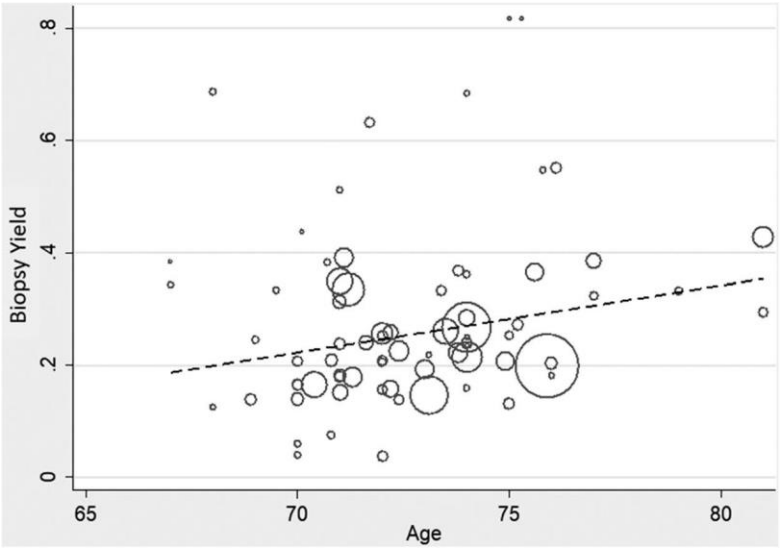
Figure 15. Histogram of the Yield of Temporal Artery Biopsy from 113 Studies



Initial analysis was performed with Stata 14.2 (StataCorp LLC, College Station, TX, USA) using a random-effects meta-analysis of proportions (metaprop) with Freeman–Tukey double arcsine transformation to stabilize the variances and exact confidence intervals (Nyaga, Arbyn and Aerts, 2017). Stata was used to perform a random effects meta-regression of the aggregate-level data (metareg). If heterogeneity exceeded 75%, we would also compare the results with MetaXL 5.3 (EpiGear International Pty Ltd) fixed-effect inverse variance heterogeneity model (IVHet) with double arcsine prevalence transformation, 0.5 continuity correction, and normalized prevalence (Doi *et al.*, 2015). If heterogeneity exceeded 90%, we would report the median yield and interquartile range. When available, the pre-specified

predictors of patient age, proportion of females, specimen length, bilateral TABx, ACR scores greater than or equal to three, vision symptoms, duration of steroid use prior to TABx, study size, decade of study, and use of arterial imaging (ultrasound or MRI) were recorded from each study for metaregression. A p-value < 0.05 was considered statistically significant. The utility rate of TABx by country and yield from first decade versus second decade of reports were also compared. The I^2 statistic of 92% suggested that heterogeneity was too large to perform meta-analysis. As such the median and interquartile range were reported. Notwithstanding metagression was performed. On univariate metaregression, age was the only statistically significant patient factor associated with TABx yield (see Figure 16).

Figure 16. Random effects metaregression of the yield of temporal artery biopsy versus age



4.3 Incidence of GCA in Ontario

Kingston, Ontario, Canada has a prominent medical centre (Queens University) that is relatively isolated from other medical facilities. The incidence study was approved by the REBs at Michael Garron Hospital and at Queens University and compliant with the Declaration of Helsinki. In Kingston, ON TABx were only performed at two medical facilities and there was a well-contained catchment area as the next closest surgical centre was at least 100 kilometres away. Thus, most if not all the cases of biopsy-proven GCA from Kingston would be captured. A chart review for all TABx cases from the Kingston hospitals (Kingston General Hospital and Hotel Dieu Hospitals) was completed for the 48-month period

from October 2011 to September 2015 inclusive. Only patients with residence postal codes within the federal electoral districts of Kingston and the Islands, and the adjoining districts of Leeds-Grenville Lanark-Frontenac, and Hastings-Lennox and Addington were included in this study. The population of the Kingston catchment area was calculated by averaging the data from the 2011 and 2016 Canada Census data (Government of Canada, 2019). Because GCA rarely is seen before the 6th decade of life, only individuals 50 years of age and over were tabulated in each electoral district for the population denominator. A query to the private pathology labs (Life Labs-CML and Dynacare) and the Quinte Health System was also made to see if any patients with Kingston postal codes had TABx submitted outside of the Kingston hospital system. In the second part of this study, we used the 2016 Canada census data, provincial billing data, and a meta-analysis of the positive yield of TABx series performed in Ontario to estimate the incidence of GCA in Ontario, Canada. The Ontario billing code for TABx is Z815A, but there was no accompanying pathology database that identified positive versus negative biopsies. To estimate the incidence of biopsy-proven GCA in Ontario, we determined the number of patients who underwent TABx (code Z815A) from July 1, 2015, to June 30, 2017. The population denominator of Ontarians 50 years of age or older was tabulated from the 2016 Canada Census Profile. The expected positive yield (utility rate) of TABx for our province was calculated from review of the Ontario TABx series in the literature, Kingston data, and a Toronto hospital pathology audit (D. Munoz, personal communication, TABx pathology service audit 2012–2017, St. Michael's Hospital, Toronto, 2017). All published English language articles on GCA and TABx were reviewed from 1981–2017 and studies performed in Ontario, Canada were retained.

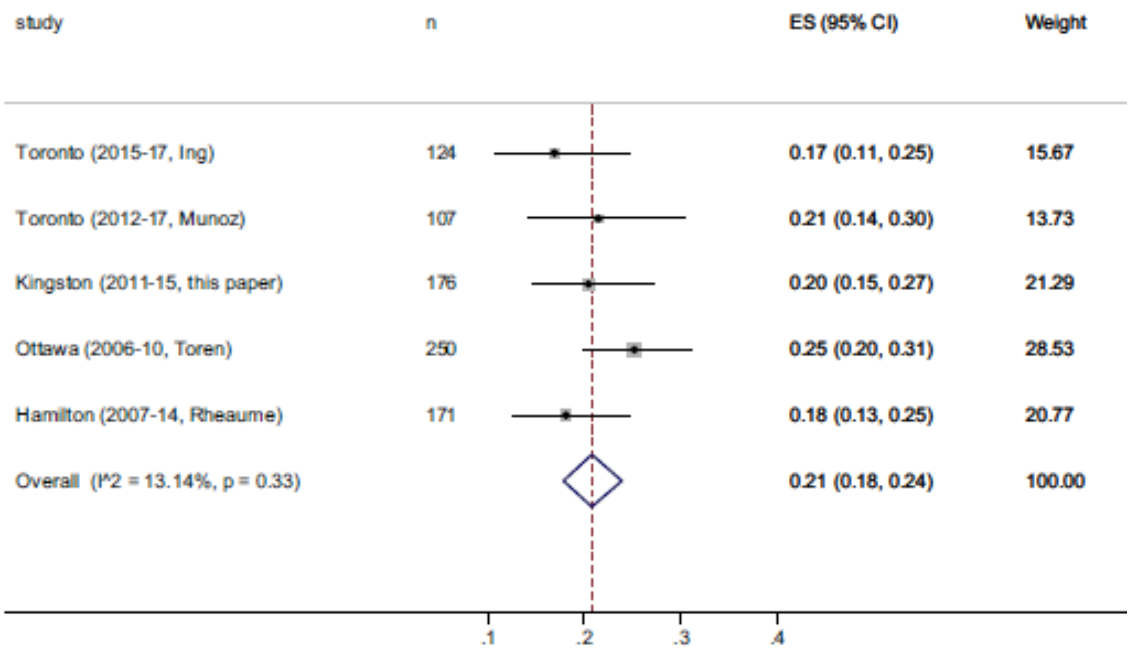
For the pathology audit, the population denominator at risk was ascertained using the postal codes of patients with biopsy-proven GCA from Kingston and the corresponding population denominator listed in the Canada census federal electoral district data at the time the TABx were performed. This self-contrived temporal geocoding technique is relatively simple, but has not been documented on Google Scholar and Pubmed literature search. Averaging the figures between the 2011 and 2016 Canada census data, the population of individuals 50 years of age or older with postal codes corresponding to the Kingston catchment area yielded the population denominator of 179,503 individuals. During the 4-year study period, 176 patients underwent TABx in Kingston, and 36 had biopsy-proven GCA. One subject with biopsy-proven GCA resided in the Northumberland-Pine Ridge federal electoral district and was

excluded from the analysis. From a pathology audit of temporal artery biopsies (TABx) in Kingston, ON, and federal census data, the minimum cumulative annual incidence of biopsy-proven GCA was 4.9 per 100,000 individuals over the age of 50 years.

Ontario, Canada has universal health care with a single party provincial payer, but it does not have a centralized registry or database for GCA or the results of TABx. Provincial billing data for the number of TABx performed is available. For billing purposes, rheumatologists in Ontario code cases of GCA using the 3-digit International Statistical Classification of Diseases, Ninth Edition (ICD-9) diagnostic codes as either code 446 "polyarteritis nodosa and allied conditions" or code 447 "other disorders of the arteries and arterioles." The Ontario billing system does not use the more specific ICD-9 four-digit code for GCA, which is 446.5. This makes it difficult to separate GCA from other vasculitides with billing data. Furthermore, ophthalmologists may code their patients with GCA as primary ophthalmic disorders using ICD-9 codes such as optic neuropathy. All patients undergoing TABx procedures (Z815A) who were billed were identified, but there was no pathology database that identified which biopsies were positive. As such, we derived the expected positive yield of TABx from the meta-analysis of 5 series of TABx performed in Ontario, Canada. Statistical analysis was performed with Stata 14.2 (StataCorp LLC, College Station, TX) using a meta-analysis of proportions (metaprop) with a random effects analysis. Random effects meta-analysis of the five Ontario series of TABx from Toronto, ON (Ing, Pagnoux, *et al.*, 2018) (D. Munoz, personal communication), Ottawa, ON, (Ing *et al.*, 2017) Hamilton, ON, (Rhéaume *et al.*, 2017) and Kingston, ON.(the present study) found the positive yield of TABx in Ontario to be 0.21 (95% CI0.18–0.24) with I^2 13.1% (

Figure 17)

Figure 17. Random effects meta-analysis of the positive yield of temporal artery biopsy in Ontario, Canada.



The pooled estimate for the utility rate of temporal artery biopsy in Ontario, Canada was 21%.

In part due to skip lesions or false-negative TABx, the use of BPGCA to determine incidence may underestimate the number of cases of GCA compared with studies that also include clinically diagnosed GCA. The diagnosis of BPGCA relies on properly performed surgery with, adequate length specimens that also are appropriately interpreted by the pathologist.

4.4 Practice Preference Survey: Temporal Artery Biopsy versus Doppler Ultrasound in the Work-up of Giant Cell Arteritis

An REB-approved online survey of ophthalmologists and neurologists in North America, Europe and, Israel was conducted in May and June 2019. Canadian rheumatologists were also canvassed.

The survey instrument was Survey Planet, (https://surveyplanet.com/). The three study questions were: 1) What test do you currently use to confirm the diagnosis of giant cell arteritis? 2) Where do you work? and 3) What is your primary speciality? The available responses to each question are shown in Appendix D and at https://s.surveyplanet.com/UJ2kjVmw6. The survey did not advance until all questions were answered, and the software prevented double entries from the same computer or internet protocol (IP) address.

Practitioners with membership in neuro-ophthalmology (European Neuro-ophthalmology Society, North American Neuro-ophthalmology Society) and oculoplastic surgery societies (American Society of Oculoplastic and Reconstructive Surgery, Canadian Society of Oculoplastic and Reconstructive Surgery) were targeted as these specialists were most likely to encounter patients with GCA. The survey was also sent to a group of Canadian rheumatologists from Ontario, Canada. To optimize the response rate, the survey was kept anonymous, designed to be completed in 25 seconds, incorporated a logo, avoided questions about age or years in practice (Fan and Zheng, 2010). Also, on the internet lines that allowed mass emailing, requests for survey responses were canvassed at least twice on two separate dates. Respondents could free text additional details, and their email address if they desired. The results of the European and Israeli physicians were pooled as a group.

The survey margin of error was determined from the survey sample size, the percentage of the sample that chose a particular answer, and the estimated population size using the calculator from https://www.surveysystem.com/sscalc.htm. The margin of error was reported as a 95% confidence interval. Two-sample tests of proportions were used to compare regional and practice speciality preferences.

4.5 Geoepidemiologic Analysis of Incidence Rates: Zoster versus GCA

The IR_{GCA} was searched for on PubMed, Embase, and Google Scholar from inception to July 1, 2017, using the search terms: incidence, epidemiology, country, temporal arteritis and GCA. The same search was repeated using herpes zoster in place of the arteritis terms.

The country-specific IRs for subjects 50 years of age and older were recorded per 100,000 population for GCA, and per 1,000 person-years for HZ. If IRs were provided for multiple years, the results were averaged.

The IR_{GCA} in Japan was calculated using Koboyashi's reported prevalence rate of 1.47 per 100,000 in subjects aged 50 years or older, with the average age of onset of 71.5 years (Kobayashi *et al.*, 2003). Lifespan is thought not to be affected by GCA unless the patient has aortic aneurysm or dissection (Kermani *et al.*, 2013). The average life expectancy in Japan is 83.3 years (United Nations, 2015). As GCA is a rare disease and recurrent, the IR was estimated as the prevalence rate/duration of disease =1.3 per million subjects 50 years or older.

Because the peak onset of GCA is in the 8th decade (Gonzalez-Gay *et al.*, 2010), we also examined the IR of HZ in 70-year-olds. If the age brackets straddled our chosen age cut-offs, the IR values from the two adjacent brackets were averaged. Only countries/regions that had IRs available for both GCA and HZ were used for analysis. Paired *t*-test was used to examine the time difference in year of publication between the GCA and HZ studies for each country. There was inadequate information in the GCA articles to consistently calculate the within-study standard errors needed for meta-regression. Pearson product-moment correlation coefficients and linear regression with and without robust standard errors were performed. White's test was used to test for heteroscedasticity. All statistical tests were conducted with Stata 14.2 (StataCorp LP, College Station, TX, USA), and a two-sided $p<0.05$ was considered statistically significant.

Apart from Olmsted County and the United Kingdom, the availability of IR_{GCA} and IR_{HZ} from the same time frame and corresponding geographic region was limited. Eight of the 14 countries (57%) (see Appendix E) were overlapping in the time frame of the corresponding GCA and HZ studies. On paired *t*-test, the GCA studies were published on average 4.5 years before the HZ studies ($p=0.09$). A published IR_{GCA} for Iceland was available. The IR_{HZ} for Iceland was only available for the 60-year age group only (4.7 per 1,000), but not the 50-year-old or 70-year-old age groups, and as such was not used.

Pearson product-moment correlation coefficient (*r*) comparing IR_{GCA} with: IR_{HZ} in 50-year-olds was -0.51 (p=0.07), and IR_{HZ} in 70-year-olds was -0.40 (p=0.16). Linear regression with robust standard errors showed a regression coefficient (β) -2.92 (95% CI -5.41, -0.43; p=0.025) between the IR_{GCA} 50-year-olds, and the IR_{HZ} in 50-year-olds. For the IR_{HZ} in 70-year-olds, no statistically significant linear dependence of the mean IR_{GCA} on IR_{HZ} was detected (β=-1.78, 95% CI -4.10, 0.53; p=0.12). White's test did not suggest heteroscedasticity. Subgroup regression analyses of the per-country IR_{GCA} and IR_{HZ}, with and without overlapping timeframes were not statistically significant and did not show a positive regression coefficient.

When the incidence of GCA and zoster was replotted with a local polynomial smoothed line and 95% confidence interval, no consistent biologic gradient between the incidence rates of GCA and zoster was seen.

Figure 18. Incidence rate of GCA versus Zoster in subjects greater than age 50 years per country with a local polynomial smoothed line and 95% confidence interval.

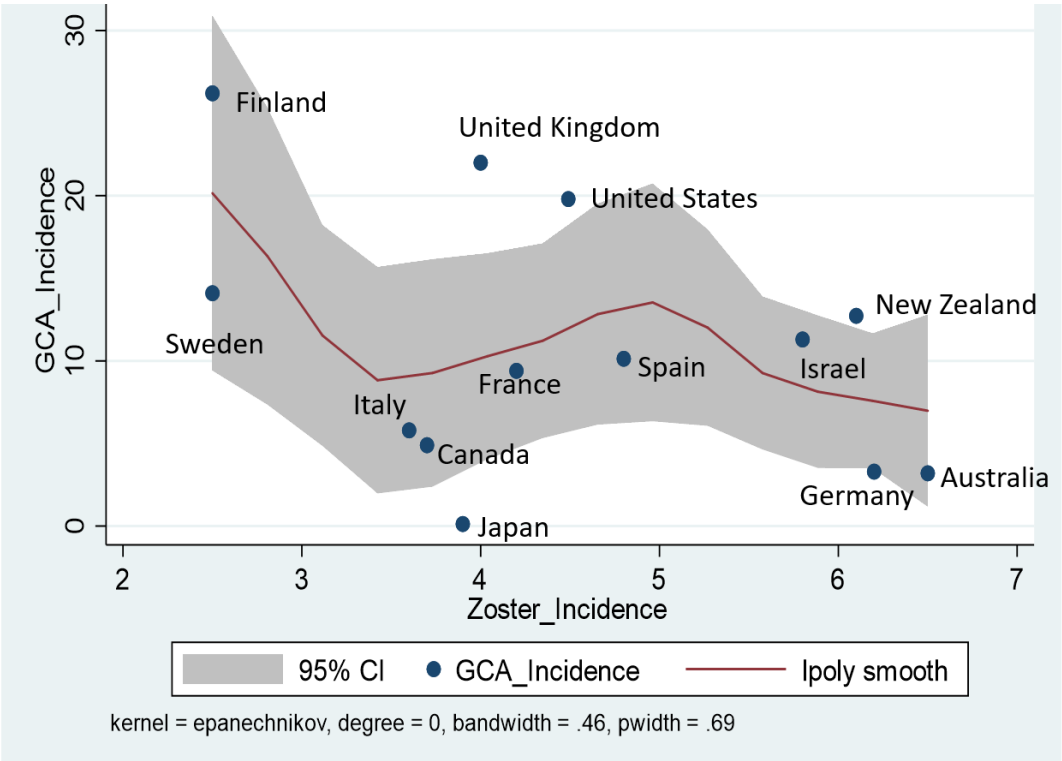


Table 7. Summary of Methodology Used in Each Publication

ABBREVIATED PUBLICATION TITLE (with clickable link)	**METHODOLOGY** Study design, n= number of subjects *Statistics [Statistics Program]*
DIAGNOSIS OF GCA: STATISTICAL PREDICTION MODELS	
Multivariable prediction model for suspected GCA. 2017 (P-LR)	Retrospective chart review cohort study at 7 medical centres (n = 530 complete cases). TRIPOD-compliant CRP and ESR were right-skewed and therefore log-transformed *Logistic Regression* *Internal Validation (10-fold cross-validation and bootstrap)* *External Validation (geographic holdout)* *[Stata 14.2, JMP Pro 13.2]*
Nomogram to Visually Interpret a Prediction Model for GCA. Clin Ophthal, 2018	In Stata the "nomolog" command was entered after logistic regression (n=530) *Logistic regression, Kattan Nomogram [Stata 14.2]*
Aids to statistics literacy for ophthalmologists. Can J Ophthal, 2016	Review and Summary of Literature
Support Vector Machines to predict TABx outcomes. Can J Ophthal, 2019	Data from the P-LR multicentre retrospective chart review (n=530 complete cases). A training set was tuned with radial basis kernel function. ROC of SVM and LR models were compared. *Support Vector Machines, Logistic Regression, DeLong's test [Stata 14.2 and R]*
Neural network and Logistic Regression prediction models for GCA. Clin Ophthal, 2019	Retrospective chart review cohort study from 14 international medical centres (n = 1,201 complete cases). TRIPOD-compliant. The 10 predictor variables from the P-LR model were retained. *Logistic Regression: clustered by centre, ESR and CRP were log-transformed* *Neural Network: one hidden layer with 4 nodes, ESR and CRP had Johnson transformation* *Internal Validation (10-fold cross-validation and bootstrap)* *External Validation (geographic holdout)* *Decision Analysis Curves to verify utility of the model* *[Stata 15.1, JMP Pro 13.2]*
DIAGNOSIS OF GCA: TEMPORAL ARTERY BIOPSY	
Systematic Review Yield of TABx for Suspected GCA. Neuroophthal, 2018	Systematic review of the literature (n = 113 articles) Relevant articles were sourced from PubMed, Embase, Cochrane Central Register of Controlled Trials, Google Scholar, Open Grey, and hand search from 1 January 1998 to 31 December 2017, using the search terms ("giant cell arteritis OR temporal arteritis") AND "biopsy". The study was registered on PROSPERO. *Random effects Meta-analysis of Proportions and Meta-Regression [Stata 14.2]*
Local anaesthesia and anxiolytic techniques for oculoplastic surgery. Clin Ophthal, 2019	Literature review
New oral anticoagulants and oculoplastic surgery. Can J Ophthal, 2014	Literature review

Practice Preferences: Temporal Artery Biopsy versus Doppler Ultrasound in the Work-up of Giant Cell Arteritis	Online survey instrument: Survey Planet https://s.surveyplanet.com/UJ2kjVmw6 The ophthalmology and neuro-ophthalmology speciality societies in North America and Europe and the Canadian Rheumatology society were canvassed by email as these were the specialists most likely to encounter GCA. We did not receive any responses from EULAR. Where possible, the techniques described by Fan and Zheng were used to optimize survey response. *Survey margin of error (95% confidence intervals) https://www.surveysystem.com/sscalc.htm* *Two sample tests of proportions [Stata 14.2]*
DIAGNOSIS OF GCA: Differential Diagnosis	
Overlap syndrome: granulomatosis with polyangiitis and GCA, Can J Ophthal, 2013	Case Report, Review of literature
Systemic amyloidosis mimicking GCA. Ophthalmic Surg Lasers, 1997	Case Report, Review of Literature
EPIDEMIOLOGY OF GCA	
Incidence of GCA in Ontario, Canada. Can J Ophthal, 2019	Cross-sectional study to determine incidence of GCA. Dual methods employed: 1) Retrospective pathology audit, Kingston, ON with postal code information to geocode population denominators in the Canada Census (n=172) 2) Provincial Billing Data to determine number of patients undergoing TABx (n=2,404) along with random effects *Meta-analysis of TABx yield from Ontario, CA studies, Incidence estimate with 95% confidence interval [Stata 14.2]*
Herpes zoster and GCA: a geo-epidemiologic study. Clin Ophthal, 2018	Ecological study with geographic comparison of the incidence rates of herpes zoster and GCA from literature review ("n" =14 countries) *Linear regression, Pearson product motion correlation t-test analysis of incidence rates from different time periods versus same time period [Stata 14.2]*
IMPACT	
Bloodwork statistical prediction model for GCA. Int Med J, 2018	Letter to the Editor, Critique of Literature
Comments on (Laskou's) GCA probability score. Clin Exp Rheumatol, 2019	Letter to the Editor, Critique of Literature
Comments on Moraña, Arch Soc Esp Oftalmol	Letter to the Editor, Critique of Literature
Diplopia and GCA, J Neuro-Ophthal, 2019	Letter to the Editor, Critique of Literature, *Logistic Regression [Stata 14.2]*
CROSS-CUTTING OR SUPPORTING ARTICLES	

Neuro-ophthalmic History, emedicine chapter, updated Nov 2018	Literature review
Neuro-ophthalmic Exam, emedicine chapter, updated Jul 2019	Literature review
DCT versus NCT in Older Patients with Headache/Vision Loss. Open Ophthal J, 2018	Prospective Cohort study, Single Centre (n=106) *Bland Altman plots [Stata 14.2]*
Lower OPA with DCT is associated with biopsy-proven GCA. Can J Ophthal, 2018	Prospective validation study, Single Centre (n= 109 complete cases) Logistic *regression [Stata 14.2]*

AAO = American Academy of Ophthalmology; DCT = dynamic contour tonometry; GCA = giant cell arteritis; LR = logistic regression; NCT = non-contact tonometry; ON = Ontario; OPA = ocular pulse amplitude; Ophthal = Ophthalmology; TABx = temporal artery biopsy; TRIPOD = compliance with guidelines for transparent reporting of multivariable prediction models for individual prognosis and diagnosis, with missing data analysis

Chapter 5. IMPACT

The impact of the doctoral research is presented in the categories of:

i) Clinical impact
ii) conference presentations
iii) professional networks, teaching opportunities and award nominations
iv) publication metrics and literature citations
v) invited paper and requested article reviews
vi) critique of the GCA literature, based on the thesis work

i) The NN-LR prediction model with its favorable decision curve analysis and geographic external validation has direct, immediate clinical application for the triage of patients with suspected GCA. Unlike clinical intuition, which may be prone to bias, the prediction model incorporates ten variables including symptoms, signs, and blood tests to provide an objective pretest probability for GCA. The pretest probability is helpful for shared decision-making with patients suspected to have GCA, and in such algorithms as the one used in the British Society of Rheumatology Guidelines for GCA (Mackie *et al.*, 2020) [see Figure 19 below]. The prediction model can decrease the number of TABx performed on low risk subjects with a tripartite benefit. Fewer patients will undergo a low yield invasive procedure. Surgeons will have time to perform more productive clinical activities, and medical funding can be redirected for greater utility.

Since patients and some clinicians may not comprehend the statistical details of the NN-LR article a plain language summary and explanatory video are available online, along with the link to the calculator. (The underlined elements in the previous sentence are clickable links.)

ii) The research has been presented at international, national and local venues. The logistic regression and nomogram were introduced at the 2018 North American Neuro-ophthalmology Society Meeting (Torun *et al.*, 2018). The clinical application of the GCA prediction models was presented at two recent Canadian Ophthalmological Society (COS) Meetings, (Ing *et al.*, 2017; Ing, 2019a) and a recording of the NN-LR presentation is online. The research methodology of the GCA prediction models was discussed at the University of Toronto Ophthalmology Research Day in fall 2017 and fall 2018. The University of Toronto was ranked 21st in the World University Rankings in 2019 (Times Higher Education, 2019).

iii) Professional networks and teaching opportunities beget the potential to disseminate scholarly work and influence present and future generations of physicians. The co-authors of the NN-LR paper were from the eight dominant medical schools in Canada, along with contributors from Harvard, Johns Hopkins, and the Mayo Clinic. The co-authors were enlisted through my membership in nine ophthalmic speciality organizations. The internet lines of these professional organizations facilitated the exchange of opinions on the prediction models and epidemiology of GCA as well as practice preferences in the work-up of GCA.

The University of Toronto is Canada's largest medical school with numerous opportunities to interact with fellows, residents, and medical students and to participate in post-graduate medical education forums. Residents and medical students participated in the data collection of three of the thesis publications and presented two of them as posters at the June 2018 Canadian Ophthalmologic Society meeting (Lahaie Luna, Ing and ten Hove, 2018; Wang, Benard-Seguin and Ing, 2018).

The influence of the GCA research is supported by nominations for the 2020 Bressler Prize in Vision Science, and the 2020 Harvard Chan Alumni Award of Merit.[8]

[8] The Bressler award is an annual $54,000 prize offered by the Lighthouse Guild in New York, NY to a "clinician or scientist whose leadership, research and service have led to substantive advancements in the understanding of vision loss, treatment of eye disease, or the rehabilitation of people with vision loss" (Lighthouse Guild, 2019). My nomination was supported by Dr. Neil Miller, the Frank B. Walsh Professor of Neuro-Ophthalmology and Professor of Ophthalmology, Neurology & Neurosurgery at the Johns Hopkins University School of Medicine in Baltimore, Maryland. The Harvard Chan Alumni Award of Merit was put forth by my MPH classmates.

iv) The topic of GCA has an eminent impact in the medical literature. In August 2019, GCA was assigned a SciVal Topic Prominence percentile of 97.060, on Scopus, which indicates a high "momentum, movement or visibility of a collection of documents with a common intellectual interest" (Elsevier, 2019).

My Scopus h-index is 11. All the major thesis works were published since February 2019. The Scopus field-weighted citation impact (FWCI) [9] was available for six of the thesis publications in July 2019, with a mean of 2.57+/-1.56 and median 2.43. A FWCI value greater than 1.00 means that the document is more cited than expected according to the average. For example, a score of 1.44 means that the outputs have been cited 44% more times than expected (USC Australia, 2018).

Table 8. Article Citations and Journal Metrics as of July 2019

Article	Citations in the Literature Google Scholar/Scopus	Field-Weighted Citation Impact (July 2019)	Total Article View Metrics (Dove Press, July 2019)
Neural network and logistic regression diagnostic prediction models for giant cell arteritis: development and validation. Ing EB, Miller NR, Nguyen A et al Clin Ophthalmol. 2019 Feb 21;13:421-430	-	-	4,703
The incidence of giant cell arteritis in Ontario, Canada. Ing EB, Lahaie Luna G et al. Can J Ophthalmol. 2019;54(1):119-124	2/1	4.85	
Does herpes zoster predispose to giant cell arteritis: a geo-epidemiologic study. Ing EB, Ing R, Liu X, Zhang A, Torun N, Sey M, Pagnoux C. Clin Ophthalmol. 2018 Jan 11;12:113-118.	6/4	3.08	5,729
Systematic Review of the Yield of Temporal Artery Biopsy for Suspected Giant Cell Arteritis. Ing EB, Wang DN, Kirubarajan A et al. Neuroophthalmology. 2018 Jun 19;43(1):18-25.	1/1	2.43	

[9] "The Field-Weighted Citation Impact shows how well cited this document is when compared to similar documents. It accounts for: the year of publication, document type, and disciplines associated with its source. The FWCI is the ratio of the document's citations to the average number of citations received by all similar documents over a three-year window. Each discipline makes an equal contribution to the metric, which eliminates differences in researcher citation behavior" (Scopus, 2015)

The Use of a Nomogram to Visually Interpret a Logistic Regression Prediction Model for Giant Cell Arteritis. Ing EB, Ing R. Neuroophthalmology. 2018 Feb 5;42(5):284-286	3/2	1.57	
Bloodwork statistical prediction model for giant cell arteritis. Ing E., Intern Med J. 2018 May;48(5):607-608	2/1	1.24	
Multivariable prediction model for suspected giant cell arteritis: development and validation. Ing EB, Lahaie Luna G, Toren A, et al Clin Ophthalmol. 2017 Nov 22;11:2031-2042	16/12	4.20	6,955
New oral anticoagulants and oculoplastic surgery. Ing E, Douketis J, Can J Ophthalmol, 2014: 49(2):123-7.	13/7		
Polyangiitis overlap syndrome with granulomatosis with polyangiitis (Wegener's) and giant cell arteritis. Ong Tone S, Godra A, **Ing E**. Can J Ophthalmol. 2013 Feb;48(1):e6-8	3/4	0.63	
Systemic amyloidosis with temporal artery involvement mimicking temporal arteritis. Ing EB, Woolf IZ, Younge BR, Bjornsson J, Leavitt JA. Ophthalmic Surg Lasers. 1997 Apr;28(4):328-31	18/17	-	

Table 9. Journal Rank of Ophthalmology Publications

Journal	2018 Scimago Journal Rank
Current Opinion in Ophthalmology	1.299 (Q1)
Clinical Ophthalmology	0.994 (Q1)
Journal of Neuro-ophthalmology	0.625 (Q2)
Canadian J Ophthalmology	0.578 (Q2)
Neuro-ophthalmology	0.286 (Q3)

v) The journal, Current Opinion in Ophthalmology annually reviews the topic of GCA by inviting an author to comment on literature from the previous year. I was invited to be the lead author of the fall 2019 review of GCA, on the topic "Advances in the Diagnosis of Giant Cell Arteritis" and discussed many of the thesis publications. Current Opinion in Ophthalmology is one of the top quartile journals in the field of ophthalmology with an impact factor of 2.824, and SciMago Rank 1.299.

I was invited to review three articles on GCA by the *Canadian Journal of Ophthalmology* in February 2017 (Weis *et al.*, 2017), *BMC Geriatrics* in May 2019 (González-Gay *et al.*, 2019), and the *Journal of Headache and Pain* in September 2019. The article by Weis et al

did not have internal validation, and I was able to provide the authors with the Stata code to complete a cross validation. The last article I reviewed was accepted in March 2020, and concerned the European Headache Federation guidelines for neurologists managing GCA. My comments are listed in Appendix I.

vi) I published five critiques of the GCA literature, which supports the ability for "independent critical power". Three of the letters commented on alternative statistical models for GCA.

The critique of Oh et al's article (Oh, Wong, Andrici, *et al.*, 2018) commented that logistic regression requires complete case analysis, and that reported sample sizes should not be inflated when there is missing data. Also, the concern for multicollinearity on multivariate analysis was expressed given the multiple lymphocyte ratio analyses (Adamczak, 2017; Ing, 2018).

The article concerning Laskou et al's GCA probability score (Laskou *et al.*, 2019) expressed the concern about overfitting because their 17-predictor variable model was developed from only 23 cases of GCA and a total dataset of 122 subjects. Furthermore, the assignment of the same arbitrary integer values to predictors of varying importance was questioned.

Moraña et al (Moraña *et al.*, 2019) asserted that prediction models may decrease the need for TABx but suggested the use of González-López's logistic regression prediction model that requires the input of the TABx length. My Letter to the Editor emphasized that logistic regression requires complete-case analysis without missing data. As such the NN-LR models that calculate GCA risk prior to the TABx result are a more rational alternative (Ing, 2019b).

My fourth Letter to the Editor concerned Ross et al's case-control study of 27 GCA subjects with diplopia, (Ross *et al.*, 2019) to estimate the differentiating features of diplopia in patients with and without GCA. The major disadvantages of case-control studies include incomplete control of extraneous variables and bias in selecting an appropriate matched comparison group (Schulz and Grimes, 2002). Given the size and design of our NN-LR retrospective cohort study, we were able to add the perspective of 40 additional patients with BPGCA and diplopia with a more accurate comparison of the features that differentiated them from the diplopia subjects without BPGCA. Although our patients with diplopia and GCA

had statistically significant greater age, jaw claudication, vision loss, ESR, CRP and platelet levels than patients with diplopia and a negative TABx, diplopia was not a statistically significant predictor for GCA on univariate or multivariable analysis. In my strabismus practice, the vast majority of patients presenting with diplopia do not have GCA. Also, diplopia may have been a weak predictor for GCA because in our study 20% of our subjects overall with BPGCA had vision loss; patients who are blind in one or both eyes are less prone to binocular diplopia.

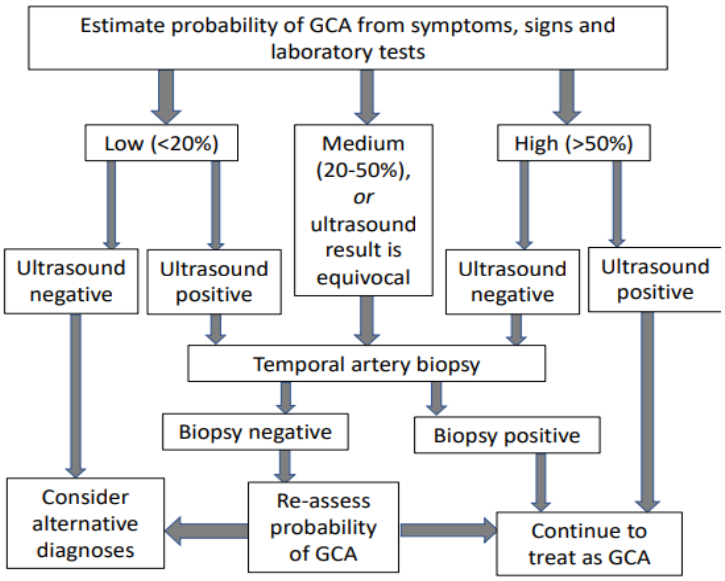
The fifth letter to the editor addressed Lyons et al "new era" in GCA (Lyons *et al.*, 2019) which suggested that TABx was no longer the gold standard for the diagnosis of GCA. However at least one meta-analysis (Rubenstein *et al.*, 2019) and another Bayesian analysis (Niederkohr and Levin, 2007) support the higher sensitivity and specificity of TABx relative to ultrasound. The possibility of false-positive ultrasound was mentioned and advantages of tissue diagnosis for diseases that mimic the symptoms and signs of GCA, and the high initial cost of point-of-care ultrasound equipment were discussed. My comment on the suboptimal TABx from the TABUL study (7% missed biopsies, and 43% TABx less than 1 cm) was acknowledged by the UK authors who responded, "Sadly, this reflects routine care within the normal NHS [National Health Service] practice" (Mollan *et al.*, 2019).

Lastly, the recently published British Society of Rheumatology (BSR) guideline (Mackie *et al.*, 2020) recommended "Patients with suspected GCA should have a confirmatory diagnostic test. This could be either a temporal artery biopsy at least 1cm in length, or an ultrasound of the temporal and axillary arteries, or both." I agree with this recommendation.

Figure 1 of the 2020 BSR guideline for suspected cranial GCA (designated Figure 19 in this thesis) advocates the use of clinician judgment to triage patients into low, medium and high-risk groups followed by ultrasound. The BSR further stated that "various clinical prediction rules have been proposed to assist clinicians in the estimation of the probability of GCA; the performance of a clinical prediction rule developed in another setting should ideally be checked using local audit data prior to adopting into local clinical practice." Outwardly this seems prudent, but the bias in using clinician judgment to risk stratify GCA more than likely exceeds any potential bias from a multi-centre, prediction model with external validation, such as the NN-LR because:

Figure 19. British Society of Rheumatology (BSR) 2020 algorithm for suspected giant cell arteritis

Figure 1. A possible approach to using rapid-access vascular ultrasound to assist in clinical diagnostic decision-making in suspected cranial GCA.



i) Expertise in vascular ultrasound is highly operator dependent (Landau, Savino and Gruber, 2013). False-positive ultrasound tests can occur with atherosclerosis (De Miguel *et al.*, 2018) and other conditions (Fernández *et al.*, 2019) between 4.3-10% of cases.

ii) Clinical judgment is usually not as accurate as a prediction algorithm (Ayres, 2007; The Medical Futurist, 2016; Parikh, 2018). Humans cannot accurately, simultaneously weight multiple variables, especially when there are non-linear relationships. No matter how experienced clinicians believe they are, humans are prone to cognitive errors and bias.

I suggested to the BSR that a more judicious position statement would be to caution against the use of prediction rules derived from small numbers of patients, without external validation,

or non-compliance with the TRIPOD guidelines. The NN-LR rule was developed from the data of multiple centres in North America, and the external validation set included patients from Switzerland.

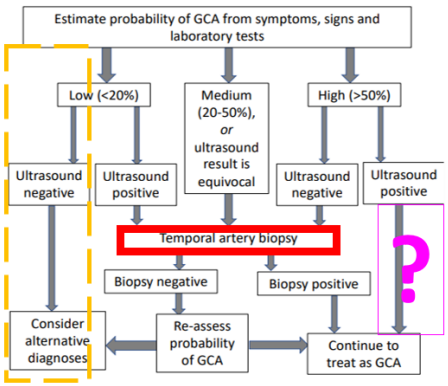
Figure 20 shows the congruency of the BSR guidelines and NN-LR in the regions of the orange dashed outlines. A disadvantage of the BSR risk category designations is that they are arbitrary. Given the catastrophe of possible bilateral vision loss from undiagnosed GCA some may feel the upper limit of "low risk" for GCA should be less than 20%. To help physicians calibrate their numeric clinical judgments on risk, a table of risk scores generated from the NN-LR model for hypothetical GCA clinical scenarios is provided in Appendix F.

The BSR guideline to avoid TABx in patients at high risk for GCA given a positive ultrasound (pink question mark at the bottom left of Figure 20) is controversial. If the BSR persists on the exclusive use of ultrasound for this category of patients it would be safer if *bilateral*, circumferential US haloes of thickness 0.7 mm or greater (Pouncey *et al.*, 2018) were required to forego TABx. Ideally all patients consigned to long term glucocorticoids should have biopsy confirmation of disease due to the potential risks of glucocorticoids. Ultrasound can be misleading (De Miguel *et al.*, 2018; Fernández *et al.*, 2019). The pathology from TABx may occasionally reveal a myriad of alternative diagnoses including syphilis, sarcoid and amyloidosis (see Section 2.2.1 page 35).

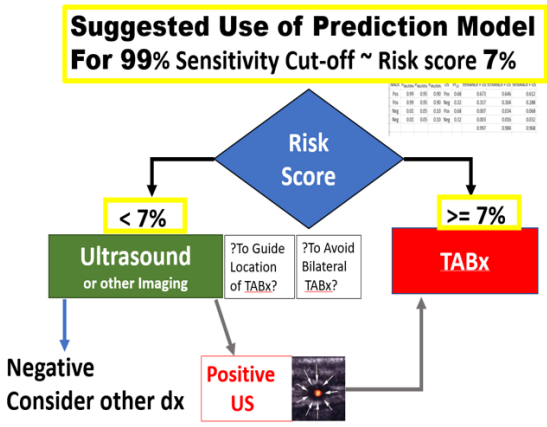
Figure 20. Comparison of Neural Network-Logistic Regression Calculator with the British Society of Rheumatology (BSR) 2020 Guidelines for GCA

BSR Guidelines

Figure 1. A possible approach to using rapid-access vascular ultrasound to assist in clinical diagnostic decision-making in suspected cranial GCA.



NN-LR Calculator



In summary, the impact of the thesis work on GCA is evidenced by the publications, presentations, critiques of the GCA literature/guidelines, and nomination for the Bressler Prize in Vision Research. The NN-LR model confirms the importance of platelets over ESR and CRP, and the need to include platelets in the core data set for GCA treatment and research, a point that was not appreciated in Table 1 of the 2018 EULAR recommendations (Ehlers *et al.*, 2019). Most importantly the NN-LR model shifts the paradigm of clinical diagnosis from reliance on clinical intuition or subjective estimations of probability, (Mackie *et al.*, 2020) to clinical judgment assisted by an objective, externally validated risk stratification.

Chapter 6. CRITICAL REFLECTIONS AND FUTURE WORK

Critical reflections on the research work included: i) the need to decrease the barriers to de-identified health care data, and the importance of electronic health records. ii) the obligation for robust, independent assessment of peer-reviewed literature iii) the perception of the GCA literature by different medical specialties may be biased and iv) the resistance of clinicians to using computerized algorithms.

i) Although a doctoral degree emphasizes independent and scholarly work, collaboration is required especially for data acquisition in the modern era. The most difficult aspects of the research were the delay in ethics board approval from collaborating institutions, although the

data were de-identified. “Dissatisfaction with the [ethics board] review process, particularly the time interval from submission to decision, is common within the research community” (Page and Nyeboer, 2017). The protection of patient privacy, patient safety and autonomy are paramount. Paradoxically, the convoluted access to non-sensitive, de-identified retrospective data to qualified and vetted health care researchers is a barrier to safeguarding and improving the health care of patients. To improve future research accessibility, citizens could be given the option to post their de-identified health care data for research, much like the presently available organ and tissue donor registration programs (Government of Ontario Health and Wellness, 2019). I suggested that the provincial and federal health agencies establish a publicly available database for research, (see Appendix G) that would be free of charge to researchers. This database could dovetail with existing patient-oriented research organizations such as the Strategy for Patient-Oriented Research in Canada (Aubin, Hebert and Eurich, 2019).

The adaptations required to carry out the incidence of GCA in Ontario study were complex. Despite Ontario, Canada having a universal health care system, it has no mechanism to enumerate the number of positive TABx performed in its pathology labs. With the increasing use of electronic medical records, future researchers will hopefully have better access to such data.

ii) When evaluating the performance of TABx as a test, competent execution of the biopsy must be ensured with procurement of an adequate length specimen, and appropriate interpretation by the pathologist. This sine qua non must be considered even when interpreting influential, peer-reviewed publications such as TABUL (Luqmani *et al.*, 2016). Critical deficiencies in the TABx technique were not listed in the abstract of the TABUL study. TABUL is 237-page report, and one must delve into the document to discover that 7% of the attempts at TABx were missed, and when an arterial specimen was obtained 43% were shorter than the 1 centimetre length suggested by the British Society of Rheumatology guidelines. The ultrasounds in TABUL were performed at a high standard, but the TABx were subpar; any claims of the comparative diagnostic accuracy of the two techniques are biased (Rubenstein *et al.*, 2019). Articles that repeatedly quote the TABUL study as justification for bypassing TABx (Lyons *et al.*, 2019) are unsettling, especially given the possibility of false-positive ultrasounds and glucocorticoids side effects.

Notwithstanding, the increased use of imaging methods to diagnose GCA in the future is anticipated. This is only partly due to the diffusion of innovation (Rogers, 1983) as ultrasound for the diagnosis of GCA has been described at least since 1981 (Dany *et al.*, 1981). Rather, the use of imaging will expand if it becomes more difficult to obtain timely and properly performed TABx (Mollan *et al.*, 2019). The number of TABx performed annually in Ontario, Canada may be declining, (Micieli, Micieli and Margolin, 2015) at least in part because they are not well remunerated throughout North America. In my locale surgeons often decline referrals to perform this procedure, or are not provided sufficient hospital resources to perform the procedure in a timely fashion.

iii) The neuro-ophthalmology and rheumatology communities may perceive the GCA literature from different perspectives. Most ophthalmologists see patients with the cranial arteritis variant of GCA, who require high dose glucocorticoids to avert vision loss. However, internal medicine specialists are more frequently referred patients with polymyalgia rheumatica, or the limb claudication and pyrexia of unknown origin variants of GCA, that may respond to lower dose glucocorticoids (Fraser *et al.*, 2008). After publication of the P-LR article, a reviewer unknowingly opined that "the model authors are ophthalmologists and thus are focusing on patients who present with cranial symptoms" (Holliman, 2018). The reviewer did not realize we had rheumatology and neurology coauthors, that the ophthalmic surgeons in the study were the primary biopsy service for many of the rheumatologists at their respective institutions, and that hospital chart reviews incorporated all patients who underwent TABx regardless of which service performed the biopsy. Furthermore, all the non-biopsy 1990 American College of Rheumatology classification criteria for GCA were incorporated in the P-LR model. Although the referral service was not indicated for every patient in the database of our publications, where the information was available, 52% of the P-LR patients were referred by rheumatologists, internal medicine specialists or primary care physicians. In the subsequent NN-LR model 46.8% of the patients were referred by non-ophthalmologists. This bolsters the generalizability of our P-LR and NN-LR models.

iv) Resistance to the use of actuarial methods by "expert specialists" has existed since Paul Meehl's "disturbing little book" in the 1950s (Meehl, 1954). As computerized algorithms improve, so must our willingness to adopt them. Robert Pearl, M.D. states, "the biggest barrier to artificial intelligence in medicine …. is a medical culture that values doctor intuition over evidence-based solutions. Physicians cling to their independence and hate being told what to

do." (Pearl, 2018) No prediction models are perfect and artificial intelligence (AI) will not replace physicians, but AI can make doctors better (Parikh, 2018). The role of prediction algorithms is to objectively guide clinical judgment.

Areas for future research endeavour include: a) Optimization of the diagnostic yield of TABx and quality control in the interpretation of TABx b) Optimization of the NN-LR model and c) the incorporation of imaging results with the NN-LR model to determine the post-test probability of GCA.

a) The yield of TABx may increase with standardization of the pathology reading process and special stains. Towards this end we will need to survey Canadian pathologists to ascertain the average length of the specimen they receive, the percentage of bilateral specimens, the number of sections they initially perform, if the artery is initially sectioned entirely, the number of sections that are initially examined, and whether or not further sections or special stains are ordered if the initial pathology appears unrevealing. The survey has been developed and soon to be launched is at https://s.surveyplanet.com/lYLQOF7uv Having a centralized quality-control consensus centre for TABx interpretation would also be an asset if funds permitted.

b) The thesis prediction models could be bolstered by larger sample sizes, further external validations, the prospective collection of information and a statistical analysis to account for multiplicity errors. The response categories of the presently binary variables could be increased. For example, for jaw claudication (JC), three response levels could be used: definitely not JC, possible JC, and highly likely JC. Additional predictors might include neck pain, body mass index, and smoking. Practical reasons were provided to exclude polymyalgia rheumatica as a predictor (Section 4.1.1, page 56) but formal testing would help settle any controversy. With greater study numbers more hidden layers could be added to the neural network, to reduce overfitting of the data. The performance of the NN-LR prediction models could be examined in conjunction with dynamic contour tonometry (Ing, Pagnoux, *et al.*, 2018), wide-field swept-source OCT angiography (Tran *et al.*, 2018), ultrasound, MRI or genetic tests such as HLA-DRB1*04 (Carmona, González-Gay and Martín, 2014). A Bayesian updating approach might improve the spatial and temporal transferability of the prediction models (Xu *et al.*, 2014).

The use of a false discovery rate (FDR) instead of traditional p-values to analyze the statistical models would decrease the possibility of errors from multiple testing. [10] The FDR is the expected proportion of false positives among all positives, or the expected proportion of false predictions divided by the total number of predictions, and has more power than the conservative Bonferroni method (Jafari and Ansari-Pour, 2019).

c) To determine the post-test probability of GCA following ultrasound or MRI, the NN-LR pre-test probability could be combined with the sensitivity and specificity values from recent meta-analyses of imaging (Duftner *et al.*, 2018; Rinagel *et al.*, 2019). Likelihood ratios are derived by Bayes Theorem as outlined in Appendix J (https://preview.tinyurl.com/y6hxlbl9) .

The penultimate research development in the diagnosis of GCA, which is beyond the scope of this thesis, would be the development of a highly specific and sensitive serology and genetic markers to diagnose or predict GCA without the need for TABx or ultrasound.

Chapter 7. CONCLUSIONS

GCA is a potentially vision-threatening emergency that also may cause aortitis, stroke or occasionally death. GCA is the most common primary vasculitis in the elderly, and a burgeoning public health concern in our ageing population.

A summary of the knowledge contributions from the published works include:

1) The incidence of biopsy-proven GCA in Ontario, Canada is 4.9 per 100,000 individuals over 50 years of age. The incidence figure is useful for epidemiologic and public health planning purposes.
2) Ecologic analysis of the incidence rates of herpes zoster versus GCA from different countries showed an inverse relationship and suggests that zoster is unlikely to be a strong immunopathogenic trigger for the development of GCA.
3) Temporal artery biopsy (TABx) remains the current reference standard confirmatory test for GCA. Perioperative anticoagulant and local anaesthetic issues should be considered prior to TABx. Although Doppler ultrasound is becoming increasingly utilized, false-positive imaging results are worrisome. Our 2019 survey showed that over 90% of North American ophthalmologists and rheumatologists prefer TABx over

[10] Using JMP Pro's false discovery rate algorithm, the ESR, gender and diplopia are not statistically significant predictors for biopsy-proven GCA. The calculations are in the appendix of the NN-LR article. https://docs.google.com/document/d/1kHVMxFmFDE-1UdSGMc65juD_h5Vd7mQCvAGR3s3bPJ4/edit

ultrasound whereas 74% of European neuro-ophthalmologists prefer TABx over ultrasound.

4) GCA can have diverse systemic and ocular manifestations and can be mimicked by other diseases including amyloidosis and overlap with granulomatosis with polyangiitis. Although the result of TABx may be negative for GCA, the biopsy occasionally may disclose pathologic confirmation of other diseases that simulate the presentation of GCA.
5) Systematic review for the positive yield (utility rate) of TABx, showed marked heterogeneity with a median yield of 25% and interquartile range 0.17 to 0.34 (Ing, Wang, *et al.*, 2018). Centres with a utility rate for TABx below 17% should determine if they are performing too many biopsies, obtaining inadequate length biopsies, or perhaps incorrectly processing biopsies. The diagnostic prediction models may improve the positive yield of TABx.
6) Statistical prediction models objectively weight the multiple risk factors for GCA and usually outperform clinical "intuition". Resistance to the use of prediction algorithms in medicine does not seem uncommon. In the age of artificial intelligence, medical societies should test published diagnostic prediction models, and incorporate the best models into their societal guidelines. Diagnostic prediction rules are not infallible and are not meant to replace clinical judgment, but to enhance it.
7) Prediction models for GCA may decrease the number of TABx performed on low-risk patients, as well as the number of unnecessary glucocorticoid initiations. In our NN-LR prediction model a risk score cut-off of approximately 7% allowed for 99% sensitivity, which can be used as a triage criterion. The publications provide the first online calculators to determine the risk of GCA prior to TABx.
8) The Kattan nomogram and the online risk calculator https://goo.gl/THCnuU allow easy access to the output of the GCA risk models. A Kattan nomogram can visually illustrate the risk contribution of the predictor variables used in the logistic regression prediction models for GCA. The nomogram allows clinicians, including those without statistical expertise to comprehend the relative contribution of continuous versus binary variables, in addition to the odds ratios of logistic regression.
9) The 1990 American College of Rheumatology (ACR) classification criteria for GCA (for update in late 2019) were not intended for diagnosis, and can miss cases of GCA.

The primary 10-factor multivariable logistic regression (LR) model with area under the receiving operating characteristic curve (AUROC) = 0.82 outperformed the pre-biopsy 1990 ACR criteria with AUROC = 0.63.

10) In our final prediction models (n=1,201), with age and bloodwork maintained as continuous variables, multivariable logistic regression showed that age, platelets, jaw claudication, vision loss, log transforms of the C-reactive protein and erythrocyte sedimentation rate, headache, and clinical temporal artery abnormality were statistically significant predictors of a positive TABx ($p \leq 0.05$). Age, platelets, vision loss and jaw claudication were stronger predictors for GCA than ESR and CRP, headache and scalp tenderness.

11) Acute phase reactants are serum proteins that increase in concentration with inflammation or tissue injury and include platelets, C-reactive protein and, the erythrocyte sedimentation rate. The dominance of platelets as a predictor of GCA over CRP and ESR is not well appreciated, in part because most GCA studies dichotomize bloodwork results rather than maintaining them as continuous variables. The *mean* / median platelet level for the GCA group was *372 (+/-143 x10^{9}L) /* 342 x 10^9/L, well below the 400-450 x 10^9/L thrombocytosis cut-off used in the literature (Foroozan *et al.*, 2002). The maintenance of predictors such as age and acute phase reactants as continuous variables will optimize statistical power. If alternative risk models persist in dichotomizing platelet levels, consideration should be given to lowering the platelet cut-off level for GCA to 350 x 10^9/L rather than the traditional 400 x 10^9/L.

12) Normal serology (the combination of ESR < 50 mm/hour, plus CRP and platelets at or below their upper limit of normal) was present in 10% of the patients with biopsy-proven GCA. Twenty per cent of these seronegative patients had healed arteritis.

13) On multivariable analysis gender and diplopia were not statistically significant predictors for GCA. Seventy one percent of our patients with GCA were women, and this female preponderance is consistent in the GCA literature. However, sex was not a statistically significant predictor for a positive TABx in our studies and other LR studies. This is likely explained by the increased longevity of women versus men in population demographics. Patients with vision loss in one or both eyes usually do not have binocular diplopia. Twenty per cent of our GCA patients experienced vision

loss, and this may explain why diplopia was not a statistically significant predictor for GCA on multivariable analysis.

14) There is overlap in the presenting features of patients with and without biopsy-proven GCA, and misclassification remains a concern for all prediction models. The neural network model for GCA had fewer false negatives than its logistic regression counterpart, but a support vector machine statistical model was equivalent to logistic regression. Decision curve analysis affirms the utility of our neural network and logistic regression diagnostic prediction algorithms.
15) In the future prediction models might be combined with ocular blood flow tests, imaging studies or genetic tests to increase diagnostic accuracy and further avert vision loss, TABx and the unnecessary initiation of glucocorticoids.

In summary, GCA remains a prime emergency in ophthalmology and medicine. The thesis comes full circle as the malapropism in the 1989 New Zealand article in the preface (Figure 1) recapitulates with the identical misprint in a 2018 GCA publication from Spain (Figure 21, (González *et al.*, 2018)). These two reports not only emphasize that GCA remains a global problem but remind us that physicians and patients continue to seek alternatives to TABx like a "temporary" artery biopsy or ultrasound.

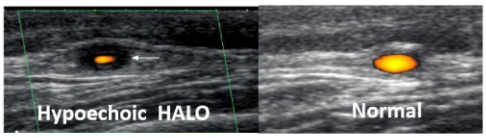
The thesis publications on diagnostic prediction rules with online risk calculator, the yield of temporal artery biopsy, the test preferences for the confirmation of GCA, the incidence of GCA in Canada, the limited relationship between herpes zoster and GCA, and the literature critiques provide new perspectives on the characteristics and management of GCA. In particular, the prediction models may help decrease the number of TABx performed in low-risk subjects.

Figure 21. Malapropism: "Temporary" artery biopsy and ultrasound study from Spain.

A Comparative Study of Doppler Ultrasound against Temporary Artery Biopsy in the Diagnosis of Giant Cell Arteritis. González Porto SA et al, Reumatol Clin. 2018 Oct 11. pii: S1699-258X(18)30187-6. [Article in English, Spanish]

FULL ENGLISH TEXT Reumatología Clínica

Suelves et al
Clin Ophthalmol, 2010



BACKGROUND: Giant cell arteritis (GCA) is a vasculitis that affects medium- and large-sized arteries. Temporal artery biopsy (TABx) is the gold standard for diagnosis. In view of the high demand for TABx, the purpose of this study is to evaluate the usefulness of Doppler ultrasonography (US) in patients with suspected GCA, to determine its sensitivity and specificity as a diagnostic test and to determine whether it would be possible to substitute US for TABx. **METHOD:** A prospective study was undertaken including 57 patients from February 2015 to July 2016, who have undergone both US and TABx. **RESULTS:** A total of 57 patients were included, 3 of whom died during the follow-up, and a patient was excluded from the study when she refused to have the biopsy. Another 21 patients were diagnosed with GCA by a rheumatologist after a minimum of 6 months of follow-up and 22 patients had positive ultrasonography, 8 of whom were diagnosed with GCA and 4 with polymyalgia rheumatica. In our study, the **sensitivity of US was 42.6%, and the specificity was 65.7%.** A total of 19 patients had a positive biopsy, all of them were diagnosed with GCA. In our study, the **sensitivity of TABx was 73.7% and the specificity was 100%.** **CONCLUSIONS:** In our study, the usefulness of US is questionable, and research about the role of US in this disease should be further studied.

This Spanish publication echoes the malapropism from the New Zealand article (Figure 1) written 30 years prior. González-Porto et al found the sensitivity and specificity of the ultrasound hypoechoic halo were both 30% less than temporal artery biopsy. Together the two "temporary" artery biopsy articles mirror the time-line of my medical career and emphasize that GCA remains a serious global concern and that we are still searching for a reliable but less-invasive procedure to confirm the diagnosis of GCA 30 years later (González *et al.*, 2018). https://www.ncbi.nlm.nih.gov/pubmed/30318270

REFERENCES

Adamczak, D. (2017) 'The Role of Toll-Like Receptors and Vitamin D in Cardiovascular Diseases—A Review', *Int J Mol Sci*, 18(11), p. 2252.

Allison, P. (2015) *What's so special about logit*, *Statistical Horizons*. Available at: https://statisticalhorizons.com/whats-so-special-about-logit (Accessed: 12 June 2020).

Astion, M. *et al.* (1994) 'Application of neural networks to the classification of giant cell arteritis', *Arthritis Rheum*, 37(5), pp. 760–770.

Aubin, D., Hebert, M. and Eurich, D. (2019) 'The importance of measuring the impact of patient-oriented research', *CMAJ*, 191(31), pp. E860–E864.

Ayres, I. (2007) 'Chapter 5. Experts Versus Equations', in *Super Crunchers*. New York: Bantam Dell, pp. 103–128.

Banerjee, P., Petrou, P. and Plant, G. (2014) 'Diagnostic and treatment challenges in giant cell arteritis', *Lancet*, 383(9936), p. 2210.

Bardi, M. and Diamantopoulos, A. (2019) 'EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice summary.', *Radiol Med*, 124(10), pp. 965–972.

Bilyk, J. *et al.* (2018) 'The Utility of Color Duplex Ultrasonography in the Diagnosis of Giant Cell Arteritis: A Prospective, Masked Study. (An American Ophthalmological Society Thesis).', *Trans Am Ophthalmol Soc*, 115, p. T9.

Bower, E. (2018) *GP: Babylon's AI 'outperforms average doctor' in MRCGP exam*. Available at: https://www.gponline.com/babylons-ai-outperforms-average-doctor-mrcgp-exam/article/1486258 (Accessed: 2 August 2019).

Broder, M. *et al.* (2016) 'Corticosteroid-related adverse events in patients with giant cell arteritis: A claims-based analysis', *Semin Arthritis Rheum*, 46(2), pp. 246–252.

Carmona, F., González-Gay, M. and Martín, J. (2014) 'Genetic component of giant cell arteritis', *Rheumatology*, 53(1), pp. 6–18.

Chao, C. *et al.* (2014) 'Serum vitamin D levels are positively associated with varicella zoster immunity in chronic dialysis patients', *Sci Rep*, 4, p. 7371.

Christodoulou, E. *et al.* (2019) 'A systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction models', *J Clin Epidemiol*, 110(Jun), pp. 12–22.

Collins, G. *et al.* (2015) 'Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): the TRIPOD statement', *BMJ*, 350, p. g7594.

Cristaudo, A., Mizumoto, R. and Hendahewa, R. (2016) 'The impact of temporal artery biopsy on surgical practice', *Ann Med Surg*, 11, pp. 47–51.

Cumberland, P. *et al.* (2014) 'Ophthalmic statistics note: the perils of dichotomising continuous variables', *Br J Ophthalmol*, 98(6), pp. 841–843.

Danesh-Meyer, H. *et al.* (2000) 'Low diagnostic yield with second biopsies in suspected giant cell arteritis', *J Neuroophthalmol*, 20, pp. 213–215.

Danesh-Meyer, H. (2012) ‘Temporal artery biopsy: skip it at your patient’s peril’, *Am J Ophthalmol*, 154(4), pp. 617–619.

Dany, F. *et al.* (1981) ‘[Doppler examination in temporal arteritis. Preliminary results (author’s transl)]’, *J Mal Vasc*, 6(4), pp. 273–7.

Dasgupta, B. *et al.* (2010) ‘BSR and BHPR guidelines’, *Rheumatology*, 49(8), pp. 1594–1597.

Davies, C. and May, D. (2011) ‘The role of temporal artery biopsies in giant cell arteritis’, *Ann R Coll Surg Engl*, 93(1), pp. 4–5.

Dejaco, C. *et al.* (2017) ‘The spectrum of giant cell arteritis and polymyalgia rheumatica: revisiting the concept of the disease’, *Rheumatology (Oxford).*, 56(4), pp. 506–515.

Dejaco, C. *et al.* (2018) ‘EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice’, *Ann Rheum Dis*, 77(5), pp. 636–643.

DeLong, E., DeLong, D. and Clarke-Pearson, D. (1988) ‘Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach’, *Biometrics*, 44, pp. 837–45.

Dickie, L. *et al.* (2010) ‘Vitamin D3 down-regulates intracellular Toll-like receptor 9 expression and Toll-like receptor 9-induced IL-6 production in human monocytes’, *Rheumatology*, 49(8), pp. 1466–1471.

Doi, S. *et al.* (2015) ‘Advances in the meta-analysis of heterogeneous clinical trials: the inverse variance heterogeneity model’, *Contemp Clin Trials*, 45(Pt A), pp. 130–138.

Dreiseitl, S. and Ohno-Machado, L. (2002) ‘Logistic regression and artificial neural network classification models: a methodology review’, *Journal of Biomedical Informatics*, 36(5–6), pp. 352–9.

Duftner, C. *et al.* (2018) ‘Imaging in diagnosis, outcome prediction and monitoring of large vessel vasculitis: a systematic literature review and meta-analysis informing the EULAR recommendations.’, *RMD Open*, 4(1), p. e000612.

Duke Fuqua (2007) *What’s the bottom line? How to compare models*. Available at: https://faculty.fuqua.duke.edu/~rnau/Decision411_2007/compare.htm (Accessed: 4 September 2018).

Edwards, M. *et al.* (2012) ‘The Global Epidemiology of Vitamin D Status’, *The Journal of Aging Research & Clinical Practice*.

Ehlers, L. *et al.* (2019) ‘2018 EULAR recommendations for a core data set to support observational research and clinical care in giant cell arteritis’, *Annals of the rheumatic diseases*. 2019/03/21. England, 78(9), pp. 1160–1166. doi: 10.1136/annrheumdis-2018-214755.

El-Dairi, M. *et al.* (2015) ‘Diagnostic Algorithm for Patients With Suspected Giant Cell Arteritis.’, *J Neuroophthalmol*, 35(2), pp. 246–53.

Elsevier (2019) *Topic Prominence in Science*. Available at: https://www.elsevier.com/solutions/scival/releases/topic-prominence-in-science#targetText=Topics are ranked by Prominence,or old%2C growing or declining. (Accessed: 16 August 2019).

England, B. *et al.* (2017) 'Herpes zoster and the risk of incident giant cell arteritis', *Arthritis Rheumatol*, 69(12), pp. 2351–58.

Fan, W. and Zheng, Y. (2010) 'Factors affecting response rates of the web survey: A systematic review', *Computers in Human Behavior*, 26(2), pp. 132–9.

Fernández, E. *et al.* (2019) 'OP0210 False positives of ultrasound in giant cell arteritis. Some diseases can also have halo sign', *Annals of the Rheumatic Diseases*, 78, p. 181.

Font, R. and Prabhakaran, V. (2007) 'Histological parameters helpful in recognising steroid-treated temporal arteritis: an analysis of 35 cases', *Br J Ophthalmol*, 91(2), pp. 204–9.

Foroozan, R. *et al.* (2002) 'Thrombocytosis in patients with biopsy-proven giant cell arteritis', *Ophthalmology*, 109(7), pp. 1267–71.

Fraser, J. *et al.* (2008) 'The treatment of Giant Cell Arteritis', *Rev Neurol Dis*, 5(3), pp. 140–152.

Frohman, L. *et al.* (2016) 'New developments in giant cell arteritis', *Surv Ophthalmol*, 61(4), pp. 400–21.

Gabriel, S. *et al.* (1995) 'The use of clinical characteristics to predict the results of temporal artery biopsy among patients with suspected giant cell arteritis', *J Rheumatol*, 22(1), pp. 93–96.

Ghinai, R. *et al.* (2017) 'Diagnosing Light Chain Amyloidosis on Temporal Artery Biopsies for Suspected Giant Cell Arteritis', *J Neuroophthalmol2017*, 37(1), pp. 34–9.

Gilden, D. *et al.* (2015) 'Prevalence and distribution of VZV in temporal arteries of patients with giant cell arteritis', *Neurology*, 84(19), pp. 1948–55.

Gilden, D. and Nagel, M. (2016) 'Varicella zoster virus and giant cell arteritis', *Curr Opin Infect Dis*, 29(3), pp. 275–279.

Gonzalez-Gay, M. *et al.* (2010) 'Giant cell arteritis: epidemiology, diagnosis, and management.', *Curr Respir Med Rev*, (12), pp. 436–42.

González-Gay, M. *et al.* (2019) 'Giant cell arteritis: is the clinical spectrum of the disease changing?', *BMC Geriatr*, 19(1), p. 200.

González-López, J. *et al.* (2013) 'Factors associated to temporal artery biopsy result in suspects of giant cell arteritis: a retrospective, multicenter, case-control study', *Acta Ophthalmol*, 91(8), pp. 763–8.

González-López, J. *et al.* (2014) 'A calculator for temporal artery biopsy result prediction in giant cell arteritis suspects', *Eur J Internal Med*, 25(8), pp. e98-100.

González, P. *et al.* (2018) 'A Comparative Study of Doppler Ultrasound against Temporary Artery Biopsy in the Diagnosis of Giant Cell Arteritis', *Reumatol Clin*, pii: S1699(18), pp. 30187–6.

Government of Canada (2019) *Census Profile, 2016, Kingston, City, Ontario*. Available at: https://www12.statcan.gc.ca/census-recensement/2016/dp-pd/prof/details/page.cfm?Lang=E&Geo1=CSD&Code1=3510010&Geo2=PR&Code2=35&SearchText=Kingston&SearchType=Begins&SearchPR=01&B1=All&GeoLevel=PR&GeoCode=3510010&TABID=1&type=0 (Accessed: 5 August 2019).

Government of Ontario Health and Wellness (2019) *Organ and tissue donor registration*. Available at: https://www.ontario.ca/page/organ-and-tissue-donor-registration (Accessed: 1 August 2019).

Grimes, D. (2008) 'The Nomogram Epidemic: Resurgence of a Medical Relic', *Ann Intern Med*, 149(273–275), p. 4.

Grossman, C. *et al.* (2016) 'Baseline clinical predictors of an ultimate giant cell arteritis diagnosis in patients referred to temporal artery biopsy', *Clin Rheumatol*, 35(7), pp. 1817–1822.

Gruener, A. *et al.* (2019) 'Association of Giant Cell Arteritis With Race', *Association of Giant Cell Arteritis With Race*, Epub ahead.

Grzybowski, A. and Justynska, A. (2013) 'Giant cell arteritis with normal ESR and/or CRP is rare, but not unique!', *Eye (Lond)*, 27(12), pp. 1418–1419.

Harvard Health Publishing and Harvard Medical School (2010) *Harvard Men's Health Watch. Mars vs. Venus: The gender gap in health*. Available at: https://www.health.harvard.edu/newsletter_article/mars-vs-venus-the-gender-gap-in-health (Accessed: 14 August 2019).

Hassane, H. *et al.* (2018) 'Co-Presentation of Giant Cell Arteritis and Granulomatosis with Polyangiitis: A Case Report and Review of Literature', *Am J Case Rep*, 19, pp. 651–5.

Hayreh, S. S., Podhajsky, P. A. and Zimmerman, B. (1998) 'Occult giant cell arteritis: Ocular manifestations', *American Journal of Ophthalmology*, 125(4), pp. 521–526. doi: 10.1016/S0002-9394(99)80193-7.

Hedges, III, T., Gieger, G. and Albert, D. (1983) 'The clinical value of negative temporal artery biopsy specimens', *Arch Ophthalmol*, 101(8), pp. 1251–4.

Holbrook, A., Krosnick, J. and Pfent, A. (2007) 'The causes and consequences of response rates in surveys by the news media and government contractor survey research firms', in Lepkowki, J. et al. (eds) *Advances in Telephone Survey Methodology*. New York: Wiley.

Holliman, K. (2018) *The Rheumatologist: Experts Discuss Proposed Giant Cell Arteritis Risk Tool*. Available at: https://www.the-rheumatologist.org/article/experts-discuss-proposed-giant-cell-arteritis-risk-tool/5/ (Accessed: 4 August 2019).

Hunder, G. *et al.* (1990) 'The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis', *Arthritis Rheum*, 33(8), pp. 1122–8.

Hunder, G. (1998) 'The use and misuse of classification and diagnostic criteria for complex diseases', *Ann Intern Med*, 129(5), pp. 417–8.

Husain, R. *et al.* (2008) 'Ocular ischaemic syndrome secondary to occult giant cell arteritis', *Neuro-Ophthalmology*, 32(6), pp. 295–298.

Hussain, O. *et al.* (2016) 'Diagnosis of giant cell arteritis: when should we biopsy the temporal artery?', *Br J Oral Maxillofac Surg*, 54(3), pp. 327–30.

Ing, E. *et al.* (1996) 'The Yield of Temporal Artery Biopsy in Patients with Suspected Giant Cell Arteritis', in. Ottawa: Canadian Ophthalmic Society Meeting.

Ing, E. *et al.* (1997) 'Systemic amyloidosis with temporal artery involvement mimicking

temporal arteritis', *Ophthalmic Surg Lasers*, 28(4), pp. 328–31.

Ing, E. (2016) 'Aids to statistics literacy for ophthalmologists', *Can J Ophthalmol*, 51(5), pp. e142-3.

Ing, E. *et al.* (2017) 'Multivariable prediction model for suspected giant cell arteritis: development and validation', *Clin Ophthalmol*, 11(Nov), pp. 2031–42.

Ing, E. (2018) 'Bloodwork statistical prediction model for giant cell arteritis', *Intern Med J*, 48(5), pp. 607–8.

Ing, E., Ing, R., *et al.* (2018) 'Does herpes zoster predispose to giant cell arteritis: a geo-epidemiologic study', *Clin Ophthalmol*, 12, pp. 113–8.

Ing, E., Pagnoux, C., *et al.* (2018) 'Lower ocular pulse amplitude with dynamic contour tonometry is associated with biopsy-proven giant cell arteritis', *Can J Ophthalmol*, 53(3), pp. 215–21.

Ing, E., Wang, D., *et al.* (2018) 'Systematic Review of the Yield of Temporal Artery Biopsy for Suspected Giant Cell Arteritis', *Neuroophthalmology*, 43(1), pp. 18–25.

Ing, E., Sambhi, G., *et al.* (2019) 'Comments on the giant cell arteritis probability score', *Clin Exp Rheumatol*.

Ing, E. (2019a) 'Do you have to do that Temporal Artery Biopsy? Neural Network and Logistic Regression Prediction Models for Giant Cell Arteritis', in. Quebec City: Canadian Ophthalmological Society.

Ing, E. (2019b) 'Letter to Editor: Neural network and logistic regression predictive calculator for giant cell arteritis', *Arch Soc Esp Oftalmol*, p. pii: S0365-6691(19)30235-7.

Ing, E., Philteos, J., *et al.* (2019) 'Local anesthesia and anxiolytic techniques for oculoplastic surgery', *Clin Ophthalmol*, 13, pp. 153–60.

Ing, E., Miller, N., *et al.* (2019) 'Neural network and logistic regression diagnostic prediction models for giant cell arteritis: development and validation', *Clin Ophthalmol*, 13, pp. 421–30.

Ing, E. (2019c) 'Orbital Surgery: Pitfalls & Pearls', in. Orlando: North American Society of Academic Orbital Surgeons.

Ing, E., Xu, Q., *et al.* (2019) 'Practice Preferences: Temporal artery biopsy versus Doppler ultrasound in the work-up of giant cell arteritis', *Neuro-ophthalmology*, published. Available at: https://doi.org/10.1080/01658107.2019.1656752.

Ing, E., Su, W., *et al.* (2019) 'Support Vector Machines and logistic regression to predict temporal artery biopsy outcomes', *Can J Ophthalmol*, 54(1), pp. 116–8.

Ing, E., Lahaie Luna, G., *et al.* (2019) 'The incidence of giant cell arteritis in Ontario, Canada', *Can J Ophthalmol*, 54(1), pp. 119–124.

Ing, E. and Douketis, J. (2014) 'New oral anticoagulants and oculoplastic surgery', *Can J Ophthalmol*, 49(2), pp. 123–127.

Ing, E. and Ing, R. (2018) 'The Use of a Nomogram to Visually Interpret a Logistic Regression Prediction Model for Giant Cell Arteritis', *Neuro-Ophthalmology*, 42(5), pp. 284–6. doi: 10.1080/01658107.2018.1425728.

Islam, N. *et al.* (2003) 'Giant cell arteritis mimicking idiopathic orbital inflammatory disease', *European Journal of Ophthalmology*, 13(4), pp. 392–394. doi: 10.1177/112067210301300411.

Jafari, M. and Ansari-Pour, N. (2019) 'Why, When and How to Adjust your P Values?', *Cell Journal (Yakhteh)*, 20(4), pp. 604–7. Available at: https://www.rheumatology.org.uk/Portals/0/Documents/Guidelines/GCA/Open_Consultation_GCA_GL_Executive_Summary.pdf?ver=2019-07-02-152636-127.

Judd, C., McClelland, G. and Ryan, C. (2017) 'Logistic Regression: Dependent Categorical Variables', in *Data Analysis: A Model Comparison Approach To Regression, ANOVA, and Beyond*. 3rd edn. New York: Routledge, pp. 339–353.

Kaufman, J. and Cooper, R. (2001) 'Commentary: Considerations for Use of Racial/Ethnic Classification in Etiologic Research', *American Journal of Epidemiology*, 154(4), pp. 291–8.

Kermani, T. *et al.* (2013) 'Large-vessel involvement in giant cell arteritis: a population-based cohort study of the incidence-trends and prognosis', *Ann Rheum Dis*, 72(12), pp. 1989–1994.

Kobayashi, S. *et al.* (2003) 'Clinical and epidemiologic analysis of giant cell (temporal) arteritis from a nationwide survey in 1998 in Japan: the first government-supported nationwide survey', *Arthritis Rheum*, 49(4), pp. 594–8.

Koster, M. and Warrington, K. (2017) 'Giant cell arteritis: pathogenic mechanisms and new potential therapeutic targets', *BMC Rheumatology*, 1(2).

Lahaie Luna, G., Ing, E. and ten Hove, M. (2018) 'The incidence of giant cell arteritis in Kingston Ontario', in. Toronto: Canadian Ophthalmologic Society.

Landau, K., Savino, P. and Gruber, P. (2013) 'Diagnosing Giant Cell Arteritis: Is Ultrasound Enough?', *J NeuroOphthalmol*, 33(4), pp. 394–400.

Laskou, F. *et al.* (2019) 'A probability score to aid the diagnosis of suspected giant cell arteritis', *Clin Exp Rheumatol*, Suppl 117(2), pp. 104–8.

Lee, A. *et al.* (2017) 'Machine learning has arrived!', *Ophthalmology*, 124(12), pp. 1726–8.

Lee, J. *et al.* (2008) 'The geo-epidemiology of temporal (giant cell) arteritis', *Clin Rev Allergy Immunol*, 35, pp. 88–95.

Lee, M. *et al.* (2014) 'The use of statistical modeling to predict temporal artery biopsy outcome from presenting symptoms and laboratory results', *Acta Ophthalmologica*, 92, p. s253.

Levy, M. and Margo, C. (1994) 'Temporal artery biopsy and sarcoidosis', *Am J Ophthalmol*, 117(3), pp. 409–410.

Lighthouse Guild (2019) *Bressler Prize in Vision Science*. Available at: https://www.lighthouseguild.org/healthcare-professionals/awards/bressler-prize/ (Accessed: 31 October 2019).

Loddenkemper, T. *et al.* (2007) 'Risk factors for early visual deterioration in temporal arteritis', *J Neurol Neurosurg Psychiatry*, 78(11), pp. 1255–9.

De Lott, L. and Burke, J. (2015) 'Use of laboratory markers in deciding whether to perform temporal artery biopsy', *JAMA Ophthalmol*, 133(5), pp. 605–6.

Luqmani, R. *et al.* (2016) 'The Role of Ultrasound Compared to Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis (TABUL): a diagnostic accuracy and cost-effectiveness study', *Health Technol Assess*, 20(90).

Luque-Fernandez, M., Maringe, C. and Nelson, P. (2017) *CVAUROC: Stata module to compute Cross-validated Area Under the Curve for ROC Analysis after Predictive Modelling for Binary Outcomes*. Available at: https://www.researchgate.net/publication/316232933_CVAUROC_Stata_module_to_compute_Cross-validated_Area_Under_the_Curve_for_ROC_Analysis_after_Predictive_Modelling_for_Binary_Outcomes (Accessed: 1 September 2018).

Lyons, H. *et al.* (2019) 'A new era for giant cell arteritis', *Eye (Lond)*. doi: 10.1038/s41433-019-0608-7.

Mackie, S. L. *et al.* (2020) 'British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis', *Rheumatology*. London, pp. 1–23. doi: 10.1093/rheumatology/kez672.

Mahr, A. *et al.* (2017) 'Épidémiologie et histoire naturelle de l'artérite à cellules géantes (Horton). [Epidemiology and natural history of giant cell arteritis]', *Rev Med Interne*, 38(10), pp. 663–9.

McDonnell, P. *et al.* (1986) 'Temporal arteritis: A Clinicopathologic Study', *Ophthalmology*, 93(4), pp. 518–30.

Meehl, P. (1954) *Clinical Versus Statistical Prediction: A Theoretical Analysis and A Review of the Evidence*. Minneapolis: University of Minnesota Press. (Reprinted 2013 by Echo Point Books).

Micieli, J., Micieli, R. and Margolin, E. (2015) 'A review of specialties performing temporal artery biopsies in Ontario: a retrospective cohort study', *CMAJ Open*, 3(3), pp. E281-5.

De Miguel, E. *et al.* (2018) 'Atherosclerosis as a potential pitfall in the diagnosis of giant cell arteritis', *Rheumatology (Oxford)*, 57(2), pp. 318–321.

Mohan, S. *et al.* (2011) 'Giant cell arteritis: immune and vascular aging as disease risk factors', *Arthritis Res Ther*, 13(4), p. 231.

Moiseev, S. *et al.* (2017) 'Giant cell arteritis, infections and biologics', *Ann Rheum Dis*, 76(9), p. e29.

Moiseev, S. *et al.* (2019) 'The role of temporal artery biopsy in patients with giant-cell arteritis is debated', *Annals of the Rheumatic Diseases*, 78, p. e31.

Mollan, S. *et al.* (2019) 'Response to "Comment on 'A new era for giant cell arteritis'"', *Eye*.

Moraña, M. *et al.* (2019) 'Giant cell arteritis and usefulness of a predictive calculator', *Arch Soc Esp Oftalmol*, pii: S0365(19), pp. 30126–1.

Morton, S. *et al.* (2012) 'In the 21st Century, what is an acceptable response rate?', *Aust NZ J Public Health*, 36(2), pp. 106–8.

Mukherjee, S. (2017) 'A.I. Versus M.D.', *Annals of Medicine, The New Yorker*, March 27.

Murchison, A. *et al.* (2012) 'Validity of the American College of Rheumatology criteria for

the diagnosis of giant cell arteritis', *Am J Ophthalmol*, 154(4), pp. 722–9.

Nagel, M. *et al.* (2015) 'Analysis of varicella-zoster in Temporal Arteries Biopsy Positive and Negative for Giant Cell Arteritis', *JAMA Neurol*, 72(11), pp. 1281–7.

Neri, A. *et al.* (2013) 'Light-chain amyloidosis mimicking giant cell arteritis in a bilateral anterior ischemic optic neuropathy case.', *BMC Ophthalmol*, 13, p. 82.

Ness, T. *et al.* (2013) 'The diagnosis and treatment of giant cell arteritis', *Dtsch Arztebl Int*, 110(21), pp. 376–86.

Niederkohr, R. and Levin, L. (2007) 'A Bayesian analysis of the true sensitivity of a temporal artery biopsy', *Invest Ophthalmol Vis Sci*, 48(2), pp. 675–80.

Nyaga, V., Arbyn, M. and Aerts, M. (2017) *METAPROP_ONE: Stata module to perform fixed and random effects meta-analysis of proportions*. Available at: https://ideas.repec.org/c/boc/bocode/s457861.html (Accessed: 1 August 2018).

Oh, L., Wong, E., Andrici, J., *et al.* (2018) 'Full blood count as an ancillary test to support the diagnosis of giant cell arteritis', *Intern Med J*, 48(4), pp. 408–13.

Oh, L., Wong, E., Gill, A., *et al.* (2018) 'Value of temporal artery biopsy length in diagnosing giant cell arteritis', *ANZ J Surg*, 88(3), pp. 191–5.

Ong Tone, S., Godra, A. and Ing, E. (2013) 'Polyangiitis overlap syndrome with granulomatosis with polyangiitis (Wegener's) and giant cell arteritis', *Can J Ophthalmol*, 48(1), pp. e6-8.

Ortega-Loubon, C., Culquichicón, C. and Correa, R. (2017) 'The Importance of Writing and Publishing Case Reports During Medical Training', *Cureus*, 9(12), p. e1964.

Ortiz-Ospina, E. and Beltekian, D. (2018) *Our World in Data. Why do women live longer than men?* Available at: https://ourworldindata.org/why-do-women-live-longer-than-men (Accessed: 14 August 2019).

Page, S. and Nyeboer, J. (2017) 'Improving the process of research ethics review', *Res Integr Peer Rev*, 2(14). doi: 10.1186/s41073-017-0038-7.

Parikh, R. (2018) *MIT Technology Review. AI can't replace doctors. But it can make them better*. Available at: https://www.technologyreview.com/s/612277/ai-cant-replace-doctors-but-it-can-make-them-better/ (Accessed: 5 August 2019).

Pearl, R. (2018) *Forbes. Artificial Intelligence In Healthcare: Separating Reality From Hype*. Available at: https://www.forbes.com/sites/robertpearl/2018/03/13/artificial-intelligence-in-healthcare/#5b2c3ac91d75 (Accessed: 5 August 2019).

Pieri, A. *et al.* (2013) 'Temporal artery biopsy: are we doing it right?', *Int J Health Care Qual Assur*, 26(6), pp. 559–63.

Poillon, G. *et al.* (2019) 'Increased diagnostic accuracy of giant cell arteritis using three-dimensional fat-saturated contrast-enhanced vessel-wall magnetic resonance imaging at 3 T', *Eur Radiol*, (published online ahead of print Dec 6, 2019). doi: 10.1007/s00330-019-06536-7.

Pouncey, A. *et al.* (2018) 'Temporal artery ultrasound versus temporal artery biopsy for giant cell arteritis (Diagnostic Protocol)', *Cochrane Database of Systematic Reviews*. doi: 10.1002/14651858.cd013199.

Price, N. and Clearkin, L. (1994) ‘Thrombocytosis and giant cell arteritis’, *Lancet*, 343(8898), p. 672.

Prior, J. *et al.* (2017) ‘Diagnostic delay for giant cell arteritis - a systematic review and meta-analysis’, *BMC Med*, 15(1), p. 120.

Quinn, E. *et al.* (2012) ‘Temporal artery biopsy is not required in all cases of suspected giant cell arteritis’, *Ann Vasc Surg*, 26(5), pp. 649–54.

Ramstead, C. and Patel, A. (2007) ‘Giant cell arteritis in a neuro-ophthalmology clinic in Saskatoon, 1998–2003’, *Can J Ophthalmol*, 42(2), pp. 295–8.

Ranganathan, P., Aggarwal, R. and Pramesh, C. (2015) ‘Common pitfalls in statistical analysis: Odds versus risk’, *Perspect Clin Res*, 6(4), pp. 222–224.

Rhéaume, M. *et al.* (2017) ‘High-Resolution Magnetic Resonance Imaging of Scalp Arteries for the Diagnosis of Giant Cell Arteritis: Results of a Prospective Cohort Study.’, *Arthritis Rheumatol*, 69(1), pp. 161–8.

Rieck, K. *et al.* (2011) ‘Evaluation for clinical predictors of positive temporal artery biopsy in giant cell arteritis’, *J Oral Maxillofac Surg*, 69(1), pp. 36–40.

Rinagel, M. *et al.* (2019) ‘Diagnostic performance of temporal artery ultrasound for the diagnosis of giant cell arteritis: a systematic review and meta-analysis of the literature’, *Autoimmun Rev*, 18(1), pp. 56–61.

Robin, X. *et al.* (2011) ‘pROC: an open-source package for R and S+ to analyze and compare’, *BMC Bioinformatics*, 12, p. 77.

Rodriguez-Valverde, V. *et al.* (1997) ‘Risk factors and predictive models of giant cell arteritis in polymyalgia rheumatica’, *Am J Med*, 102(4), pp. 331–6.

Rogers, E. (1983) *Diffusion of Innovations*. 3rd edn. New York: The Free Press (Macmillan Publishing).

Ross, A. *et al.* (2019) ‘Retrospective, Multicenter Comparison of the Clinical Presentation of Patients Presenting With Diplopia From Giant Cell Arteritis vs Other Causes’, *J Neuroophthalmol*, 39(1), pp. 8–13.

Rubenstein, E. *et al.* (2019) ‘Sensitivity of temporal artery biopsy in the diagnosis of giant cell arteritis: a systematic literature review and meta-analysis’, *Rheumatology (Oxford)*, (Sep14), p. pii: kez385. doi: 10.1093/rheumatology/kez385.

Sadun, A. and Gordon, L. (2020) ‘Should Tocilizumab Be Used Routinely in New Patients With a Diagnosis of Giant Cell Arteritis?’, *J Neuroophthalmol*, 40(1), pp. 117–121.

Schulz, K. and Grimes, D. (2002) ‘Case-control studies: research in reverse’, *Lancet*, 359(9304), pp. 431–4.

Serrano Alcalá, E. *et al.* (2019) ‘Orbital Magnetic Resonance Imaging to unmask giant cell arteritis TT - Resonancia magnética orbitaria para desenmascarar arteritis de células gigantes’, *Radiologia*. Spain, pp. S0033-8338(19)30170–5. doi: 10.1016/j.rx.2019.11.006.

De Smit, E. *et al.* (2016) ‘Giant cell arteritis: ophthalmic manifestations of a systemic disease’, *Graefes Arch Clin Exp Ophthalmol*, 254(12), pp. 2291–2306.

De Smit, E., Palmer, A. and Hewitt, A. (2015) 'Projected worldwide disease burden from giant cell arteritis by 2050', *J Rheumatol*, 42(1), pp. 119–125.

Smith, J., Israel, C. and Harner, R. (1967) 'Syphilitic temporal arteritis', *Arch Ophthalmol*, 78(3), pp. 284–8.

Solans-Laque, R. *et al.* (2018) 'Giant cell arteritis with normal inflammatory markers at diagnosis', *Annals of the Rheumatic Diseases*, 77, p. 1490.

Statistics Canada (2017a) *Age and sex, and type of dwelling data: Key results from the 2016 Census*. Available at: https://www150.statcan.gc.ca/n1/daily-quotidien/170503/dq170503a-eng.htm (Accessed: 14 August 2019).

Statistics Canada (2017b) *Statistics Canada Census Profile, 2016 Census,Ontario,Canada.* Available at: https://www12.statcan.gc.ca/census-recensement/2016/dp-pd/prof/details/page.cfm?Lang=E&Geo1=PR&Code1=35&Geo2=PR&Code2=01&Data=Count&SearchText=ontario&SearchType=Begins&SearchPR=01&B1=All&TABID=1 (Accessed: 21 July 2019).

Stone, J. *et al.* (2017) 'Trial of Tocilizumab in Giant-Cell Arteritis', *N Engl J Med*, 377(4), pp. 317–28.

Stuart, R. (1989) 'Temporary artery biopsy in suspected temporal arteritis: a five year survey', *N Z Med J*, 102(874), pp. 431–3.

Terrades-Garcia, N. and Cid, M. (2018) 'Pathogenesis of giant-cell arteritis: how targeted therapies are influencing our understanding of the mechanisms involved', *Rheumatology (Oxford)*, 57(suppl 2), pp. ii51–ii62.

The Medical Futurist (2016) *Can An Algorithm Diagnose Better Than A Doctor?* Available at: https://medicalfuturist.com/can-an-algorithm-diagnose-better-than-a-doctor (Accessed: 4 August 2019).

Times Higher Education (2019) *The World University Rankings University of Toronto*. Available at: https://www.timeshighereducation.com/world-university-rankings/university-toronto (Accessed: 1 August 2019).

Torun, N. *et al.* (2018) 'Poster 236: The utility of nomograms for suspected giant cell arteritis', in. Waikoloa Village: North American Neuro-ophthalmology Society.

Torun, N. and Ing, E. (2008) 'Neuro-Ophthalmologic Emergencies', *Focal Points, American Academy of Ophthalmology*, XXVI(9).

Tran, A. *et al.* (2018) 'Swept-Source Optical Coherence Tomography Angiography of an Amalric Choroidal Infarction in a Rare Presentation of Giant Cell Arteritis With Bilateral Corneal Edema', *Ophthalmic Surg Lasers Imaging Retina*, 49(10), pp. e157-60.

Turesson, C. *et al.* (2019) 'Swedish Society of Rheumatology 2018 guidelines for investigation, treatment, and follow-up of giant cell arteritis.', *Scand J Rheumatol*, 48(4), pp. 259–65.

United Nations (2015) *World Population Prospects: The 2015 Revision. Volume 1. Comprehensive Tables, World Population Prospects: The 2015 Revision. Volume 1. Comprehensive Tables*.

USC Australia (2018) *Research Metrics*. Available at: https://libguides.usc.edu.au/researchmetrics/researchmetrics-field-weighted-citation-impact (Accessed: 1 August 2019).

Vergouwe, Y. *et al.* (2005) 'Substantial effective sample sizes were required for external validation studies of predictive logistic regression models', *Journal of Clinical Epidemiology*, 58(5), pp. 475–83.

Vickers, A. and Elkin, E. (2006) 'Decision curve analysis: a novel method for evaluating prediction', *Med Decis Making*, 26(6), pp. 565–74.

Visser, P. *et al.* (1996) 'Mail surveys for election forecasting? An evaluation of the Colombia Dispatch Poll', *Public Opin Q*, 60, pp. 181–227.

Waldman, C., Waldman, S. and Waldman, R. (2013) 'Giant cell arteritis', *Med Clin North Am*, 97(2), pp. 329–35.

Wang, D., Benard-Seguin, E. and Ing, E. (2018) 'The yield of temporal artery biopsy for suspected giant cell arteritis: A meta-analysis', in. Toronto: Canadian Ophthalmologic Society.

Wang, X. *et al.* (2019) 'Exploring the role of programmed cell death protein 1 and its ligand 1 in eye diseases', *Crit Rev Clin Lab Sci*, 56(1), pp. 18–32.

Weis, E. *et al.* (2017) 'Development of a predictive model for temporal artery biopsies.', *Can J Ophthalmol*, 52(6), pp. 599–605.

Weyand, C., Berry, G. and Goronzy, J. (2018) 'The Immunoinhibitory PD-1/PD-L1 pathway in inflammatory blood vessel disease', *J Leukoc Biol*, 103(3), pp. 565–75.

Weyand, C. and Goronzy, J. (2014) 'Giant-cell arteritis and polymyalgia rheumatica', *N Engl J Med*, 371(1), pp. 50–7.

Weyand, C., Liao, Y. and Goronzy, J. (2012) 'The immunopathology of giant cell arteritis: diagnostic and therapeutic implications', *J Neuroophthalmol*, 32(3), pp. 259–65.

Xu, C. *et al.* (2014) 'Using the Bayesian updating approach to improve the spatial and temporal transferability of real-time crash risk prediction models', *Transportation Research Part C*, 38, pp. 167–76.

Zlotnik, A. and Santos, V. (2013) 'Stata logistic regression nomogram generator', in. Madrid: Stata.com.

APPENDIX

Appendix A. Over-the-counter medications with potential anticoagulant effect, from Table 3 in publication: (Ing and Douketis, 2014)

Table 3—Herbal and homeopathic supplements that can cause bleeding
Vitamin E
Gingko
Ginger
Ginseng
Glucosamine
Onion *(Allim cepa)*
Green tea *(Camellia sinensis)*
Chondroitin
Fish oil
Licorice
Oil of wintergreen *(methyl salicylate)*
Red chili pepper *(Capsaicin)*
Chinese agrimony *(Agrimonia pilosa)*
Arnica Montana
Danshen
Saw palmetto *(Serenoa repens)*
Grape seed extract
Scutellaria baicalensis
Devil's claw *(Harpagophytum procumbens)*
Horseradish *(Armoracia rusticana)*
Trifolate orange *(Poncirus trifolitata)*
Horse chestnut seed *(Aesculus hippocastanum)*
Bladderwrack *(Fucus vesiculosus)*
Feverfew *(Tanacetum parthenium)*
Bromelain
Lonicera japonica
Geum japonicum
Turmeric root *(Curcuma longa, Curcuma aromatica)*
Fritillaria cirrhosa
Coleus *(Solenostemon)*
Turmeric root *(Curcuma longa/aromatica)*
Evening primrose *(Oenothera biennis)*
Guarana *(Paullinia cupana)*
Dong quai *(Angelica sinensis)*
Reishi fruit *(Ganoderma lucidum)*
Horsetail rush *(Equisetum)*
Cayenne fruit *(Capsicum frutescens)*
St. John's Wort *(Hypericum perforatum)*
Papain *(Carica papaya)*
Cat's claw *(Uncaria tomentosa)*
Anise *(Pimpinella anisum)*
White willow *(Salix alba)*
Celery *(Apium graveolens)*
Chinese peony *(Paeoniae rubra)*
Guggul *(Commiphora wightii)*
Bilberry *(Vaccinium myrtillus)*

Appendix B. The Incidence of GCA in different countries from Table 1 (Ing, Lahaie Luna, *et al.*, 2019)

Table 1 Incidence rates of giant cell arteritis and herpes zoster per country

Country	GCA study: year published (study period)/region	IR_{GCA}	HZ study: year/region	IR_{HZ50}	IR_{HZ70}	Time overlap
Norway, B+C[37]	2014 (2006–2012)/South	21	2016 (2008–2012)/National[38]	2.8	7.0	Yes
Finland, B+C[39]	1992 (1984–1988)/West Nyland	26.2	2010 (2000–2006)/Tuusula, Kangasala, Salo[40]	2.5	6.5	No
Sweden, B[41]	2015 (1997–2010)/Skane	14.1	2013 (2006–2010)/National[42]	2.5	8.0	Yes
United Kingdom, B+C[43]	2006 (1990–2001)/National	22	2003 (1991–2000)/National[44]	4.0	9.3	Yes
USA, C[45]	2015 (2000–2009)/Olmsted Cty	19.8	2016 (1945–2007)/Olmsted City[46]	4.5	8.4	Yes
Spain, B[47]	2007 (1981–2005)/Lugo	10.13	2013 (2007–2010)/Valencian Community[48]	4.8	9.8	No
New Zealand, B[49]	2011 (1996–2005)/Otago	12.73	2014 (2009–2013)/Lower Hutt[50]	6.1	7.3	No
Israel, B+C[51]	2007 (1980–2004)/Jerusalem	11.3	2013 (2006–2010)/Tel Aviv[52]	5.8	11.8	No
Canada, B[53]	2007 (1998–2003)/Saskatoon	9.4	2011 (1992–2010)/Ontario[54]	3.7	7.4	Yes
France, B+C[55]	1982 (1970–1979)/Loire-Atlantique	9.4	2010 (2005–2007)/National[56]	4.2	8.7	No
Italy, B+C[57]	2017 (1986–2012)/Reggio Emilia	5.8	2010 (2003–2005)/National[58]	3.6	7.7	Yes
Australia, B[59]	2013 (1992–2011)/Adelaide	3.2	2008 (1998–2006)/National[60]	6.5	11.5	Yes
Germany, C[61]	2005 (1998–2002)/Schlewig-Holstein	3.3	2011 (2007–2008)/National[62]	6.2	11.3	No
Japan, Cal[7]	2003 (1998)/National	0.13	2009 (1997–2006)/Miyazaki[63]	3.9	7.4	Yes

Notes: B, biopsy proven; C, clinical criteria for diagnosis; Cal, calculated from published prevalence rate; Time overlap, the incidence rates for GCA and HZ were from the same time period.

Abbreviations: GCA, giant cell arteritis; IR, incidence rate; IR_{GCA}, giant cell arteritis incidence rates per 100,000 subjects, 50 years of age or older; HZ, herpes zoster; IR_{HZ50}, herpes zoster incidence rates in 50-year-old subjects per 1,000 person years; IR_{HZ70}, herpes zoster incidence rates in 70-year-old subjects per 1,000 person years.

Appendix C, Research Degree Declaration Form RD12A

Kingston University Research

RD12a

RESEARCH DEGREE CANDIDATE'S DECLARATION FORM
(Please complete in black ink or type)

Note: This form must be submitted to the Faculty Office with the candidate's thesis.

Name of Candidate: ...Edsel B. ING ..... **Student ID No: K1930416**

Degree for which dissertation/thesis is being submitted: PhD by Publication

1. **Material submitted for another award**

I declare that no material contained in the thesis has been used in any other submission for an academic award.

2. **Plagiarism**

*I declare that all material contained in the thesis is my own original work, and that any references to or use of other sources have been clearly acknowledged within the text.

Note that an electronic copy of your thesis may be requested for use with plagiarism detection software.

3. **Contact details for future correspondence**

Please check and update your contact details by logging in to OSIS.

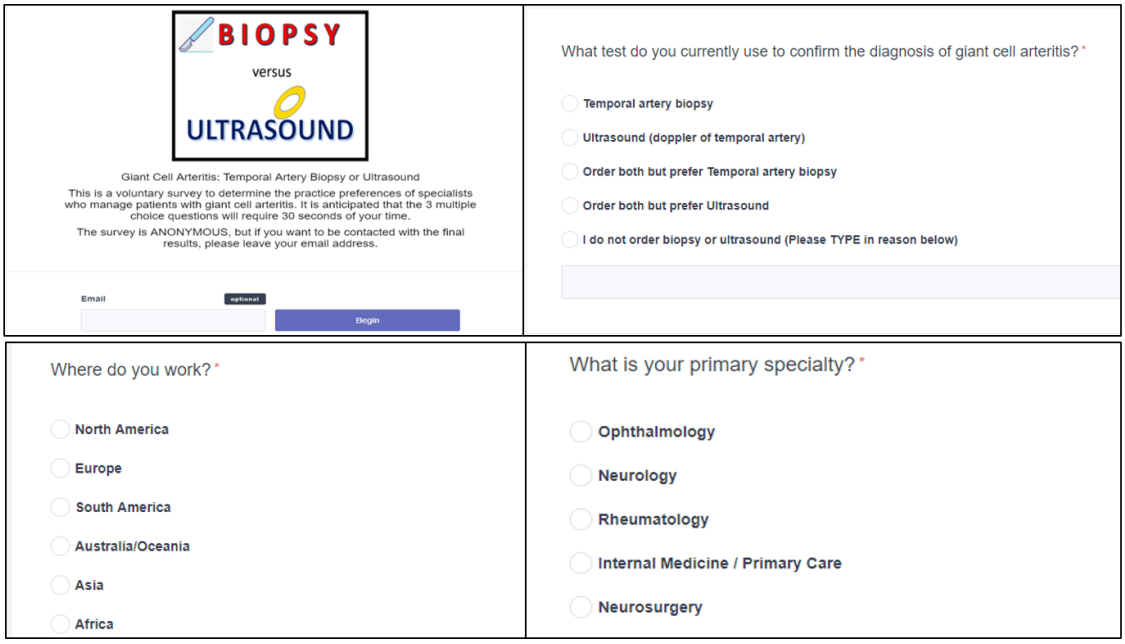
4. **Signature of Candidate**
5.

. **Date August 2, 2019 .....**

GRS July 2018

Appendix D: Practice Preference Survey Temporal artery biopsy versus Ultrasound

Appendix D1: Survey Questions



Appendix D2: Estimation of Survey Response Rate

Calculations

NANOS members: 627 American + 55 Canadian = 682

ASOPRS members: 669 American + 28 Canadian = 697

Overlaps in NANOS & ASOPRS estimated at 5%: (682+697)*.95 = 1,310

Ont-Eye internet line ophthalmologists: 463-16-14 = 433

2018 communication with website moderator: 16 NANOS members overlap in Ont-Eye;
14 ASOPRS overlaps in Ont-Eye

EUNOS member: 244 - 4 NA = 240 recipients

Ontario rheumatologists: 270 according to College of Physicians and Surgeons website

Best denominator estimate =2,253

406 (NA + Europe & Israel) respondents/2253 = 18.0% response rate overall

Abbreviations

NANOS = North American Neuro-Ophthalmology Society

ASOPRS = American Society of Ophthalmic Plastic & Reconstructive Surgery

Ont-Eye = Eye Physicians and Surgeons of Ontario

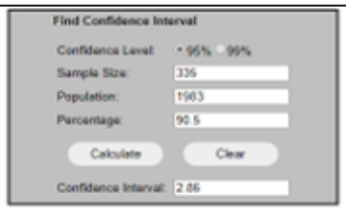
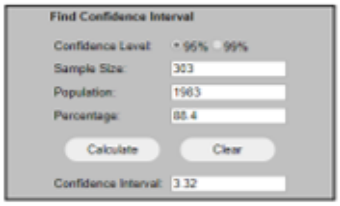
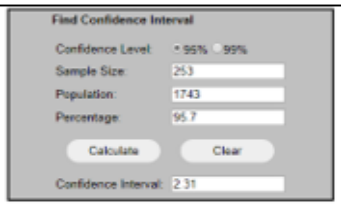
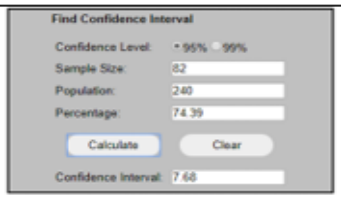
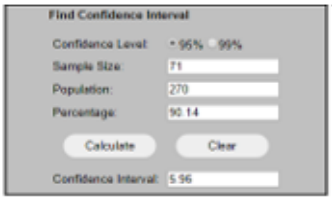
EUNOS = European Neuro-ophthalmology Society

NA = North American

CPSO = College of Physicians and Surgeons of Ontario

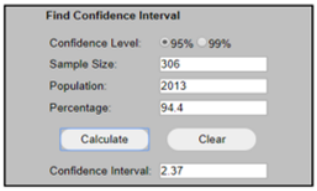
Appendix D3: Calculation of Survey 95% Confidence Intervals

Calculation of survey 95% confidence intervals was done using the online tool: https://www.surveysystem.com/sscalc.htm

Result	Sample Size Calculator
303/335 O&N NA +Europe (90.5% prefer TABx). Total estimated 1,983 O&N NA+Europe 95% CI is +/-2.9%	
A total of 303 O&N in NA & Europe preferred TABx. 88.4% used TABx exclusively 95% CI is +/-3.32%	
253 North American O&N / total 1743 O&N in North America with 95.58% choosing TABx 95% CI is +/-2.31%	
82 European O&N / total 240 O&N in Europe with 74.39% choosing TABx 95% CI is +/-7.7 %	
64/71 rheumatologists in survey (90.14% prefer TABx). There are 270 provincially registered rheum 95%CI is +/- 6.0%	

64/71 rheumatologists in NA plus 242/253 O&N in NA prefer TABx.

NA survey population was estimated at 2013.



Appendix D4: Statistical Tests for Regional Differences in O&N Preference for TABx

Chi Square Test

	Region		
	Europe	**North America**	**Total**
Neither	1	9	10
TABx	61	242	303
US	20	2	22
Total	82	253	335

Pearson $Chi^2 = 56.7492$ Pr = < 0.001

Conventional 2 Sample Tests of Proportions

Although the test is not adjusted for survey weighting, given the 21% difference and survey confidence intervals, there would be no change in the inference.

Two-sample test of proportions — x: Number of obs = 253; y: Number of obs = 82

	Mean	Std. Err.	z	P>|z|	[95% Conf.	Interval]
x	.9565217	.012821			.931393	.9816505
y	.7439024	.0482007			.6494307	.8383742
diff	.2126193	.0498768			.1148626	.310376
	under Ho:	.0373514	5.69	0.000		

diff = prop(x) - prop(y) z = 5.6924

Ho: diff = 0

Ha: diff < 0 Ha: diff != 0 Ha: diff > 0

Pr(Z < z) = 1.0000 Pr(|Z| > |z|) = 0.0000 Pr(Z > z) = 0.0000

Appendix D5: Statistical Tests for Specialty Differences in Preference for TABx

ConfirmTestCATEGORY	SpecialtyCAT Neurology	Ophthal..	Rheumat..	Total
Neither	0	10	3	13
Temporal artery bio..	34	269	64	367
Ultrasound (doppler..	3	19	4	26
Total	37	298	71	406

```
. prtesti 37 34 298 269, count
Two-sample test of proportions                     x: Number of obs =       37
                                                   y: Number of obs =      298
------------------------------------------------------------------------------
             |       Mean   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
           x |   .9189189   .0448743                      .8309669    1.006871
           y |   .9026846   .0171692                      .8690335    .9363356
-------------+----------------------------------------------------------------
        diff |   .0162344   .0480467                     -.0779354    .1104041
             |  under Ho:   .0512348     0.32   0.751
------------------------------------------------------------------------------
        diff = prop(x) - prop(y)                                      z =   0.3169
    Ho: diff = 0

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(Z < z) = 0.6243         Pr(|Z| > |z|) = 0.7513          Pr(Z > z) = 0.3757


. prtesti 71 64 298 269, count
Two-sample test of proportions                     x: Number of obs =       71
                                                   y: Number of obs =      298
------------------------------------------------------------------------------
             |       Mean   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
           x |   .9014085   .0353795                      .8320659     .970751
           y |   .9026846   .0171692                      .8690335    .9363356
-------------+----------------------------------------------------------------
        diff |  -.0012761   .0393254                     -.0783526    .0758003
             |  under Ho:   .0391853    -0.03   0.974
------------------------------------------------------------------------------
        diff = prop(x) - prop(y)                                      z =  -0.0326
    Ho: diff = 0

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(Z < z) = 0.4870         Pr(|Z| > |z|) = 0.9740          Pr(Z > z) = 0.5130


. prtesti 71 64 37 34, count
Two-sample test of proportions                     x: Number of obs =       71
                                                   y: Number of obs =       37
------------------------------------------------------------------------------
             |       Mean   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
           x |   .9014085   .0353795                      .8320659     .970751
           y |   .9189189   .0448743                      .8309669    1.006871
-------------+----------------------------------------------------------------
        diff |  -.0175105   .0571438                     -.1295102    .0944892
             |  under Ho:   .0587721    -0.30   0.766
------------------------------------------------------------------------------
        diff = prop(x) - prop(y)                                      z =  -0.2979
    Ho: diff = 0

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(Z < z) = 0.3829         Pr(|Z| > |z|) = 0.7658          Pr(Z > z) = 0.6171
```

Appendix E. Correlation and Linear Regression of the Incidence Rates of GCA versus Herpes Zoster, Table 2 from the publication: (Ing, Ing, *et al.*, 2018)

Table 2 Correlation and linear regression of the incidence rates of giant cell arteritis versus herpes zoster

Zoster incidence rate age groups	Number of countries	Correlation coefficient	Regression coefficient	*p*-value, R^2	*p*-value with robust SE	*p*-value for white's test
50-year-olds, all countries	14	−0.51	−2.92	p=0.07, R^2=0.26	p=0.025	p=0.28
70-year-olds, all countries	14	−0.40	−1.78	p=0.16, R^2=0.16	p=0.12	p=0.42
50-year-olds, time overlap	8	−0.38	−2.66	p=0.35, R^2=0.14	p=0.06	p=0.12
70-year-olds, time overlap	8	−0.15	−0.88	p=0.72, R^2=0.02	p=0.69	p=0.88
50-year-olds, no overlap	6	−0.80	−4.24	p=0.06, R^2=0.63	p=0.05	p=0.93
70-year-olds, no overlap	6	−0.74	−2.63	p=0.09, R^2=0.54	p=0.14	p=0.09

Notes: Correlation coefficient, Pearson product-moment correlation coefficient (*r*); regression coefficient, linear regression coefficient; time overlap, the incidence rates for GCA and HZ were from the same time period; no overlap, the incidence rates for GCA and HZ were from different time periods.
Abbreviations: GCA, giant cell arteritis; HZ, herpes zoster; SE, standard error.

Appendix F. Hypothetical Clinical Scenarios showing the Risk Score Predictions of the Neural Network and Logistic Regression Models for High, Medium and Low risk GCA

Scenarios	Case	LR, Normal Vision	LR, Vision Loss	NN, Normal Vision	NN, Vision loss
i) 90F, HA+, TAabn, JC+, Dip- Plat475, ESR90, CRP/ULN 4	1	0.820	0.921	0.800	0.871
ii) 80F, HA+, TAabn, JC+, Dip- Plat 399, ESR60, CRP/ULN3	2	0.596	0.791	0.623	0.830
iii) 80F, HA+, TAabn, JC+, Dip- Plat 250, ESR 50, CRP/ULN 2	3	0.378	0.610	0.378	0.734
iv) 80M, HA-, TAnl, JC+, Dip- Plat 250, ESR49, CRP/ULN 2	4	0.217	0.416	0.379	0.609
v) 80F, HA+, TAabn, JC-, Dip- Plat 250, ESR49, CRP/ULN2	5	0.170	0.344	0.216	0.499
vi) 80F, HA+, TAnl, JC-, Dip- Plat 250, ESR49, CRP/ULN 2	6	0.119	0.257	0.116	0.318
vii) 65F, HA+, TAnl, JC-, Dip- Plat 250, ESR49, CRP/ULN 2	7	0.054	0.127	0.044	0.176
viii) 65F, HA-, TAnl, JC-, Dip+ Plat 250, ESR55, CRP/ULN 1.5	8	0.029	0.072	0.103	0.186
ix) 50M, HA-, TAnl, JC-, Dip- Plat 390, ESR55, CRP/ULN 2	9	0.033	0.080	0.057	0.140
x) 50M, HA-, TAnl, JC-, Dip- Plat 250, ESR55, CRP/ULN 2	10	0.017	0.042	0.045	0.080
xi) 50M, HA-, TAnl, JC-, Dip+ Plat 250, ESR 55, CRP 1	11	0.014	0.036	0.081	0.158
xii) 50F, HA-, TAnl, JC-, Dip- Plat 800, ESR49, CRP/ULN 1	12	0.136	0.288	0.079	0.256
xiii) 50F, HA-, TAnl, JC-, Dip- Plat 250, ESR49, CRP/ULN 2	13	0.013	0.032	0.028	0.067
xiv) 50F, HA-, TAnl, JC-, Dip- Plat 250, ESR 55, CRP/ULN 1	14	0.011	0.027	0.027	0.058

Legend for Appendix F
LR = logistic regression; NN = neural network
M = male; F = female
HA - = no headache; HA+ = headache present
TAnl = no temporal artery abnormality; TAabn = temporal artery abnormality
JC- =no jaw claudication; JC+ = jaw claudication present
Dip- = no diplopia; Dip+ = diplopia
Plat = platelets x 10^9/L
ESR = erythrocyte sedimentation rate mm/ hr
CRP / ULN = C-reactive protein divided by upper limit of normal for each lab

Appendix G. Citizen Research Participant Registry

Contact us: Organ and tissue donor registration

There are many ways to contact us.

Phone numbers

Telehealth Ontario

Toll-free: 1-866-797-0000

For general inquiries, call:
ServiceOntario

Tel: 416-314-5518

Toll-free: 1-866-532-3161

TTY: 1-800-387-5559

Hours of operation: Monday to Friday, 8:30am - 5:00pm.

Address

ServiceOntario

M-1B114, Macdonald Block
900 Bay Street
Toronto ON M7A 1N3

If you are **mailing health card forms**, see ServiceOntario, Health Card Services for the address of your local OHIP office.

Send us an email

Message

please don't include any personal or financial information

Would the government of Ontario consider a Research Database Registration Program, akin to the Organ Donor Registration program? Researchers would still have to be trained and vetted, but approval time for projects could be decreased.

Would you like a reply?

(•) Yes ( ) No

see the service standards for how long it will take to get a reply

Email

you will receive a confirmation email

Required

Optional information

Name

Edsel B Ing

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Ministry of Health
Ministry of Long-Term Care

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You may find an answer to your questions here:

- Understanding Health Care in Ontario
- Ontario Health Insurance (OHIP)
- Health Card Renewal Appointment Booking
- Changing your home address on your health card online
- Ontario's Public Drug Programs
- Assistive Devices Program
- Seniors' Care
- Healthy Living

Service Standards and Accessibility:

- Accessible Customer Service Policy
- Common Service Standards
- Ministry of Health and Long-Term Care Service Standards

We welcome your feedback

What is your message about?

General questions or comments

Please enter your message here:

For privacy and security reasons, do not include personal health information such as health card numbers in your e-mail.

Subject:	re: Ontario Patient Database Registry
Comments:	Would you consider establishing a Research Database Registration Program, akin to your Organ Donor Registration? Only de-identified data should be available and researchers would still have to be trained and vetted, but the approval time for

re: Citizen Registry for Health Care and Social Research

christine.elliott@pc.ola.org

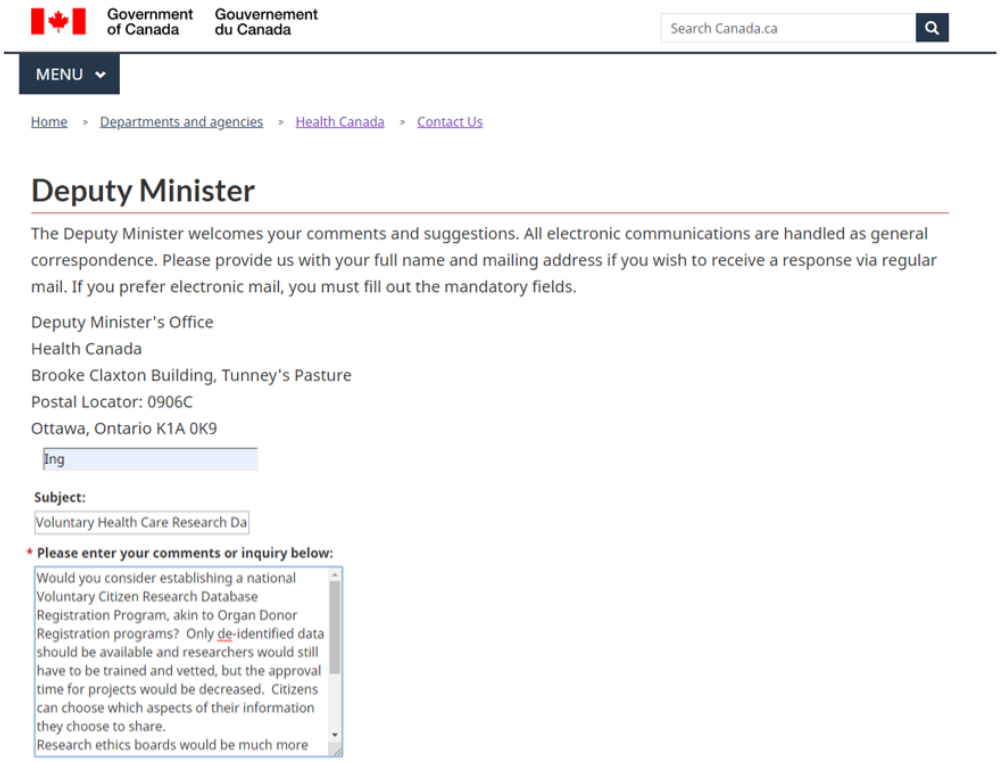
re: Citizen Registry for Health Care and Social Research

Dear Minister Elliott

Would you consider establishing a Voluntary Citizen Research Database Registration Program, akin to your Organ Donor Registration? Only de-identified data should be available and researchers would still have to be trained and vetted, but the approval time for projects would be decreased. Citizens can choose which aspects of their information they choose to share.

Research ethics boards would be much more inclined to grant permission for projects where citizens have voluntarily offered the use of their de-identified data. Alternative resources such as the ICES database are very expensive to use (about $10,000 per query) which most health care students and clinicians cannot afford.

--
Edsel Ing MD, FRCSC, MPH, CPH, MIAD
Michael Garron (Toronto East General) Hospital
Associate Professor, University of Toronto, Ophthalmology



Appendix H. TRIPOD Checklist downloaded from the EQUATOR network.

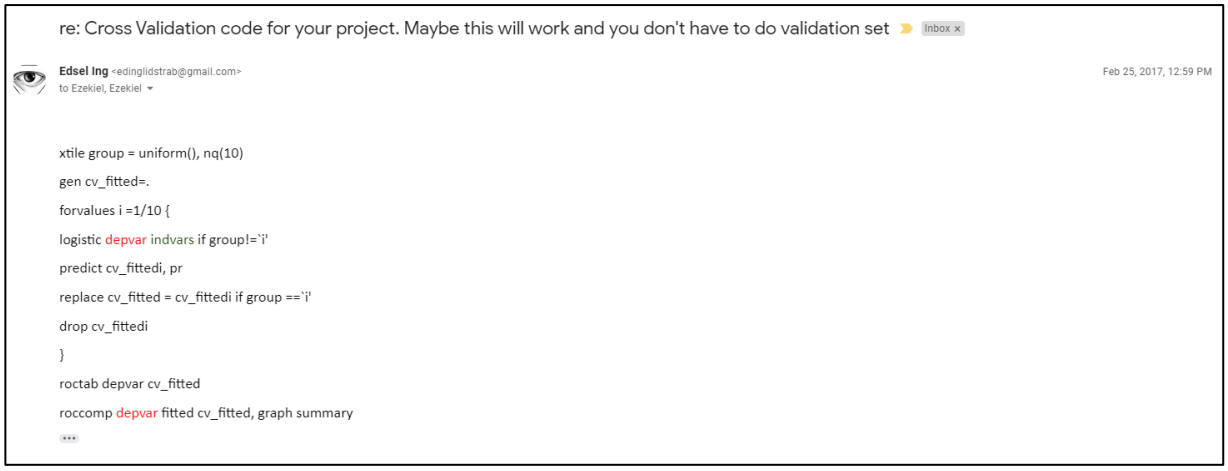
https://www.equator-network.org/reporting-guidelines/tripod-statement/

TRIPOD Checklist: Prediction Model Development

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	
	5b	Describe eligibility criteria for participants.	
	5c	Give details of treatments received, if relevant.	
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	
	6b	Report any actions to blind assessment of the outcome to be predicted.	
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	
Sample size	8	Explain how the study size was arrived at.	
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	
Risk groups	11	Provide details on how risk groups were created, if done.	
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	
Model development	14a	Specify the number of participants and outcome events in each analysis.	
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	
	15b	Explain how to the use the prediction model.	
Model performance	16	Report performance measures (with CIs) for the prediction model.	
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	
Implications	20	Discuss the potential clinical use of the model and implications for future research.	
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	
Funding	22	Give the source of funding and the role of the funders for the present study.	

Appendix I. GCA Article Reviews

Review for *Canadian Journal of Ophthalmology* in February 2017 (Weis *et al.*, 2017),

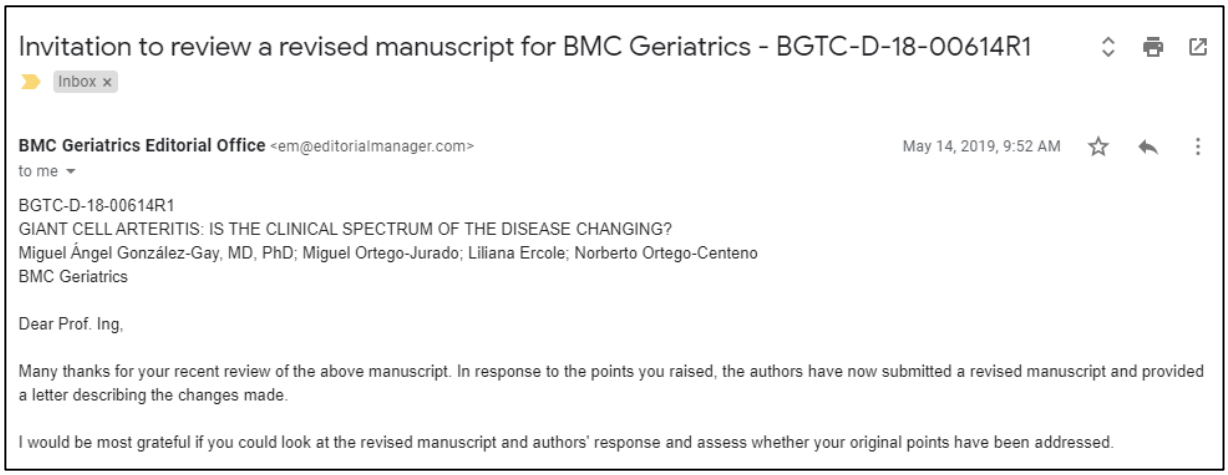


re: Cross Validation code for your project. Maybe this will work and you don't have to do validation set Inbox ×

Edsel Ing <edinglidstrab@gmail.com> Feb 25, 2017, 12:59 PM
to Ezekiel, Ezekiel

```
xtile group = uniform(), nq(10)
gen cv_fitted=.
forvalues i =1/10 {
logistic depvar indvars if group!=`i'
predict cv_fittedi, pr
replace cv_fitted = cv_fittedi if group ==`i'
drop cv_fittedi
}
roctab depvar cv_fitted
roccomp depvar fitted cv_fitted, graph summary
```

Review for *BMC Geriatrics* in May 2019 (González-Gay *et al.*, 2019)



Invitation to review a revised manuscript for BMC Geriatrics - BGTC-D-18-00614R1

Inbox ×

BMC Geriatrics Editorial Office <em@editorialmanager.com> May 14, 2019, 9:52 AM
to me

BGTC-D-18-00614R1
GIANT CELL ARTERITIS: IS THE CLINICAL SPECTRUM OF THE DISEASE CHANGING?
Miguel Ángel González-Gay, MD, PhD; Miguel Ortego-Jurado; Liliana Ercole; Norberto Ortego-Centeno
BMC Geriatrics

Dear Prof. Ing,

Many thanks for your recent review of the above manuscript. In response to the points you raised, the authors have now submitted a revised manuscript and provided a letter describing the changes made.

I would be most grateful if you could look at the revised manuscript and authors' response and assess whether your original points have been addressed.

Review for *Journal of Headache and Pain* in September 2019 (article accepted March 2020)

Thank you for your review for The Journal of Headache and Pain - let us know how we can improve the reviewing process Inbox ×

The Journal of Headache and Pain Editorial Office <em@editorialmanager.com> Fri, Sep 27, 6:33 PM (9 days ago)

to me

TJHP-D-19-00243
European Headache Federation guidelines for neurologists managing giant cell arteritis
The Journal of Headache and Pain

Dear Dr. Ing,

Thank you very much for your review of manuscript TJHP-D-19-00243, 'European Headache Federation guidelines for neurologists managing giant cell arter

We greatly appreciate your assistance.

Best wishes,

Paolo Martelletti, MD
The Journal of Headache and Pain
https://thejournalofheadacheandpain.biomedcentral.com/

Reviewer Recommendation and Comments for Manuscript Number TJHP-D-19-00243
European Headache Federation guidelines for neurologists managing giant cell arteritis

Original Submission
Edsel Ing

Recommendation: Minor revisions

Transfer Authorization	**Response**
If this submission is transferred to another publication, do we have your consent to include your identifying information?	Yes
If this submission is transferred to another publication, do we have your consent to include your original review?	Yes

Custom Review Question(s):	**Response**
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Quality of written English Please indicate the quality of language in the manuscript:	Not suitable for publi
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6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

Reviewer Blind Comments to Author:

I respectfully suggest the following suggestions:

Abstract: Do not glucocorticoids remain the first line initial treatment of GCA, with tocilizumab as an adjunct? The abstract seems to imply that tocilizumab is the new single agent initial treatment for GCA, which I do not think is correct.

Page 4 On the spectrum of GCA do you include fever of unknown origin and occult presentations?

Page 6 Instead of reference 25 from author E. Ing (n = 530), use the more comprehensive update from the same author (n=1,201), Ing EB et al, Clin Ophthalmol. 2019 Feb 21;13:421-430. The update shows that on multivariable logistic regression, new onset headache has an odds ratio of 1.540 (p value of 0.035) which I feel qualifies new onset headache as better than a "modest" discriminator for GCA.

Page 7 Diagnosis of GCA
Studies have shown that artificial intelligence and actuarial models are superior to clinical intuition for medical diagnosis (Meehl, 1954) (Ayres, 2007) (The Medical Futurist, 2016) (Mukherjee, 2017) because humans cannot objectively or accurately weigh the multiple, often non-linear risk factors for GCA as well as a judiciously formulated statistical model. The risk calculator may help avert temporal artery biopsy (and increase the yield of ultrasound) in patients determined to be at low risk for GCA.
Although risk models are not infallible they objectively risk stratify patients prior to temporal artery biopsy or ultrasound. PET and MRI are studies that cost hundreds to thousands of dollars. Free online risk calculators for GCA that have been externally validated, and follow the TRIPOD transparent reporting guidelines merit consideration in the diagnosis of GCA. e.g. Ing EB et al, Clin Ophthalmol. 2019 Feb 21;13:421-430

Ayres, I., 2007. Chapter 5. Experts Versus Equations. In: Super Crunchers. New York, New York: Bantam Dell, pp. 103-128.
Meehl, P., 1954. Clinical Versus Statistical Prediction: A Theoretical Analysis and A Review of the Evidence. Minneapolis: University of Minnesota Press. (Reprinted 2013 by Echo Point Books).
Mukherjee, S., 2017. A.I. Versus M.D.. Annals of Medicine, The New Yorker, Volume March 27.
The Medical Futurist, 2016. Can An Algorithm Diagnose Better Than A Doctor?. [Online]
Available at: https://medicalfuturist.com/can-an-algorithm-diagnose-better-than-a-doctor
[Accessed 4 Aug 2019].

Page 8 Laboratory markers:
ESR, CRP and platelets are all acute phase reactants. The platelet level must be specifically mentioned as it is the strongest bloodwork predictor for GCA. Reference 25 used by the authors graphically shows the importance of platelets in comparison to ESR and CRP. Pubmed search of the recent GCA literature will reveal numerous other references indicate the importance of a "relative thrombocytosis" for GCA. Because the odds ratio of platelets seems small in papers such as Clin Ophthalmol, 2019, on examination of an odds ratio summary table, the average reader may not realize the importance of platelets as a continuous versus binary predictor variable.
The latter is a very valuable clinical point which I did not appreciate for 25 years, until I started examining risk models as an adjunct to "clinical intuition". Clinicians should refrain from dichotomizing continuous variables such as bloodwork results, as much valuable information is lost. In a study of 1,201 temporal artery biopsy patients, the average platelet value of the positive biopsy group was 372 x 109/L compared to 283 x 109/L in the negative biopsy group. However, clinicians tend to use a platelet cut-off of 400 x 109/L for the diagnosis of GCA. Once again, the value of an objective risk calculator is shown. The same thinking applies to age, which has an exponential risk for GCA.

Page 9 re: ultrasound
Dr. Luqmani is one of the authors in this headache paper as well as the lead author of the TABUL study which is an excellent ultrasound paper. However, with all due respect in the TABUL study, the very low quality of the temporal artery biopsies is not a fair comparison with the very high quality ultrasound

performance. In 7.3% of the TABUL study subjects, instead of a temporal artery specimen, structures such as veins, fat, muscle or nerve were harvested. This is an unacceptable failure rate. Of the temporal artery specimens obtained in the TABUL study, a remarkable 43% were less than 1 cm in length, which is also glaringly substandard (see British Society of Rheumatology guidelines). Unfortunately, these important details were not mentioned in the abstract of the TABUL study.
If the EHF GCA mentions the TABUL study, it should emphasize the deficiencies of the temporal artery biopsies in the TABUL study, so as not to propagate misinformation about temporal artery biopsy.
Please note that as a reviewer I have no financial interests whatsoever in performing temporal artery biopsy, or suggesting that temporal artery biopsy be continued over ultrasound. However, having only TABUL abstract when it was initially published, I was completely misled regarding its conclusions until I delved in to the 238 page pdf document.

Furthermore, the authors should comment on this meta-analysis which shows poor sensitivity and specificity of the hypoechoic halo compared to temporal artery biopsy.
Autoimmun Rev. 2019 Jan;18(1):56-61. doi: 10.1016/j.autrev.2018.07.012. Epub 2018 Nov 5.
Diagnostic performance of temporal artery ultrasound for the diagnosis of giant cell arteritis: a systematic review and meta-analysis of the literature.
Rinagel M1, Chatelus E1, Jousse-Joulin S2, Sibilia J1, Gottenberg JE1, Chasset F3, Arnaud L4.
Based on a total of 20 studies, the sensitivity and specificity of hypoechoic halo compared to positive temporal artery biopsy were respectively of 68% (95% CI: 57-78) and 81% (95%CI: 75-86).

Page 10
The EULAR recommendations (Dejaco, et al., 2018) stress that CDUS must be properly performed by experienced ultrasonographers. The possibility of false positive ultrasound results should be clearly stated with references.
Dejaco, C. et al., 2018. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Ann Rheum Dis, 77(5), pp. 636-643.

Incidentally, a 2019 practice pattern survey, for publication in October 2019, found that 74% of European neuro-ophthalmologists and over 90% of North American neuro-ophthalmologists prefer temporal artery biopsy over ultrasound for the work-up of giant cell arteritis.

Page 13
When ophthalmic symptoms are present, glucocorticoid treatment should be initiated and ophthalmic consultation should be obtained.

Treatment: Provide the reference for 40 mg oral prednisone treatment, which I presume is in the rheumatology literature. The ophthalmology literature suggest that the minimum vision protective prophylactic dose for suspected GCA is 1 mg/kg (i.e. closer to 60 mg) oral prednisone, with higher dose i.v. glucocorticoid for patients who already have vision symptoms.

Page 15 Provide a reference for the proton pump inhibitor statement given Jones' article
Jones MG, Tsega S, Cho HJ. Inappropriate Prescription of Proton Pump Inhibitors in the Setting of Steroid Use: A Teachable Moment. JAMA Intern Med. 2016;176(5):594-595.
doi:10.1001/jamainternmed.2016.0603
The literature suggests no benefit from PPI prophylaxis in patients taking systemic corticosteroids without concomitant NSAID use. Furthermore, PPIs have been linked to numerous adverse events. Studies5 show a 2- to 3-fold increase in renal disease such as acute kidney injury in PPI users compared with nonusers and a 74% higher risk of developing Clostridium difficile infection. In addition to these adverse effects, the case described herein highlights the dermatologic drug reactions that may stem from PPI use.

Appendix J. The Post-test probability of GCA after Imaging or Negative Biopsy

Abstract submitted to the Canadian Ophthalmological Society, Nov 4, 2019.

https://preview.tinyurl.com/y6hxlbl9

The Post-Test Probability of Giant Cell Arteritis after Ultrasound, MRI, or Negative Biopsy

Purpose: Temporal artery biopsy (TABx) is the traditional reference standard confirmatory test for giant cell arteritis (GCA), but is invasive and time-consuming. Doppler ultrasound and MRI have been suggested as alternatives to TABx. We determine the post-test probability of giant cell arteritis (GCA) using a pre-test clinical risk calculator in combination with the published sensitivity and specificity of ultrasound, MRI imaging and TABx.

Study Design: Literature Review and Probability Calculations

Methods: An externally validated multivariable prediction model for biopsy-proven GCA (https://goo.gl/THCnuU) was used to determine the pre-test probability for GCA ($P_{Pre\text{-}Test}$). The sensitivity and specificity of the doppler ultrasound and MRI from published meta-analyses was used to calculate positive and negative post-test probabilities ($P_{Post\text{-}Test}$). The sensitivity of TAB from meta-analysis and Bayesian analysis was used to compute a negative post-test probability, with the presumed specificity of TABx of 100%. The $P_{Post\text{-}Test}$ was derived using (http://getthediagnosis.org/calculator.htm) derived from the formulae: Pre-Test Odds = $P_{Pre\text{-}Test}$ /(1 - $P_{Pre\text{-}Test}$); LR+ = sensitivity / (1-specificity); LR- = (1-sensitivity) / specificity; Post-Test Odds = Pre-Test Odds * Likelihood ratio; $P_{Post\text{-}Test}$ = Post-Test Odds/(1 + Post-Test Odds)

Results: The sensitivity, specificity of ultrasound, MRI, and TABx were obtained from the meta-analyses of Duftner et al (2018), Rinagel et al (2019), Rubenstein et al (2019) and a Bayesian analysis by Niederkohr (2007) were charted online along with the calculated $P_{Post\text{-}Test}$ for imaging and negative TABx. The data table is at https://preview.tinyurl.com/y6hxlbl9

Conclusions: Although calculations that combine the results of series with clinically-diagnosed GCA and biopsy-proven GCA may be biased, the $P_{Post\text{-}Test}$ for GCA following imaging studies can objectively guide clinician and patient decisions whether to continue on glucocorticoids, obtain TABx, or both. Ultrasound of the temporal artery is very operator dependent and additional imaging of the axillary arteries or occipital arteries, and unilateral or bilateral circumferential haloes of 0.7 mm thickness or greater may alter expected results.

Following a unilateral negative TABx, the negative $P_{Post\text{-}Test}$ may direct decision-making with regards to contralateral biopsy or discontinuation of glucocorticoids. However, biopsy length, unilateral versus bilateral biopsy, and completeness of pathologic exam may potentially influence the negative $P_{Post\text{-}Test}$.

Pre-Test Probability = result from the NN-LR calculator = $P_{NN\text{-}LR}$

Pre-Test Odds = $P_{NN\text{-}LR}/(1 - P_{NN\text{-}LR})$

LR+ = sensitivity / (1-specificity)

LR- = (1-sensitivity) / specificity

Post-Test Odds = Pre-Test Odds * Likelihood ratio

Post-Test Probability = Post-Test Odds/(1 + Post-Test Odds)

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Institution name	Kingston University, London, UK
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