Incidence and Prevalence of Uveitis in Veterans' Affairs Medical Centers of the Pacific Northwest

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A Thesis

Presented to the Department of Public Health and Preventative Medicine

and the Oregon Health & Science University

School of Medicine

In partial fulfillment of

the requirements for the degree of

Masters in Public Health

June 2006

School of Medicine
Oregon Health & Science University

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ACKNOWLEDGEMENTS

This thesis is dedicated to my wife, Naomi Suhler, and our three children, Kayla, Benjamin, and Sophia, without whose patience, support, love, and indulgence of time away from family this project could never have been completed.

This work would not have been possible without the mentoring, tutelage, availability, and patience of the three members of my thesis committee, Drs. Donald Austin, Dongseok Choi, and James Rosenbaum. Thank you all very much for your support and guidance.

Michael Lloyd, MD provided invaluable assistance in database construction, obtaining multiple IRB approvals, and numerator data gathering, cleaning, and deidentification. Gene Weast provided significant early assistance in the initial construction of the Access database program which allowed identification of cases. Jim Jackson, BSN, RN, BBA gave invaluable assistance in obtaining and interpreting the FY03 and FY04 denominator data from the VISTA/CHIPS data warehouse. David Hickam, MD, MPH and David Gritz, MD, MPH both provided valuable advice in the early stages of the project. I would never have been able to begin the MPH degree without the support and encouragement of Joseph Robertson, MD, MBA, and David Wilson, MD during my fourth year of ophthalmology residency at OHSU from 1999-2000. The VA Medical Center Operations Team and Eye Clinic, led by Floss Mambourg, RN, MS, MPA, CNAA and Iva Walker, respectively, both have been incredibly supportive of my desire to complete this project, in particular during the first half of 2006. Lastly, I would like to

thank my parents, Marilyn and Keith McFatridge and Jerry Suhler, for their love, support, and encouragement over the duration of my academic career. Thanks very much to all of you- this project and degree would not have been possible without your support.

ABSTRACT

Purpose: to ascertain the frequency of uveitis in VA patients in the Pacific Northwest, and to compare the disease rates to those reported in previously published epidemiologic studies.

Methods: The medical records of 152,267 patients seen at 6 Veterans' Affairs Medical Centers (VAMCs) in Oregon and Washington during Fiscal Year 2004 were searched for ICD9 codes related to uveitis. Cases were reviewed and classified anatomically, by associated systemic disease, and as incident or prevalent. Only definite cases were used for disease rate calculations.

Results: This study found an crude incidence of 25.6 cases/100,000 person-years and crude prevalence of 69 cases/100,000 persons. The most common anatomic location for uveitis was anterior. About half of cases were idiopathic, with HLA-B27 related diseases the most common identified etiology. There was no statistical evidence of increased or decreased incidence with age, although uveitis appeared to be more prevalent in the younger age groups.

Conclusion: Our data are consistent with the majority of published population-based studies on the epidemiology of uveitis but significantly lower than that reported in a recently published study from Kaiser Permanente. The signficance of and possible explanations for the differences between our data and that published by the Kaiser group are discussed.

Background and Overview of Literature:

A. Overview of Uveitis and Description of Public Health Import

Uveitis is a term which is used to describe a heterogenous set of disease entities having in common inflammation of the uveal tract, the vascular tunic of the inner eye, which is comprised of the iris, ciliary body, and choroid. In the middle part of the 20th century, most cases of uveitis were thought to be due to infectious diseases such as tuberculosis or syphilis. It is clear that with improvements in public health and improvement of infectious disease diagnosis and treatment, that the true prevalence of these as causative agents of uveitis has declined; it is equally apparent that many uveitic entities that were ascribed to infections were in fact manifestations of immune-mediated disease, the recognized leading cause of uveitis today[1,2].

Inflammation of different parts of the uveal tract may present with clinical inflammatory disease with widely variable clinical presentations. For example, intraocular inflammation restricted to the iris, which is in the anterior segment of the eye, causes a disease phenotype referred to as iritis, which is classified anatomically as anterior uveitis. Similarly, inflammation restricted to the posterior choroid, with or without inflammation of the overlying retina, would be referred to as a choroiditis or chorioretinitis, defined anatomically as a posterior uveitis. In addition to anatomic classifications, uveitis is commonly classified with regards to duration of disease, rapidity of onset, laterality, presence or absence of inflammation of contiguous ocular structures such as the cornea or

sclera, and a number of other clinical characteristics. These classification criteria have importance not only with regards to prognosis for visual outcome and development of complications, but also may serve as useful adjuncts to the diagnosis of systemic diseases which frequently accompany uveitis. For example, the uveitis caused by ankylosing spondylitis is more commonly associated with an acute presentation, anterior location, and unilateral disease which may alternate eyes in discrete flares but is less commonly simultaneously bilateral, whereas the uveitis from sarcoidosis is much more likely to be chronic, bilateral, and involve the posterior segment, often with findings of chorioretinal granulomata. Greater knowledge of the relative prevalence of subsets of uveitis is therefore of use in targeting health care and research resources towards diseases and interventions with the greatest likelihood of achieving significant improvements in public health.

Uveitis is a significant public health problem, with published series estimating that uveitic diseases may account for as much as 10% of legal blindness in Western countries [3,4], and indicating visual impairment in 30% of affected individuals[5]. More common causes of legal blindness include age-related macular degeneration, glaucoma, and diabetic retinopathy. Due to the relative youth of the majority of patients diagnosed with uveitis, however, the cost to society in terms of lost productive person-years of sight due to uveitis has been found to be similar to diabetic retinopathy, despite the greater population prevalence of the latter[4].

B. Review of the Epidemiologic Literature

Despite the demonstrated public health importance of the uveitic diseases, surprisingly few United States population-based epidemiologic studies have been published in the peer-reviewed literature to ascertain the population frequency of uveitis. Indeed, many population-based studies on causes of incident and prevalent blindness in the United States and other countries fail to list uveitis at all, preferring instead to categorize the reasons for loss of vision in patients with uveitis by the uveitic structural complication which led to decreased vision, including retinopathy, retinal detachment, glaucoma, corneal damage, or cataract[4].

In 1962, Darrell and colleagues published what, until recently, was the only US population-based epidemiologic study of uveitis in the peer-reviewed literature[6]. This study, which quantified the incidence and prevalence of uveitis in Rochester, Minnesota, a small community of approximately 30,000 residents whose medical care was felt to be exclusively delivered by practitioners affiliated with the Mayo Clinic. Cases were identified by cross-referencing 53 diagnostic codes possibly associated with uveitis against a database of IBM punchcards on all Rochester residents from 1945 to 1955, and then manually reviewing all identified charts to verify the diagnosis of uveitis, subclassified by accepted anatomic criteria at that time. Using this method, Darrell calculated an incidence rate of 17 cases per 100,000 person-years of follow-up, with 10-year prevalence of uveitis calculated at 200 cases per 100,000 population. The annual prevalence would be lower than this number, but was not provided; extrapolating 17

incident cases per 100,000 person-years each of the 10 years and a stable population (there is no commentary in the article to support these assumptions), however, one could surmise an approximate prevalence in the first year of 47 cases/100,000 population. A strength of this study was its advanced, for that time, data retrieval system and the captured nature of the study population; however, its findings are limited by small population size and lack of ethnic diversity due to the mostly Caucasian makeup of the study population.

Numerous subsequent population-based European studies on the epidemiology of uveitis have reported similar incidence rates as Darrell's initial study. Vadot and collagues reported on a French population with incidence of 17/100,000 person-years and prevalence of 38/100,000 population[7]. Mortensen reported an incidence of 14/100,000 person-years in Denmark[8]. Miettenen[9] and Paivonsalo-Heitanen[10], in study periods separated by 20 years, reported an incidence of 19.6 and 22.2 per 100,000 person-years, respectively, in the populations of Northwest and Southwest Finland, also respectively, with the latter study reporting a prevalence of 61-76 cases per 100,000 population. A slightly higher incidence of 25/100,000 person-years was found in the Bantu-speaking African black population in Johannesburg, South Africa[11]. With exceptions noted, most of the above studies only attempted to quantitate rates of incident disease and did not provide prevalence data in the studied populations. All of the above studies found that the preponderance of cases were diagnosed in the 25-to-44 year age group, and that cases were predominantly anterior in location.

In March 2004, Gritz and Wong published the second US population-based epidemiologic study of the incidence and prevalence of uveitis, and the first in approximately 40 years. This study, which they titled the Northern California Epidemiology of Uveitis (NCEU) study[12], attempted to ascertain the incidence and prevalence of uveitis in the Kaiser Permanente population of Northern California during the one year period between July 1, 1998 and June 30, 1999. Gritz and Wong performed a computerized search of the electronic medical records of 729,048 patients enrolled during the study period at 6 Kaiser Permanente facilities providing eye care in the Northern California region for the presence of 31 ICD-9 codes which might suggest a diagnosis of uveitis. All identified records were then reviewed by one of the two investigators to definitely confirm the diagnosis of uveitis. Using this methodology, the investigators described a three-fold increase in incidence compared to the Darrell study from 1962, with a calculated annual incidence rate of 52.4 cases per 100,000 person-years. In addition, the NCEU study documented an increasing incidence of uveitis with age, with highest prevalence in the age group over 65, which is counter to the experience of most uveitis specialists and that of all of the published reports listed previously. The reported annual prevalence in the NCEU study of 115/100,000 is the highest published in any study to date, although Darrell's study reported a 10-year prevalence of 200 cases/100,000 population. The Kaiser study was important not only due to the results suggesting higher frequency of disease, but also due to the size and diversity of its patient population, both significantly greater than other published studies. Additionally, it was the first modern cross-sectional epidemiologic study in uveitis performed since the advent of computerized medical records, allowing for surveying of a large population

using computerized billing codes that might suggest a diagnosis of uveitis. In addition, each chart was reviewed by an experienced investigator, with all questionable cases reviewed by two uveitis specialists, ensuring accurate identification of cases. The diagnosis of uveitis was made using strictly defined criteria for incident and prevalent disease, as well as for classification of disease anatomically. The published commentary on the NCEU study recommended further population-based studies to validate their findings, including a specific query about the generalizability of the NCEU results to VA populations[13].

Another recent population based study of the incidence and prevalence of uveitis in elderly (>65 years old) patients on Medicare was published by Reeves and colleagues in February 2006[14], in which Medicare claims were reviewed to ascertain the cases, with no review of the source records to verify the diagnosis of uveitis. This methodology makes the findings difficult to compare to the studies of Darrell and Gritz, where rigorous review of charts culled out the majority of identified charts as falsely positive for the diagnosis of uveitis. Reeves' study found an average annual incidence of 341/100,000 person-years and cumulative 10-year prevalence of uveitis at 1231 cases/100,000 at the end of the 10-year study period. By comparison, the NCEU study reported incidence of 102.8/100,000 PY and prevalence of 234.6/100,000 population in the 65+ age group. Despite this study's methodologic issues, it further raises the issue of a potential increase in the incidence and prevalence of uveitis among the elderly compared to that reported in previous studies.

In summary therefore, only two US population-based studies on the incidence and prevalence of uveitis have been published that verified all identified cases by record review. The first, by Darrell in 1962, is in general agreement with numerous published studies from Europe and one study from Africa, finding incident rates fairly tightly grouped between 14 and 25 incident cases per 100,000 person-years, with greatest incidence in younger patients. Gritz's study in 2004 was drawn from a larger, more ethnically diverse population and found significantly higher incidence rates and annual prevalences than all previous studies, with highest incidence and prevalence found in the oldest age groups. The finding of increasing incidence and prevalence with age is in sharp contradistinction to the previous literature and general conventional wisdom of uveitis specialists, both of which have indicated a peak in incident and prevalent disease in young adulthood which wanes with age. Reese's study, with the above noted caveats relating to differing methodology, supports the finding of disparity in estimates of uveitis disease frequency in older adults initially reported by Gritz. Given the aging of the population, increased uveitis in the elderly would be of obvious public health import.

This study, therefore, sought to study the population incidence and prevalence of uveitis in the patients receiving medical care at one of the six VA Medical Centers (VAMCs) in the states of Washington and Oregon, and to compare the overall age- and gender-specific measures obtained with those from the recently published NCEU study.

C. Rationale for Study of Uveitis Epidemiology in the VA system

There are a number of factors which make the VA population a particularly advantageous group on which to conduct population-based epidemiologic research. The VA population comprises a large and discrete group of patients who tend to receive their interdisciplinary medical care within the VA system. The VA uses the same computerized patient records system (known by the acronym CPRS) at all of its medical centers and providers within the system have significant incentive to complete electronic encounter forms containing diagnostic codes pertaining to the diagnosis bringing patients to clinic, as completion of this data is directly linked to medical center reimbursement and is closely monitored and reinforced by the senior management of the respective VAMCs. In addition, VA Medical Centers are grouped into Veterans Integrated Service Networks (VISNs), which are comprised of numerous community-based outpatient clinics and smaller VA Medical Centers which refer more complicated cases to tertiary centers within the same VISN.

This study was based in VISN 20, which comprises eight main VAMCs in the Pacific Northwest, six of which are geographically related by location within Oregon and Washington, and work in an interrelated fashion. The VAMCs in Seattle (Puget Sound or PS) and Portland (PDX) serve as tertiary referral centers for smaller VAMCs in Spokane (SPO), Walla Walla (WW), Roseburg (ROS), and White City (WC). Two additional VAMCs that are part of VISN20 include centers in Boise and Anchorage, which were excluded from this study due to the fact that they utilize increased levels of non-VA fee

care and function in a less inter-related fashion with the tertiary centers, making it more likely that incident or prevalent cases might be treated outside the VA system.

All clinical and billing information from the CPRS system is downloaded to a central database storehouse, known as the Consumer Health Information and Performance Set, or CHIPS. In the CHIPS database, patients are given a unique VISN ID (VID) number, eliminating the likelihood of counting uveitis patients with encounters at multiple hospitals as multiple patients (or for that matter, doubly counting patients with more than one name entry (i.e. Bob or Robert) or diagnosis code (i.e coded as uveitis at one visit and iritis the next). With regards to data relating to the size of the population in study, comprising the denominator of incidence and prevalence calculations, the VA database of total enrollees and users is closely and accurately tracked, as individual VA Medical Centers are reimbursed by VA Central Office in significant part based on the number of unique patients seen in a given fiscal year, extending from October to September in the federal budgetary cycle.

Disadvantages of using the VA population include the fact that its population is predominantly male and older than the general population, though both of these population disparities should lessen over the coming decades with the influx of veterans from more recent conflicts. Despite these limitations, the VA's computerized medical record system and central databases, combined with the relatively self-contained and comprehensive nature of care delivered within the system, make it an excellent setting for epidemiologic studies.

The specific aims of this cross sectional study, therefore, were as follows:

1. to utilize retrospectively collected data accrued in the VA CPRS and stored in CHIPS to ascertain the incidence and prevalence of uveitis and other ocular inflammatory diseases in VISN 20 during Fiscal Year 2004 (FY04), which extends over the time period from October 1, 2003 to September 30, 2004.
2. to compare the FY04 incidence and prevalence of uveitis in crude and age- and gender-adjusted forms to that found in the recent study by Gritz and colleagues from the Northern California Kaiser system, which found a significantly higher incidence of uveitis than prior epidemiologic studies. The study hypothesis is that there will be a significant difference in the incidence of prevalence of uveitis in the two populations. For the purposes of statistical testing of this hypothesis, therefore, the null hypothesis of this study is that the incidence and prevalence in the two populations are equivalent; therefore, the alternative hypothesis, which would be supported by rejection of the null hypothesis, is that a statistically significant difference between the two populations exists.
3. to ascertain the relative frequency of uveitides within the VA populations by anatomic location, etiologic diagnosis, age, gender, and other characteristics.

Methods:

This study was approved by the Institutional Review Boards and Research and Development Committees of the Portland VAMC, the Puget Sound VA Medical Center, and the VISN 20 IRB, which has jurisdiction over research studies performed on patients seen at the White City, Roseburg, Walla Walla, and Spokane VAMC facilities. All IRBs gave permission for querying of the CHIPS database to ascertain possible cases of uveitis, and also gave permission for more detailed medical record review using the facilities' specific CPRS systems. All IRBs also waived the requirement for informed consent in this non-interventional chart review study.

The data ascertainment for this study can be broken down generally into searches for two sets of statistics, relating to the numerator and denominator of our disease estimates. The numerator statistics is an exact count of the numbers of definite cases of uveitis identified from the large database of potential subjects seen at the six VISN facilities being studied. A computerized search strategy using Microsoft Access (Redmond, WA) was designed to query the VISN20 CHIPS database for all ICD-9 codes which could possibly be associated with the diagnosis of uveitis, and to cross-reference all such patients against patients with a clinic visit or "stop" code indicating they had been seen during the study period in a VISN20 ophthalmology or optometry clinic. An augmented version of the ICD-9 codes utilized by Gritz[12] was, with our additions to the list of ICD-9 codes based on careful review of all potential uveitis-indicating codes listed in the CPRS system. *The original and augmented list of codes are referenced in Appendices A and B,*

respectively. Augmentation of the list was necessary due to the presence of numerous ICD-9 codes within CPRS that could clearly be used to indicate uveitis cases which were present on the list of codes used in the NCEU study, perhaps owing to differences in the ICD-9 code lists available to providers using the computerized medical record systems at Kaiser in 1999 and the VA in 2004. The criteria were purposefully inclusive of numerous codes that were likely to have relatively low yield for uveitic cases (orbital inflammation, sarcoidosis, HIV) to ensure as best possible that no cases of uveitis confirmable by medical record review would be missed.

The specific criteria used to define uveitis cases in this study are based on consensus standards arrived upon by the Standardization of Uveitis Nomenclature workgroup in 2005[15], and are listed in Appendix C. All cases identified as potential patients with uveitis were reviewed by an ophthalmologist who had been rigorously trained in the application of the various criteria defined in Appendix C. All equivocal cases were reviewed by a second ophthalmologist with subspecialty training in uveitis and adjudicated between the two ophthalmologists, with definite cases requiring concurrence of both ophthalmologists. Only definite cases were utilized in disease frequency calculations. Definite cases were subdivided into one of three mutually exclusive categories to indicate their "incident status": incident, prevalent, and inactive prevalent cases. Only cases that were confirmed as incident during the study period were used for incidence calculations. Cases that were classified as prevalent were those that had uveitis that was either active or requiring treatment during FY04, but which was diagnosed prior to the study period. All cases which were classified as either incident or prevalent

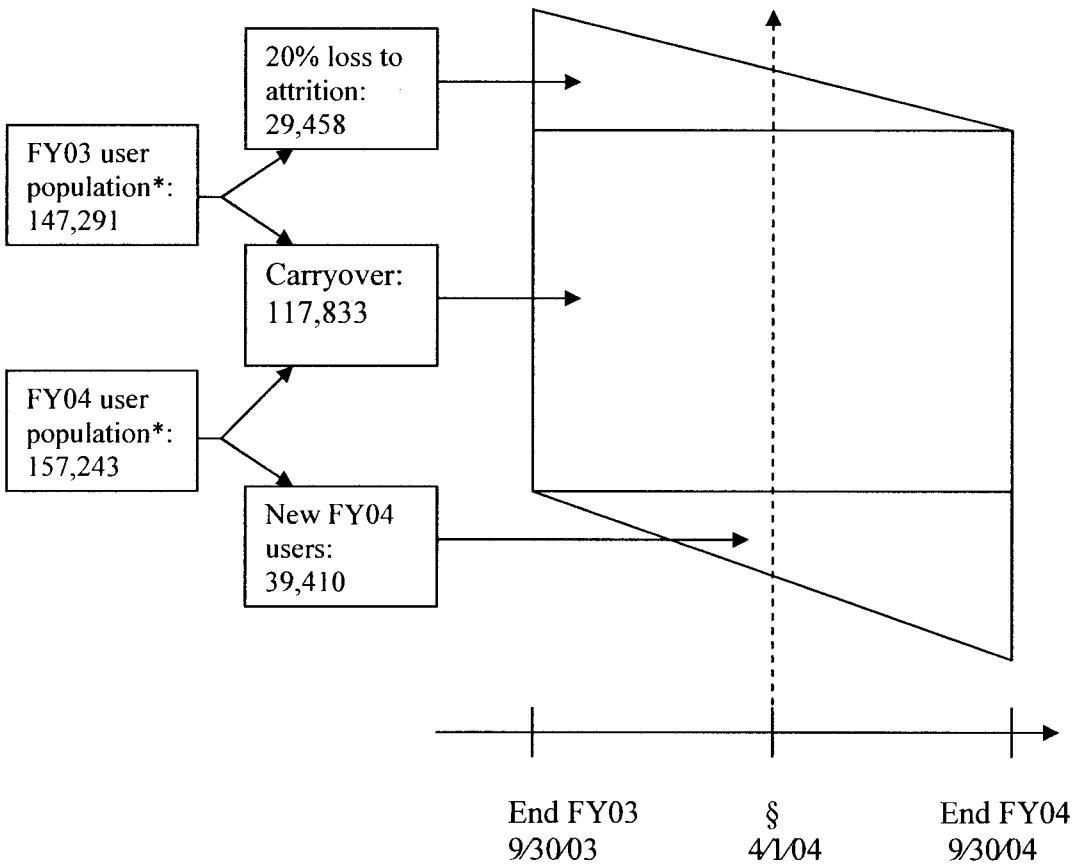
represent prevalent disease during FY04, and therefore were utilized for prevalence calculations. Gritz's study excluded inactive prevalent cases from disease frequency calculations, so to allow comparability to Gritz's data, inactive prevalent cases were not used in calculation of the primary outcomes and for testing against null hypothesis that incidence and prevalence would be equivalent to the Gritz study. The criteria for confirmation of the diagnosis of uveitis and for subclassification as incident, prevalent, or inactive prevalent disease are listed in Appendix C as well.

All of the CPRS data described above were abstracted directly from CPRS into a secure, password protected Microsoft Access (Redmond, WA) database which was kept on a password protected computer in the investigator's locked office. The data were carefully cleaned using VIDs to eliminate duplicative patient records. Once data collection was complete, the patient's name and other linking identifiers were removed in favor of a coded identifier to which only the investigator has a linking document. The data were then transferred into SPSS for greater ease of data analysis. Both the Excel and SPSS databases used for data analysis had all identifiable personal health information removed.

The denominator is an estimate derived from the total number of persons enrolled in the study period before, during, and after the study period of FY04 to attempt to model as best as possible the actual person-time spent by veteran users in the VISN 20 health care system during FY04. To ascertain these data, the CHIPS database was surveyed to determine the total number of unique patients who accessed the six participating VISN facilities for care during FY03 and FY04. During FY03-FY05, data collected on the

VISN20 Decision Support Systems website indicates that the average total unique population seen in VISN 20 facilities grew approximately 10% per year, while approximately 20% of all patients enrolled in a given year did not return for care in the following year. The CHIPS database search revealed that the number of veteran users attending the six study facilities at the end of FY03 was 147,291, and the number enrolled at the end of FY04 was 157,243. We assumed that all patients listed as users at the end of FY03 and FY04 contributed 12 months of person-time, while all individuals either leaving during FY04 or newly entering (i.e. not present at the end of FY03) would contribute, on average, six months of person-time. A reasonable estimate of person-time, therefore, was calculated by averaging the year-end population from the two years, leading to a person-time estimate of 152,267 person-years for FY04. This calculation is illustrated step-by-step in FIGURE 1. For similar reasons, this number (152,267) is a reasonable estimate of the actual size of the user population of the population at the midpoint of the study period, assuming constant influx and efflux of patients between end of FY03 and FY04, and was utilized as the denominator for prevalence calculations as well.

FIGURE 1: Diagrammatic Representation of Study Person-Time and Population Estimation



Legend:

horizontal axis- time (FY ends marked)

vertical (dotted) axis- size of population at selected time point

area within box represents total person-time during FY04- assumptions include stable rate of influx and efflux during year

* fiscal year end total user populations

§ FY04 midpoint

Person-time estimate and midpoint population estimate:

- 117,833 + [(29,458+39,410)/2]= 152,267
- Similar methodology used for age, gender specific subgroups.

Enrolled patients who did not utilize the VA system in FY 2004 were not counted in the denominator, nor were they available to be identified as cases in the numerator. Similarly to the Darrell and Gritz studies, patients were also subdivided into age strata: 25 to 44, 45 to 64, and 65+. The two referenced studies also had age groups from 0-14 and 15-24, which are not significantly represented in the VA population. Similarly to the overall population and person-time calculations, all age- and gender-specific data were created by averaging the size of the specific populations at the ends of FY03 and FY04, yielding a reasonable estimate of both overall person-time for incidence calculations and midpoint study period (April 1, 2004) population for prevalence calculations in each age/gender category.

Incidence and prevalence data were calculated using only definite cases. Incidence was calculated by dividing the number of definite incident cases by the person-time denominator and multiplying the quotient by 100,000, yielding the number of incident cases per 100,000 person-years. Prevalence data were calculated using the total number of definite prevalent cases for FY04 (including incident cases), dividing by the number of users at the study midpoint as calculated above, and then multiplying by 100,000, yielding the number of prevalent cases per 100,000 persons. Age and gender specific data were compared in crude and adjusted form using Fisher's Exact test or chi-squared testing, as appropriate. All statistical calculations were performed using Microsoft Excel 2003 (Redmond, WA) and SPSS Version 12.0 (Chicago, IL), as well as selected online statistical modules[16,17]

Results:

We identified a study population of 152,267 using the above defined methodology. Age and VISN facility demographics are shown in Table 1. Males comprised the majority of all age groups and were 92% of our study population, although in the younger age-groups women comprised a higher portion of the population. The overall gender breakdown by age is illustrated in Table 2. Out of this pool of subjects, our Microsoft Access-based search engine found 509 patient records indicating a potential diagnosis of uveitis.

After record review, 126 subjects were judged to have had definite uveitis, of whom 105 had definite prevalent disease. Of these 105 prevalent cases, 39 were definitely incident. An additional 21 patients were found to have inactive prevalent (IP) disease. Fourteen (14) patients were found to have possible uveitis but did not have definite evidence of disease. Neither inactive prevalent (IP) nor possible cases were used for population disease rate or ratio calculations. The mean age was 58 (SD 14); the youngest identified patient with uveitis was 28, and the oldest was 86, so age-specific disease rate calculations were performed only for the 25-44, 45-64, and 65+ age groups; however, all patients, including those under 25, were counted in the denominator for overall population disease rates.

Using only definite incident cases, the overall study population incidence rate was 25.6 cases per 100,000 person-years (95% confidence interval 18.8-35.0 cases/100,000 person-years). Using definite prevalent cases recorded in FY04, prevalence was

calculated at 69.0 cases per 100,000 population (95% confidence intervals: 57-83 cases/100,000 population).

TABLE 1: Number of Veteran Users* of the Six VISN20 Study Facilities, by Age Strata (years)

	<25	25-44	45-64	65+	Total
Portland, OR	280	4,747	19,685	16,982	**41,694**
Roseburg, OR	79	1,397	7,948	9,762	**19,185**
VA Puget Sound, WA	334	8,454	26,127	18,476	**53,391**
Spokane, WA	76	1,735	7,490	7,526	**16,826**
Walla Walla, WA	55	874	4,719	6,909	**12,556**
White City, OR	32	621	3,615	4,349	**8,617**
Total	**855**	**17,828**	**69,583**	**64,003**	**152,267**

* Users are defined as individual patients who utilized VA services at least once during FY04 and indicated the listed VISN20 facility as their primary site of care

TABLE 2: Veteran Users* of the Six VISN20 Study Facilities by Gender

	<25	25-44	45-64	65+	total
Males	485	13,791	64,006	61,862	140,145
Females	369	4,036	5,577	2,140	12,122
Total	**855**	**17,828**	**69,583**	**64,003**	**152,267**

* Users are defined as individual patients who utilized VA services at least once during FY04 in VISN20 facilities, as defined in Figure 1.

Table 3 breaks down incidence and prevalence into age- and gender-specific rates and proportions. Female subjects accounted for only 1 of 39 incident cases and 7 of 105 total cases identified in the study population. Fisher's exact testing comparing overall and age-stratified incidence and prevalence between genders did not yield significant differences. There was no statistically significant difference in incidence of uveitis in the three studied age strata overall or for either gender. A trend indicating increased

prevalence in the younger age groups was observed (logistic regression test for trend, p value =0.052).

TABLE 3: Crude Incidence Rates and Prevalence of Uveitis Among Veterans Seen in the Six VISN20 Study Facilities in FY04, by Age Stratum and Gender

All subjects:	**25-44**	**45-64**	**65+**	**all**
Number of Incident Cases	4	17	18	39
Number of Prevalent Cases	18	50	37	105
***Number of Inactive Prevalent (IP) cases**	4	12	5	21
Incidence (per 100,000 person-years)	**22.4**	**24.4**	**28.1**	**25.6**
Prevalence (per 100,000 population)	**101.0**	**71.9**	**57.8**	**69.0**
***Prevalence (Inclusive of IP cases)**	**123.4**	**89.1**	**65.6**	**82.7**

Females only:	**25-44**	**45-64**	**65+**	**all**
Number of Incident Cases	1	0	0	1
Number of Prevalent Cases	3	3	1	7
***Number of Inactive Prevalent (IP) cases**	1	1	0	2
Incidence (per 100,000 person-years)	**24.8**	**0.0**	**0.0**	**8.2**
Prevalence (per 100,000 population)	**74.3**	**53.8**	**46.7**	**57.7**
***Prevalence (Inclusive of IP cases)**	**99.1**	**71.7**	**46.7**	**74.2**

Males only:	**25-44**	**45-64**	**65+**	**all**
Number of Incident Cases	3	17	18	38
Number of Prevalent Cases	15	47	36	98
***Number of Inactive Prevalent (IP) cases**	3	11	5	19
Incidence (per 100,000 person-years)	**21.8**	**26.6**	**29.1**	**27.1**
Prevalence (per 100,000 population)	**108.8**	**73.4**	**58.2**	**69.9**
***Prevalence (Inclusive of IP cases)**	**130.5**	**90.6**	**66.3**	**83.5**

* IP (inactive prevalent) cases not used in rate calculations for purpose of comparison to other studies; included here for illustrative purposes only.

Breakdown of cases by anatomic criteria subclassified by age and incident or prevalent status is listed in Table 4. The vast majority (94.9%) of incident cases were anterior uveitis (37 anterior; 1 intermediate; 1 indeterminate, 0 for posterior or panuveitis). A similar, but less decided trend, was seen for non-incident prevalent cases, with 46 of 66 cases (69.7%) anterior in location (4 intermediate, 10 posterior, and 6 panuveitis). For all prevalent cases, 83 of 105 cases (79.0%) were anterior in location. Incident and prevalent uveitis cases are subclassified by etiologic cause in Table 5A, and subclassified further by age in Table 5B. The most common etiology of uveitis overall and in all age groups was idiopathic (26/39 incident cases; 48/105 overall). The most common identifiable secondary causes for incident uveitis were herpesvirus infections (7 total: 4 zoster, 3 simplex) and seronegative spondylarthropathies (4 total: 3 reactive arthritis and 1 Crohn's disease). Most common identifiable causes of prevalent disease were HLA B27+/seronegative spondylarthropathies (25 total: 7 AS, 7 ReA, 1 Crohn's disease; 1 psoriatic arthritis, 9 B-27+ not otherwise specified) and CMV retinitis (6 cases; none incident). Perhaps unsurprisingly, CMV retinitis predominantly occurred in the younger age groups (5 cases in 25-44 range, one in 45-64, none in 65+), and herpes zoster appeared somewhat more frequently in the eldest group (4/37 cases in 65+, 2/50 in 45-64, 0/18 in 25-44.

TABLE 4: Incident and Prevalent Uveitis Cases in Study Population by Anatomic Location, Subclassified by Age Strata

Anatomic classification		Age Stratum			Total
		25-44	45-64	65+	
Anterior	Incident	4	16	17	37
	Prevalent	11	41	31	83
Intermediate	Incident	0	1	0	1
	Prevalent	0	4	1	5
Posterior	Incident	0	0	0	0
	Prevalent	6	2	2	10
Panuveitis	Incident	0	0	0	0
	Prevalent	1	3	2	6
Indeterminate	Incident	0	0	1	1
	Prevalent	0	0	1	1
Total	**Incident**	**4**	**17**	**18**	**39**
	Prevalent	**18**	**50**	**37**	**105**

TABLE 5: Incident and Prevalent Uveitis cases in VISN20 Study Population by Etiology

A: All Age Strata

	incident	prevalent
idiopathic	26	48
HLA-B27 related	4	25
HLA-B27 NOS	*0*	*9*
anklyosing spondylitis	*0*	*7*
Crohn's disease	*1*	*1*
psoriatic arthritis	*0*	*1*
reactive arthritis	*3*	*7*
herpes simplex	4	7
herpes zoster	3	6
zoster keratouveitis	*3*	*5*
acute retinal necrosis (HZV)	*0*	*1*
CMV retinitis	0	6
sarcoidosis	1	3
multiple sclerosis	0	3
Behcet's	0	2
unusual postoperative	1	1
birdshot choroidopathy	0	1
histoplasmosis	0	1
rheumatoid arthritis (sclerouveitis)	0	1
VKH	0	1
Total	39	105

NOS= not otherwise specified; HZV=herpes zoster virus; CMV=cytomegalovirus; VKH=Vogt-Koyanagi-Harada disease

B: Subdivided by Age Strata

Age stratum	secondary cause	incident	prevalent
25-44	idiopathic	2	5
	HLA-B27 related	2	5
	HLA-B27 NOS	*0*	*3*
	Crohn's disease	*1*	*1*
	reactive arthritis	*1*	*1*
	CMV retinitis	0	5
	Behcet's	0	2
	multiple sclerosis	0	1
	Total	4	18
45-64	idiopathic	11	21
	HLA-B27 related	1	16
	HLA-B27 NOS	*0*	*4*
	anklyosing spondylitis	*0*	*6*
	psoriatic arthritis	*0*	*1*
	reactive arthritis	*1*	*5*
	herpes simplex	2	4
	sarcoidosis	1	3
	herpes zoster	1	2
	acute retinal necrosis (HZV)	*0*	*1*
	zoster keratouveitis	*1*	*1*
	multiple sclerosis	0	2
	unusual postoperative	1	1
	CMV retinitis	0	1
	Total	17	50
65+	idiopathic	13	22
	herpes zoster	2	4
	herpes simplex	2	3
	HLA-B27 related	1	4
	HLA-B27 NOS	*0*	*2*
	anklyosing spondylitis	*0*	*1*
	reactive arthritis	*1*	*1*
	birdshot choroidopathy	0	1
	histoplasmosis	0	1
	rheumatoid arthritis (sclerouveitis)	0	1
	VKH	0	1
	Total	18	37

The overall incidence and prevalence determined in this study were compared to the corresponding measures from the Gritz/NCEU and Darrell studies (Table 6). Statistical comparison of crude incidence and prevalence reveals that the incidence and prevalence of uveitis ascertained in this study was roughly half that seen in the NCEU study, and that this difference was highly statistically significant (Fisher's exact test, $p<.00$). Comparison of crude data between the current study and Darrell's study revealed statistically equivalent incidence rates ($p=0.07$) nearing significance indicating a lower incidence in Darrell's study. The present study had approximately one-third the amount of prevalent disease identified in Rochester, but the prevalence rates from that study are not strictly comparable to ours, as the Darrell data represent prevalent cases collected over a 10-year period. Annual prevalence in the NCEU study was significantly greater than that ascertained by our study as well.

TABLE 6: Disease Frequencies from Current Study compared to Gritz (2004) and Darrell (1962)

A. Incidence

	Incident cases	Person-years	Incidence rate (per 100000 PY)	P-value *
Current VA study	39	152,267	25.6	*reference*
Gritz	382	729,048	52.4	.00
Darrell	52	298,850	17.4	.07

B. Prevalence

	Prevalent cases	Population Size	Prevalence (per 100,000 pop.)	P-value *
Current VA study	105	157,243	69.0	*reference*
Gritz	844	731,898	114.5	.00

* by χ^2 testing

Given the NCEU study findings of higher incident rates in females and the elderly, and due to the relative paucity of females in the VA cohort, direct adjustment for age and gender was performed to see if this difference would be maintained. After direct age and gender adjustment to the VA population distribution, the incidence in the NCEU cohort actually went up significantly, more than doubling from the crude incidence of 52.4 to an adjusted rate of 124.2 cases per 100,000 person-years, which is significantly greater than the rate found in the current study (Table 7B; p-value <.00 by χ^2 testing). Similar crude and age-adjusted comparisons were also made to the data from Darrell's study based in Rochester, which demonstrated similar response to age adjustment, with incidence rising from 17 to 36 cases per 100,000 person-years after direct age and gender adjustment (Table 7C). Age and gender-adjustment was also performed for prevalence, with findings in Tables 8 demonstrating significant elevation of annual prevalence after age and gender adjustment for the Gritz study; the Darrell study reports only ten-year prevalence, and therefore does not provide comparable data to the annual prevalences reported in the current VA study and that of Gritz.

TABLE 7:

A: Comparative Crude Age- and Gender-Specific Incidence Rates from Current Study, Gritz/NCEU (2004), and Darrell (1962)

	Current VA study			Gritz			Darrell		
	Person-Time	# Cases	Incidence	Person-Time	# Cases	Incidence	Person-Time	# Cases	Incidence
0-14 M	0	0	n/a	66,838.2	4	6.0	3,350	4	11.9
15-24 M	485	0	0.0	42,024	8	19.0	1,593	2	12.6
25-44 M	13,791	3	21.8	111,973	56	50.0	4,011	14	34.9
45-64 M	64,006	17	26.6	91,565	71	77.5	2,906	6	20.6
65+ M	61,862	18	29.1	39,161	31	79.2	1,183	1	8.5
total M	140,144	38	27.1	351,561.2	170	48.4	13,043	27	20.7
0-14 F	0	0	n/a	64,178.7	5	7.8	3,272	0	0.0
15-24 F	369	0	0.0	44,538	15	33.7	3,197	7	21.9
25-44 F	4,036	1	24.8	117,986	52	44.1	4,910	12	24.4
45-64 F	5,577	0	0.0	101,416	80	78.9	3,692	3	8.1
65+ F	2,140	0	0.0	49,368	60	121.5	1,771	3	16.9
total F	12,122	1	8.2	377,486.7	212	56.2	16,842	25	14.8
total	152,266	39	25.6	729,047.9	382	52.4	29,885	52	17.4

*Incidence calculated as number of new cases per 100,000 person-years

B: Incidence Data from Gritz and Darrell After Direct Age and Gender Adjustment to VA Study Population Standard

		Gritz		Darrell	
	Population Standard Person-Time (VA)*	Adjusted§ # Cases	Age-Adjusted Incidence	Adjusted§ # Cases	Age-Adjusted Incidence
0-14 M	0	0.0		0.0	
15-24 M	485	0.1		0.1	
25-44 M	13,791	6.9		4.8	
45-64 M	64,006	49.6		13.2	
65+ M	61,862	49.0		5.2	
total M	140,144	67.8		29.0	
0-14 F	0	0.0		0.0	
15-24 F	369	0.1		0.1	
25-44 F	4,036	1.8		1.0	
45-64 F	5,577	4.4		0.5	
65+ F	2,140	2.6		0.4	
total F	12,122	6.8		1.8	
total	152,266	189.1	**124.2**	56.0	**36.8**

* standard population chosen for purpose of direct adjustment was actual FY04 VA population, stratified by age and gender as above

§ Adjusted cases calculated from product of actual study (Gritz/Darrell) age and gender-specific incidence rates times actual size of referent VA population in same age/gender group

TABLE 8:

A: Comparative Crude Age- and Gender-Specific Prevalence Ratios from Current Study and Gritz/NCEU

	Current (VA) study			Gritz/NCEU		
	Population	# Cases	Prevalence	Population	# Cases	Prevalence
0-14 M	0	0	n/a	67,222.5	4	6.0
15-24 M	485	0	0.0	42,171	10	23.7
25-44 M	13,791	15	108.8	112,524	104	92.4
45-64 M	64,006	47	73.4	91,830	157	171.0
65+ M	61,862	36	58.2	39,233	61	155.5
total M	140,144	98	69.9	35,2980.5	336	95.2
0-14 F	0	0	n/a	64,580	5	7.7
15-24 F	369	0	0.0	44,868	25	55.7
25-44 F	4,036	3	74.3	118,424	126	106.4
45-64 F	5,577	3	53.8	101,599	205	201.8
65+ F	2,140	1	46.7	49,447	147	297.3
total F	12,122	7	57.7	378,918	508	134.1
total	152,266	105	69.0	731,898.5	844	115.3

Prevalence calculated by number of prevalent cases per 100,000 population

B. Prevalence Data from Gritz After Direct Age and Gender Adjustment to VA Study Population Standard

	Gritz/NCEU		
	Population Standard (VA)*	# Cases §	Adjusted Prevalence
0-14 M	0	0.0	
15-24 M	485	0.1	
25-44 M	13,791	12.7	
45-64 M	64,006	109.4	
65+ M	61,862	96.2	
total M	140,144	133.4	
0-14 F	0	0.0	
15-24 F	369	0.2	
25-44 F	4,036	4.3	
45-64 F	5,577	11.3	
65+ F	2,140	6.4	
total F	12,122	16.3	
total	152,266	390.2	256.3

* standard population chosen for purpose of direct adjustment was actual FY04 VA population, stratified by age and gender as above

§ adjusted cases calculated from product of actual study (Gritz) age and gender-specific prevalence ratios times actual size of referent VA population in same age/gender group

Discussion:

The first two specific aims of this study were to ascertain the incidence and prevalence of uveitis in the VA population, and to compare these disease rate and frequency estimates to those from the Gritz/NCEU study in crude and age/gender-adjusted form. The crude incidence rates we found in our study of the VA population were lower by approximately half than the corresponding data ascertained by Gritz in the NCEU study, and are statistically congruent with the findings of the crude incidence data published in the other epidemiologic studies from the US, Europe, and Africa. Those collected studies reported incidence rates ranging from 14 to 25 cases per 100,000 person-years, consistent with our calculated incidence of 25.6/100,000 person-years. With regards to the second specific aim, therefore, the null hypothesis of equivalent crude incidence and prevalence of uveitis between the current study and the Gritz/NCEU study was rejected. This hypothesis was even more strongly rejected after age and gender adjustment, which led to a further effective increase in incident and prevalent disease in the NCEU study. This increase after adjustment was due to the much higher population proportion in the oldest age groups at the VA compared to Kaiser, combined with the higher rates of incidence in these older age groups at Kaiser compared to the VA. The higher proportion of elderly patients in the VA overwhelmed the effect of a much smaller female population at the VA than at Kaiser, which alone would have actually lowered the adjusted Kaiser figures.

Our third specific aim was to characterize other factors relating to incident and prevalent uveitis in the VA population. The studies of Gritz and Reeves suggested that uveitis incidence increases with increasing age, which is contrary to the findings of most

previously published epidemiologic studies, which found a preponderance of incident cases affecting the age group from 25 to 44. Our study did not wholly agree with either of these divergent trends, finding roughly equivalent (and statistically indistinguishable) incidence of disease across the three age strata principally represented in our population. However, the prevalence of uveitis in our population seemed to be higher in the younger age strata, which is similar to the findings of the other epidemiologic studies published prior to 2004.

The predominant anatomic classification of uveitis in our series was anterior uveitis in all age and gender subgroups, consistent with previous literature on the anatomic distribution of uveitis cases in the general practice of ophthalmology[18]. Almost half of all cases were idiopathic. It is worth noting that idiopathic disease in this study represents patients who received extremely variable evaluation from ophthalmologists and optometrists spread over the six VISN facilities; the rate of idiopathic disease, which is higher than might be expected in a tertiary care clinic, may be due in part to this factor. The most common identifiable secondary causes of uveitis in our population were the B-27 related seronegative spondylarthropathies (reactive arthritis, ankylosing spondylitis, inflammatory bowel disease from Crohn's disease or ulcerative colitis, and psoriatic arthritis), which are most commonly associated with acute anterior uveitis. In this study, there was no evident trend for greater infectious uveitis in older patients than in younger patients to explain differential incidence or prevalence in this or other studies, although the subsets of infectious uveitis differed between age groups, with relatively more

herpesvirus uveitides in older patients and more CMV retinitis seen in younger HIV + patients.

In population-based epidemiologic studies such as this, definition of the population at risk is often difficult, but is of paramount importance. There are a number of biases relating to our denominator data that could conceivably skew our incidence and prevalence estimates either higher or lower. Our denominator was the population of veteran users, defined as all veteran patients who utilized VA services during FY04, including those who accessed the system for primary care, specialty services, or pharmacy. The population of users of the VA is a subset of a larger group of individuals who are enrolled in the VA system during a given fiscal year, whether or not they actually make use of this service. The six VISN20 facilities had an enrollee population of 253,577 in FY04, which included the 152,267 users who made up our midpoint study population, as well as an additional 101,210 individuals, who were enrolled at the VA but did not use any VA services during the study period. Many veterans who are enrolled at the VA are dually enrolled in other health care plans, including Medicare, Medicaid, and with private providers using a variety of third-party payors. It is very likely that true cases of definite uveitis exist in the unobserved population of "non-using enrollees". There is no way using available data to estimate the uveitis disease burden in that group, or whether it is higher, lower, or equal to observed disease rates in the measured population of patients who were users during FY04. If these "non-using enrollees" were counted in our denominator estimates of person-time, and if we make the unlikely assumption that there were no actual uveitis cases in the non-using population, our

estimates of incidence and prevalence would be reduced to 15.4 cases/100,000 person-years and 41 cases/100,000, respectively. The above estimates, while substantially lower than those calculated in our study using the "user" population, are still within the range of values published in the collected epidemiologic studies referenced previously. It is clear that using enrollees as the denominator would substantially and artificially reduce the estimates of disease risk in our study population. Conversely, however, the selection of users rather than enrollees as the denominator for this study would be expected to artificially raise disease estimates to some degree, as there will be some non-using enrollees who did not use VA services that should be appropriately included in the population at risk. As this assumption biases our estimates of disease toward the null hypothesis (that of no difference in disease incidence or prevalence between the studies), however, this is felt to be the more conservative approach, as well as being more defensible based on the known characteristics of the VA population discussed further below. Comparison of the crude incidence and prevalence in this study with users and enrollees used as the denominator may be found in Table 9.

TABLE 9: Comparative Crude Age- and Gender-Specific Prevalence Ratios from Current Study Using Enrollees and Users as the Denominator

	25-44	45-64	65+	total	p-value*
	4	17	18	39	
Prevalent Cases	18	50	37	105	
Users (U)	**17,828**	**69,583**	**64,003**	**152,267**	
Enrollees (E)	**40,512**	**112,042**	**99,706**	**253,577**	
Incidence (U)	**22.4**	**24.4**	**28.1**	**25.6**	**.612**
Prevalence (U)	**101.0**	**71.9**	**57.8**	**69.0**	**.052**
Incidence (E)	**9.9**	**15.2**	**18.1**	**15.4**	**.292**
Prevalence (E)	**44.4**	**44.6**	**37.1**	**41.4**	**.444**

* Logistic regression test for trend comparing incidence and prevalence across three measured age strata

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The above discussion clearly demonstrates the potential biases of using the enrollee and user populations as denominators in calculating the uveitis disease burden in our study population. The decision to employ the user population as the denominator was felt to be most appropriate in this study for a number of reasons, including some which relate to fundamental differences between the Kaiser and VA systems. The Kaiser system is a system primarily elected by employed individuals for coverage of themselves and/or their families using a workplace benefit. Employed individuals can be shown to have a greater likelihood of being healthy than non-employed individuals, and thereby are less likely to visit any doctor, at Kaiser or otherwise. One therefore would surmise that utilizing user status in the Kaiser population would lead to a significant underestimate of the size of the true population at risk, leading to an overestimate of true population disease rates or proportions. Such an assumption would be true, but to a lesser effect, at the VA as well, which has an older and sicker population than Kaiser. One could additionally argue that nearly all individuals with true incident or prevalent disease who have chosen and paid

for Kaiser as their preferred provider of health benefits would be captured in the Kaiser database, as Kaiser enrollees are economically discouraged from accessing health care providers outside the system without prior authorization from their Kaiser providers, who typically would document the presence of the condition prior to out-of-system referral.

The VA, by contrast, is a health care system made up of individuals who have "paid" on the front end by virtue of their military service for a lifetime of entitlement to the benefit of federally provided (or at very least, heavily subsidized) health care. The provision of this benefit is only maintained by individuals who apply for and are enrolled in the VA system, and who renew the benefit every two years by accessing the system. The majority of these individuals are also eligible for other federal benefits, including Medicare and Medicaid, and unlike the situation at Kaiser, there is no economic disincentive for dually benefited veteran patients to go back and forth between VA and private care. There is, however, a significant negative effect for enrollees in the VA who allow their enrollment status to lapse, regardless of whether or not they actually use the system, as becoming re-enrolled may be difficult. The VA has very little data on the health status of enrollees versus users. It is certain that some non-using enrollees with definite uveitis received care for this condition outside the VA system; some of our possible/non-definite cases which were not used for incidence and prevalence calculations fit this criterion. What is uncertain, and impossible to estimate, is whether the incidence and prevalence of disease in the enrollees who did not utilize VA services is equal or unequal to that seen in users, or the magnitude or direction of any difference between the two groups. What is certain, given the above, however, is that utilizing

enrollees as our denominator would significantly and artifactually reduce our calculated incidence and prevalence, due to our inability to track the number or proportion of incident or prevalent cases occurring in the enrolled population who did not use the VA for health care during the study period, and the certainty that cases that were counted in the denominator would be missed in the numerator.

Given all of these factors, the most conservative way to calculate disease rates in the population of individuals who choose the VA as their primary source of health care provision is to utilize users as the denominator data, even though it is possible that such methodology will lead to an overestimation of the population risk or rate of disease with the awareness that excluding all non-users will lead to an overestimation of incidence and prevalence of uncertain magnitude. By choosing to accept users as the population, we accept a risk of overestimating true disease rates, rather than underestimating them. As noted previously, this decision would have the effect of lessening the likelihood of a type I error with regard to the null hypothesis of equivalent incidence and prevalence with the NCEU study (i.e. finding a true difference between the two studies when one does not truly exist). Despite the probable effect of the bias of utilizing the user population in increasing incidence and prevalence estimates, however, the null hypothesis of equivalent incidence and prevalence with the NCEU study was still rejected.

With regard to numerator data, our search strategy should have captured all cases of incident and active prevalent disease. Inactive prevalent cases were not used in this study, to maintain consistency with the methods in the Gritz/NCEU study, which only

counted as prevalent cases those which either were actively inflamed or which required treatment during the study period. Any cases missed by our strategy would, almost by definition, meet our criteria for inactive prevalent disease, which would not affect our calculated rates as these cases were excluded from incidence and prevalence calculations. To confirm that this assumption was true, a second database search was performed of the Portland and Puget Sound data, using a more specific subset of uveitis codes and removing the requirement for an ophthalmic or optometric clinic visit, with the goal of capturing data on patients whom were coded as having uveitis by primary care providers who had either minimally active disease or disease managed outside the VA. This search strategy did not add any incident cases, and accounted for less than 5% of our prevalent cases. It is also possible that actual cases of uveitis are present within the user population that received eye care outside the VA; this would lead to an underestimate of incidence and prevalence regardless of the denominator used.

One could certainly argue that any person diagnosed with an immune-mediated disease such as uveitis, whether actively inflamed or not, should be counted as having prevalent disease for life, as they are always at theoretical (or greater) risk for recurrence of disease, requiring lifetime surveillance by eye care providers. For this reason, this study counted and reported inactive prevalent cases to allow comparison by both methods for future researchers, although they were not used as part of the primary outcome calculations of this study. It is additionally important to document inactive prevalent cases since as treatments for uveitis improve, the proportion of patients with inactive

prevalent disease will also hopefully increase and become a more important part of characterizing population disease burden.

Although we found statistically equivalent incidence rates in the three studied groups, it is worth noting that we did find a trend of borderline significance indicating decreasing prevalence of disease in the older populations (see Table 9), which is somewhat consistent with the collective experience of the previous published epidemiologic studies, and counter to the experience of the NCEU study. Since prevalence is the product of incidence and duration, this finding is counter-intuitive. A number of explanations for this are possible. One plausible explanation would be that younger patients with uveitis are more likely to have persistent disease than older patients. Another, more ominous explanation would be that there is an increased risk of mortality in older individuals who might develop uveitis as a surrogate marker for systemic disease. Although there is no definitive evidence for either hypothesis at this time, they merit further study. One theory reconciling Darrell's highest incidence in the 1950s among 25 to 44 year olds and Gritz's highest incidence in 65+ year olds in a study 40 years later would be a birth cohort effect; however, the relatively consistent finding of highest incident uveitis in 25 to 44 year olds in epidemiologic studies published over the last 40 years argue against this.

Given the significant disparity between the incidence and prevalence data found in this study and the NCEU study, which was made more significant by age- and gender-adjustment, it is appropriate to consider reasons for the disparity. As noted previously,

most of the biases relating to our estimate of population at risk would have had the effect of increasing disease burden estimates, biasing our estimates toward the null hypothesis of no difference. The studies were methodologically similar and verified all cases by record review, although it is somewhat more likely that users of the VA would receive initial and ongoing management of eye problems outside their primary health care system than would Kaiser patients. It is possible that VA providers are underascertaining or undercoding cases, or that Kaiser providers are overascertaining or overcoding them; however, this is impossible to determine by chart review, and there is no obvious reason why providers in the two systems would be differentially likely to diagnose or code cases. An obvious difference between the two groups relates to the ethnic composition of the cohorts. The current study population, based in the Pacific Northwest, is comprised predominantly of individuals of European ancestry, similarly almost all of the populations studied. The NCEU study had a significantly higher proportion of non-white subjects. In his discussion, Gritz indicated this disparity as a possible explanation for at least some of the disparity between his study and others previously published. Socioeconomic factors may also play a role in the disparity. The primarily urban and employed enrollees in this study population may be more likely to present for initial evaluation of incident or follow-up of prevalent uveitis than the older, less employed, and more rural VA population. In addition, as the Kaiser population is more likely to be employed, and by virtue of this, is more likely to be systemically healthy. If unknown or unmeasured confounders relating to systemic health (for example, a more robust immune system) increase likelihood of developing uveitis, these could partially explain the

differences between our study and the NCEU study. These hypotheses could be more critically assayed in future epidemiologic studies of the VA or other populations.

Summary and Conclusions:

In conclusion, the null hypothesis that incidence and prevalence of uveitis would be statistically indistinguishable from that ascertained in the Gritz study was strongly rejected. Crude uveitis incidence was about half that seen in the Gritz study, and slightly more than seen in the Darrell study, although age- and gender-adjustment revealed that the current VA study had significantly less incident disease than either of the previous US cohorts. Similarly to previous studies, the preponderance of disease was anterior in location, and most prevalent disease occurred in younger patients, although incident disease was evenly distributed among the age groups.

Ability to generalize this study to the population as a whole is somewhat limited by the age and predominantly male character of our population, as well as the relative lack of ethnic diversity in the Pacific Northwest compared to Northern California and the United States as a whole. It will be instructive to re-examine this population in the next decades as an influx of veterans from contemporary wars replace the older generations, with greater numbers of younger and female patients entering the VA population. Comparative studies, either to other VISNs or well-defined populations outside the VA system, would also be instructive in arriving at an estimate of uveitis prevalence that might better reflect the general population. A study of the VA population in Northern California might be particularly instructive in comparison with the Kaiser data from the same region, and perhaps in validating the findings of the current study in the Pacific Northwest region. For maximal benefit in the current VA population, increasing study

should be prioritized towards epidemiology, diagnosis, and treatment of idiopathic and anterior uveitis, and perhaps into investigating the paradigms for evaluation of "idiopathic" uveitis utilized in VISN20 facilities. Additional prospective or retrospective studies might also be dedicated to ascertaining risk factors for the development of incident disease, including military exposure histories. No data on clinical outcomes of uveitis were gathered in this study, and correlation of population disease burden to actual impact on the studied population in lost vision, functional ability, or need for medical or surgical intervention would also be instructive.

This study is the first to attempt to ascertain the incidence and prevalence of uveitis in the VA population, and continued work in cohorts such as this and others should be valuable in enhancing understanding of the epidemiology of uveitis in veterans and in the general population as a whole.

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Appendix A:

Uveitis Codes utilized by Gritz and Wong, Ophthalmology 2004

APMPPE/white dot chorioretinopathy	363.15
CMV chorioretinitis	363.20, 078.5
Choroid disorder	363.9
Eales disease/ retinal vasculitis	362.18
Episcleritis	379.00
Eyelid, inflammatory lesion	373.9
Harada disease	363.22
Herpes (cornea)	054.43
Herpes (eye)	053.29
Herpes simplex (eye)	054.49
Immunodeficiency/HIV (AIDS)	042
Infection, retina, choroid, vitreous (eye)	360.00
Inflammation, uveitis disorders	364.3
Iridocyclitis (acute/subacute)	364.00
Iritis	364.3
Nasolacrimal/external eye, inflamm lesion	375.9
Optic neuropathy/neuritis	377.39
Orbit/sinus inflammatory lesion	376.00
Pars planitis, posterior cyclitis	363.21
Presumed Ocular Histo Syndrome	115.92
Postoperative endophthalmitis	360.19
Retinitis/choroiditis	363.20
Sarcoid	135
Sclera disorder	379.19
Scleritis	379.00
Toxocara	128.0
Toxoplasmosis	130.9
Uveitis, uveitis/other	364.3, 564.3

Appendix B:

Uveitis Codes added to list in Appendix A for current study:

Degen of Pupillary Margin	364.55
Fuch's	364.21
Primary Iridocyclitis	364.01
Recurrent Iridocyclitis	364.02
Secondary Iridocyclitis-Noninfectious	364.04
Pupillary Abnormality	364.75
Anterior Synechiae	364.72
Posterior Synechiae	364.71
Pseudotumor	376.11
Optic Papillitis	377.31
Pupil Abnormality	379.40
Keratitis	370.9
Herpes Zoster	053.21
Glaucoma associated with ocular inflamm	365.62
Uveomeningoencephalic syndrome	363.22/363.24
Sympathetic Ophthalmia	360.11
Serpiginous Ulcer	370.04
Intermediate Uveitis	364.10
Posterior Uveitis	364.20
Disseminated choroiditis and chorioretinitis	363.11
Focal choroiditis and chorioretinitis	363.03
Posterior scleritis	379.07
Scleritis NEC, other	379.09
Anterior scleritis	379.03
Brawny scleritis	379.06
Scleritis with corneal involvement	379.05
Chronic uveitis	364.10
Uveitis due to secondary syphilis	091.50
Hypopyon	364.05
Syphilis	097.9
Neurosyphilis	094.9
Tuberculosis, NEC or ocular	011.90, 017.00, 017.30
Cataract in inflammatory ocular disorders	366.32
Chronic inflammatory disorder, orbit	376.10
Disorders/visual pathways assoc. w/ inflamm disorders	377.63
Behcet syndrome	136.1
Band keratopathy	371.43

Appendix C:

Criteria utilized to define uveitis diagnoses in this study (modified from Gritz and Wong, Ophthalmology 2004, and SUN working group, Am J Ophthalmol 2005:

General criteria:

Uveitis:
defined as clinical evidence of intraocular inflammatory disease, not primarily due

1. to proximate (<3 months) trauma or surgery.
2. to bacterial or fungal keratitis (viral keratitis is allowed if the iridocyclitis is clinically significant in the opinion of the evaluating provider i.e. sufficient to require treatment)

Epidemiologic Case Definitions:

Incident disease: disease which was new in onset during the study period (FY04), or newly diagnosed without structural complications clearly indicating prior disease

Prevalent disease: incorporates both incident cases and cases with onset prior to FY04. All prevalent cases were noted to have active inflammation during FY04, or disease which was quiescent due to ongoing treatment.

Inactive Prevalent disease: prevalent cases in which there was no active intraocular inflammation off therapy, where there is clear historical information and/or structural sequelae of uveitis confirming the prior diagnosis.

N.B. although the designation of incident vs. prevalent disease should be made based on the patient's presentation within the study period (FY04), ophthalmology/optometry notes pre- or post-dating the index visit may be referenced if available within the CPRS system to further clarify the nature of disease.

Definite vs. Possible Disease: Only definite disease which meets the above and below criteria will be utilized in calculations of incident or prevalent disease frequencies. All non-definite cases will be characterized as possible cases and will not be used in disease.

Anatomic criteria:

Anterior Uveitis:
Inflammation primarily located in the anterior segment of the eye (anterior to the lens). Spillover vitreous cell or macular edema is permissible.

Intermediate Uveitis:
Inflammation primarily located in the vitreous cavity of the eye (anterior to the lens). Spillover anterior inflammation, macular edema, optic nerve edema, and peripheral retinal vasculitis is permissible.

Posterior Uveitis:
Inflammation primarily located in the retina or choroid. Spillover vitritis is permissible.

Panuveitis:
Inflammation meeting collective criteria for all three of the above is required to diagnose panuveitis.

Unilateral: involving one eye at onset of clinical disease. "Flip-flopping" disease which has initial onset in one eye, and "flips" to the opposite eye in discrete attacks may still be classified as unilateral.

Bilateral: involving both eyes simultaneously.

Duration/Acuity Criteria:

Acute vs. Chronic Duration: disease duration of < vs. > 3 months.

Sudden vs. Insidious Onset: relating to rapidity of onset of disease; as described subjectively by patient.

Other Features:

Granulomatous Inflammation: inflammation in the eye with the clinical appearance of intraocular granulomas, including granulomatous keratic precipitates, iris nodules, or chorioretinal nodules. Note that histopathologic confirmation is not required.

Presence or Absence of Associated Systemic Disease: if a putatively causative systemic disease was identified during the workup for uveitis, it was listed in our database. Idiopathic cases were listed as such. For purposes of this study, idiopathic cases could be either those whom did not have a workup, or those whose workups were negative.

Age: age of all patients was calculated and recorded as of the midpoint of FY04 (April 1, 2004).

Gender: self-explanatory.

If insufficient historical data was present in the chart to conclusively define one of the above criteria, it was listed as "indeterminate".

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