The Advantages and Disadvantages of Being Left Handed in a Right Handed Scientific Universe

Amy C. Justice, MD, MSCE, PhD
Professor of Medicine and Public Health
Leadership in Biomedicine Lecture
January 11, 2016
Yale University School of Medicine
What is life like for a left handed person?
“Facts” About Lefties

• ~10% of US population are lefties
  – 5 of last 7 (71%) US presidents were lefties
  – 40% of schizophrenics/schizo affectives are lefties

• Causes not well understood
  – Genetics explains ~25% of handedness
    (less than for height or intelligence)
  – Linked to stress in pregnancy
    (low birth weight and older maternal age)

• 30% of lefties are “right brained”

http://www.cnn.com/2015/11/03/health/being-left-handed-health-impact/
My Experience

• We live in a right handed world:
  – Scissors, computer desks, lecture hall flip desks, etc.

• My Germanic grandmother
  – “Mark of the devil” “clumsy”
  – Tied my left hand behind my back
  – ‘Couldn’t’ teach me because I used the wrong hand

• I said, “Show me and I will figure it out.”

• She also said, repeatedly, “it is a man’s world.”
Being the youngest of six taught me how important it was to align my needs with those of others as well as how to gauge their mood!
Harvard/Radcliffe College

• Nearly flunked out
  – Math TA used me to tell when “everyone” got it
  – Academic Dean told me to drop Pre Med

• Got an amazing tutor
  – Worked hard
  – Grades dramatically improved
  – Became a tutor
  – Got the tutoring award

• Aced MCATS
College taught me to stop asking whether I deserved to be there and to instead take full advantage of whatever opportunities I was given.
“Gap Year”

• Patient Advocate at Harvard Health Services
• Lived in a cooperative household
• Applied to medical school
• Traveled in Peru and Bolivia

• Chose Yale over Harvard because of:
  – Small class size
  – Yale System
  – Thesis requirement
Classmates taught me as much as the professors about life, medicine, and science.
The First Question
DM a 26 year old black woman with tattoos and track marks, presents with delirium

• Lumbar puncture positive for cryptococcus
The patient asks,

“How long do I have? I know I have AIDS and it is going to kill me, but I need to make plans for myself and my two kids.”

The medical student says,

“I don’t know. But I will find out... “
Alvan Feinstein ‘87-89

- 1 hour/wk for two years
  - Developing chart review
  - Interpreting results
  - Editing first scientific writing

- RWJ Scholars (Jack Hughes and Patrick O’Connor) advised me how to stay out of trouble

- Presented the work at Thesis Day and Dr. Relman, Editor of NEJM, suggested we submit it

- During my internship, ARF writes the manuscript
A NEW PROGNOSTIC STAGING SYSTEM FOR THE ACQUIRED IMMUNODEFICIENCY SYNDROME

Amy G. Justice, M.D., Alvan R. Feinstein, M.D., and Carolyn K. Wells, M.P.H.

Abstract An improved prognostic staging system is needed for patients with the acquired immunodeficiency syndrome (AIDS). To construct such a system, we analyzed the course of 117 consecutive adults who received a diagnosis of AIDS at Yale-New Haven Hospital from 1981 through 1987. The staging system was developed from the data on the first 76 patients, confirmed in the remaining 41 patients, and then applied to the entire cohort.

The staging system, which is based on physiologic deficits rather than demographic or diagnostic features, gives one point for each of the following: severe diarrhea or serum albumin level under 2.0 g per deciliter, any neurologic deficit, arterial oxygen tension of 50 mm Hg or less, hematocrit below 30 percent, lymphocyte count below 150 per microliter, white-cell count below 2500, and platelet count below 140,000. The total score determines the presence of Stages I (0 points), II (1 point), or III (2 to 7 points). The three stages had distinctive prognostic gradients in our cohort. For patients in Stages I, II, and III, the median survival times were 11.6, 5.1, and 2.1 months, respectively, with one-year survival rates of 50, 30, and 8 percent. When the staging system was tested with a proportional-hazards model, no other descriptive or laboratory variable added any additional predictive power.

Although this new staging system requires further validation in other populations, we believe it will be useful in evaluating new therapies and improving the precision of prognosis in patients with AIDS. (N Engl J Med 1989; 320:1388-93.)

• Severe Diarrhea or albumin<2 g/dL
• Any neurologic deficit
• O2<50 mm Hg
• Hematocrit <30%
• Lymph Count <150/mL
• WBC <25000/mL
• Platelets<140K/mL

Referenced 126 times, once last year
"The work being done on your marriage—are you having it done, or are you doing it yourselves?"
1988-1995: Seven Years at the University of Pennsylvania
## Staging System in New Data

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<th>Score</th>
<th>YNHH ‘81-88</th>
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<td>N</td>
<td>117</td>
<td>104</td>
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<tr>
<td>Mortality</td>
<td>42%</td>
<td>20%</td>
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<tr>
<td>ROC Area</td>
<td>.85</td>
<td>.69</td>
<td>.63</td>
<td>.66</td>
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</table>

*Inpatient or 30 day mortality

Next Questions: How Do You...

• Test validity of a prognostic system?

• Maximize the chances that your prognostic system will hold up in new patient samples?
The Development, Validation, and Evaluation of Prognostic Systems: An Application to the Acquired Immunodeficiency Syndrome (AIDS)

A Dissertation in Health Systems for the Graduate Group in Managerial Science and Applied Economics (Wharton School of Management, University of Pennsylvania) 1996
Two Ideas

- Can approach evaluation of prognostic information like that of diagnostic tests

- HIV is not just a disease of immunodeficiency
Figure 4.2. Complex Pathophysiologic Model

CONCEPTUAL MODEL OF HIV
Project

• Developed 3 alternative systems using 3 approaches to weighting variables
  – Recursive partitioning analysis
  – Neural networks
  – Conventional regression techniques
• Validated in 5 independent samples
• 8 chapters, 2 years
• System validated well, never published
Assessing the Generalizability of Prognostic Information

Amy C. Justice, MD, PhD; Kenneth E. Covinsky, MD, MPH; and Jesse A. Berlin, ScD

Physicians are often asked to make prognostic assessments but often worry that their assessments will prove inaccurate. Prognostic systems were developed to enhance the accuracy of such assessments. This paper describes an approach for evaluating prognostic systems based on the accuracy (calibration and discrimination) and generalizability (reproducibility and transportability) of the system's predictions. Reproducibility is the ability to produce accurate predictions among patients not included in the development of the system but from the same population. Transportability is the ability to produce accurate predictions among patients drawn from a different but plausibly related population. On the basis of the observation that the generalizability of a prognostic system is commonly limited to a single historical period, geographic location, methodologic approach, disease spectrum, or follow-up interval, we describe a working hierarchy of the cumulative generalizability of prognostic systems.

This approach is illustrated in a structured review of the Dukes and Jass staging systems for colon and rectal cancer and applied to a young man with colon cancer. Because it treats the development of the system as a "black box" and evaluates only the performance of the predictions, the approach can be applied to any system that generates predicted probabilities. Although the Dukes and Jass staging systems are discrete, the approach can also be applied to systems that generate continuous predictions and, with some modification, to systems that predict over multiple time periods. Like any scientific hypothesis, the generalizability of a prognostic system is established by being tested and being found accurate across increasingly diverse settings. The more numerous and diverse the settings in which the system is tested and found accurate, the more likely it will generalize to an untested setting.

Your secretary just called to say that a favorite patient of yours (a 45-year-old high school teacher) with colon cancer dropped off his surgical and pathologic reports. She reminds you that he is scheduled this afternoon for a second opinion about his prognosis. Scanning the reports, you note that the surgeon staged the cancer at Dukes stage C1 on the basis of negative margins and 1 positive out of 28 lymph nodes and that the pathologist staged the microscopic tissue at Jass stage IV. You are not sure how to translate these stages into useful prognostic information for your patient.

Time is short. You log on to MEDLINE, type "Dukes and Jass," and select the years 1966 to 1997. The combined terms generate 18 references (1–18). Of these, 4 are independent reports of observed mortality rates (8, 11, 17, 19). You also track down the original reports of the Dukes and Jass systems (20, 21) and learn that both systems were developed at St. Mark's Hospital in London more than 30 years ago (20, 21). The Dukes system is based on histology and extent of local, lymphatic, and venous spread seen in the surgical specimen (20), and the Jass system is based on microscopic pathologic staging (21). However, the reported mortality rates by stage for these systems vary widely. How do you tell which report and which system are most likely to pertain to a 45-year-old teacher from Cleveland, Ohio?

Physicians are frequently asked for prognostic assessments and often worry that their assessments
What I Didn’t Have in 1996

• Data!
  – More variables (CD4, HIV-1 RNA, and others needed to reflect cumulative injury)
  – Bigger samples, wider diversity of sites and subjects

• Collaborators
  – Programming and statistical experts
  – Clinical experts

• Faster, stronger, smarter computers

• Buy in from stakeholders
Perceived Patient Outcomes in 1996

HIV

Treatment

Comorbid Medical and Psychiatric Disease
Spading the Ground and Waiting...

Veterans Aging Cohort Study (VACS)
Building Cross Cohort Collaborations
Veterans Aging Cohort Study (VACS)

1. Understand role of aging, comorbidity, treatment toxicity and substance use in determining outcomes with HIV infection

2. Develop interventions to improve patient outcomes
VHA Health Information System

Electronic Medical Record
- Inpatient/Outpatient
- Laboratory Data
- Pharmacy Data (centralized)
- Pathology
- Radiology
- Progress Notes

Administrative Record (centralized)
- Diagnostic Codes
- Procedure Codes
- Utilization
- Mortality

VACS Database

Patient Survey
- Adherence
- Alcohol Use
- Drug Use
- Quality of Life
- Health Behaviors
- Provider Relationship

Substudies
- Telephone Interviews
- Blood Samples
- DNA Samples
- Neurocognitive
- Psychiatric Testing
- Focus Groups

Provider Surveys
- Adherence
- Comorbidity
- Health Behaviors
- Provider Characteristics
Funding VACS

• ‘96-97 Preliminary data Cleveland VA
• ‘97 NIA KO8 CDA not funded
• Fall ‘97 RWJFS CDA funded
• Summer ’98 NIA CDA also funded
• Started 3 VA site study of HIV+ patients
  – Cleveland, Manhattan, and Houston
  (site PIs contributed their time)
  – Supported my salary, 3 part time coordinators
Cross Cohort Collaborations

• Needed to reproduce VA findings outside VA

• Joined cross cohort collaborations (~30-60,000 subjects in each)
  – ART-CC: Largely European, 19 cohorts
  – HIV Causal: Largely European, 10 cohorts
  – NA-ACCORD: North American, 21 cohorts
Collateral Benefits

• Began to see my work through reviewer’s eyes

• Learned standard approaches to limitations (missing data, confounding by intention)

• Gained a reputation for:
  – Playing well in the sandbox
  – Careful data analyses

• Learned who could help me solve problems
“After complimenting her child on his excellent behavior on their ride home from day care, Sharon realizes she has forgotten him.”
Percentage of Adults Living with HIV Aged 50+ By Year and Region

Source: UNAIDS 2012 estimates.
Stakeholder Buy In (Finally!)

- The fundamental nature of HIV care has changed

- We must address conditions:
  - Caused or exacerbated by HIV
  - Caused or exacerbated by treatment
  - Representing cumulative injury from aging, HIV, comorbid disease and treatment

- But, how do we integrate and prioritize care without an integrated measure of risk?
The Holy Grail?

**Veterans Aging Cohort Study Risk Index (VACS Index)**

An index composed of routinely collected laboratory values that accurately predicts all cause mortality among those with HIV infection.

How Can We Monitor Aging with HIV?

Components of VACS Index

• Age

• HIV Biomarkers: HIV-1 RNA, CD4 Count

• General Biomarkers: Hemoglobin, HCV, Composite markers for liver and renal injury

• Assessed among those initiating treatment

• Adjusted to predict among those on treatment
Composite Biomarkers

\[
\text{FIB 4} = \frac{\text{AGE} \times \text{AST}}{\text{PLT} \times (\text{ALT}^{1/2})}
\]  

\[
e\text{GFR} = 186.3 \times \text{CREAT}^{-1.154} \times \text{AGE}^{-0.203} \times \text{FEM} \_\text{VAL} \times \text{BLACK} \_\text{VAL}
\]

FEM \_VAL = 0.742 if female, 1 if male

BLACK \_VAL = 1.21 if black, 1 otherwise


<table>
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<th>Biomarkers of General Organ System Injury</th>
<th>Index Score</th>
<th>Restricted</th>
<th>VACS</th>
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<td><strong>Age (years)</strong></td>
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<td>&lt;50</td>
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<td>50 to 64</td>
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<td>&gt; 65</td>
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<tr>
<td><strong>CD4 cells/mm³</strong></td>
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<td>≥ 500</td>
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<td><strong>HIV-1 RNA copies/ml</strong></td>
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<td>≥ 1x10⁵</td>
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<td>&gt; 3.25</td>
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<td><strong>eGFR mL/min</strong></td>
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<td>≥ 60</td>
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<td>45 to 59.9</td>
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<td>&lt; 30</td>
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<td><strong>Hepatitis C Infection</strong></td>
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VACS Index Highly Predictive of Long Term (5 Year) All Cause Mortality

A. NA-ACCORD (N= 10835)
B. VACS (N=5066)
C. Men (N = 12785)
D. Women (N = 3116)
E. Age < 50 years (N = 11191)
F. Age > 50 years (N = 4710)
G. Black (N= 5878)
H. White (N = 6079)
I. Undetectable VL (N=8715)
J. Detectable VL (N= 7186)

Justice AC et al. *Can the Veterans Aging Cohort Study (VACS) Index Improve Clinical Judgment?* CROI 2013 [Poster] Under Review
Veterans Aging Cohort Study (VACS)

The Veterans Aging Cohort Study (VACS) is a prospective, observational cohort study of HIV-positive and an age/race/site matched control group of HIV-negative veterans in care in the United States. The study's aim is to understand the role of comorbid medical and psychiatric disease in determining clinical outcomes in HIV infection. It is funded primarily by the National Institute on Alcoholism and Alcohol Abuse, National Institutes of Health. The study has a special focus on the role of alcohol use and abuse in determining clinical outcomes.

The VACS study is built around the Veterans Health Administration (VA), the largest integrated health-care system in the United States, providing care to 5.6 million patients annually. The VA is also the largest single provider of HIV care in the nation, serving 15,000 HIV-positive veterans in 2003. The VA provides inpatient and outpatient medical care, pharmacy, mental-health services, substance-abuse treatment, long-term care, homeless care, and hospice services. The VA also has a national, fully electronic medical-record system that includes all routine clinical data, administrative data, and comprehensive follow-up data for mortality, as the VA pays some burial expenses for veterans.
National VACS Project Team
### Table: Funding Summary

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<td>HL126555</td>
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- **Note:** VACS Survey enrollment began in June 2002 and is ongoing. Additional sites were added (Dallas) in 2012 and (Nashville) in 2015. Follow-up surveys began in December 2003 and occur every 12-18 months. VACS Virtual Cohort enrollment began in 1996 and is ongoing. Solid dark lines show mortality and electronic medical record follow-up.
Impact: Aging and HIV Infection

VACS Publications by Year

VACS Citations by Year

Table 3. VACS Training Activities by Academic Affiliation of Mentor

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<th>Junior Investigator</th>
<th>Coordinating Center (Yale)</th>
<th>VACS Survey*</th>
<th>Pulmonary or CVD Study</th>
<th>Affiliated Mentors</th>
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<td><strong>11</strong></td>
<td><strong>13</strong></td>
<td><strong>14</strong></td>
<td><strong>157</strong></td>
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*Survey site academic affiliates include Emory, UCLA, Baylor, University of Texas Southwestern, NYU, Mount Sinai, George Washington, University of Maryland, and University of Pittsburgh

- >250 publications
- >10,000 citations
- >150 trainees
- Largest cohort of HIV+ in North America
- VACS publications have shaped the discussion of HIV and aging
Another Sign of Productivity
What About DM?

DM died 6 months after admission--years before cART and the VACS Index. Had she received cART, she would be 56 years old and experiencing comorbidities of aging in combination with likely HCV co-infection. Optimal management might include treatment of HCV with newly available agents while monitoring her VACS Index score to minimize toxicity and maximize clinical benefit.
Next Questions?

Epidemiology in the Era of Big Data
“...we really do have essentially free and ubiquitous data...the complimentary scarce factor is the ability to understand that data and extract value from it.”

--Hal Varian

Google’s Chief Economist
What Constitutes “Big” Health Data?

- Administrative/billing data
- Electronic medical records
- Radiological images
- Biometrics (fitbit, telemedicine, etc.)
- Metabolomic and Genomic data
- Geospatial data
Electronic Medical Records the Norm

Left: The EMR adoption rate for hospitals was obtained from the Optum Institute. The figure for physician offices was obtained from the Kalorama Information. Right: The installation time frame of different EMR components in hospitals was calculated based on data obtained from the Healthcare Information and Management Systems Society.
Smart Phones the Norm

Adults Who Own a Smartphone

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-29 years</td>
<td>85</td>
</tr>
<tr>
<td>30-49 years</td>
<td>79</td>
</tr>
<tr>
<td>50-64 years</td>
<td>54</td>
</tr>
<tr>
<td>65+ years</td>
<td>27</td>
</tr>
</tbody>
</table>

Use of Smart Phone in Last Year

<table>
<thead>
<tr>
<th>Activity</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Get info about a health...</td>
<td>62</td>
</tr>
<tr>
<td>Do online banking</td>
<td>57</td>
</tr>
<tr>
<td>Look up real estate...</td>
<td>44</td>
</tr>
<tr>
<td>Look up info about a job</td>
<td>43</td>
</tr>
<tr>
<td>Look up government...</td>
<td>40</td>
</tr>
<tr>
<td>Take a class/get...</td>
<td>30</td>
</tr>
<tr>
<td>Submit job application</td>
<td>18</td>
</tr>
</tbody>
</table>

# EHR Methods Generalize

<table>
<thead>
<tr>
<th>Title</th>
<th>PI</th>
<th>Funding</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ERCHIVES</strong> (Electronic Retrieved Cohort of HCV Infected Veterans)</td>
<td>A. Butt</td>
<td>NIH/Industry</td>
<td>600,000</td>
</tr>
<tr>
<td><strong>WVCS</strong> (Women Veterans Cohort Study)</td>
<td>C. Brandt/S. Haskell</td>
<td>VA Merit</td>
<td>&gt;1 million</td>
</tr>
<tr>
<td><strong>MSD</strong> (Musculoskeletal Disorders Cohort)</td>
<td>R. Kerns/C. Brandt/J. Goulet</td>
<td>VA Center Grant</td>
<td>4.4 million</td>
</tr>
<tr>
<td><strong>VOCAL</strong> (Veterans Outcomes and Costs Associated with Liver Disease)</td>
<td>T. Taddei/D. Kaplan</td>
<td>Industry</td>
<td>55,000 cirrhotics &amp; 7,000 HCC</td>
</tr>
<tr>
<td><strong>1945-65 Birth Cohort</strong></td>
<td>J. Lim/A. Justice</td>
<td>GI Pilot &amp; VA Program Funds</td>
<td>6 million</td>
</tr>
</tbody>
</table>
VA Million Veteran Program RFA

- VA Funded Initiative to enroll and genotype 1 million veterans with links to EHR and survey data via corporate data warehouse (CDW)

- Has enrolled 300,000 veterans with links to EHR

- Our project will use EHR phenotypes of multi substance use (alcohol, tobacco, and prescription opioids) developed and validated in VACS

- Team: W Becker, K Xu, J Gelernter, H Kranzler, H Zhao, A Justice, P Miller, M Gerstein, and D Federman with advice from J Concato

- Innovation: longitudinal, repeated measures of quantity and frequency of substance use rather than DSM categories of multiple substance use
“...Data is the sword of the 21st century, those who wield it well, the Samurai.”

--Internal email to Google employees
Jonathan Rosenberg
Past Senior Vice President for Product Management
Google
Why I Love Research

• Designing studies and interpreting data are highly creative processes

• You can be wrong which makes being right so much more fun!

• Team science is immensely rewarding

• You must master your ego or it will master you

• The work can help large numbers of people
What About Being Female in a Male Scientific Universe?

• There are advantages and disadvantages

• The secret is to:
  – Mine the advantages—you see the world differently
  – Persevere through the disadvantages—discrimination is real and pervasive, but difficult to prove
  – Use your anger, pain, and frustration to fuel harder and smarter work
  – Collaborate, collaborate, collaborate
  – “The best revenge is living well.”
Privilege is invisible to those who have it.

--Michael Kimmel, PhD
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- **Participating VA Medical Centers**: Atlanta (D. Rimland*, V Marconi), Baltimore (M Sajadi, R Titanji), Bronx (S Brown, Y Ponomarenko), Dallas (R Bedimo), Houston (M Rodriguez-Barradas, N Másózera), Los Angeles (M Goetz, D Leaf), Manhattan-Brooklyn (M Simberkoff, D Blumenthal, H Leaf, J Leung), Pittsburgh (A Butt, K Kraemer, M Freiberg, E Hoffman), and Washington DC (C Gibert, R Peck)
- **Core and Workgroup Chairs**: C Brandt, J Edelman, N Gandhi, J Lim, K McGinnis, KA Oursler, C Parikh, J Tate, E Wang, J Womack
- **Staff**: H Bathulapalli, T Bohan, J Ciarleglio, A Consorte, P Cunningham, L Erickson, C Frank, K Gordon, J Huston, F Kidwai-Khan, G Koerbel, F Levin, L Piscitelli, C Rogina, S Shahrir, M Skanderson
- **Major Collaborators**: VA Public Health Strategic Healthcare Group, VA Pharmacy Benefits Management, Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), Yale Center for Interdisciplinary Research on AIDS (CIRA), Center for Health Equity Research and Promotion (CHERP), ART-CC, NA-ACCORD, HIV-Causal
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*Indicates individual is also the Chair of a Core or Workgroup
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