Exploring the Relationship between Cyanobacterial Toxins and Human Diseases in Florida

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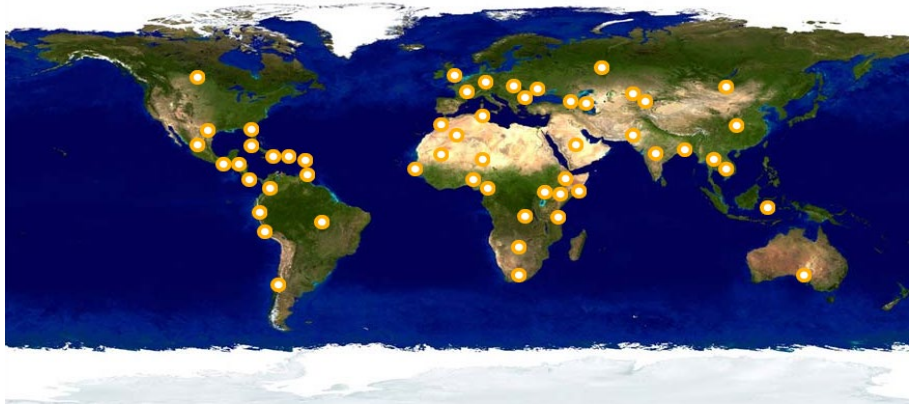
UF COLLEGES OF MEDICINE, VETERINARY MEDICINE, AND IFAS

UF Emerging Pathogens Institute

- Created in 2006 with $60 million appropriation from Florida state legislature, to conduct basic and applied research on human, animal, and plant pathogens
- Over 200 affiliated faculty members, from 11 UF colleges (including medicine, public health, veterinary medicine, and agriculture)
- Collaborations in over 70 countries, reflecting the global nature of work with pathogenic microorganisms

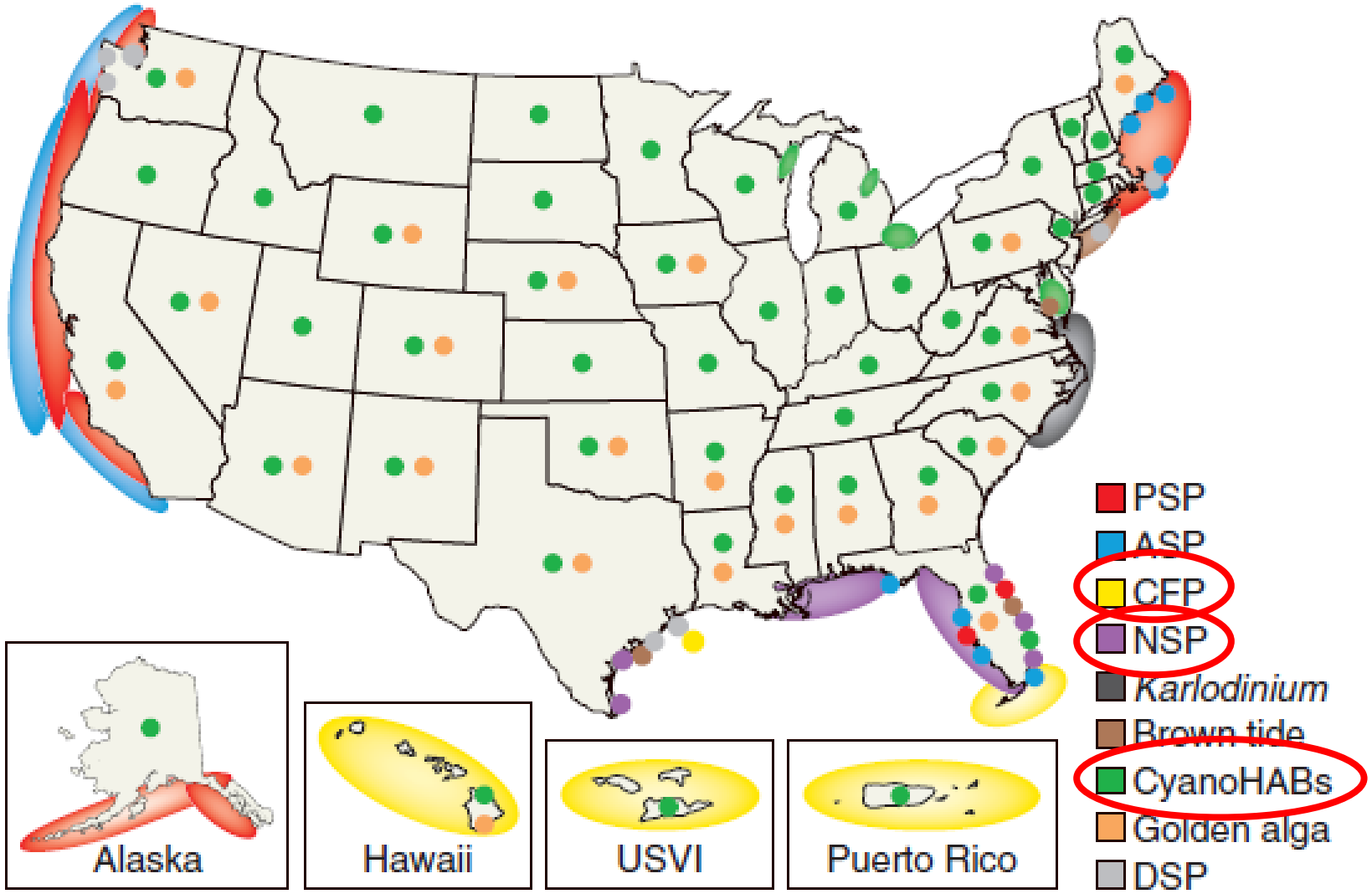
- Team within EPI, working in collaboration with UF Center for Environmental and Human Toxicology, with substantial expertise with emerging harmful algal species:
  - Studies of ciguatera in Florida and the USVI
  - Studies of Amnesic Shellfish Poisoning/domoic acid in Pacific Northwest



SYNDROME	CAUSATIVE ORGANISMS	TOXIN PRODUCED	CLINICAL MANIFESTATIONS
Ciguatera fish poisoning	*Gambierdiscus* spp. and others	ciguatoxins	Acute gastroenteritis followed by paresthesias and other neurologic symptoms
Paralytic shellfish poisoning	*Alexandrium* spp. and others	saxitoxins	Acute paresthesias and other neurologic manifestations; may progress rapidly to respiratory paralysis
Neurotoxic shellfish poisoning	*Karenia brevis*	brevetoxins	Gastrointestinal and neurologic syndromes; formation of toxic aerosols by wave action can produce respiratory irritation and asthma-like symptoms
Diarrhetic shellfish poisoning	*Dinophysis* spp.	okadaic acid and others	Acute gastroenteritis, abdominal pain
Amnesic shellfish poisoning	*Pseudo-nitzschia* spp.	domoic acid	In acute cases, gastroenteritis followed by memory loss, neurologic manifestations; may progress to amnesia, coma, and death; chronic, low-level exposure may result in mild memory loss
Azaspiracid shellfish poisoning	*Azadinium* spp. and others	azaspiracid	Acute gastroenteritis, abdominal pain
Cyanobacteria	*Lyngbya* spp. *Microcystis* spp.	lyngbyatoxin A, debromaplysia-toxin microcystins, ? BMAA	Swimmers itch, particularly in inguinal area; sore eyes, ears; headache; possibly gastrointestinal symptoms Liver damage; neurodegenerative diseases

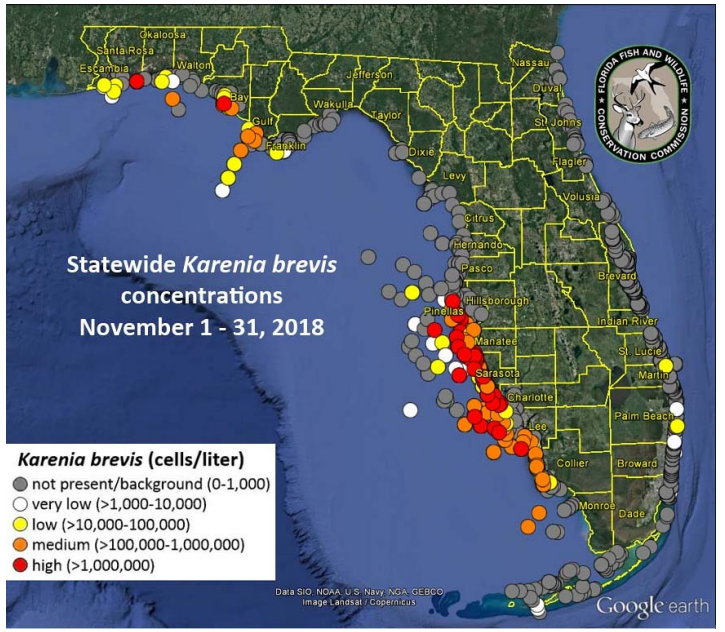
HABS in the United States

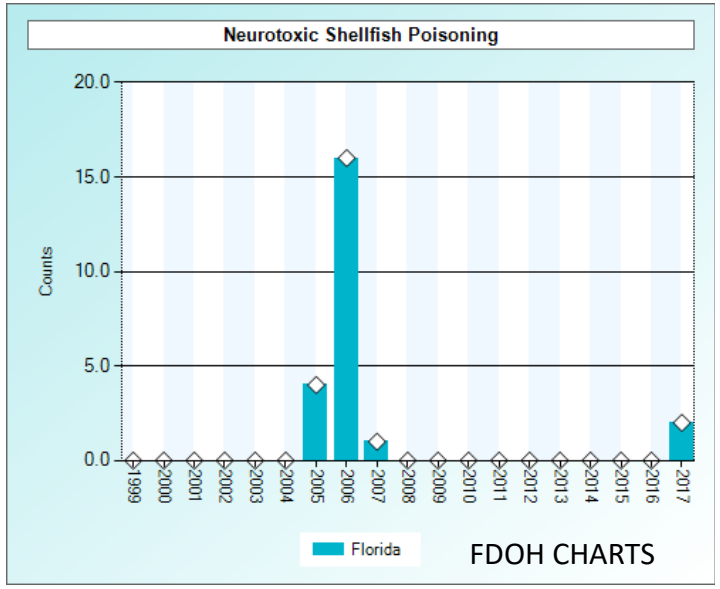
(from: National Office for Harmful Algal Blooms, Woods Hole Oceanographic Institute)



HABs of Greatest Concern in Florida

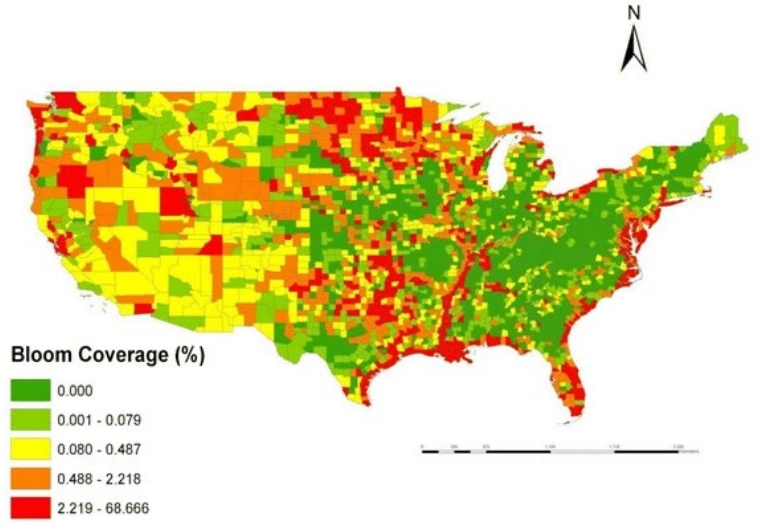
- Ciguatera
  - Illness associated with large, predatory reef fish; most common among fishermen going to Bahamas (34% of cases), Florida Keys (20%)
  - Incidence, 2007-2011:
    - Florida: FDOH confirmed cases 0.2/100K population; with corrections for under-reporting, 5.6 cases/100K population
    - Monroe County: FDOH confirmed cases 3/100K; corrected for under-reporting 84/100K (Radke *et al*)
  - Diagnosis based on clinical presentation: typical pattern of gastrointestinal and neurologic symptoms
- NSP/Brevetoxin
  - Problems along west and east coast of Florida, with regular environmental monitoring by Florida Fish and Wildlife
  - Low number of reported human cases
  - Clinical symptoms reasonably well described:
    - In association with consumption of shellfish: paresthesias, gastroenteritis
    - Respiratory irritation
      - Exacerbation of asthma in patients with a history of asthma, with drop in FEV_1 (Fleming *et al* – study of 97 asthma patients on a beach with brevetoxin exposure)





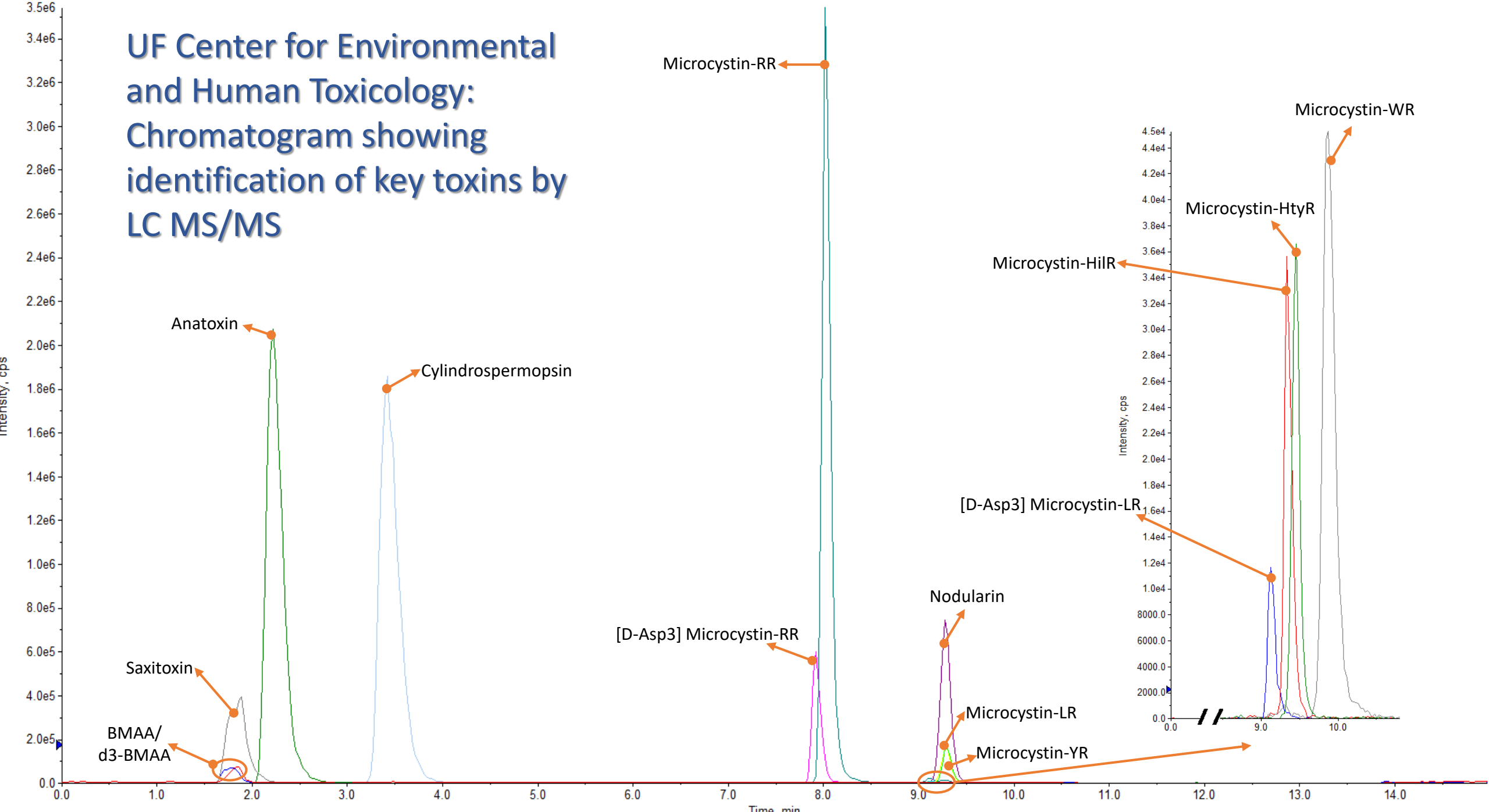
HABS of Greatest Concern in Florida - II

- Cyanobacteria
  - Widespread in U.S./Florida
  - Case reports but no incidence data on linked human illness (not reportable to FDOH)
  - Clinical presentations: diverse and poorly documented
    - Skin irritation
    - Possible liver/renal/gastrointestinal toxins (microcystins)
    - Possible neurotoxins
      - BMAA: neurodegenerative illnesses
      - Saxitoxin: PSP-like syndromes
  - Exposure data extremely difficult to obtain
    - Multiple species/strains, with differing toxin genes and expression patterns
    - Multiple toxins/toxin congeners



Bloom coverage area (percentage by county) in the US in 2005 as estimated by MERIS.

UF Center for Environmental and Human Toxicology: Chromatogram showing identification of key toxins by LC MS/MS



Microcystins

- More than 240 microcystin variants produced by cyanobacteria; MC-LR most common
  - Release occurs predominantly after cell death/lysis
- Primary exposure pathways:
  - Ingestion of contaminated drinking water
    - WHO tolerable daily intake (TDI) of 0.04 ug MC-LR/kg body weight/day
  - Inhalation and dermal contact during recreational activities
- Sublethal doses trigger cell apoptosis through formation of ROS; very high doses cause hepatic necrosis
- Selected outbreak reports:
  - 1878, Australia – lethality in livestock dosed with waterside scum
  - 1981, Australia – link between rise in liver enzymes and use of water from dam during bloom
  - 1980s, China – correlation between liver cancer and microcystin exposure
  - 2002, China – correlation with exposure and colorectal cancer
  - 2016, China – correlation with deterioration in renal function
  - 1996, Brazil – 58% mortality due to liver failure among 131 hemodialysis patients, with microcystins found in water used for dialysis
- Ecologic studies:
  - Zhang *et al*: significant association between cyanobacteria blooms and non-alcoholic liver disease, at county level in U.S.
  - Labine *et al*: no association between cyanobacterial blooms and liver cancer in Canada

BMAA

- B-N-methylamino-L-alanine (BMAA) is produced by some cyanobacteria
- Identified in cyanobacterial blooms in Florida (Florida Bay, South Biscayne Bay, Caloosahatchee River), and in fish and shellfish, with concentrations ranging from below assay detection to 7000 ug/g (Brand *et al*)
- In studies in non-human primates, caused a “dense” tauopathy, with neurofibrillary tangles, with findings similar to those seen in neurodegenerative diseases, including Alzheimer’s disease, frontotemporal dementia and early stages of ALS
- Selected ecologic studies (all of which have potential problems):
  - Association of ALS cluster with New Hampshire lake known to have a history of cyanobacterial blooms, high levels of BMAA in fish
  - Association of ALS cluster with coastal lagoon in France that has frequent cyanobacterial blooms
  - Possible association between high incidence of ALS among veterans of the 1990-1991 Persian Gulf war and exposure to cyanobacterial toxins in desert dust?

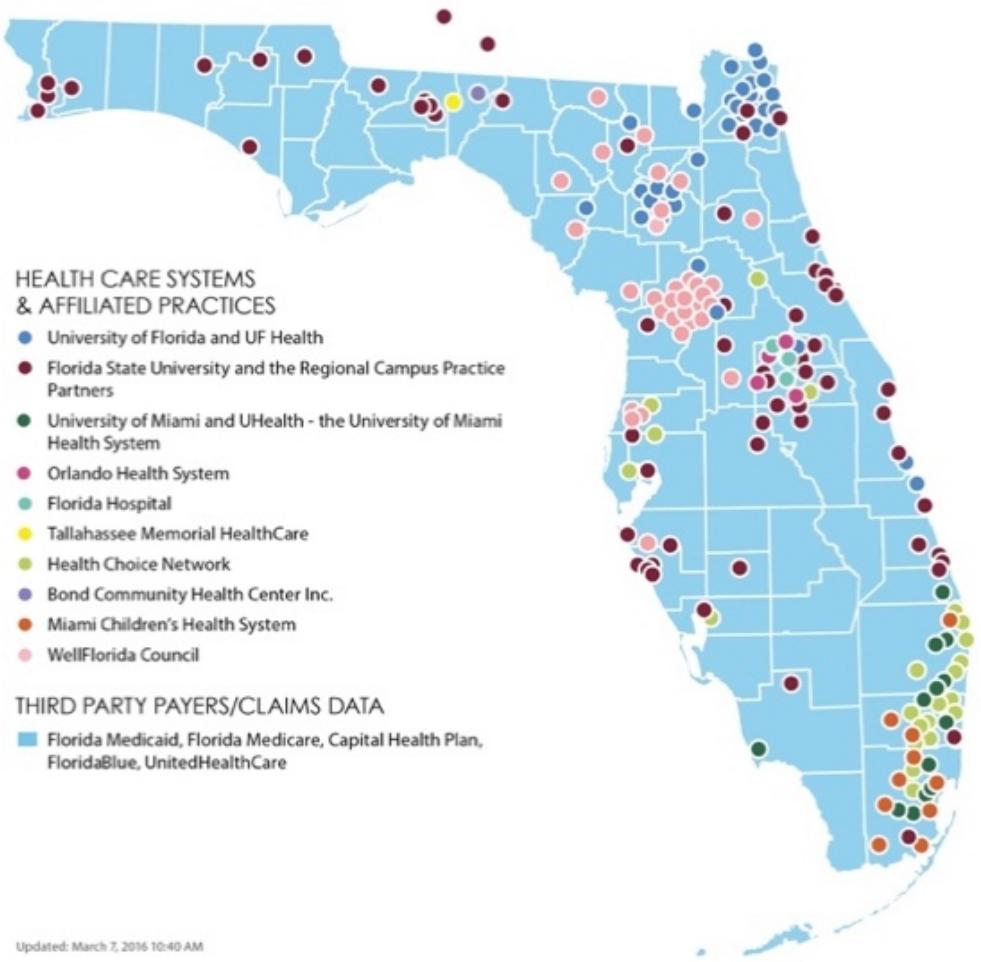


Figure 1. *OneFlorida Clinical Research Consortium Coverage Area*

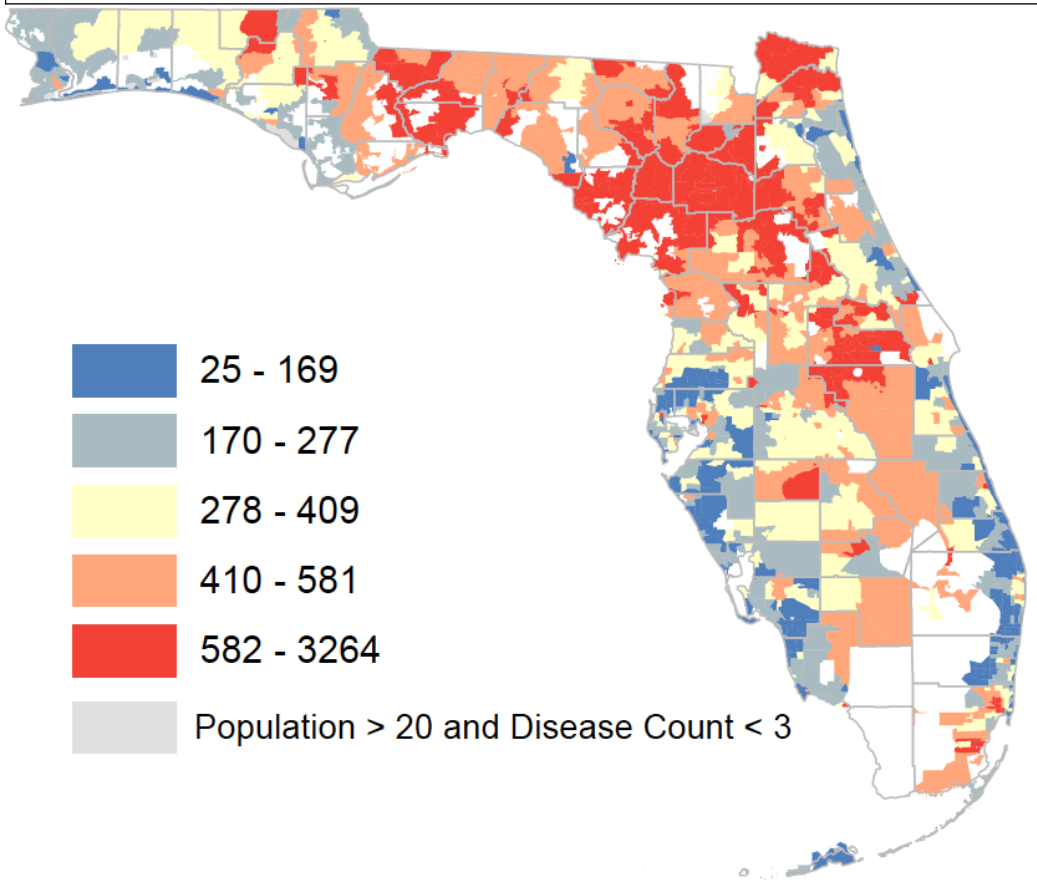
OneFlorida Clinical Research Consortium

	ICD-9-CM	ICD-10-CM	Cases
Non-alcoholic liver diseases	790.4, 570, 571.4 – 571.9, 572, 573	R74.0, K71 – K77	525,558
Paralytic shellfish poisoning	988.0	T61.78	305
Amyotrophic lateral sclerosis (ALS)	335.20, 335.21	G12.21	3,400
Alzheimer's disease	331.0	G30.0 – G30.9	98,064
Parkinson's disease	332.0	G20	50,902

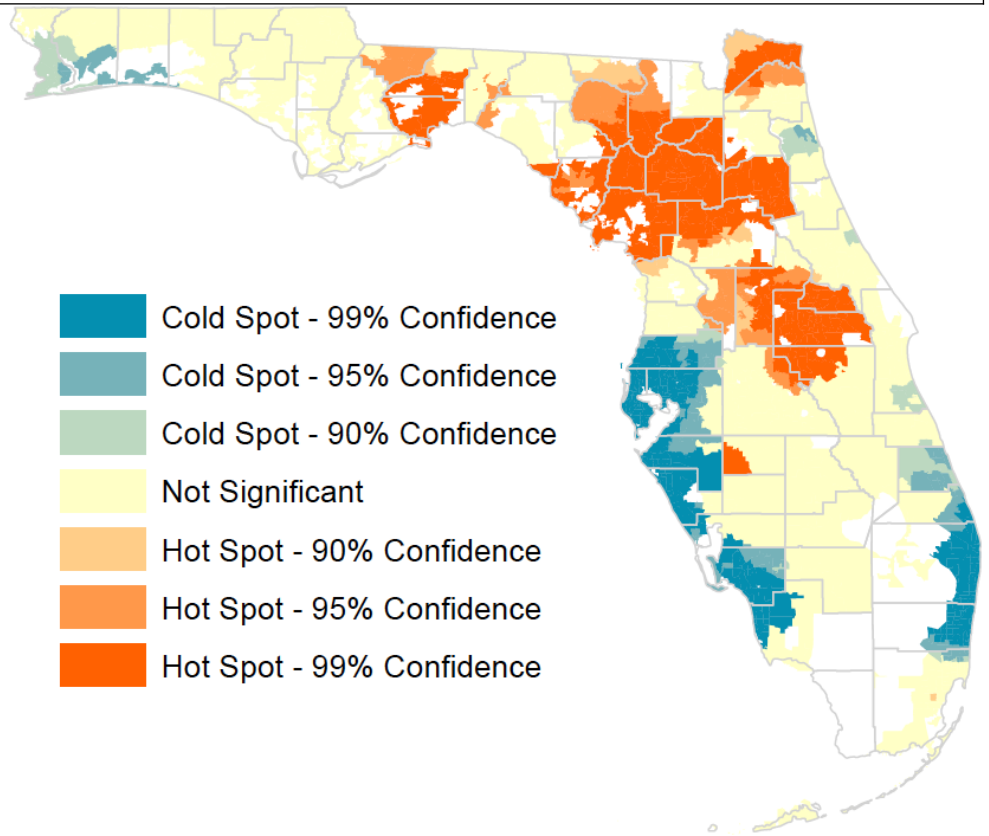
Table 1. Numbers of patients with diagnoses which have been linked with cyanobacteria-related toxins, OneFlorida EHRs 2012-2018.

Non-Alcoholic Liver Disease

Age-adjusted incidence rate by zipcode

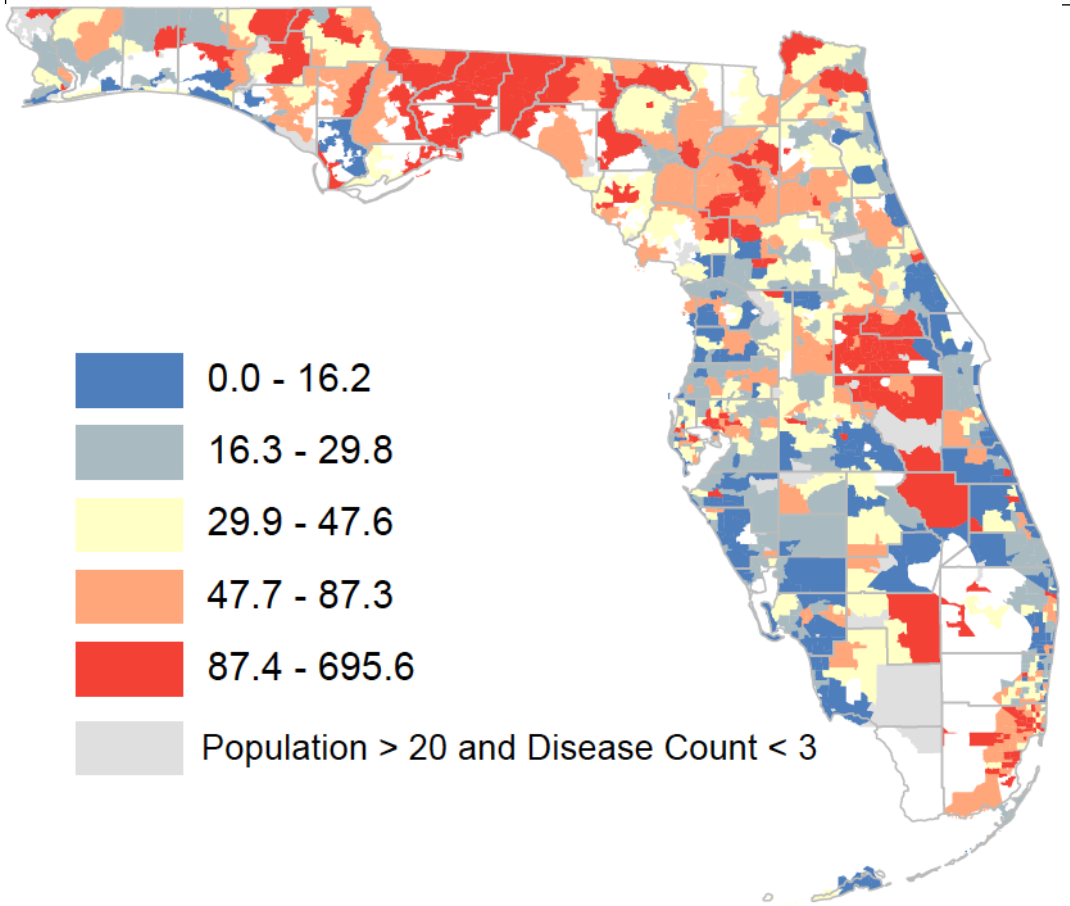


Hotspots



Alzheimer's Disease

Age-adjusted incidence rate by zipcode



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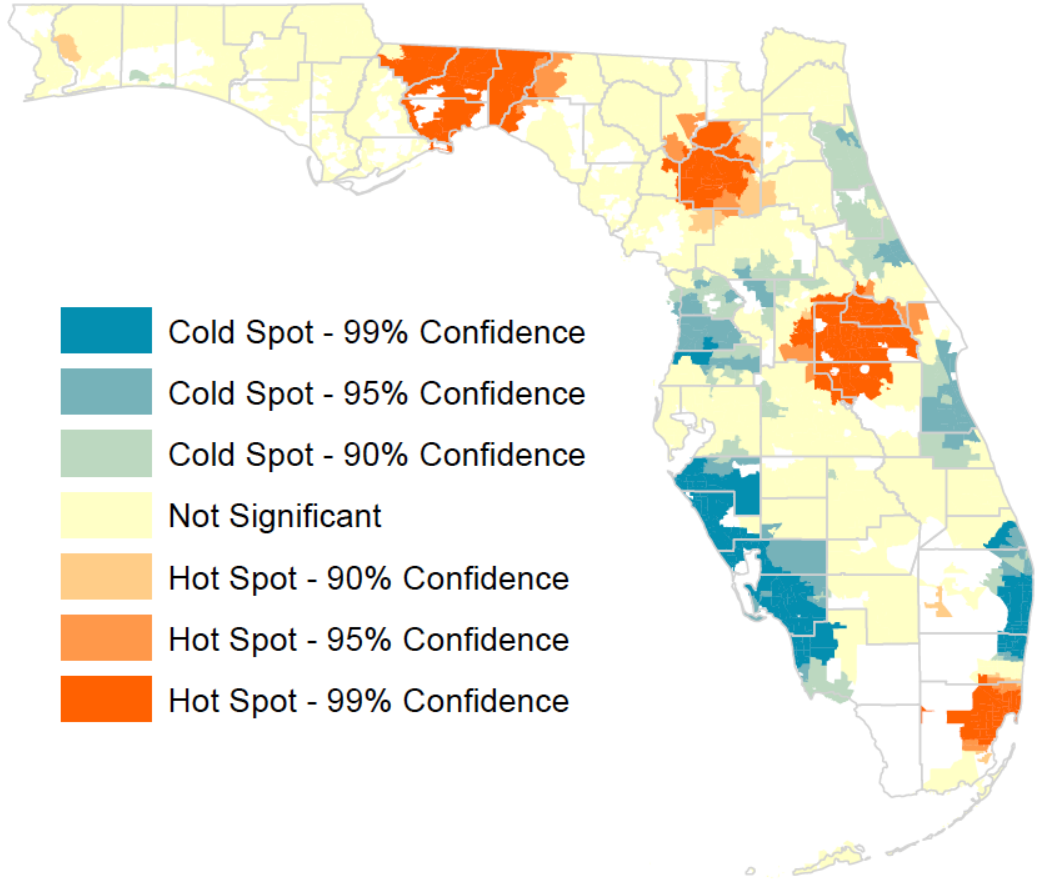
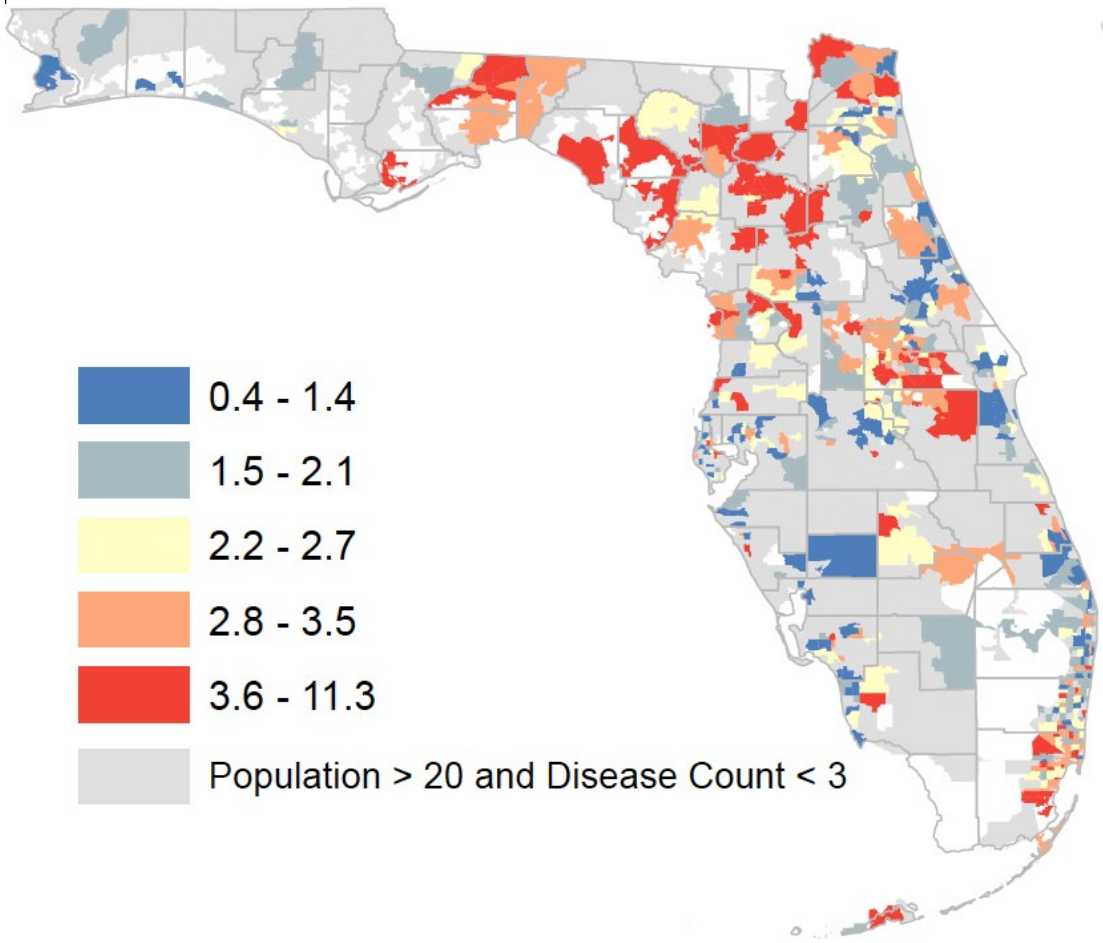
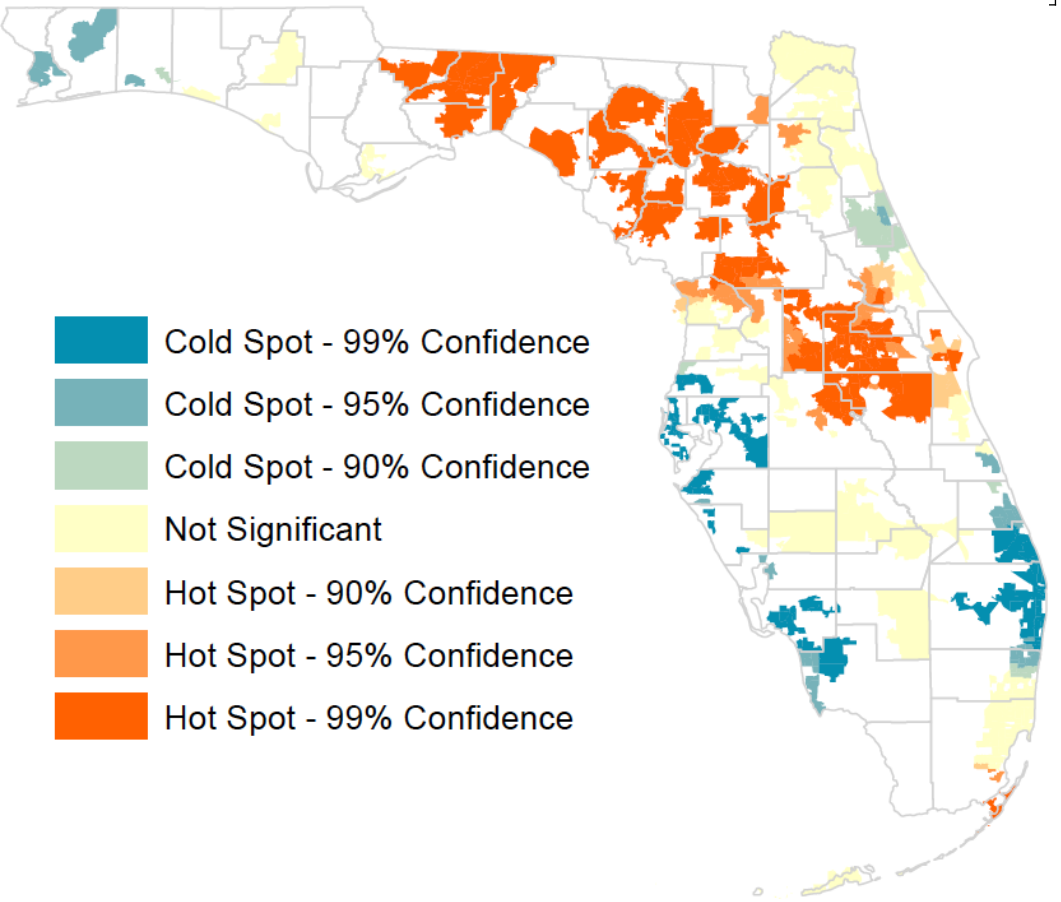


Amyotrophic Lateral Sclerosis

Age-adjusted incidence rate by zipcode



Hotspots



Assessment of Human Health Impact of HABs

- Reasonable understanding of health risk associated with ciguatera, NSP/brevetoxin-producing strains
- Much poorer understanding of human health risks associated with cyanobacteria
  - Paucity of exposure data
    - Not sure which species are causing the bloom
    - Not sure which microcystin is present, at what level, and what its toxicity is
    - Not sure if BMAA is present, and at what level
  - Difficulties inherent in associating exposures with long-term health effects (non-alcoholic liver disease, liver cancer, Alzheimer's disease, ALS)

We have the tools in Florida to do the necessary research – but research will be expensive, and take time

- *Need for careful study of HAB species and toxins present in Florida, and environmental conditions that drive toxin expression*
- *Need for further pathophysiologic/toxicologic studies to assess potential toxicity of "Florida" strains/toxins*
- *Need for clinical studies, with carefully matched exposure data*
  - *Documentation of short-term effects*
  - *Evaluation of possible long-term effects, making use of state-wide clinical databases linked with exposure data*