CONSIDER RARE

Suspecting and Diagnosing Hereditary Angioedema (HAE)

Jonathan A Bernstein, MD

Professor of Medicine
University of Cincinnati
Department of Internal Medicine
Division of Immunology, Allergy Section
Partner Bernstein Allergy Group
Partner Bernstein Clinical Research Center
Editor in Chief Journal of Asthma

Continuing Education Information

In support of improving patient care, this activity has been planned and implemented by American Academy of CME, Inc. and CheckRare CE. American Academy of CME, Inc. is Jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

American Academy of CME, Inc., designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Planner/Faculty Educator Dr. Bernstein discloses the following relevant financial relationships with ineligible companies:

- Advisory Board Consultant: Takeda/Shire, CSL Behring, KalVista, Pharming, Biocryst, Ionis, Intellia, Pharvaris, Astria and Biomarin
- Grant/Research Support: Takeda/Shire, CSL Behring, KalVista, Pharming, Biocryst, Ionis, Intellia, Pharvaris, Astria and Biomarin
- Speaker's Bureau: Pharming

Planners and reviewers for this activity have no relevant financial relationships with any ineligible companies.

All relevant financial relationships listed have been mitigated.

This program is supported by an educational grant from Takeda Pharmaceuticals U.S.A., Inc.

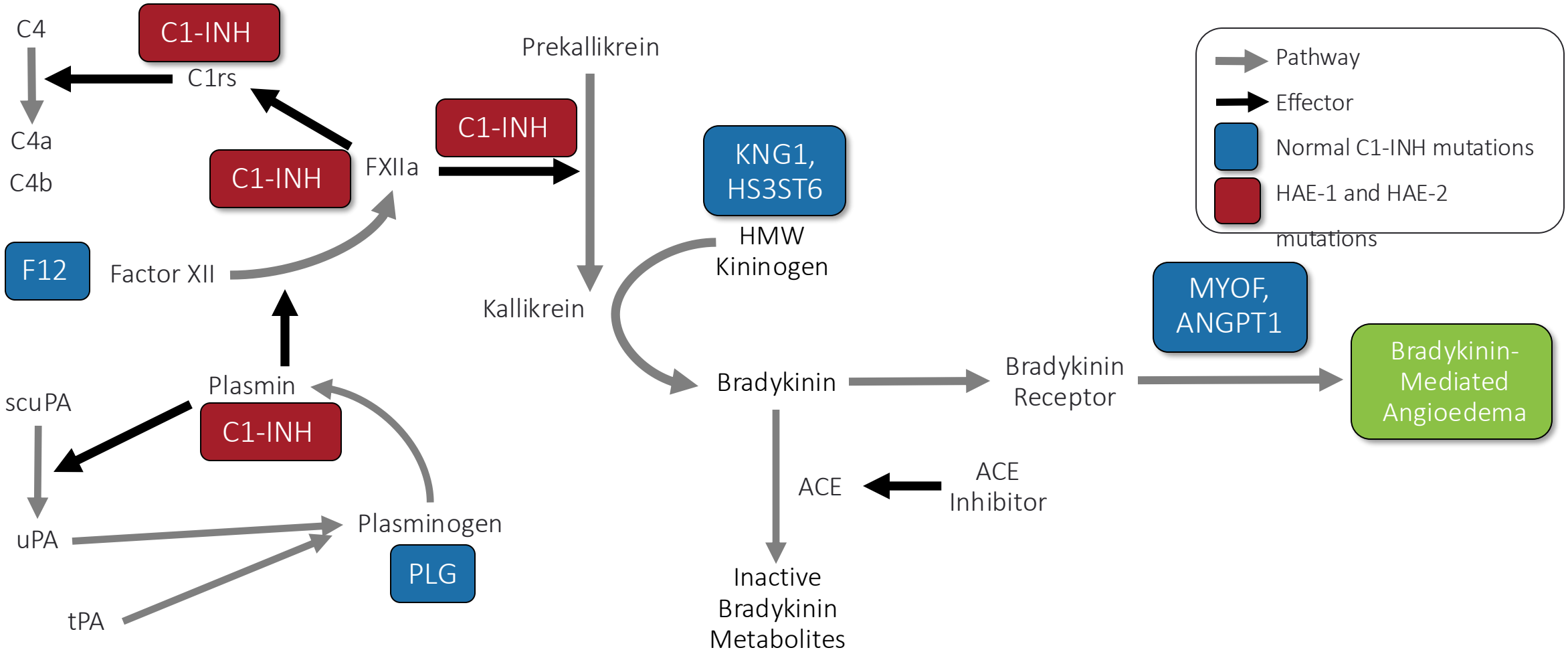
Hereditary Angioedema

- A rare genetic disorder that leads to recurrent and unpredictable episodes of angioedema
- Airway swelling can be life threatening
- Significant impact on quality of life
- Significant improvement over the past 15 years for treating both attacks and prophylaxis

	HAE-I	HAE-2	Normal C1-INH
Genes affected	SERPING1	SERPING1	Coagulation factor XII (F12) Plasminogen (PLG) Angiopioetin-1 (ANGPT1) Kininogen-1 (KNG1) Myoferlin (MYO) Heparin (HS3ST6) Other unknown genes
Gene products affected	C1-INH	C1-INH	Coagulation factor XII Plasminogen Angiopioetin-1 Kininogen-1 Myoferlin Heparin Other unknown gene products
Affect on gene product	Low C1-INH antigenic levels Functional C1-INH but insufficient amounts (leads to low function)	Normal C1-INH antigenic levels Conformational changes in C1-INH (result in dysfunctional protein, low function)	Mechanisms poorly understood Likely increased activation of contact system (F12, PLG), bradykinin activity (KNG1), or increased susceptibility to vascular leak (ANGPT1, MYO)

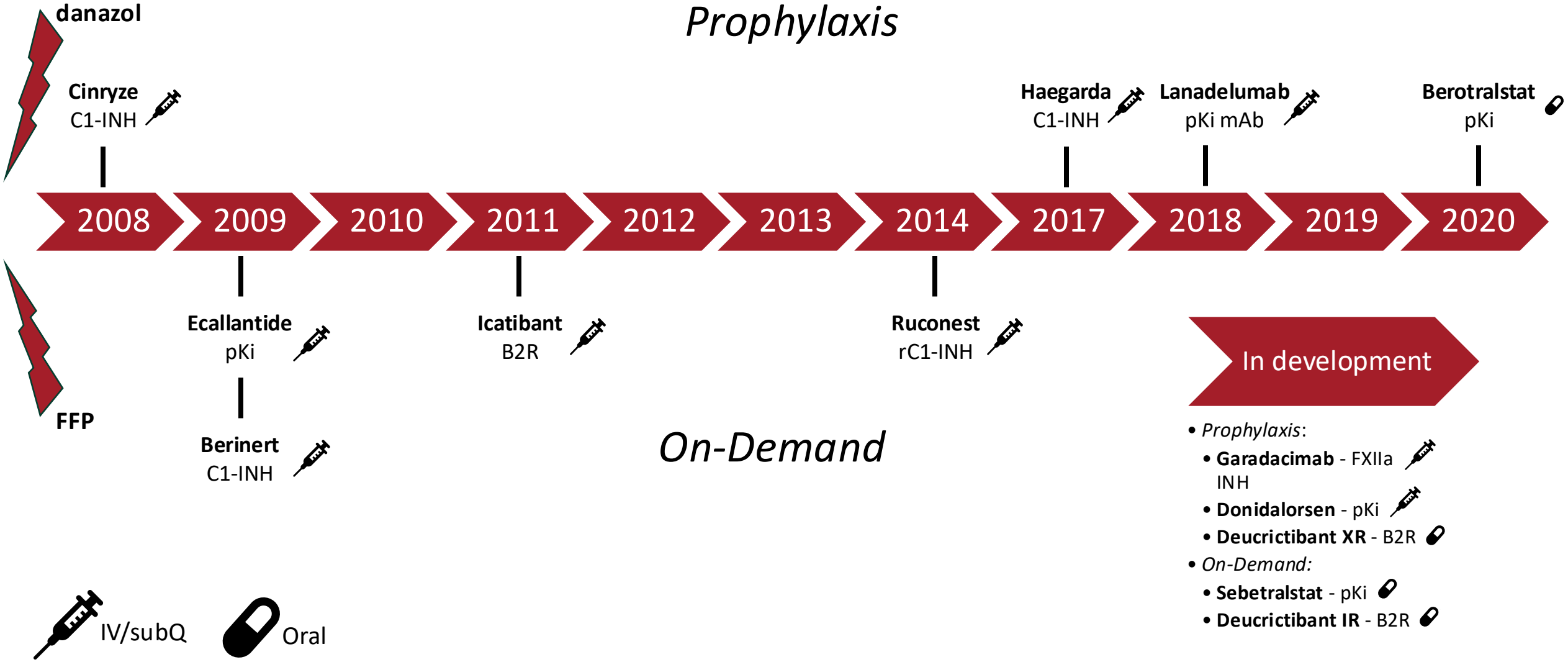
Bork K, et al. *Allergy Asthma Clin Immunol.* 2021;17(1):4.
Maurer M, et al. *Allergy.* 2022;77:1961-1990.
Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9:132-150.

HAE Pathophysiology



Busse PJ, et al. *N Engl J Med.* 2020;382:1136-1148
Bandy AZ, et al. *Genes Dis.* 2020;7:75-83
Santacroce R, et al. *J Clin Med.* 2021;10(9):2023.

HAE Prophylaxis and On-Demand Treatment



Diagnostic Delays Are Common

- Diagnostic delays of 5-15 years are common
- Awareness of HAE in the medical community has improved time to diagnosis but only one-third of patients with HAE are diagnosed within a year (and usually that is because of a family member being diagnosed)
- Common misdiagnoses include appendicitis, allergy, mental disorders, tonsillitis, and ‘nervous stomach’

Margeri M, et al. Clin Transl Allergy 2023. 13: e12297.
Margeri M, et al. Orphanet J Rare Dis. 2020;15:221..
Giavina-Bianchi P et al. Clinics. 2023; 2022; 77: 100023 .

Self Reflective Question

What are the benefits of an early diagnosis of HAE?

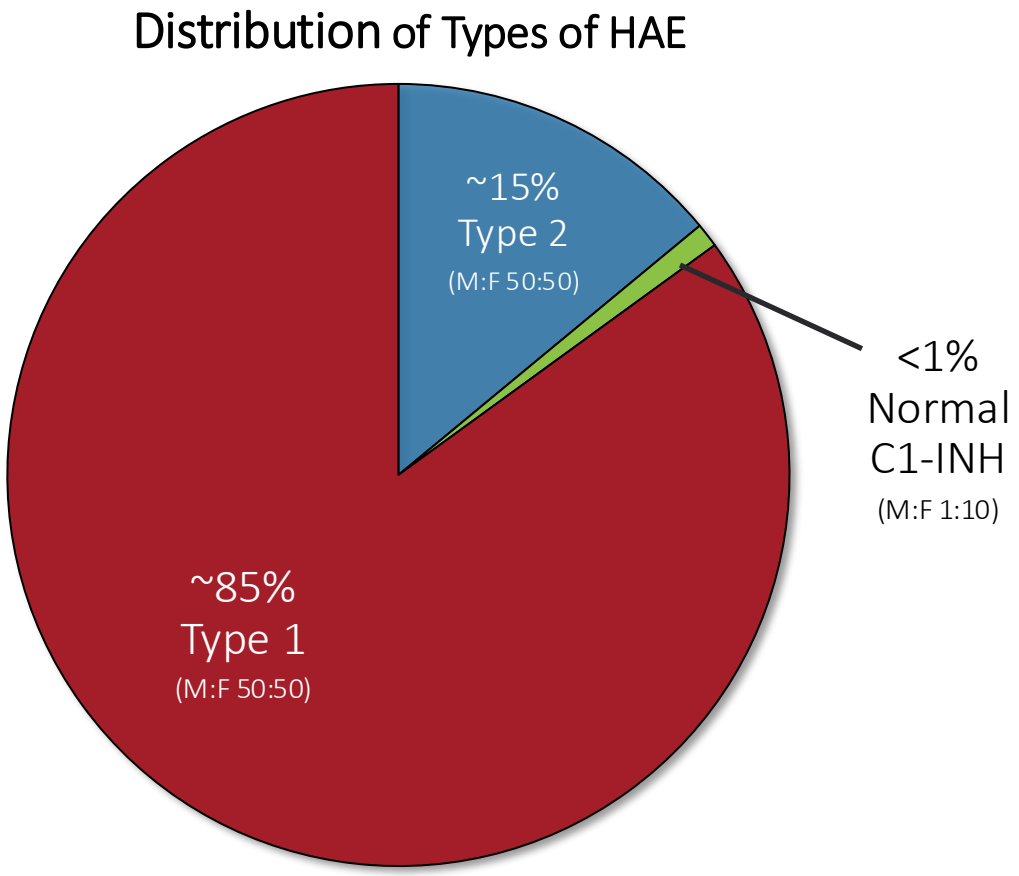
Benefits of Early Diagnosis

- Reduce unnecessary patient discomfort
- Reduced unnecessary doctor appointments
- Reduced unnecessary medical procedures
- Reduced loss of work
- Properly targeted therapies

Suspecting HAE

Onset of Symptoms

- Symptoms of HAE typically begin in childhood and worsen during puberty
- Family history of HAE (75% of cases)
  - Autosomal dominant inheritance pattern, variable penetrance
- Remaining 25% of cases have no family history of HAE
  - De novo mutations that subsequently follow autosomal dominant inheritance pattern



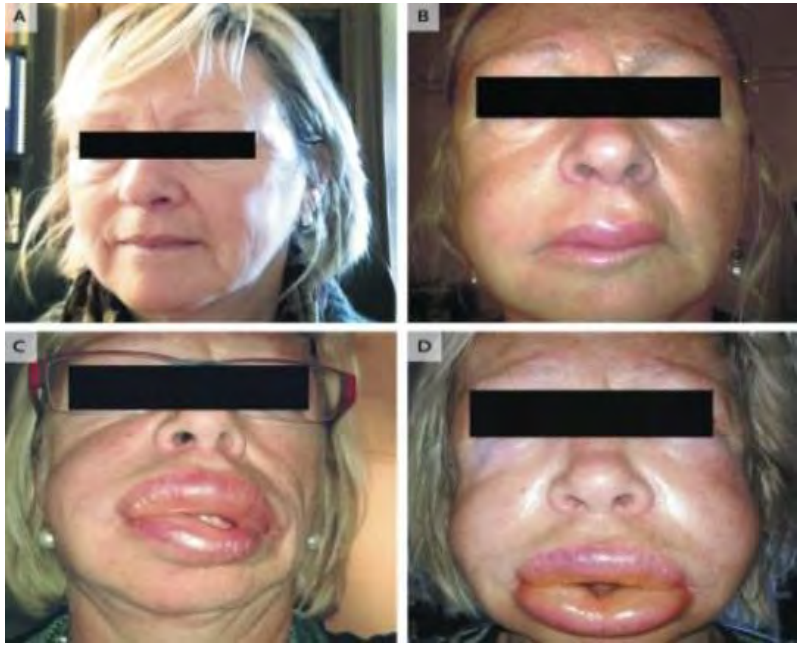
Kaplan AP, et al. *J Allergy Clin Immunol Pract*. 2020;8:892–900.
Bork K, et al. *Allergy Asthma Clin Immunol*. 2021;17(1):4.
Azmy V, et al. *Allergy Asthma Proc*. 2020;41(suppl 1):S18-S21.
Maurer M, et al. *Allergy*. 2022;77:1961-1990.
Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9:132-150.

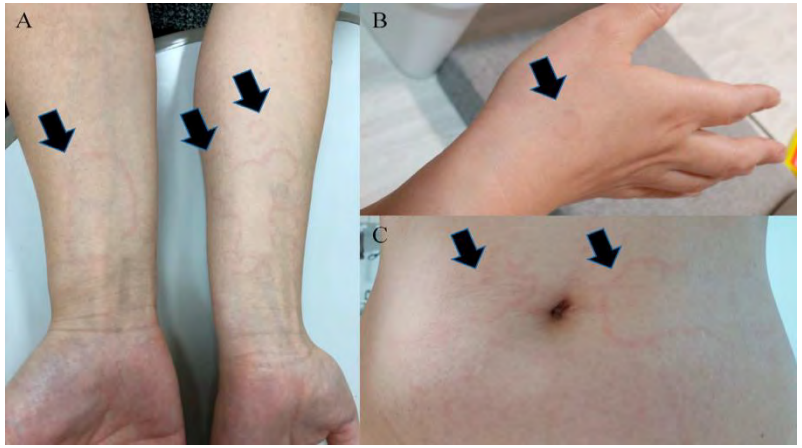
Wide Range of Symptoms

- Fluid extravasation in deep dermis, subcutaneous, or submucosal tissues

- Swelling (non-pitting, generally self-limited)
  - Affects skin and mucosal tissues
  - Any skin location (most common: face, hands, feet genitals)
  - Not accompanied by urticaria or pruritus
  - Prodromal non-itchy rash (erythema marginatum) seen in ~30% of patients
  - Depending on location, potentially can be disabling or life-threatening

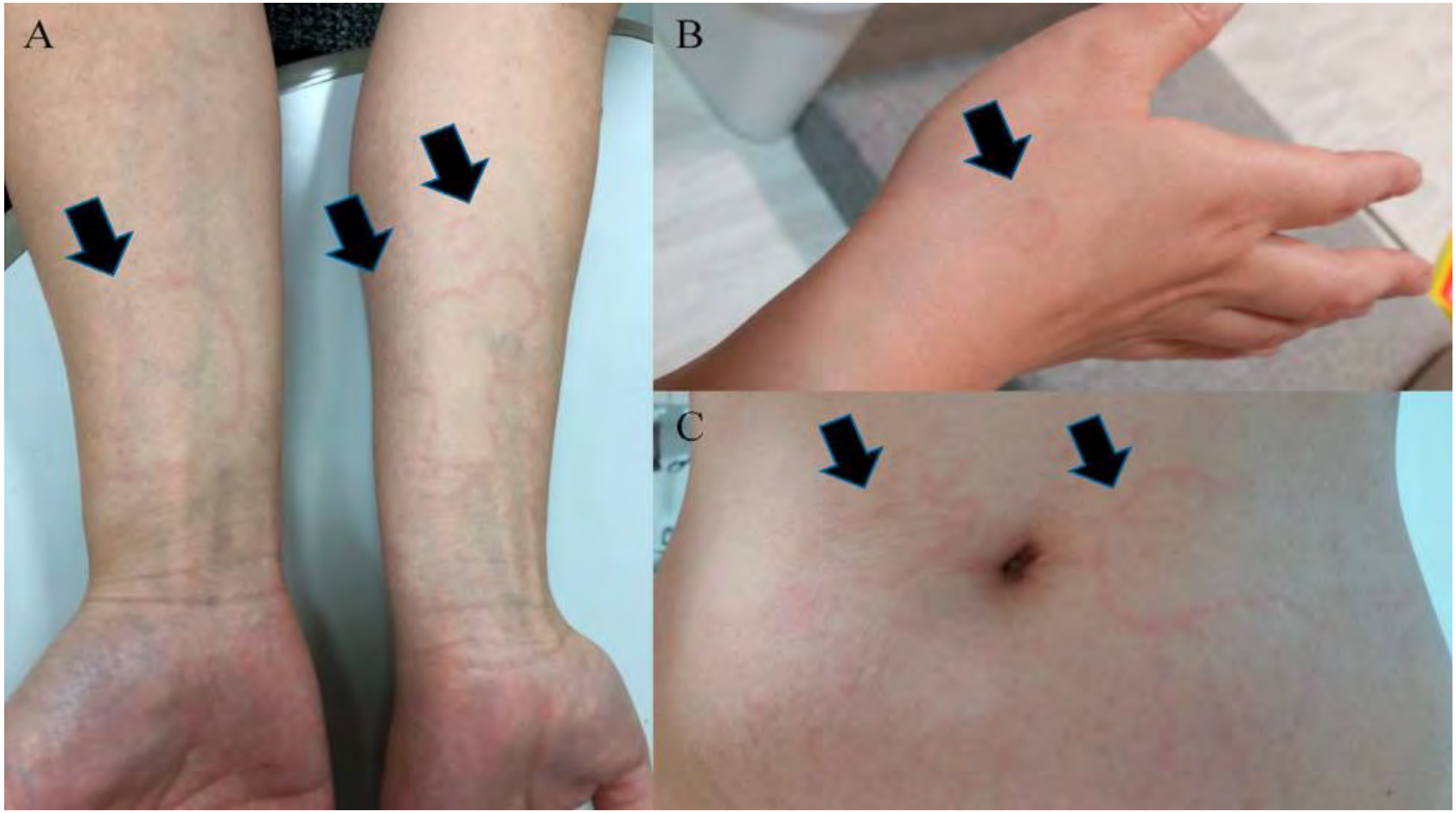
- Submucosal tissue swelling
  - Upper respiratory tract: potentially life-threatening due to asphyxiation
  - GI tract: leads to severe abdominal pain, nausea, and vomiting





Maurer M, et al. *Allergy*. 2022;77:1961-1990.
Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9:132-150.
Busse PJ, et al. *N Engl J Med*. 2020;382:1136-1148.
Sraveni et al *int Jou Hea Bio Sci.* 2021;2:56-58.
Ohsawa I et al. *World Allerg Org J.* 2021;14:100511.

Prodromal Symptoms



Ohsawa I et al. *World Allerg Org J*. 2021;14:100511.

Triggers and Patterns of Attacks

- Many episodes do not have a known trigger
- Episodes of HAE attacks
  - Frequency is highly variable
  - Many untreated patients have attacks every 1 to 2 weeks
    - Most untreated attacks last for 2 to 4 days
  - Swelling can occur in one or multiple parts of the body during an attack
  - Location and frequency of swelling
    - Varies widely within and among individuals
    - Occur from several times a week to less than once a year

Common Triggers of HAE Attacks

- Emotional or physical stress
- Minor trauma
- Surgery
- Infections (e.g., colds, flu)
- ACE inhibitors
- Changes in estrogen levels

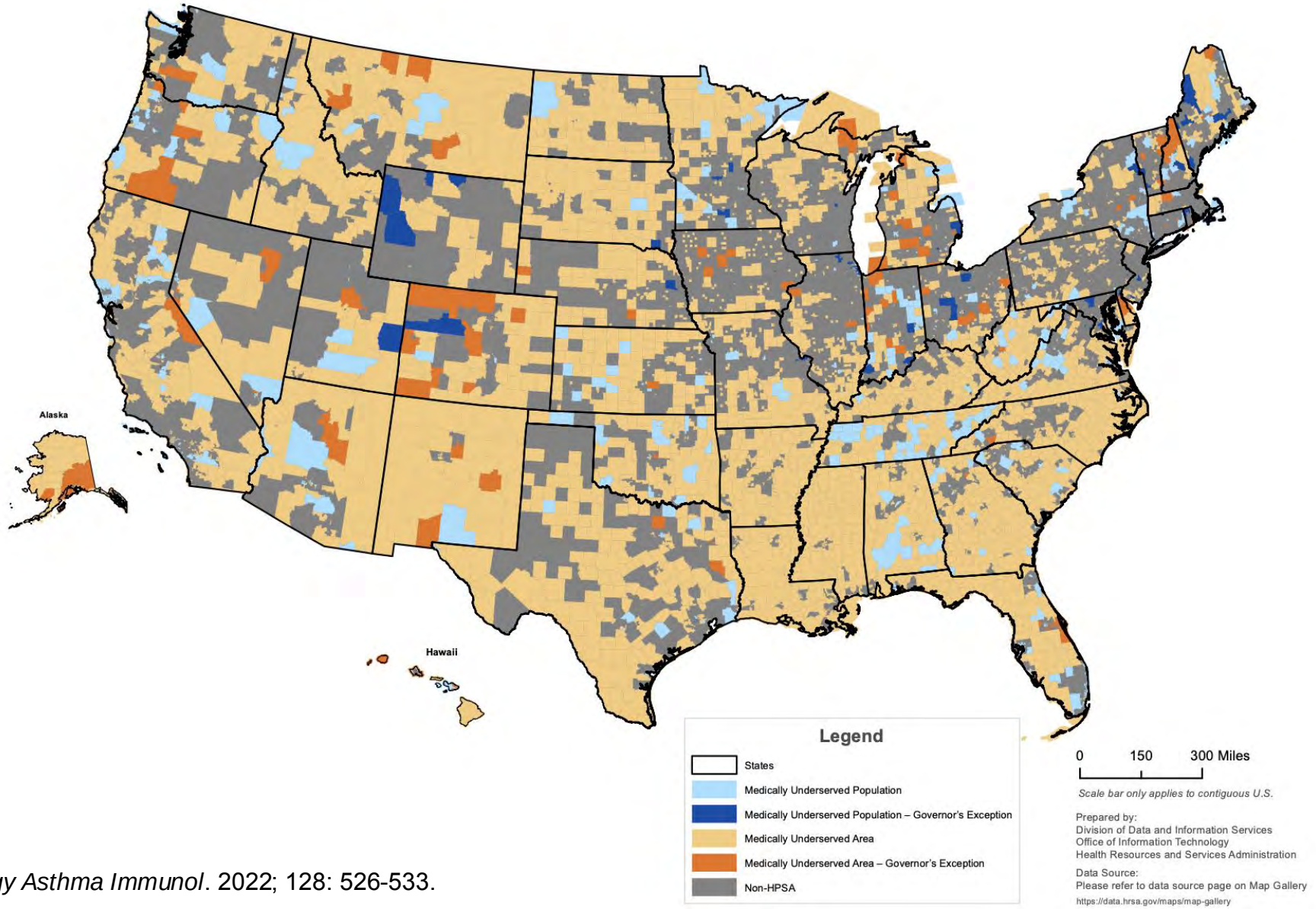
Azmy V, et al. *Allergy Asthma Proc*. 2020;41(suppl 1):S18-S21.
Bork K, et al. *Allergy Asthma Clin Immunol*. 2021;17(1):4.
Maurer M, et al. *Allergy*. 2022;77:1961-1990.
Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9:132-150.

Patient Groups at Risk for Delayed Diagnosis

- Rural communities?
- Race/ethnic inequalities?
- Data limited but there is a concern

Riedl MA et al. *Ann Allergy Asthma Immunol.* 2022; 128: 526–533.
Sylvestre S et al.. *J Allergy Clin Immunol Pract*. 2021; 9: 4441–4449.

One-Fifth of HAE Patients Live in Rural Areas



Riedl M et al. *Ann Allergy Asthma Immunol*. 2022; 128: 526-533.

HAE Real-World vs. Clinical Trial

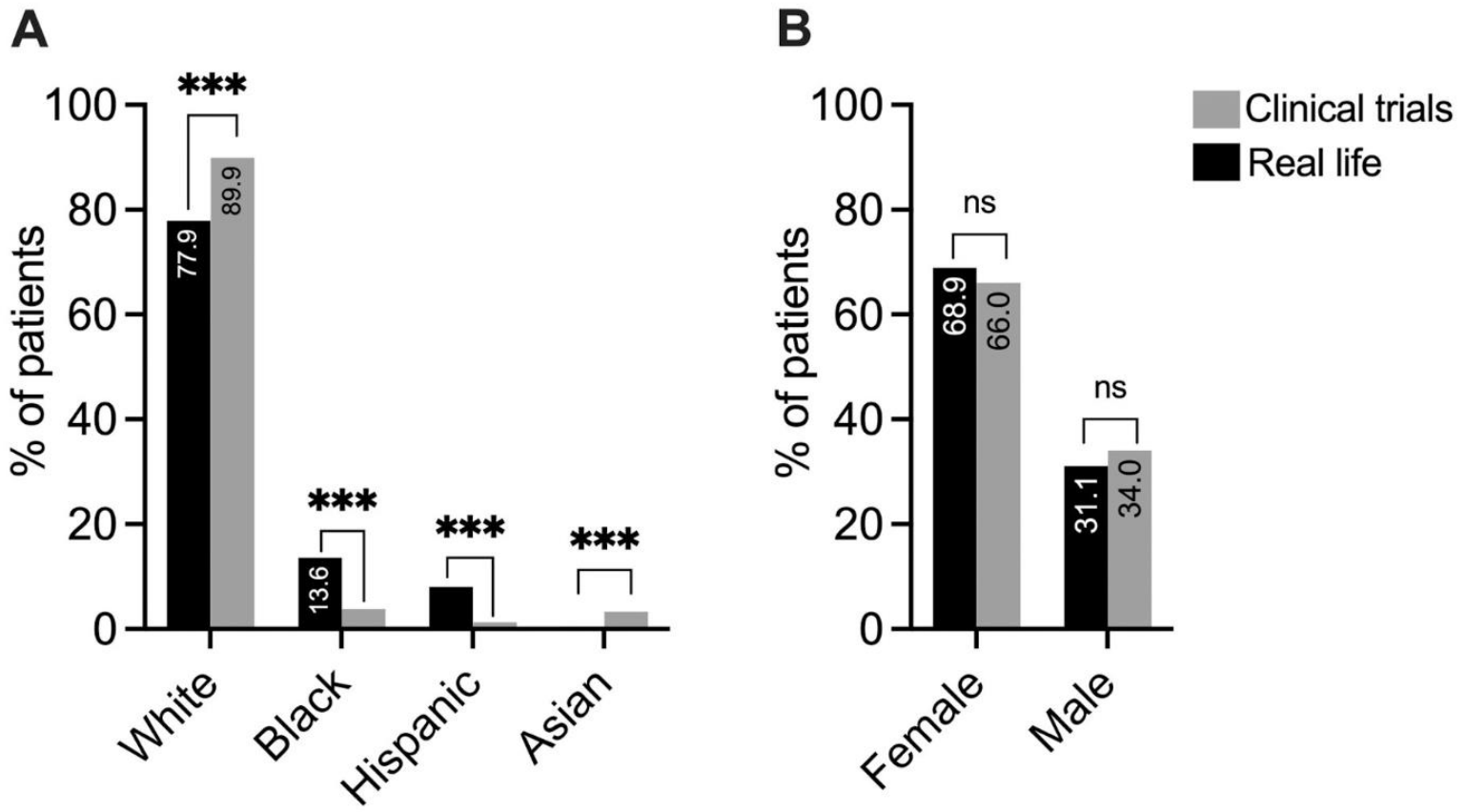
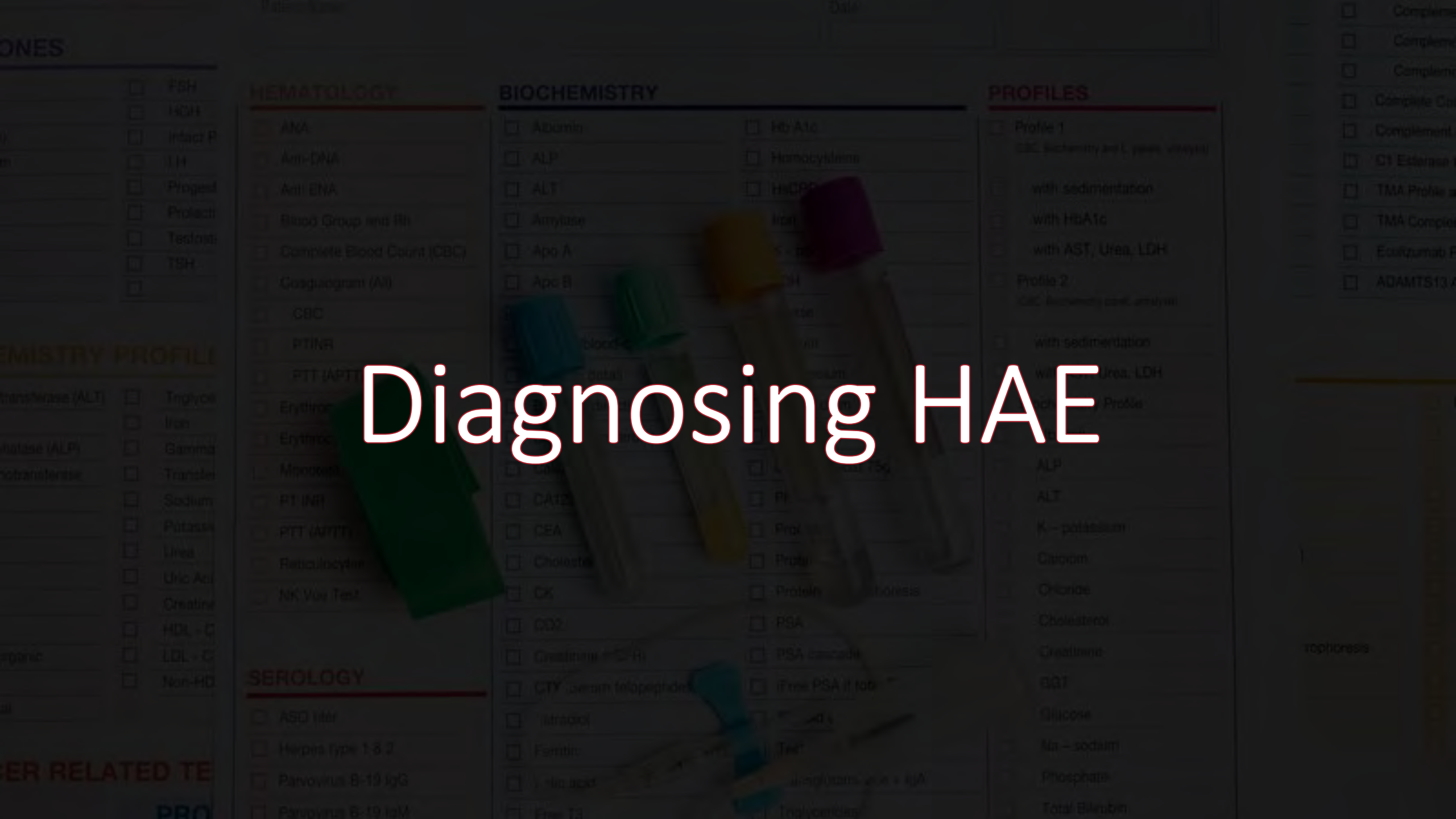


Figure 1. Race/Ethnic distribution of patients included in the clinical trials versus real life data. **(A)** There is overrepresentation of White and Asian patients and underrepresentation of Black patients and Hispanic patients in clinical trials. **(B)** The sex distribution of patients was not different between real life data and clinical trial data. ns $P > 0.05$, *$P \leq .05$, **$P \leq .01$, ***$P \leq .001$.

Sylvestre et al. J Allergy Clin Immunol Pract. 2021; 89: 444104449.



Diagnosing HAE

Self Reflective Question

Are you aware of
best practices to diagnose HAE?

Diagnostic Best Practices

Recognition of symptoms is critical for correct treatment

Common symptoms

- Recurrent, subcutaneous edema without urticaria
- Abdominal symptoms
- Upper airway symptoms

Clinical tests

- C4 and C1-INH function and antigenic level
- Genetic testing (normal C1-INH)

Screening should be performed on all first-degree relatives

Maurer M, et al. *Allergy*. 2022;77:1961-1990.
Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9:132-150.

Assessment Tools

Lab Tests

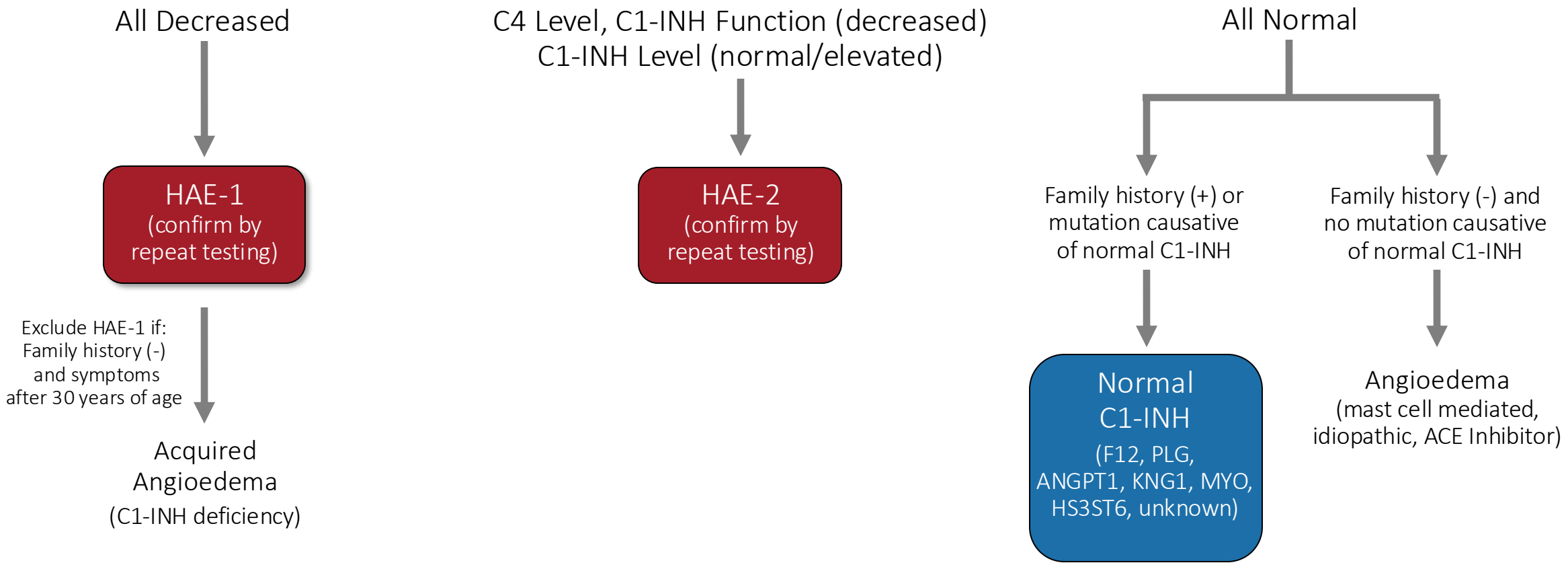
	HAE-I	HAE-2	Normal C1-INH
Serum C4 level	Low	Low	Normal
C1-INH			
Antigenic level Function	Low Low	Normal to elevated Low	Normal Normal
Genetic sequencing	Rarely needed	Rarely needed	Maybe useful (NGS assays/panel) (many mutations not yet identified)

Laboratory results must always be interpreted in conjunction with clinical history.

Maurer M, et al. *Allergy*. 2022;77:1961-1990.
Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9:132-150.

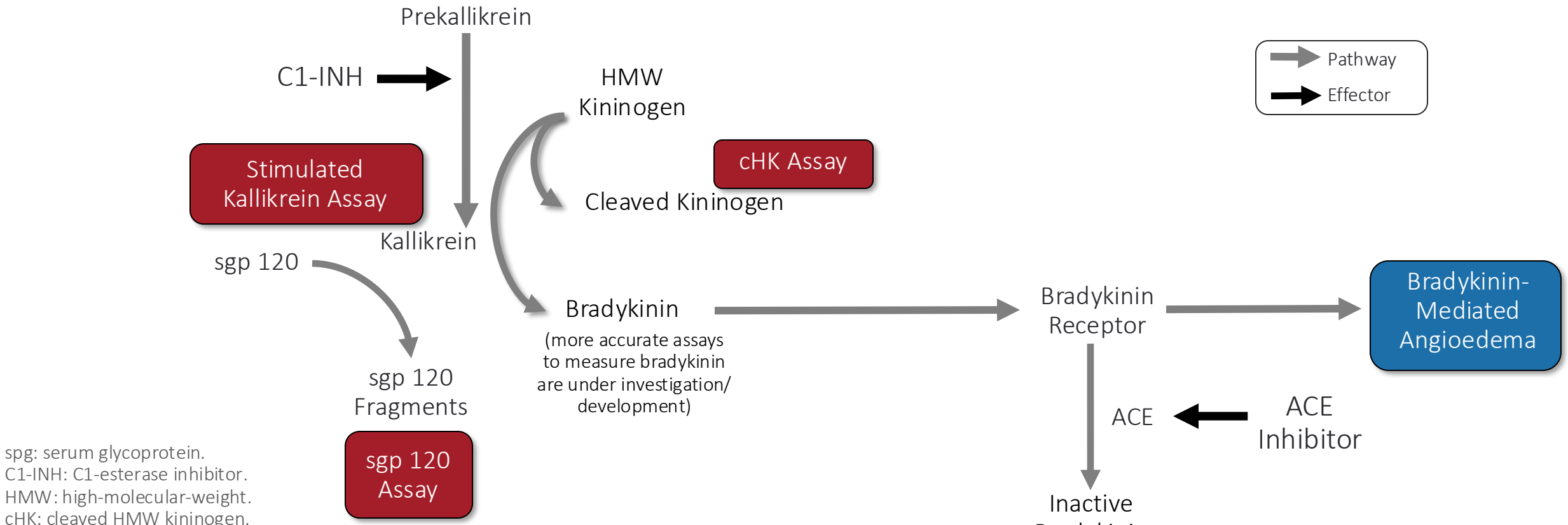
Assessment Tools and Differential Diagnosis

C4 level, C1-INH level, and C1-INH Function



Maurer M, et al. *Allergy*. 2022;77:1961-1990.

Additional Assessment Tools



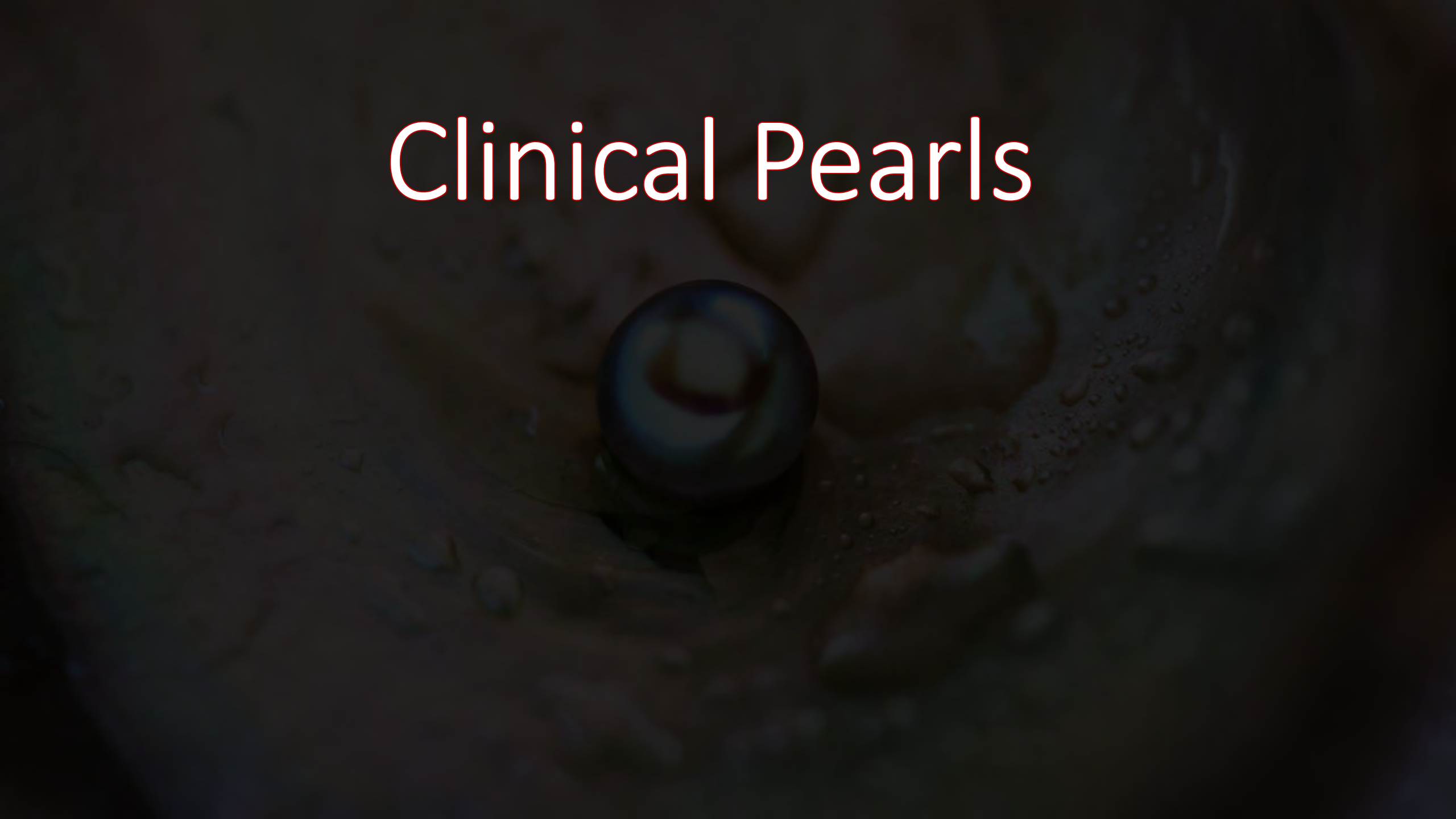
spg: serum glycoprotein.
C1-INH: C1-esterase inhibitor.
HMW: high-molecular-weight.
cHK: cleaved HMW kininogen.
ACE: angiotensin-converting enzyme.

Maurer M, et al. *Allergy*. 2022;77:1961-1990.

Further Assessment and Follow-up

- Genetic testing, if necessary
- Creating a multidisciplinary team
- Setting up a management strategy tailored to the patient

Clinical Pearls



Clinical Pearls

- Diagnostic delays are the norm for HAE. We need to do better.
- Early signs and symptoms, as well as a family history, should trigger the need for diagnostic testing.
- Diagnosis is fairly straight forward and can provide patient with a management plan that will treat HAE more efficiently and safely.