# Cure HHT Research Network Survey
# -From Bedside to Bench-


## Data summary from HHT patient, scientist, and clinician surveys

www.Cure HHT.org

cure hht
The Cornerstone of the HHT Community

# CHRN History

- The Chan Zuckerberg Initiative has selected Cure HHT as one of the 30 organizations in a two-year funding opportunity called the Rare as One Project.

- Rare as One Project seeks to lift up the work patient communities are doing to accelerate research and drive progress against rare disease. The program provides funding, tools, and capacity-building support and training.

CURE HHT
RESEARCHNETWORK

# Goals of Patient-Driven Research

- Establish a large, collaborative scientific and patient community in order to:
  - Encourage collaborations between scientists and clinicians
  - Promote data sharing and sample sharing
  - Expand to underserved areas
- Incorporate the patient voice to drive basic science research and ultimately clinical outcomes
- Develop approved treatments for HHT

# Step 1: Survey HHT Patients

- 49 Question Survey was created by Cure HHT and distributed to the community
- 1204 HHT patients and caregivers answered

- Survey topics:
  - History of HHT (symptoms, age of onset, treatments received, personal view of treatment success, quality of life)
  - Opinion of research/knowledge gaps in HHT
  - Barriers to access of care for HHT

# Step 2: Survey HHT Scientists

- 17 Question Survey was created by Cure HHT and distributed to the community
- 42 HHT scientists answered

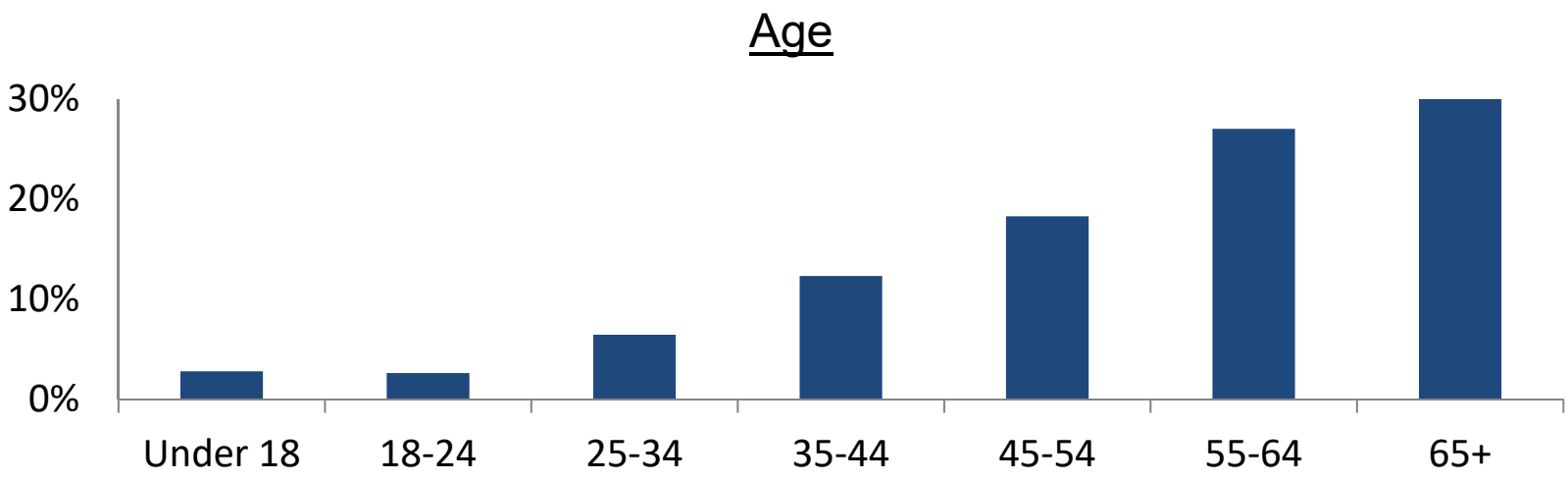
- Survey topics:
  - Area of HHT research
  - Barriers to achieve more successful research (lack of collaboration, lack of resources, etc.)
  - Perceived gaps in HHT research to improve patient outcomes
  - Ability to share/collaborate with other scientists and clinicians

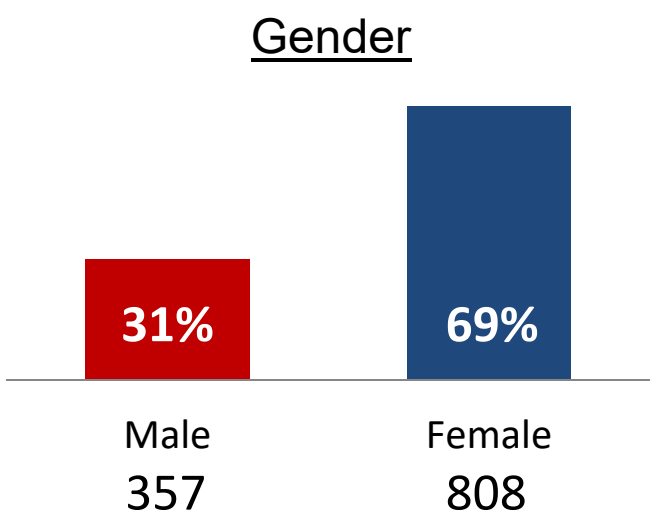
# Step 3: Survey HHT Clinicians

- 25 Question Survey was created by Cure HHT and distributed to the community
- 96 HHT clinicians answered

- Survey topics:
  - Perceived gaps in HHT research to improve patient outcomes
  - Collaborative ability/status among HHT Centers of Excellence
  - Patient priority areas to improve outcomes
  - Views on Curacao criteria for diagnosing HHT

# Patient Survey Demographics




**Race/Ethnicity**

88% White

5% Hispanic or Latino

**Residence**

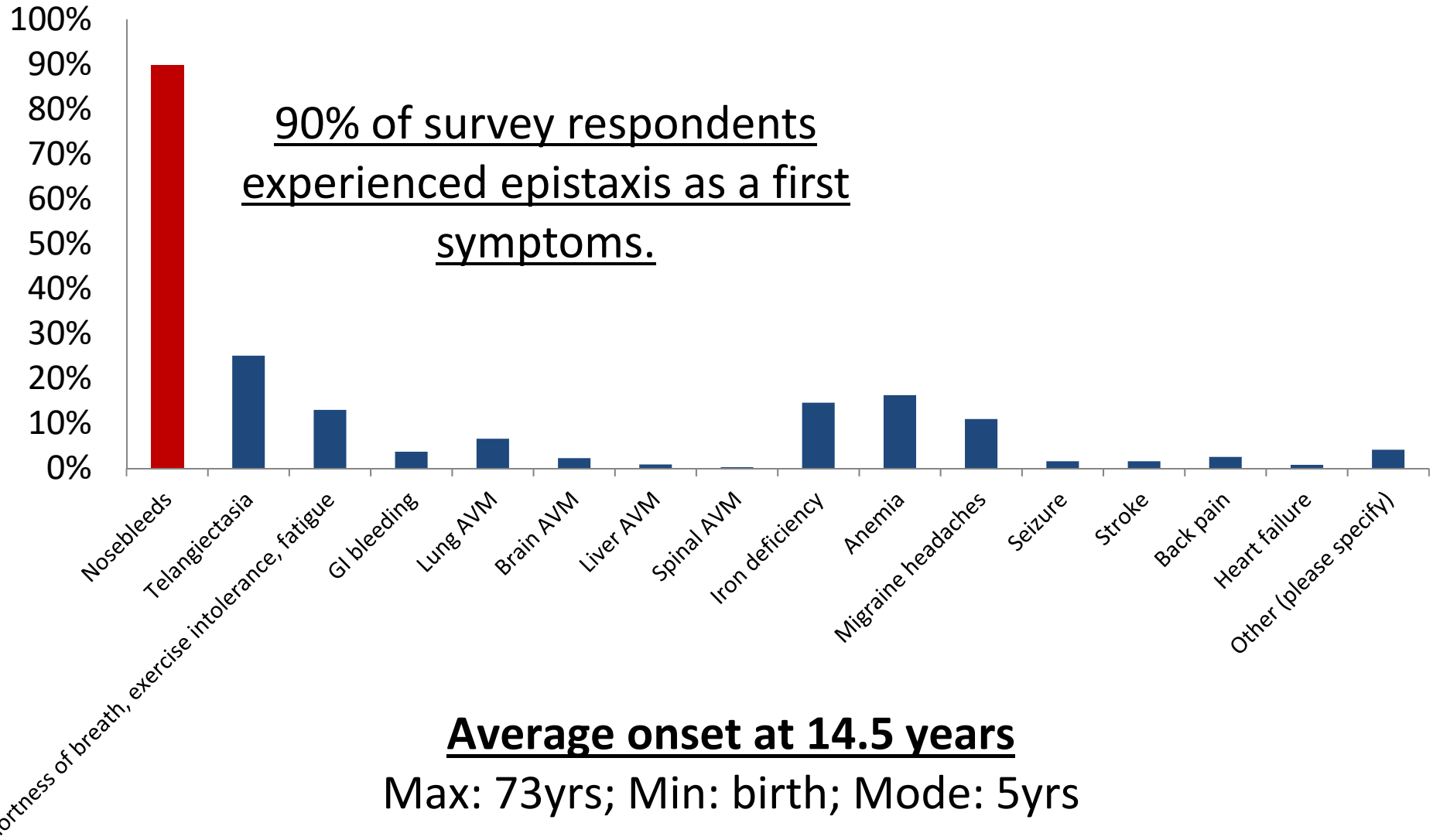
70% USA

7% UK

7% Canada

Survey was conducted in 2021 through the HHT newsletter, website, and social media platforms.

# First Symptoms of HHT

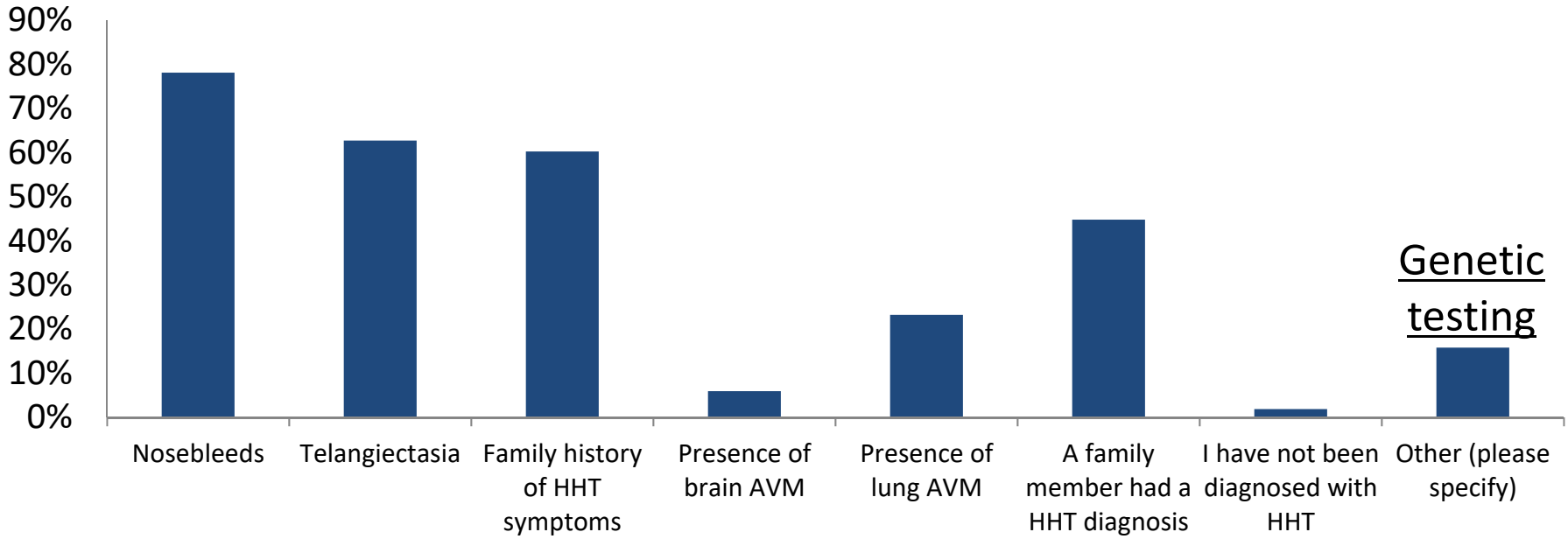



90% of survey respondents experienced epistaxis as a first symptoms.

**Average onset at 14.5 years**

Max: 73yrs; Min: birth; Mode: 5yrs

# HHT first diagnosed by ____ symptoms




- 40% diagnosed between 27-45yrs
- 28% diagnosed after 46+ yrs
- 15% diagnosed in childhood/adolescence

"We were aware nosebleeds ran in our family."

"Asthma and allergy diagnosis."

"Couldn't find a physician familiar with HHT."

**60% of patients did not seek medical attention or diagnosis for 5+ years from onset of first symptoms.**

**60% did not realize they needed to see a doctor.**

**Symptoms just 'run in the family'.**

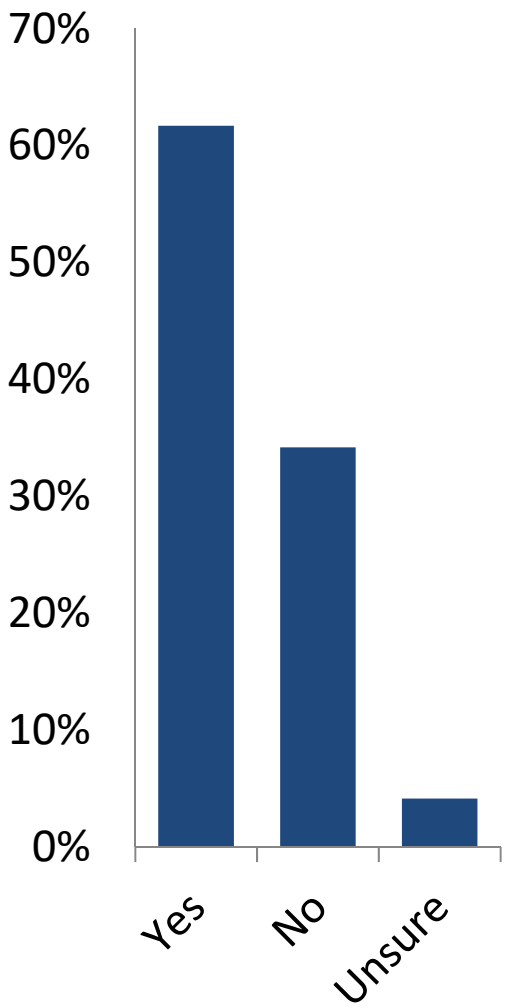
**Anxiety/fear of diagnosis or lack of insurance coverage**

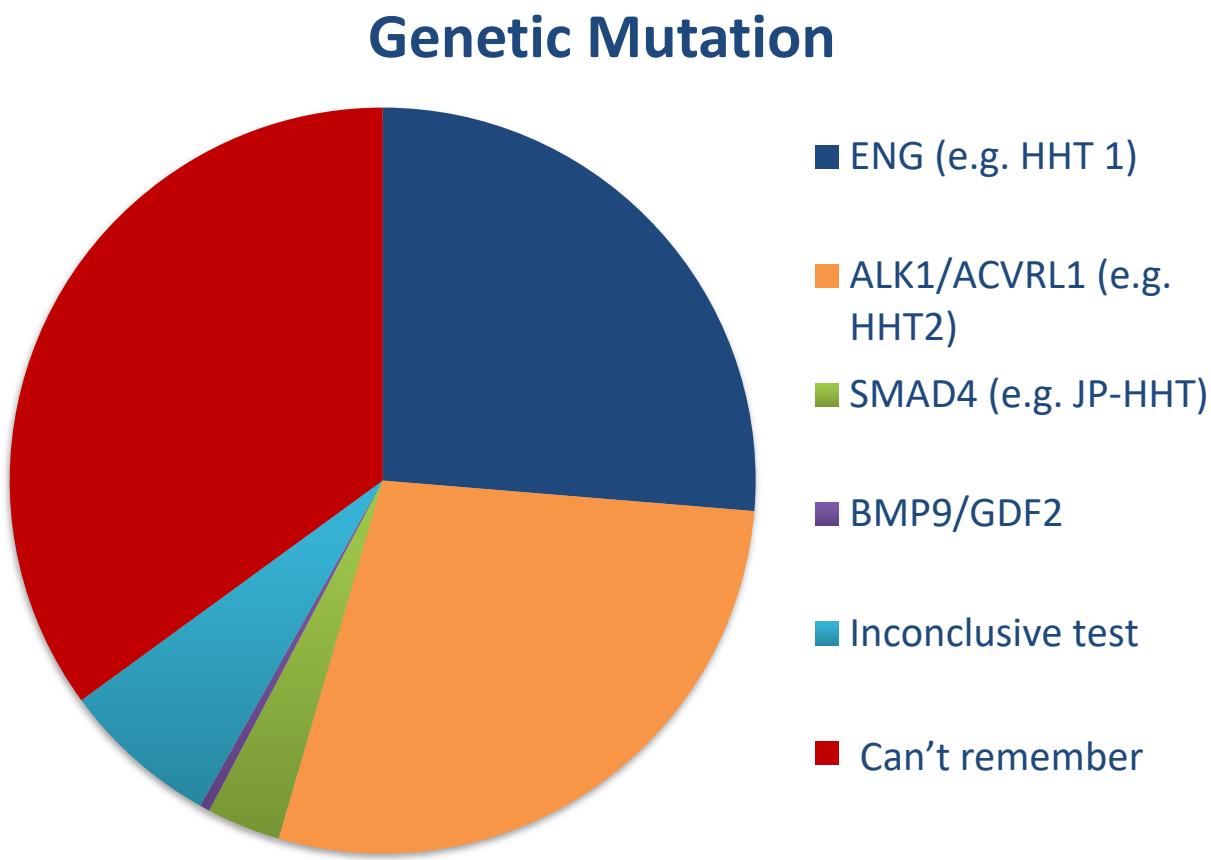
"Doctor kept giving me nose spray."

"Nosebleeds weren't severe enough."

"Unaware of HHT."

# HHT Confirmed by Genetic Testing



# Why haven't patients been tested?

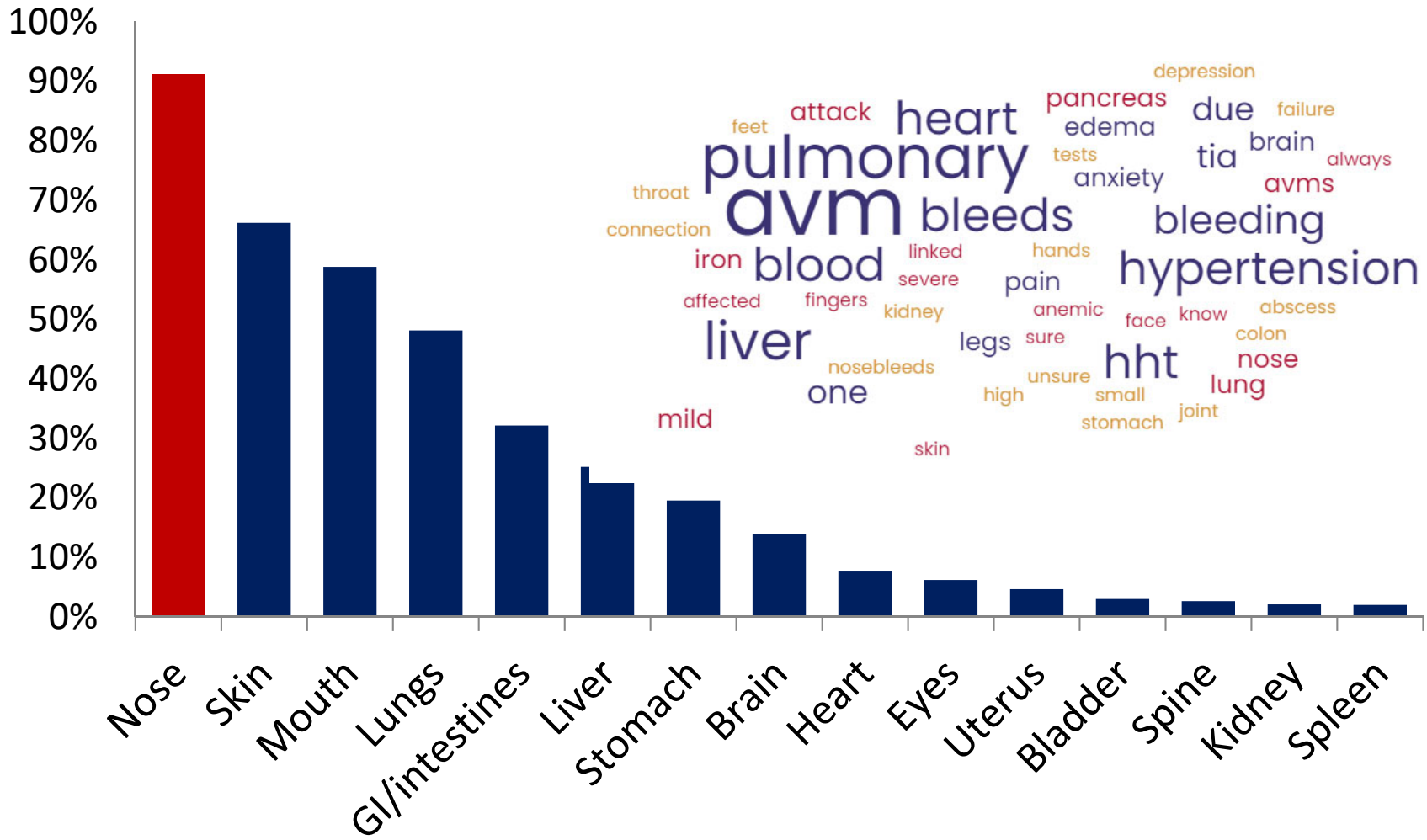
- 37% - Physician did not offer genetic testing
- 19% - Insurance did not cover genetic testing/cannot afford it
- 9% - I do not want to have genetic testing done
- 5% - I am worried about the possibility of discrimination

Other:

- Family had testing done; didn't find it necessary; had no children
- Unsure how to get testing done
- Genetic testing not offered in remote area
- Diagnosed on Curacao criteria
- Testing in progress

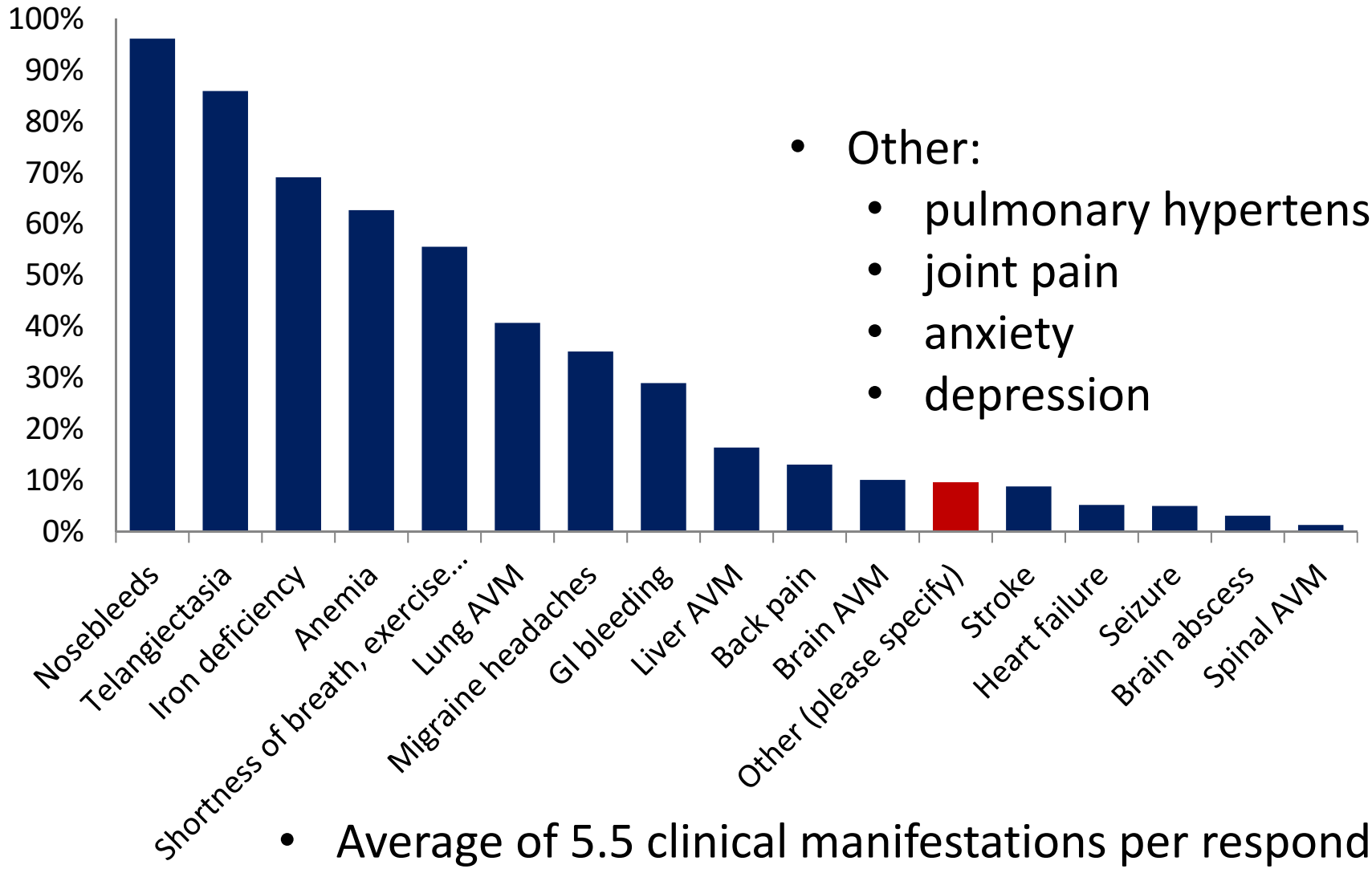
***Only 23% indicated knowledge of genetic testing being less expensive after a family member has a confirmed genetic diagnosis of HHT**

# Organs affected by HHT




- Average of 3.8 organs affected per respondent

# Clinical Manifestations of HHT



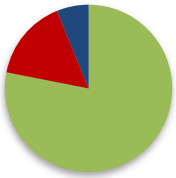

- Other:
  - pulmonary hypertension
  - joint pain
  - anxiety
  - depression

- Average of 5.5 clinical manifestations per respondent

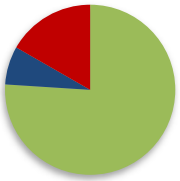
# Nosebleed Treatment Efficacy

Positive Impact | No Impact | Negative Impact

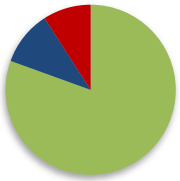
**Moisturizing Topical Therapy: 744 Patients**



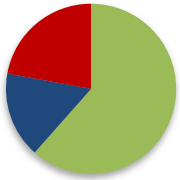
**Laser Ablation: 371 Patients**



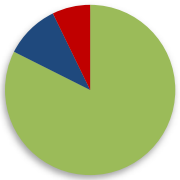
**Tranexamic Acid: 231 Patients**



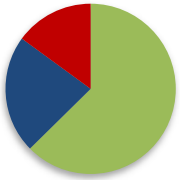
**Embolization: 208 Patients**



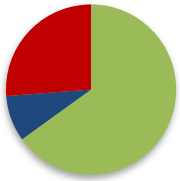
**Avastin IV: 125 Patients**



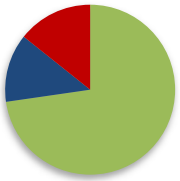
**Doxycycline: 107 Patients**



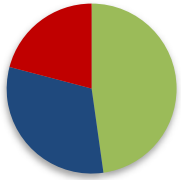
**Electrosurgery: 103 Patients**



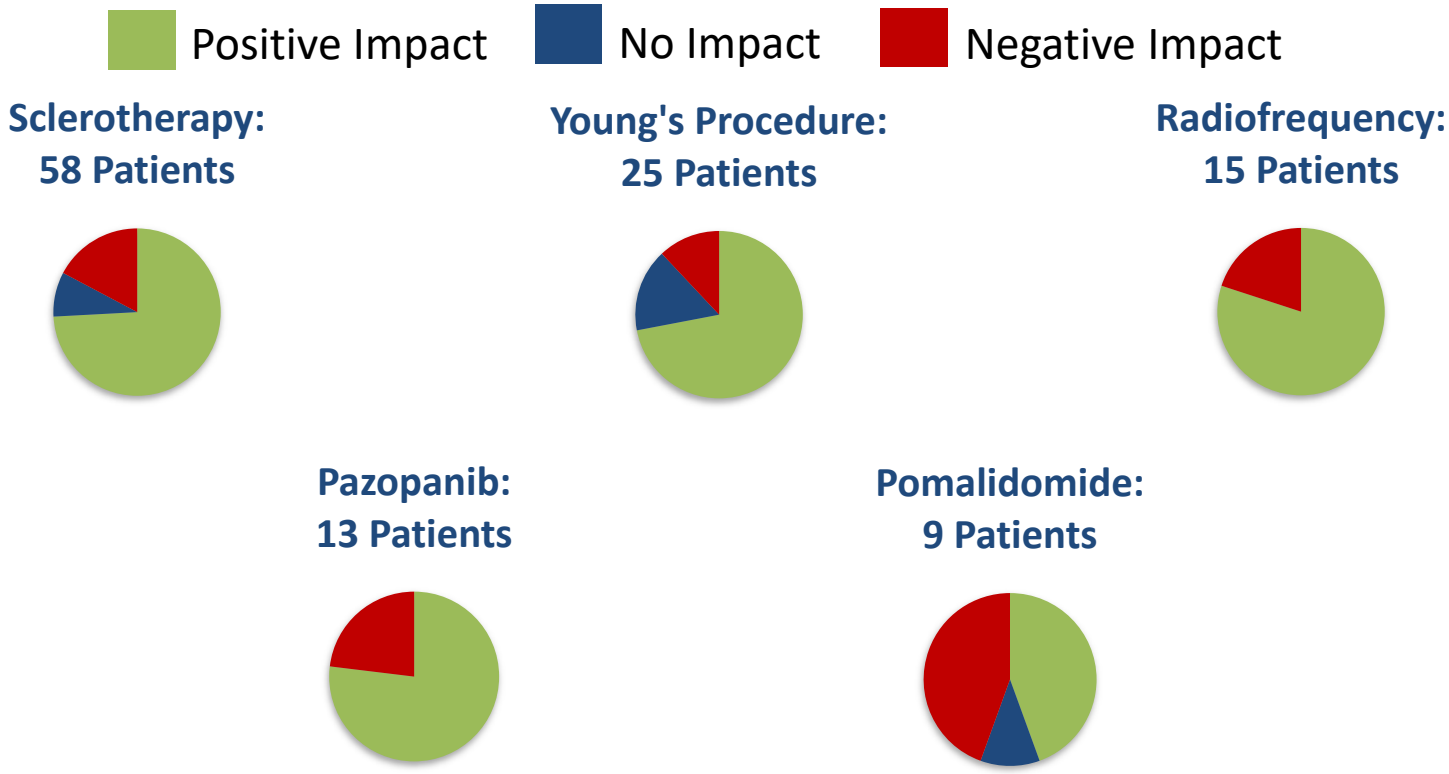
**Septodermoplasty: 77 Patients**



**Avastin Spray: 67 Patients**



# Nosebleed Treatment Efficacy

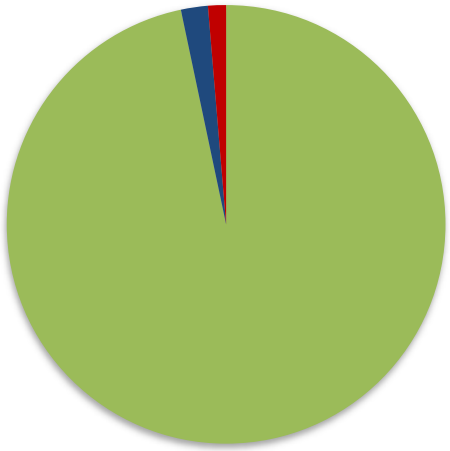



- The majority of patients have tried at least one therapeutic to reduce bleeding
  - Most therapeutics have had at least some positive impact on the patient
    - Survey respondents also indicated Tamoxifen as treatment

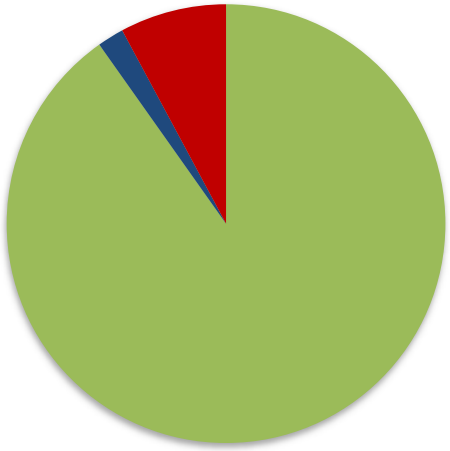
# Pulmonary AVM Treatment Efficacy

Positive Impact No Impact Negative Impact

**Embolization: 302 Patients**



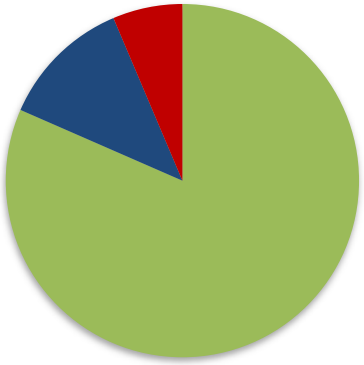
**Surgical Resection: 51 Patients**



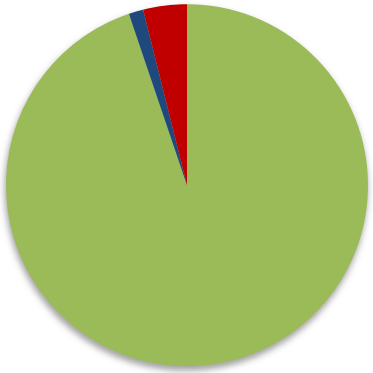
# GI Bleeding Treatment Efficacy

Positive Impact | No Impact | Negative Impact

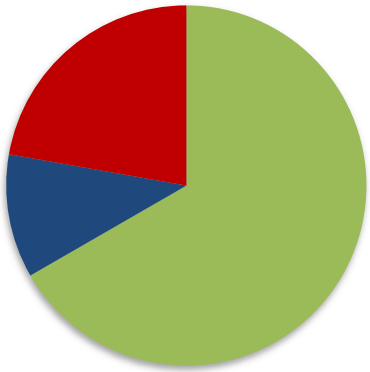
**Laser Ablation: 141 Patients**



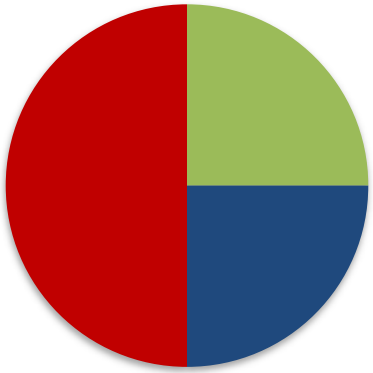
**Avastin IV: 77 Patients**



**Pazopanib: 9 Patients**



**Pomalidomide: 4 Patients**

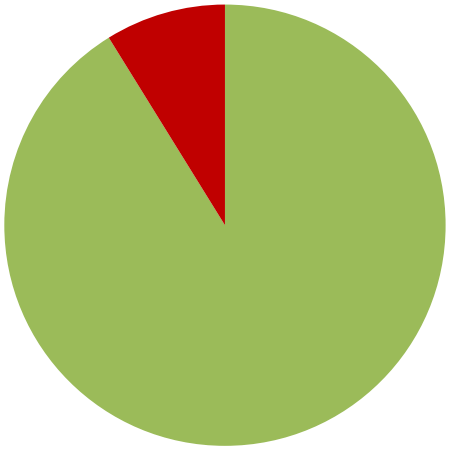


- Some survey respondents had resection of affected colon

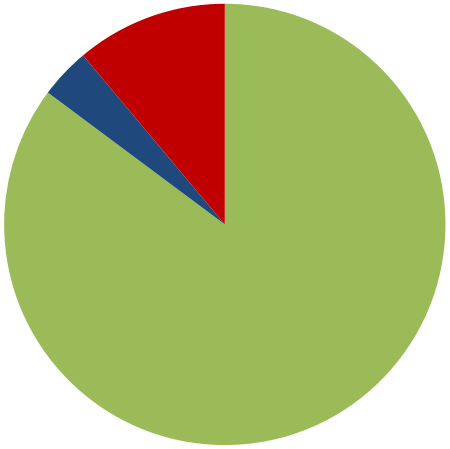
# Brain AVM Treatment Efficacy

Positive Impact | No Impact | Negative Impact

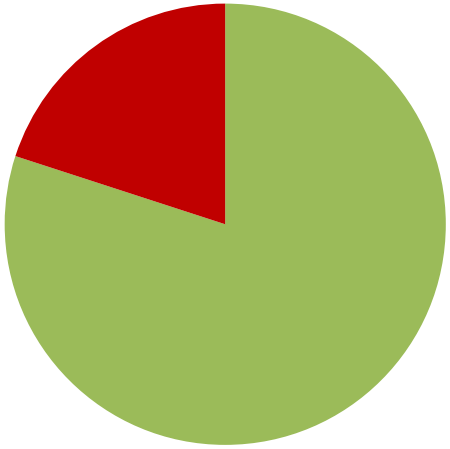
**Embolization: 34 Patients**



**Surgical Removal: 27 Patients**



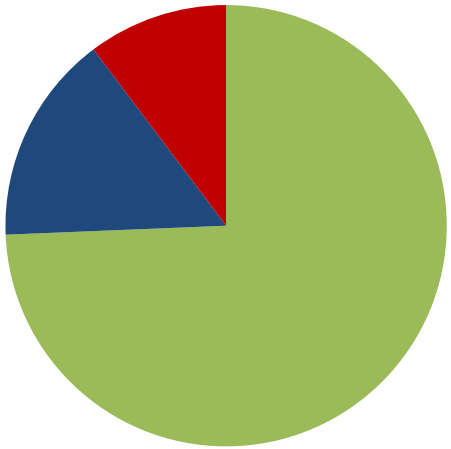
**Stereotactic Radiation: 15 Patients**



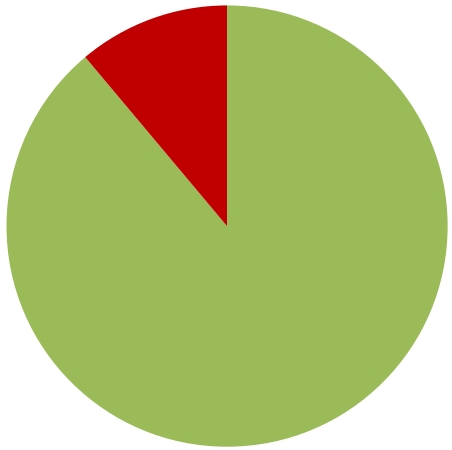
# Liver AVM Treatment Efficacy

Positive Impact No Impact Negative Impact

**Avastin IV: 39 Patients**



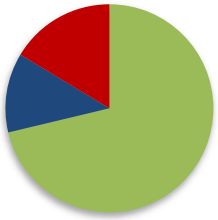
**Liver Transplant: 9 Patients**



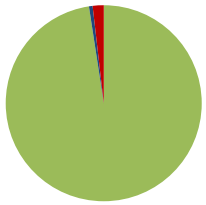
# Iron Deficiency/Anemia Treatment Efficacy

Positive Impact | No Impact | Negative Impact

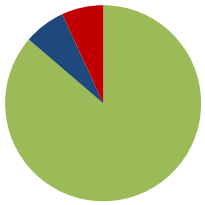
**Oral Iron: 776 Patients**



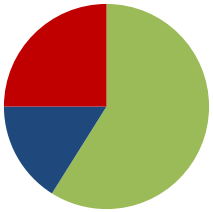
**IV Iron: 496 Patients**



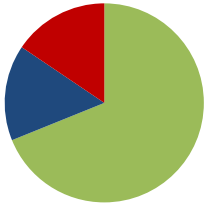
**Avastin IV: 102 Patients**



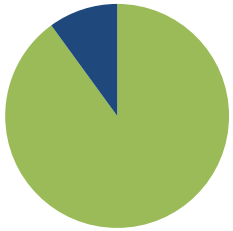
**Anticoagulation: 56 Patients**



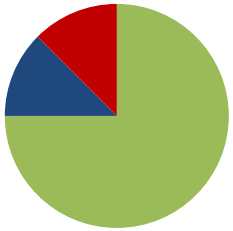
**Tamoxifen: 45 Patients**



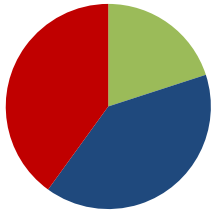
**Antiplatelet Therapy: 10 Patients**



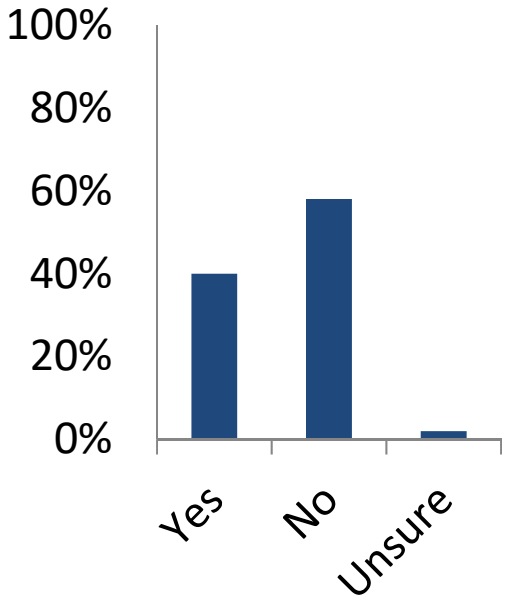
**Pazopanib: 8 Patients**

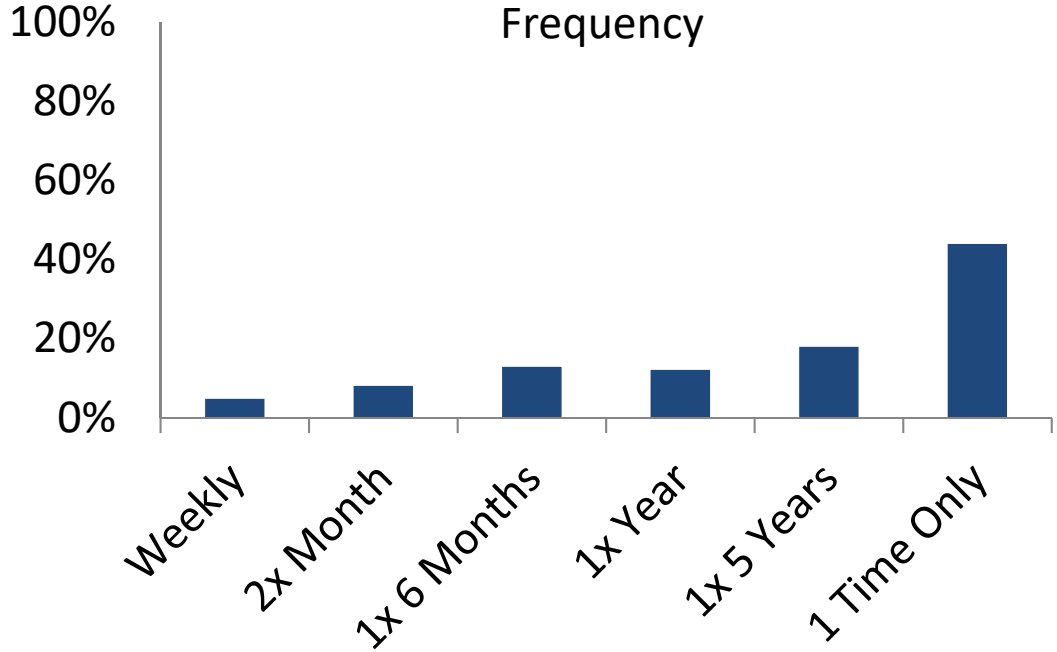


**Pomalidomide: 5 Patients**



# Blood Transfusions




**<u>Average age of transfusion: 45.7 years</u>**

Max: 80yrs; Min: 1yr; Mode: 50yrs

# Patient Perspective on HHT Research Gaps

- A cure
- Stop nose bleeding completely
- Women's issues (uterine bleeding, pregnancy, hormones)
- Gene therapy
- Dietary impacts on HHT severity
- Improve quality of life

*EDUCATION FOR HEALTHCARE PROVIDERS ABOUT HHT*

# Clinician Survey Responses

60% of clinicians say office management of epistaxis is a top area needing more research to achieve a positive impact on HHT patient outcomes

The second area of research need to achieve better patient outcomes is in standardization of protocols for management of anemia

- 96 Clinicians surveyed
- 65% located in US
- 57% treat at an HHT COE

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# Top 3 Anti-Angiogenic Areas for Improved Patient Outcomes

- **33% Development and further validation of current and new anti-angiogenic therapies for epistaxis and GI bleeding**
- **32% Refinement/development of clinical (best practice) guidelines regarding use of anti-angiogenic therapy**
- **16% Guidelines for initiation of anti-angiogenic therapy for liver AVMs in the setting of high cardiac output**
- 12% Guidelines for dose-escalation and/or therapeutic non-response to anti-angiogenic therapy of liver AVMs and high cardiac output state
- 7% Imaging predictors of response to anti-angiogenic medications in the treatment of liver AVMs

Clinician survey results

# Top 3 HHT Manifestations where successful treatment would positively impact **quality of life**

**1. Epistaxis**

**2. Iron Deficiency/Anemia from nose and GI bleeding**

**3. Fatigue**

Clinician survey results

# Clinicians rank top areas of HHT research focus areas needed to impact clinical outcomes with little consensus

1. HHT signaling pathways
2. Impact of HHT genotype on response to therapeutic agents
3. Pathophysiological basis for HHT-1 & HHT-2 phenotypic differences
4. Genotype-phenotype correlation
5. Phenotypic mimics of HHT
6. Pathophysiological basis for 'classic' HHT findings in patients with negative HHT gene testing

Clinician survey results

Epistaxis management is the top agreed area where more educational programs and collaboration are needed to manage HHT

Other answers include management of:

- Iron deficiency and anemia
- Pulmonary AVMs
- GI bleeding
- Liver AVM and high output heart failure
- Genetic testing
- Pregnancy
- Prenatal and pre-implantation testing and counseling

Clinician survey results

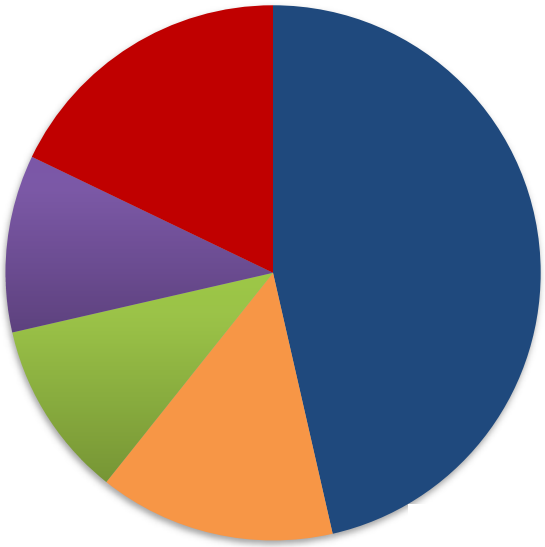
# Scientist Survey Responses on the State of HHT Research

42 Basic Scientists Surveyed

<u>Survey themes:</u>

- Area of research
- Tools/Model systems used and needed
- Perceived lack of resources/collaborations needed to advance research in the field
- Most important basic science gap

# Basic Science Areas of Research



- AVM pathways/signaling/protein function
- Genetics
- Hemodynamics
- Models of HHT
- Other

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# Scientists identify several areas with knowledge gaps (ranked order)

- Mechanistic basis for fragile vessels/differences in propensity to bleed in different vascular beds
- Preclinical models for drug discovery
- Cellular origins of AVMs
- Role of hemodynamic force in AVM development
- BMP/ALK1/ENG signaling

- Cellular origins of AVMs
- Role of hemodynamic force in AVM development
- Genetic and epigenetic mechanisms of disease (including genetic modifiers of disease)
- Biomarkers of disease
- Other signaling pathways: VEGF, PI3K/AKT/mTOR, ANG/TIE2
- Environmental modifiers of disease
- Utility of patient-derived iPSC lines
- Genotype/phenotype correlations

Scientist survey results

# Scientists agree HHT research needs:

- Biobank or access to patient samples
- Better imaging techniques
- Bioinformatics support
- More funding
- More collaboration with clinicians
- Better models of disease

Scientist survey results

# Based on Survey Results:

- 7 Topic Areas were developed as a guideline for discussion
  1. Bleeding
  2. AVM Progression
  3. Drug Therapies/Discovery
  4. Unresolved Topics in Lung AVMs
  5. Genetic Considerations in HHT Diagnosis
  6. Somatic Mutations and Genetic Mechanisms of Disease
  7. Unresolved Topics in Brain AVMs

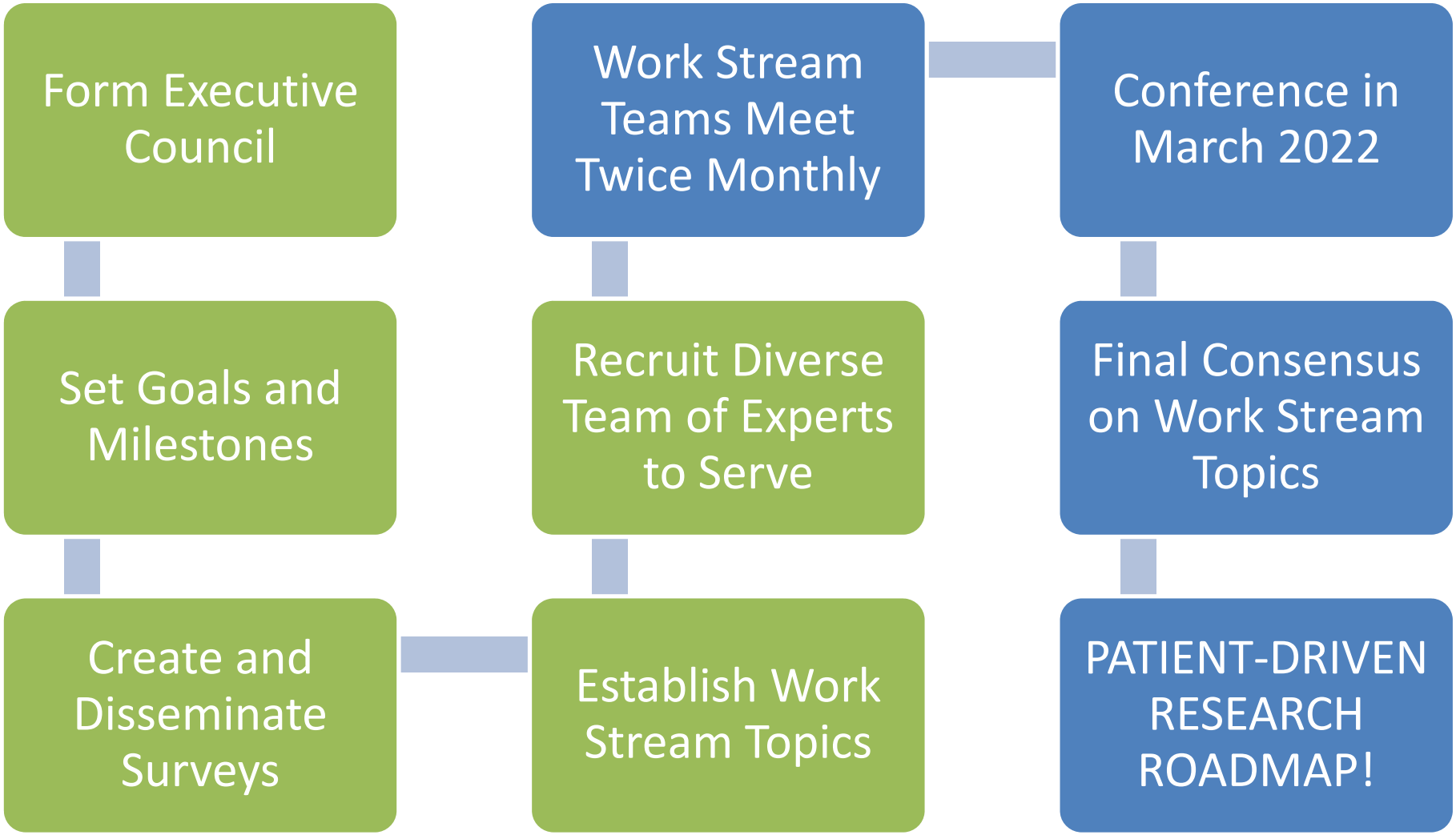
Each topic represents a Work Stream of dedicated clinicians, scientists, and patient leaders who work within the topic areas to understand the landscape of each problem and find opportunities to study these topics to impact HHT patients

# Work Stream Outcome

Develop a plan that includes the areas of consensus, areas that lack evidence or data, and a path forward to address the gaps in scientific understanding of their specific topic within HHT research.

All work streams come together to build a **Research Roadmap** to drive HHT research.

# Work Stream Progress



# Completed and In-Progress Outcomes

- Development of HHT International Challenging Case Series
- Development of virtual HHT Grand Rounds
- Formation of international HHT Center committee
- IDEAS Hub
- Development and execution of survey specifically for women's issues in collaboration with Duke University
- Development of HHT Patient Registry
- Translation of HHT materials
  - HHT Guidelines
  - Living with HHT book
  - COVID statements

# Questions

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