Hemangioma Treatment: Current practices in the use of steroids, propranolol, and laser treatment for children with PHACE syndrome

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Disclosures

No Conflicts of Interest

Grant Funding

Spirit Foundation

Greater Milwaukee Foundation

Blaser Foundation

Children's Research Institute

Dermatology Foundation

Society for Pediatric Dermatology

Food and Drug Administration-1R01FD003429-01

NIH-NIAMS-1R13AR061943-01

NIH-NIAMS-1R34AR060881-011

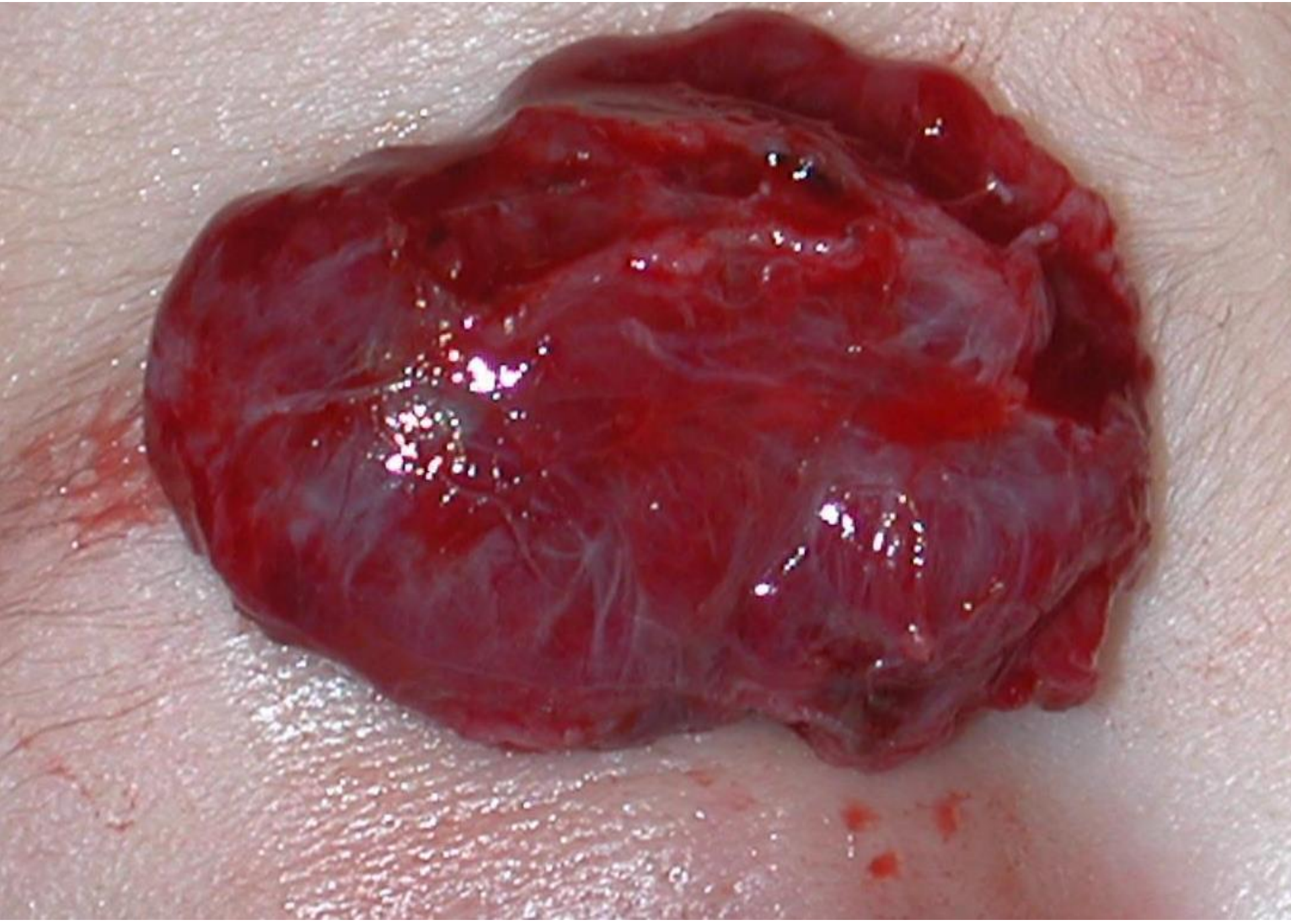
NIH-NIAMS-R01 AR064258-01A1 Siegel (PI)

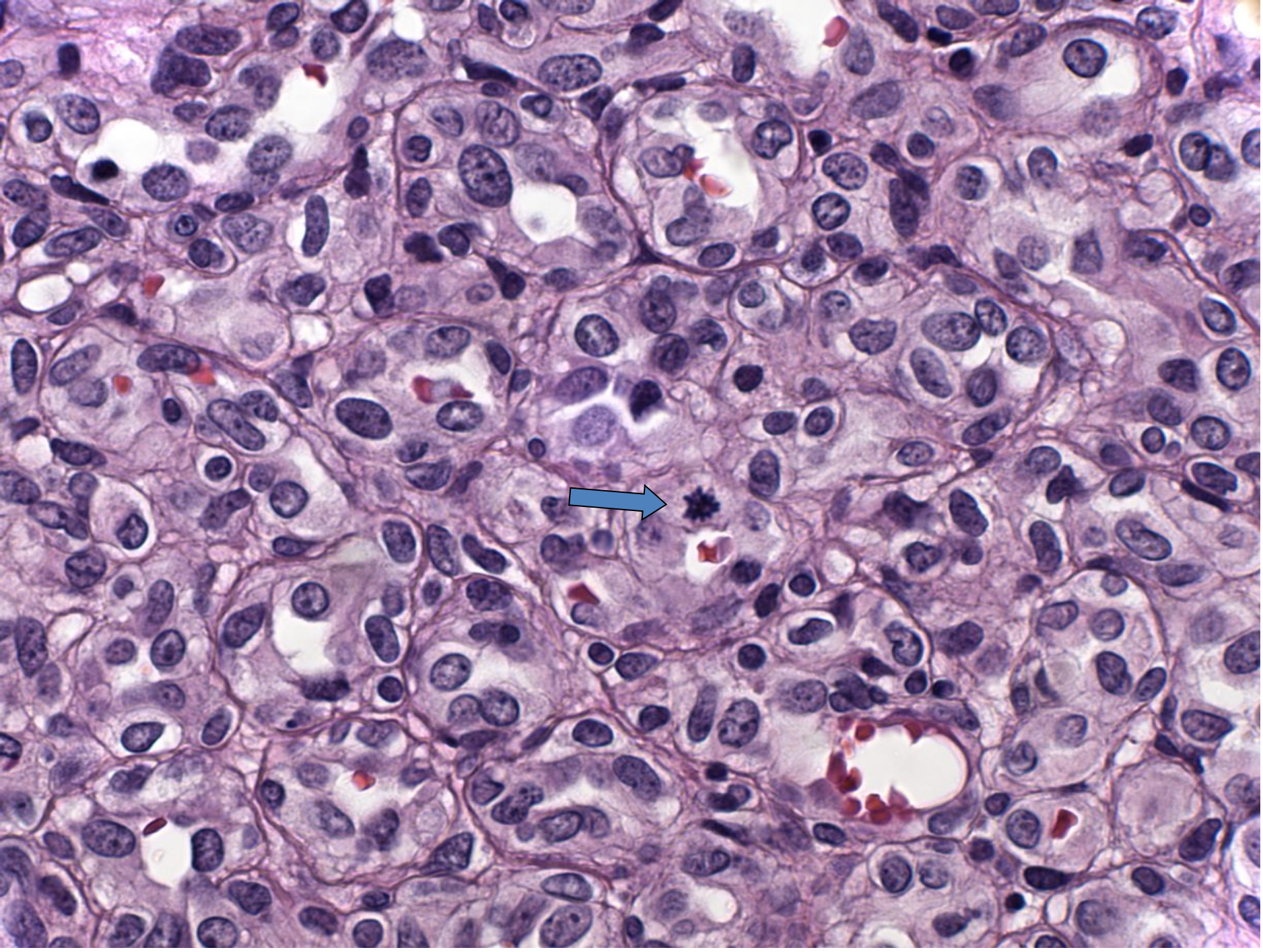
Learning Objectives

- Review treatment of infantile hemangiomas
  - How hemangiomas may be different in PHACE
- Review propranolol for infantile hemangiomas
  - Mechanism of action of propranolol
  - Special considerations in PHACE syndrome
- Introduce consensus-derived guidelines of care
- Overview of laser for infantile hemangioma

Treatment of Infantile Hemangioma

- Infantile hemangiomas are the most common tumor of childhood
  - 25% will have complications
  - 12% will require treatment with a systemic agents
- Data on pharmacologic interventions have not been generated
- Agents with reported efficacy
  - Oral steroids
  - Interferon
  - Intravenous Vincristine
  - Oral Propranolol
  - Topical timolol





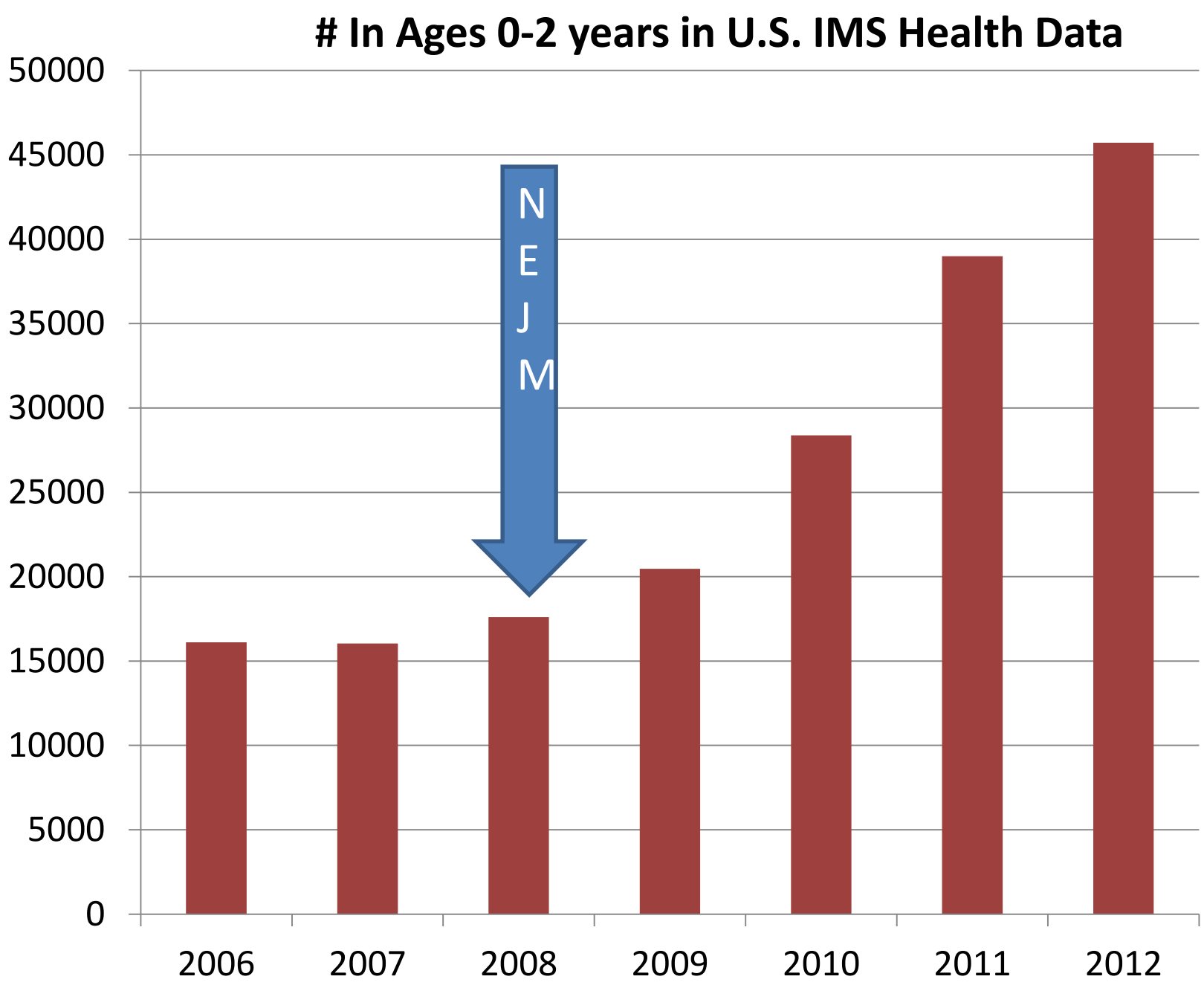
Oral Corticosteroids

- First reported 1968
- Standard of care until 2008
- 2-3 mg/kg/day
- Prolonged treatment
- Unknown efficacy
- Unknown safety

Oral Propranolol

- Synthetic, β-adrenergic receptor-blocking agent
- Blocks both β-1 and β-2 adrenergic receptors
  - Classified as non-selective
- 2008 was reported to be effective for hemangiomas
- 441 articles in pubmed
  - Not subjected to the stringency of clinical trials
  - Only a few publications are prospective and controlled
- Rapidly adopted as first line therapy

Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taïeb A. **Propranolol for severe hemangiomas of infancy. NEJM, 358:2549-51, 2008**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Rapid Adoption of Propranolol

- Previous options had significant side-effects
- Previous options were not highly effective
- Oral propranolol commercially available in US
  - Suspension 20mg/5 cc
- Propranolol previously used in infants/children for rhythm abnormalities
- Rapidly effective

Unique Circumstances

- Especially vulnerable patient population
- No FDA-approved indication for children
- Little safety data for use in infants with rhythm abnormalities
  - supraventricular tachycardia
- Exclusively used in inpatient setting with cardiac monitoring
- Guidelines for use for infantile hemangioma do not exist
  - dose initiation
  - dose escalation
  - toxicity monitoring

Oral Propranolol Adverse Events

- Low heart rate
- Low blood pressure
- Wheezing or breathing problems
- Cold feet or hands
- Low blood sugar
- Sleep disturbance
- Somnolence/sedation
- Low body temperature

Variation in Practice
Cost Analysis

• Inpatient telemedicine monitoring for 3 days • Echocardiogram • 48 hour Holter monitor	$11,270
• EKG • Cardiology consultation • Clinic visits & propranolol suspension	$1,100
• Clinic visits • Propranolol suspension	$425

NIH-NIAMS-1R34AR060881-01
Safety Monitoring for Use of Propranolol for Hemangiomas

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Initiation and Use of Propranolol for Infantile Hemangioma: Report of a Consensus Conference *Pediatrics* 2013;131;128;

- **Invited Participants**
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- Francine Blei, MD, VBINY, Dermatology
- Yvonne E. Chiu, MD, MCW, Dermatology
- Robert H. Chun, MD, MCW, Otolaryngology
- David H. Darrow, MD, EVMS, ENT
- Maria C. Garzon, MD, Columbia, derm
- Kristen Holland, MD, MCW, Dermatology
- Shawna Joachim, MCW, Study Coordinator
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- Leonardo Liberman, MD, Columbia, Cardiology
- Susan MacLellan-Tobert, MD, Gundersen, Card
- Anthony J. Mancini, MD, Northwestern, Derm
- Kari Martin, MD, MCW, Dermatology
- Jonathan Perkins, MD, Seattle, ENT
- Marcia Seefeldt, RN, MCW, Nurse Clinician
- Robert Sidbury, MD, Seattle, Dermatology
- Dawn Siegel, MD, MCW, Dermatology

Consensus Group's Aims

- Who not to use it in
  - exclusion criteria
- Pretreatment evaluation
- Safe and effective dose
- Initiation Protocol
  - Clinical setting
  - Monitoring
  - Education
- Special populations-PHACE syndrome

- December 2011
  - 85 papers in the English literature
  - 1175 patients

Complications recorded	# of patients/ Total # of patients in papers reporting said complication	Frequency (%) of complication among papers reporting said complication	Overall frequency (%) of total of 1175 patients reviewed in 85 papers
Asymptomatic hypotension or hypotension (unspecified)	33/228	14.5 %	2.8%
Symptomatic hypotension	3/46	6.5%	0.3%
Pulmonary symptoms-bronchospasm	16/201	8.0%	1.4%
Hypoglycemia	10/88	11.4%	0.9%
Asymptomatic bradycardia	11/126	8.7%	0.9%
Symptomatic bradycardia	1/2	50%	0.1%
Sleep disturbance (incl. nightmares)	44/326	13.5%	3.7%
Somnolence	26/220	11.8%	2.2%
Cool or mottled extremities	20/225	8.9%	1.7%
Diarrhea	9/53	17.0%	0.8%
GERD or GI upset	8/133	6.0%	0.7%
Hypothermia			.7%

Pre-treatment Evaluation

- The prescribing physician must perform/obtain a normal cardiovascular and pulmonary history and examination.
  - family history of heart block or arrhythmia
  - heart rate
  - blood pressure
  - cardiac and pulmonary auscultation.
- The examination should be performed by a care provider with experience in evaluating infants

The Utility of ECG Screening is Unclear

- It should be part of the pre-treatment evaluation when:
  - family history of congenital heart conditions and arrhythmias, e.g., heart block, long QT syndrome, sudden death
  - history of an arrhythmia
  - the heart rate is below normal for age, with normal values varying with age:
    - *-Newborns (0-30 days old): 70 - 190 beats per minute*
    - *-Infants (1 - 11 months old): 80-120 beats per minute*
    - *-Children 1 to 10 years: 70 - 130 beats per minute*

Initiation Guidelines

- Inpatient hospitalization recommended
  - Infants ≤ 8 weeks of corrected age, OR
  - inadequate social support
  - co-morbid conditions affecting the cardiovascular system, the respiratory system or blood glucose maintenance
- Initiate therapy on an outpatient basis with 2-3 hours clinical monitoring
  - Infants/Toddlers over 8 weeks of age with adequate social support and without significant co-morbid conditions

Monitoring

- Clinician must have experience in measuring HR & BP in infants
  - Appropriate size BP cuffs
  - Dynamap inaccurate in infants
- Heart rate more reliable
- Dose response is usually most dramatic after initial dose
- Peak effect on HR & BP is 2 hours after dose
- Recommend prolonged monitoring 2-3 hours
- Major escalation in dosage (>0.5mg/kg/day) will require monitoring for at least 2 hours

Target Dose

- 1-3 mg/kg/TID
- Titrate to hemangioma response
- Polymorphisms in beta-blocker receptors

Summary

1. There are no FDA-approved indications for propranolol in pediatric patients in the United States
2. There is significant uncertainty regarding toxicity monitoring

Initiation

1. Screen for 3rd degree heart block before starting
2. The 20 mg/5 mL preparation of propranolol is preferred
3. Propranolol dose must be titrated up to a target dose
4. Starting at 1 mg/kg/day
5. Oral propranolol be divided into three times daily
6. Target dose is 2mg/kg/day TID

Adverse Events

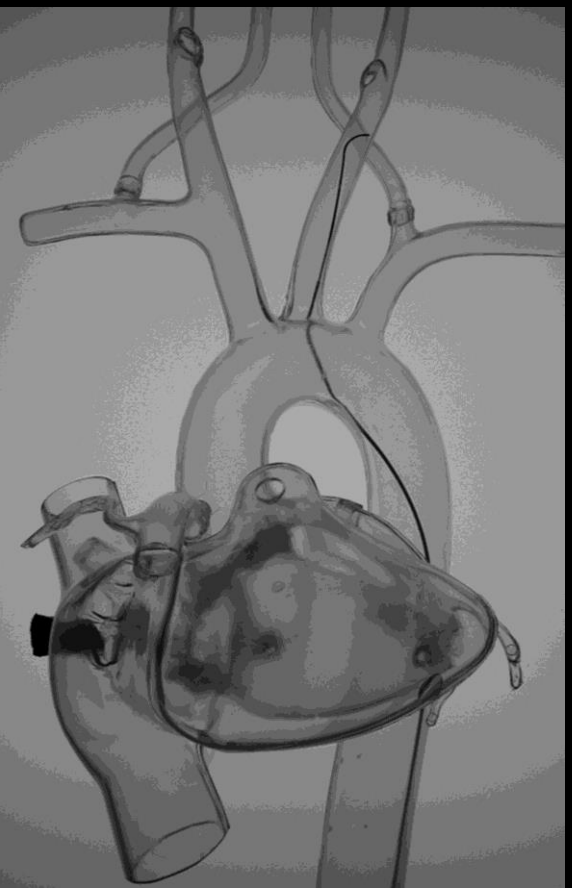
1. Hypoglycemia may be the most common serious complication
    1. Younger infants are at higher risk
    2. Most reports occur in toddlers
2. Propranolol should be discontinued during intercurrent illness
3. Bronchospasm is the most common adverse event and reason for stopping

Which Infants Are at Risk For PHACE?

- Large hemangiomas
- Segmental hemangiomas
- Head and neck hemangiomas
- Hemangioma Investigator Group
  - Enrolled 111 patients >22 cm2 head and neck
  - MRI,MRA, Echocardiogram, eye exam
  - 33% have PHACE syndrome
  - 33% have cerebrovascular anomalies
  - 19% coarctation
  - 5% had vascular ring

Arterial Anomalies PHACE Syndrome

- Common in PHACE
  - >91% cerebral or cervical arterial anomalies
  - 30% aortic arch anomalies
- Acute ischemic stroke is rare
- Will pharmacologic intervention increase risk?
  - Oral steroids
  - Oral propranolol
- Which PHACE patients are at highest risk for stroke?



Stroke in PHACE Syndrome

- Review of literature/PHACE registries
- 10 articles with 19 cases of stroke
  - 2 additional cases in our registries
- **21 cases**
- All *acute ischemic stroke*
  - Ischemia from reduced blood flow and inadequate cerebral perfusion or “demand ischemia”
- Age on onset- 13.6 months (3-60 months)
  - 24 yr old reported
- Symptoms-hemiparesis and seizures

Propranolol and PHACE Syndrome

- **Determine higher risk for demand ischemia**
  - Severe arterial anomalies
  - Long segment narrowing (>75%) or non-visualization of a major cerebral vessel

AND

  - Isolated circulation
  - Long segment narrow or non-visualization of multiple arteries
  - Cardiac or arch anomalies
  - Moyamoya disease

Risk Category	Cerebrovascular Anomalies
High 	• Multiple vessels with severe narrowing or non-visualization without adequate collateral circulation and Moyamoya disease and Cardiac or Aortic arch anomalies • Severe narrowing/stenosis[b] or non-visualization of 1 major vessel[c] without adequate collateral circulation and Moyamoya disease and Cardiac or Aortic arch anomalies • Severe narrowing/stenosis[b] or non-visualization of 1 major vessel[c] without adequate collateral circulation and Moyamoya disease • Severe narrowing/stenosis[b] or non-visualization of 1 major vessel[c] without adequate collateral circulation and Cardiac or Aortic arch anomalies • Severe narrowing/stenosis[b] or non-visualization of 1 major vessel[c] without adequate collateral circulation
Standard	• Severe narrowing/stenosis[b] of major vessels[c] *with* adequate collateral circulation • Mild narrowing/stenosis[d] of major vessels[c] *with* adequate collateral circulation • Hypoplasia, dysplasia, aberrant origin or course of major vessels[c, e] • Persistent embryonic arteries • Aberrant subclavian artery
Low	• No arterial anomalies

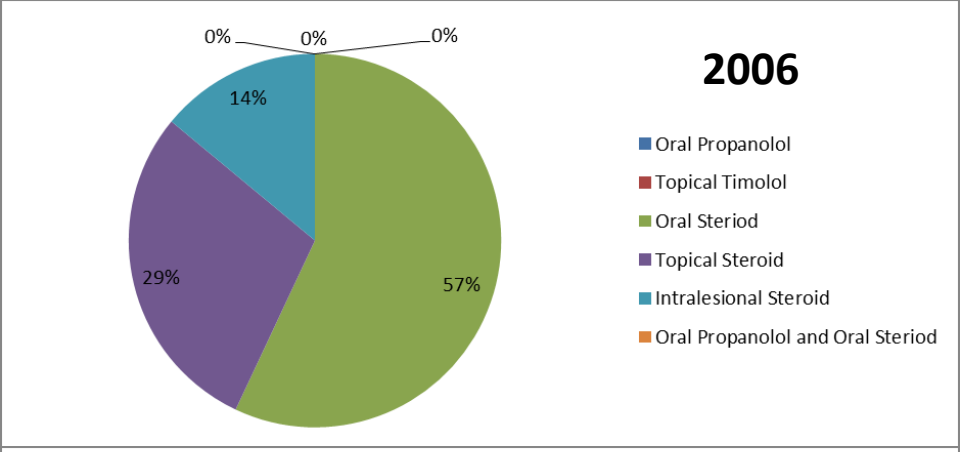
Propranolol Use in PHACE Syndrome

- Multicenter retrospective case series
  - 7 centers
- 32 patients with PHACE syndrome and arterial anomalies
- 17/32 were considered high risk for stroke
- 1/32 had a change in neurologic status
- 3/32 had worsening of ulceration

Denise Metry, MD, Ilona J. Frieden MD, Christopher Hess MD/PhD, Dawn Siegel MD, Mohit Maheshwari MD, Eulalia Baselga MD, Sarah Chamlin MD, Maria Garzon MD, Anthony J. Mancini MD, Julie Powell MD, and Beth A. Drolet MD. Propranolol Use in PHACE Syndrome with Cervical and Intracranial Arterial Anomalies: Collective Experience in 32 Infants. Pediatr Derm 2013 Jan;30(1):71-89.

Oral Propranolol Use in PHACE Syndrome

- First-line therapy
- Minimize swings in BP
  - Use lowest possible dose (<2mg/kg/day)
  - Titrate dose up slowly
  - Three times a day dosing
- Consider perfusion studies prior to initiation
- Cardiology and neurology consultation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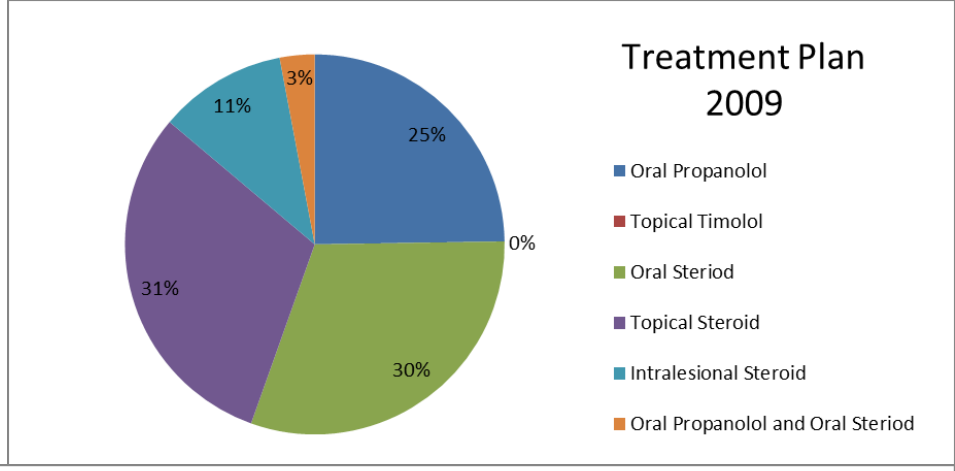
Topical Timolol
Oral Steriod
Topical Steroid
Intralesional Steroid
Oral Propanolol and Oral Steriod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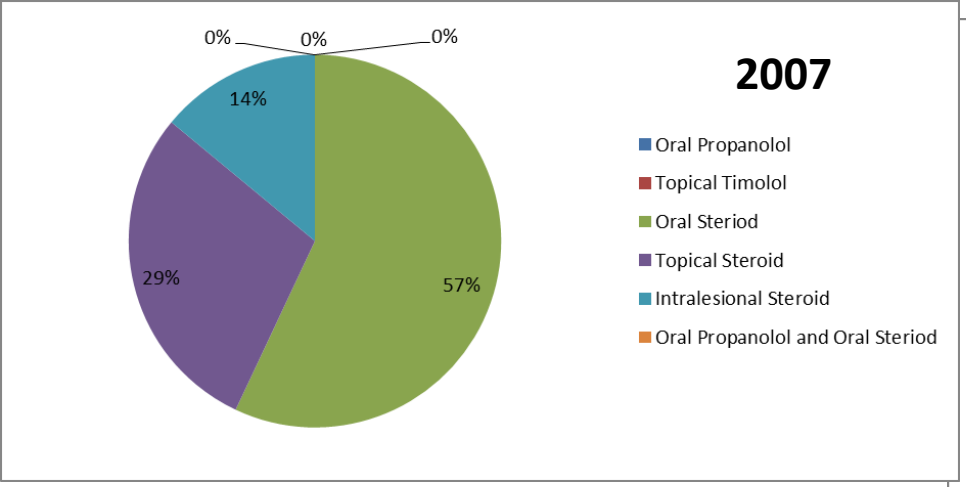
Oral Propanolol and Oral Steriod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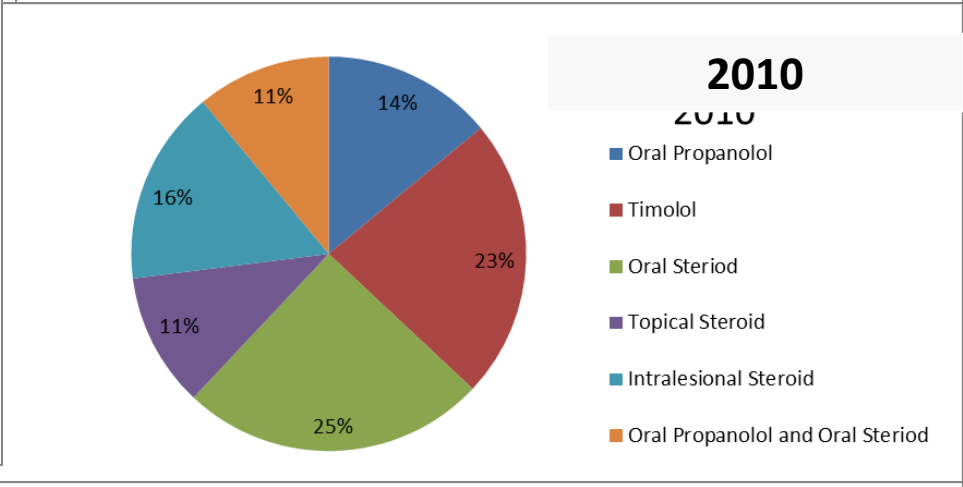
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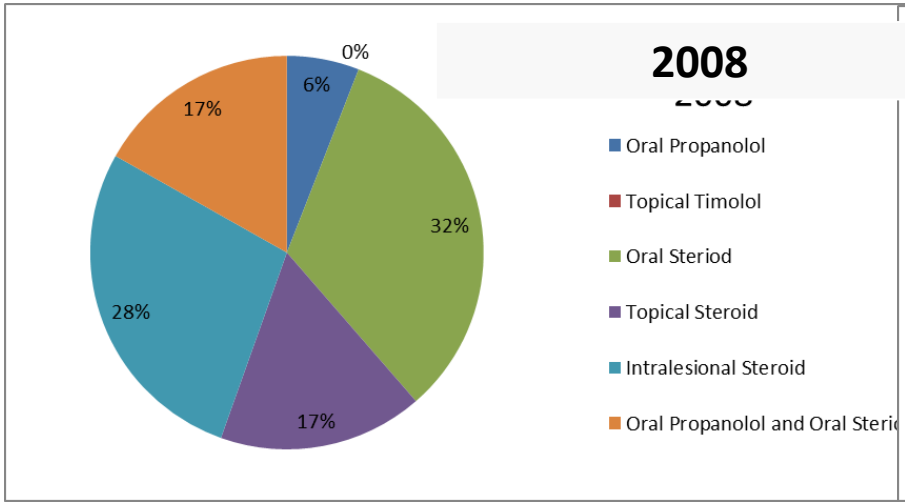
Oral Propanolol and Oral Steriod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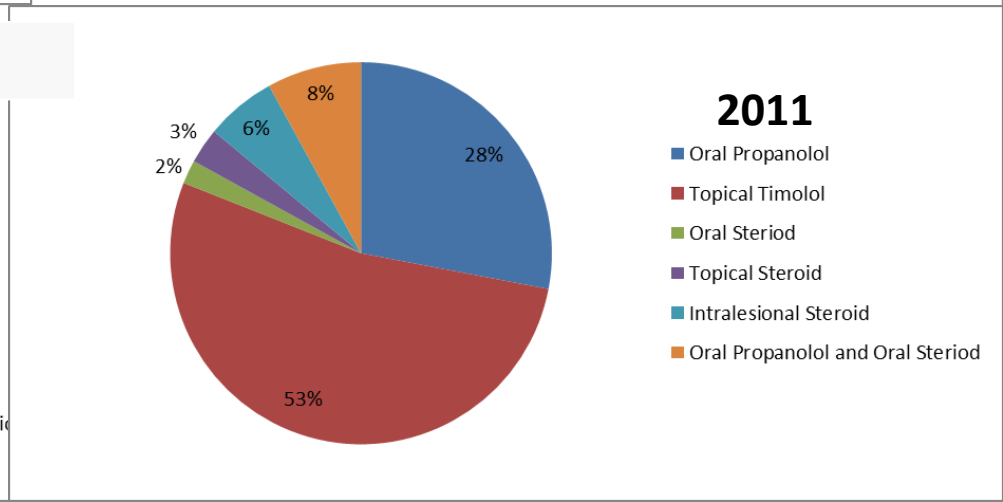
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Oral Propanolol
Topical Timolol
Oral Steriod
Topical Steroid
Intralesional Steroid
Oral Propanolol and Oral Steriod

Topical Timolol for Hemangiomas

- Topical timolol
  - Ophthalmalmic solution 0.25%, 0.5%
- Superficial hemangioma
- Early proliferative phase
- Eyelid, nasal tip, lips, genital
- Systemic absorption has been reported

Beta-blockers, Hemangiomas, and PHACE Next Steps

- Efficacy of Beta-blockers?
- Safety of Beta-blockers?
- Length of therapy?
  - Rebound growth of hemangioma
- Topical beta-blockers?

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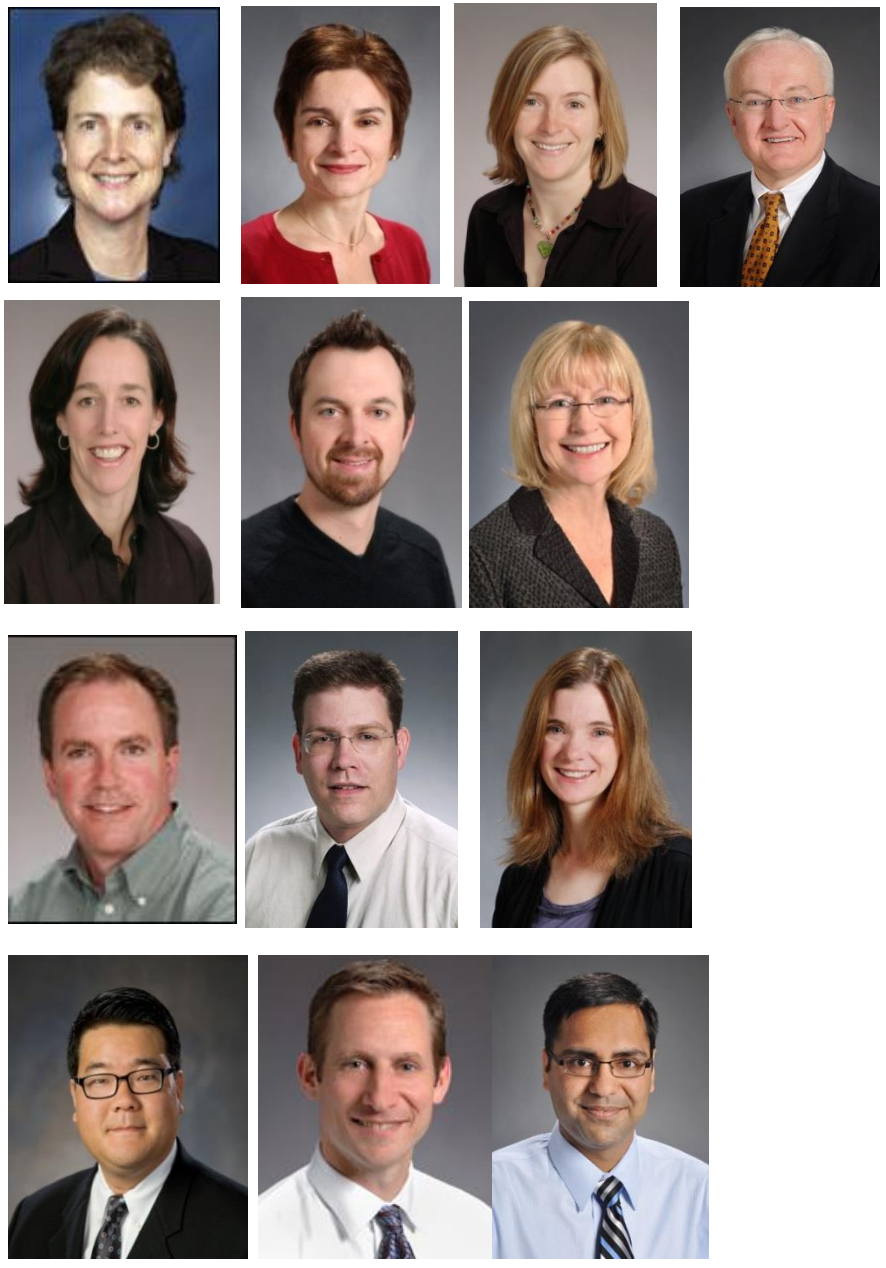
- Radiology
  - Interventional radiology
- Neuroradiology
- Hematology-Oncology
- General Surgery
- Plastic Surgery
- Hand surgery
- Otolaryngology
- Orthopedic Surgery



Birthmarks and Vascular Anomalies Program

- The represents a unique collaboration between Children's Hospital of Wisconsin and the Medical College of Wisconsin.
- To best care for you and your family, we've built an internationally respected team of doctors and researchers who share a vision to provide outstanding care. Although we treat many children, we also diagnose and treat adults.
- When you come to Children's Hospital, you can expect:
- **One-stop, convenient care**
  One benefit of coming to Children's Hospital's Vascular Anomalies Clinic is the patient can see all of his or her physicians at one visit, reducing the number of visits.
  A team of specialists will work together to discuss treatment options. This approach saves time and gives you peace of mind knowing that all of our specialists have come together to agree on a treatment plan.
- **A team that works together for your child – and for you**
  Vascular anomalies are complex and each case is unique. Our team includes medical, surgical and research experts who work together to develop a treatment plan that best addresses each patient's condition.
  - Learn more about the conditions we treat
  - Meet our birthmark treatment specialists.
- **Superior diagnostics capability**
  Our team has access to the most up-to-date technology and a wide range of resources in research, pathology, radiology and many other specialties.
- **Cutting-edge research**
  The vascular anomalies team is doing research on the causes of and potential cures for infantile hemangiomas. The research and work of our team has given several important clues to help us understand what causes infantile hemangiomas. We also have important new tools for diagnosing them.
  We use knowledge gained in the laboratory to care for infants with hemangiomas.
- **Highly specialized programs**
  To provide focused expertise, we offer a Hemangioma of Infancy Program, a Laser Program and a Surgery Program

Funding

- Dermatology Foundation
- Spirit Foundation
- Greater Milwaukee Foundation
- Blaser Foundation
- Society for Pediatric Dermatology
- Children's Research Institute
- Food and Drug Administration-1R01FD003429-01-
- NIH-NIAMS-1R13AR061943-01
- NIH-NIAMS- 1R34AR060881-01

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Vascular Anomalies Center & Broeckel & Worthey Lab

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