ICH GWAS Monthly Newsletter
Issue 3 - February 2009

In this issue:

This is the third issue of the monthly newsletter for the ICH GWAS Study Group. This newsletter is meant to be a tool to keep investigators participating in the ICH GWAS updated on all aspects of this project, including phenotyping, genotyping, data analysis and logistics.

The newsletter will be sent out to participants on the 15th of each month (or nearest workday) as an email attachment from the Program Manager at the Coordinating Center.

If you want to add topics relevant to all investigators involved in the ICH GWAS to the next newsletter, or you'd like to give general feedback to the Newsletter Design Team please contact:
Lynelle Cortellini (lcortellini@partners.org).

Please do not forget to mark your calendars with the date for the next ICH GWAS Conference Call:

Tuesday, March 24 2009
10-11 am, Eastern USA time

New Newsletter Format and Additions

We are very excited to present you the new and improved format of the ICH GWAS Newsletter. We have been working hard on creating an appealing, eye-catching graphic format for the newsletter, while also striving to improve ease of reading and information-finding.

This new format also comes with significant additions to contents. Following advice given by Investigators during the latest ICH GWAS Conference Call we have introduced **Recruitment Reports**, which will be constantly updated and available on each new issue of the newsletter.

We went even further in trying to deliver a useful, informative service for the ICH GWAS community. We have introduced a **Spotlight** section, focusing on either recently published papers relevant to the ICH GWAS or on one of our own Investigators. We hope this will prove a valuable tool in sharing information and bringing our ever-increasing group of Investigators even closer.

As usual, we'd like to hear from you all. Comments, advice and criticism are fundamental in guiding us into improving the quality of this Newsletter even more. We also welcome your contribution in the form of articles for the spotlight section (focusing on either papers or Investigators participating in the ICH GWAS), as well as proposals for new topics to be added to the contents.

For further info on this topic please contact:

Lynelle Cortellini, M.Sc.
lcortellini@partners.org

Recruitment Updates

Sites recruiting prospectively as part of GOCHA

Study site	Period	Warfarin		Non Warfarin		Total
		Case	Control	Case	Control	
Mass General Hospital	November 2008	2	1	3	-	**6**
	December 2008	-	-	2	-	**2**
	January 2009	4	2	4	-	**10**
University of Michigan	November 2008	-	6	-	-	**6**
	December 2008	-	2	-	-	**2**
	January 2009	-	-	-	2	**2**
University of Virginia	November 2008	-	-	1	-	**1**
	December 2008	1	-	4	-	**5**
	January 2009	-	-	5	-	**5**
Mayo Clinic - Jacksonville	November 2008	-	-	1	-	**1**
	December 2008	-	-	-	1	**1**
	January 2009	1	-	1	-	**2**
University of Florida	November 2008	-	-	-	-	**-**
	December 2008	-	-	-	-	**-**
	January 2009	1			1	**2**
Beth Israel Deaconess Medical Center	November 2008	2	-	1	-	**3**
	December 2008	1	1	1	-	**3**
	January 2009	-	-	2	-	**2**
Total		12	12	25	4	**53**

Sites recruiting prospectively as part of ICH GWAS

Principal Investigator		Institution	Country of Origin	Status
Last Name	First Name			
Majersik	Jennifer	University of Utah	US	Joining
Thjis	Vincent	Leuven	Belgium	Joining

Sites recruiting retrospectively as part of ICH GWAS

Principal Investigator		Institution	Country of Origin	Number of Cases	Number of Controls	Samples received by Genotyping Center
Last Name	First Name					
Lindgren	Arne	University Hospital, Lund	Sweden	250	250	
Markus	Hugh	St. George's, University of London	UK (England)	200	200	
Melander	Olle	Malmo University Hospital	Sweden	100	300	
Montaner	Joan	Vall d'Hebron Hospital	Spain	185	270	
Roquer	Jaume	Hospital del Mar	Spain	200	200	
Schmidt	Reinhold	Medical University Graz	Austria	400	1000	
Slowik	Agnieszka	Jagiellonian University	Poland	350	430	**Yes**

Please note that data presented in the table above are to be intended as estimates of the number of samples each participating center has pledged to provide for the ICH GWAS. Actual numbers of samples analyzed might vary depending on DNA and phenotype quality.

For further info on this topic please contact:

Alessandro Biffi, M.D.

abiffi@partners.org

Spotlight: Article

Eckman MH, Rosand J, Greenberg SM, Gage BF.

Cost-effectiveness of using pharmacogenetic information in warfarin dosing for patients with nonvalvular atrial fibrillation.

Ann Intern Med. 2009 - 20;150(2):73-83

BACKGROUND: Variants in genes involved in warfarin metabolism and sensitivity affect individual warfarin requirements and the risk for bleeding. Testing for these variant alleles might allow more personalized dosing of warfarin during the induction phase. In 2007, the U.S. Food and Drug Administration changed the labeling for warfarin (Coumadin, Bristol-Myers Squibb, Princeton, New Jersey), suggesting that clinicians consider genetic testing before initiating therapy. OBJECTIVE: To examine the cost-effectiveness of genotype-guided dosing versus standard induction of warfarin therapy for patients with nonvalvular atrial fibrillation. DESIGN: Markov state transition decision model.

DATA SOURCES: MEDLINE searches and bibliographies from relevant articles of literature published in English.

TARGET POPULATION: Outpatients or inpatients requiring initiation of warfarin therapy. The base case was a man age 69 years with newly diagnosed nonvalvular atrial fibrillation and no contraindications to warfarin therapy.

INTERVENTION: Genotype-guided dosing consisting of genotyping for CYP2C9*2, CYP2C9*3, and/or VKORC1 versus standard warfarin induction.

OUTCOME MEASURES: Effectiveness was measured in quality-adjusted life-years (QALYs), and costs were in 2007 U.S. dollars.

RESULTS: In the base case, genotype-guided dosing resulted in better outcomes, but at a relatively high cost. Overall, the marginal cost-effectiveness of testing exceeded $170 000 per QALY. On the basis of current data and cost of testing (about $400), there is only a 10% chance that genotype-guided dosing is likely to be cost-effective (that is, <$50 000 per QALY). Sensitivity analyses revealed that for genetic testing to cost less than $50 000 per QALY, it would have to be restricted to patients at high risk for hemorrhage or meet the following optimistic criteria: prevent greater than 32% of major bleeding events, be available within 24 hours, and cost less than $200.

LIMITATION: Few published studies describe the effect of genotype-guided dosing on major bleeding events, and although these studies show a trend toward decreased bleeding, the results are not statistically significant.

CONCLUSION: Warfarin-related genotyping is unlikely to be cost-effective for typical patients with nonvalvular atrial fibrillation, but may be cost-effective in patients at high risk for hemorrhage who are starting warfarin therapy.

ICH GWAS Conference Calls: Schedule and Information

Please mark your calendars with dates for the next ICH GWAS Conference Calls:

Tuesday, March 24 2009
10-11 am Eastern USA time

Tuesday, May 19 2009
10-11 am, Eastern USA time

As announced in an email addressed to all Investigators, we will be moving to a web-based conferencing system for the next ICH GWAS Conference Call. This means that we will be using Internet Connections and a Voice over IP provider. Still, we have arranged for Investigators who prefer to use a telephone line to join to be able to do so.

To get more information on the service we will be using you can visit:
http://www.paetec.com/

Please do not hesitate to contact us if you have any questions about the equipment needed for the Web-Conferencing (see box).

For further info on this topic please contact:
Alessandro Biffi, M.D.
abiffi@partners.org

EQUIPMENT NEEDED

In order to participate to the Conference Call over the Web (**please note that telephone conferencing will still be a possibility**) Investigators will need:

- **Internet Connection**
- **Mac or PC computer**
- **Communication set**
  This typically consists of a headset: unlike music headsets, these also include a built-in microphone for conversations. They are commercially available and can be bought both online and at electronics retailer stores.
  Alternatively, users can use speakers on their computers to listen to conversations and buy a separate stand-alone microphone to talk. However, this solution is technically not recommended. Moreover most stand-alone microphones are only available in packages that also include a web-cam, specifically intended for use in video-conferencing (which we do not plan to implement).

Large Format Newsletter in June 2009

We are very pleased to announce that we plan to release a super-sized version of the ICH GWAS Newsletter bi-yearly. The first large-format issue will be sent out to Investigators on June 2009.

This large-format version will benefit from additional spotlight articles on our Investigators and on recently published papers.

We will also host contributions from members of the Phenotyping, Imaging, Data Analysis and Genotyping Committees regarding general GWAS issue, as well as topics specifically pertaining to the ICH GWAS.

Additionally, we will take a closer look at data already available from the phenotyping and genotyping, as well as discuss additional issues concerning future efforts aimed at replicating our results and fine-mapping regions of interest. Sub-projects submitted by Investigators and approved will be detailed and discussed.

All ICH GWAS Investigators are invited to submit material and ideas for the Large Format ICH GWAS Newsletter. We really look forward to deliver an even more interesting issue of this publication.

For further info on this topic please contact:

Alessandro Biffi, M.D.
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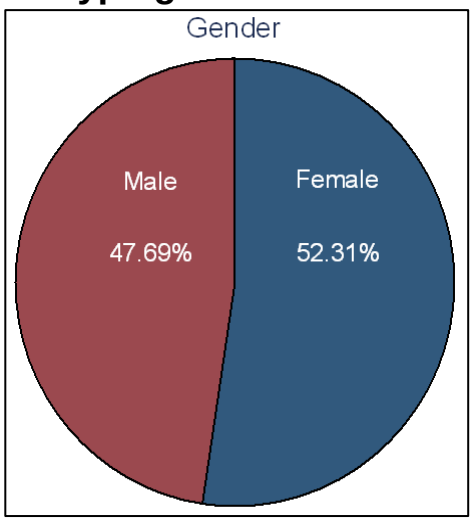
Preliminary Data: Lobar ICH Cases

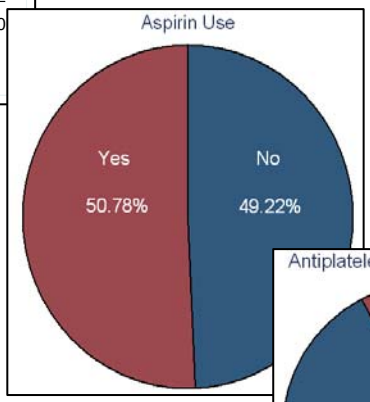
Phenotype Data from Genotyping Phase I

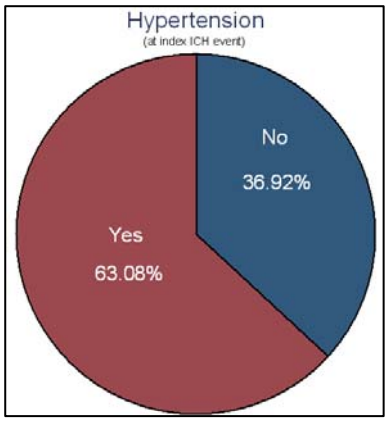
Selection Criteria:

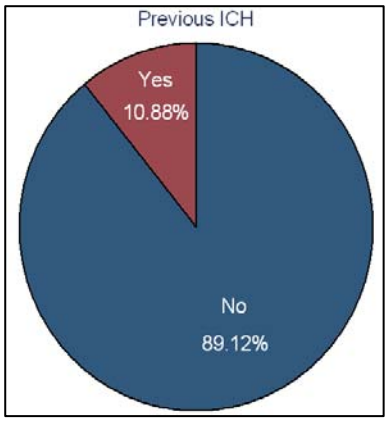
- GOCHA Samples
- Minimal GWAS data points available
- All additional data points available
- Lobar ICH
- Not on Warfarin at Index Event
- Adequate DNA concentration and volume

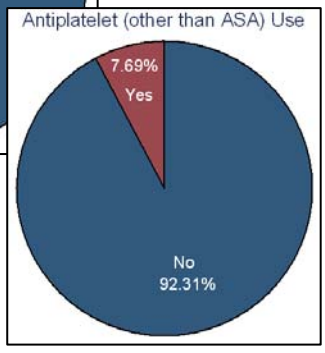
Total no. of Cases selected for Phase I Genotyping: 195

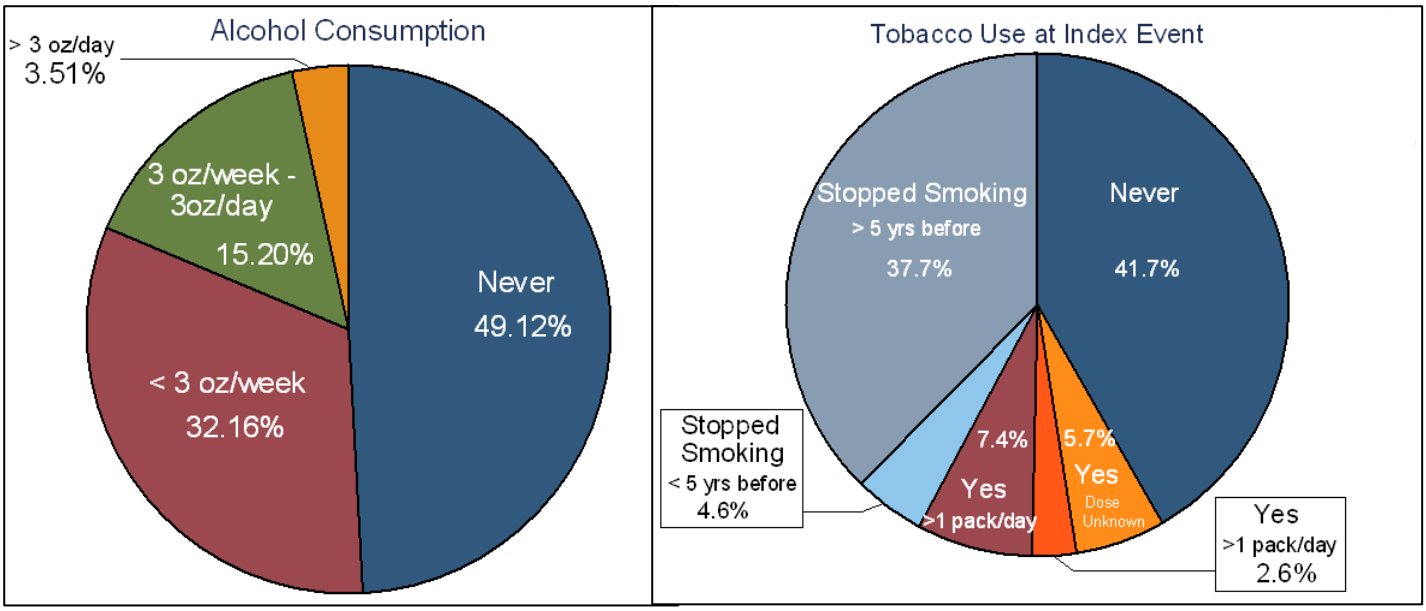


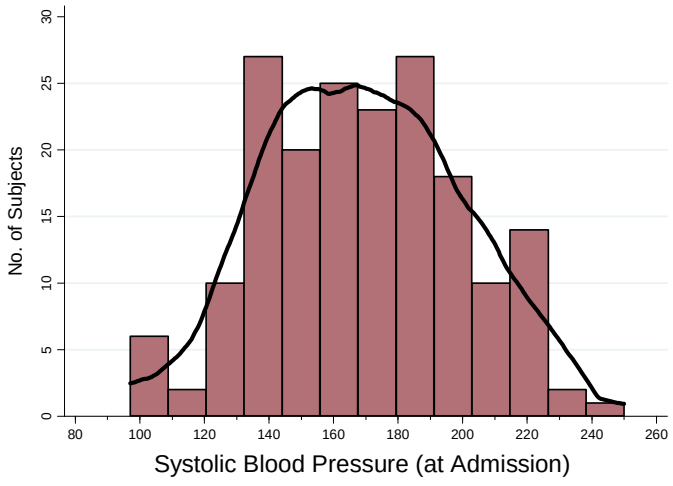




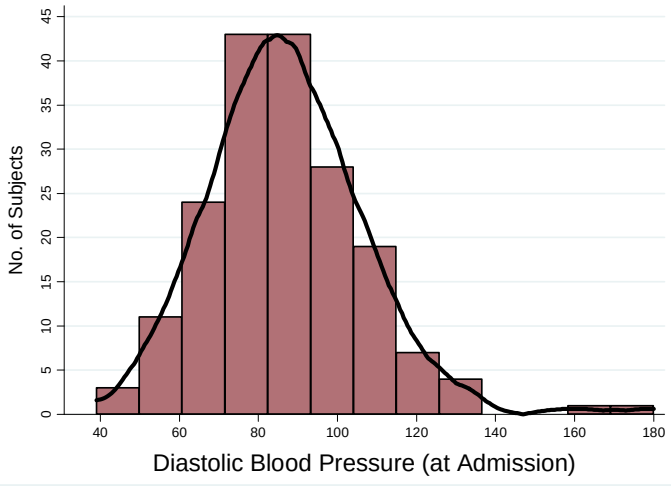








Variable	Mean ± SD
Systolic Blood pressure	168.9 ± 30.6



Variable	Mean ± SD
Diastolic Blood pressure	87.0 ± 19.9

For further info on this topic please contact:

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Sub-project Proposals

The Proposal From for Sub-projects was sent out to all Investigators on January 21st 2009. Investigators who would like to submit a proposal for a sub-project as part of the ICH GWAS should use this form. Once completed, this form needs to be sent (either by mail or electronically) to Dr. Jonathan Rosand, M.D. M.Sc. at the ICH GWAS Coordinating Center at MGH (see the contact info box for this topic).

Once this form is received, sub-projects will be reviewed and approved by the ICH GWAS Publications Committee. While a brief description of the sub-project is a required part of the form, please do not forget to list an email contact for the Principal Investigator, in case further info or additional details are needed.

Please do not hesitate to contact us at any time if you'd like to have the form re-sent to you or if you need assistance with completing it.

For further info on this topic please contact:

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