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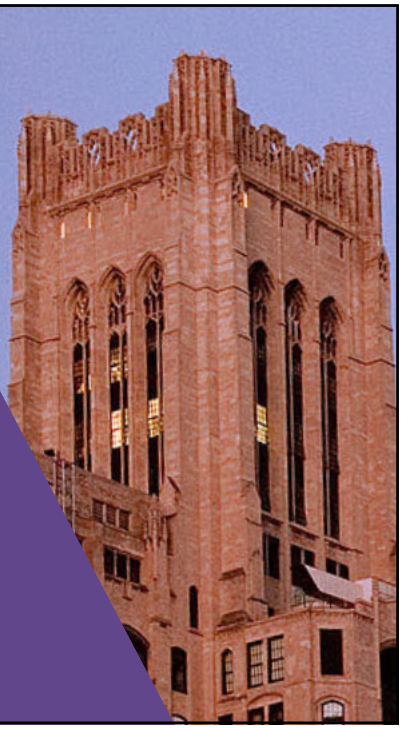

Predicting Hematoma Expansion with NeurOimaging and Bio-Markers (**PHENOM**), a FASTEST Ancillary Study

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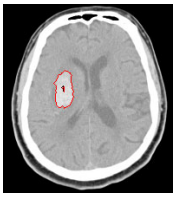
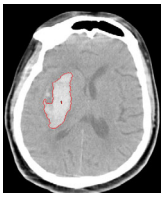
Model of ICH



Hemostasis



Care, rehab

90-180d Functional Outcomes (mRS) HRQoL (EQ5D, PROMIS)

Diagnostic CT within 2h of ICH symptoms

Follow-up CT (typically 24h)

Trials of Acute Hemostasis in ICH

A few successes, a few near misses, depending on patient selection

Trial	Intervention	Difference in Hematoma Expansion	Outcomes at 90 days	Primary Endpoint	Time from ICH symptom onset
FAST phase II	Factor VIIa	**4.5 mL (P=0.04)**	**Improved mRS**	**% change in hematoma volume (P=0.01)**	4 hours
FAST phase III		**3.7 mL (P=0.009)**	**Improved NIHSS**	mRS 0-4 vs. 5-6 (P>0.1)	
STOP-IT, SPOTLIGHT	Factor VIIa, requires Spot Sign	Not Different	Not Different	Hematoma growth >33% or 6 mL	6.5 hours
PATCH	Platelet transfusion	Not Different	**Worse**	Ordinal regression of mRS (P=0.01)	6 hours
INCH	Prothrombin Complex vs. Fresh Frozen Plasma	**14 mL (P=0.02)**	Not Different (not powered)	**Hematoma growth (P=0.0003)**	12 hours
TICH-2	Tranexamic Acid	**4.9 mL (P=0.04)**	Not Different	mRS (ordinal shift)	8 hours

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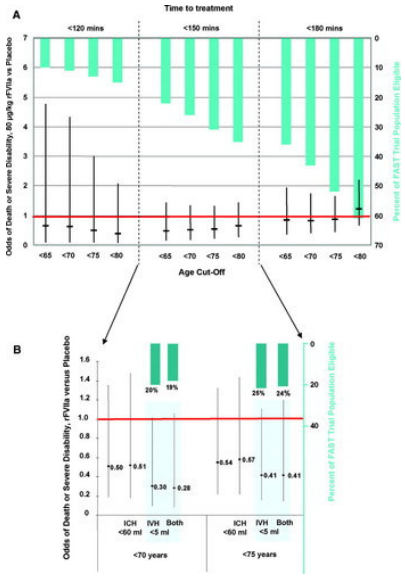
FASTEST

- Factor VII had greatest benefit in a subset of patients
  - Shorter time from symptom onset
  - Age < 80
  - No severe IVH
  - Not deeply comatose
  - Hematoma volume < 60 mL
- FASTEST selects salvageable patents who present within 2 hours of symptom onset
- Geared towards mobile stroke units
- 130 sites, many in EU, UK, Japan, Canada, and US



Stephan A. Mayer. Stroke. Can a Subset of Intracerebral Hemorrhage Patients Benefit From Hemostatic Therapy With Recombinant Activated Factor VII?, Volume: 40, Issue: 3, Pages: 833-840, DOI: (10.1161/STROKEAHA.108.524470)

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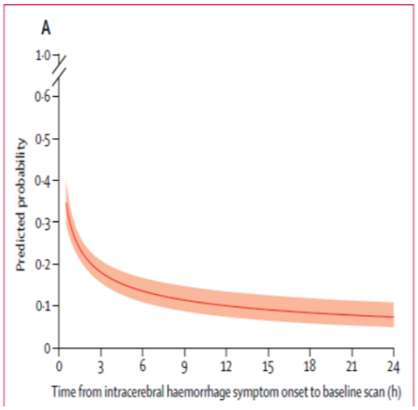
Patient Selection

Factor VII is likely to improve outcomes only in patients who will have hematoma expansion

- Patient Selection is still important in FASTEST, and for future care of patients with ICH
- Most patients in FASTEST will **not** have hematoma expansion
- Further patient selection would allow even more targeted treatment
  - Increased efficacy by treating patients most likely to benefit
  - Precluding unnecessary risks by foregoing treatment in patients unlikely to benefit (e.g., no hematoma expansion likely)
- If FASTEST is positive, identifying salvageable patients likely to benefit who do not meet the stringent criteria in future investigations (e.g., longer window)



Salman et al, Lancet Neurology 2018. Decrease in likelihood of hematoma expansion over hours from symptom onset.

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PHENOM

Predicting Hematoma Expansion with Neuro-imaging and Biomarkers

PHENOM is a FASTEST ancillary study that will improve patient selection for acute ICH treatment with hemostatic therapy using two established predictors

- Diagnostic CT (neuroimaging), obtained and centrally stored for all diagnostic and follow-up CTs for patients in FASTEST
- Biomarkers of hemostasis, which are routinely obtained at some participating centers
  - Thromboelastography
  - Platelet Activity Testing

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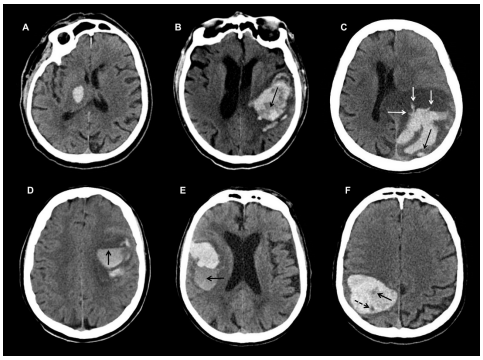
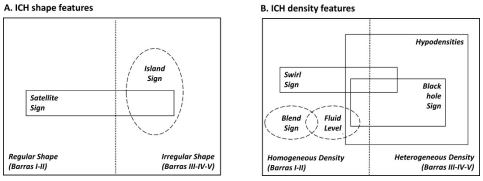
Standards for Detecting, Interpreting, and Reporting Noncontrast Computed Tomographic Markers of Intracerebral Hemorrhage Expansion





- A variety of CT appearances (black hole, blend, swirl) predict subsequent hematoma expansion
- CT appearances overlap
- Could be helpful to select patients for treatment
- (A) would be less likely to benefit than others
- Not part of FASTEST, but can be centrally adjudicated
- (CTAngios and "spot sign" not routinely measured)
- Excellent candidate for an artificial intelligence (AI) algorithm and automated detection (Dr. Luo)
- Prelim: Detecting pre-ICH anti-platelet medication

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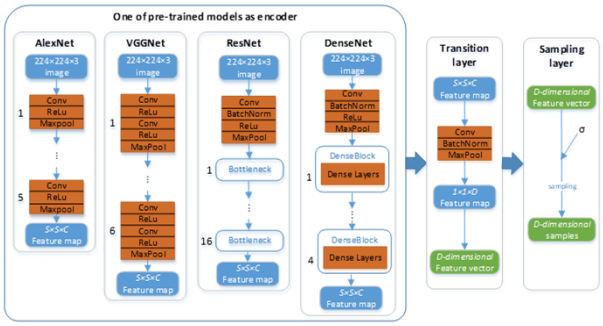
Annals of Neurology, Volume: 86, Issue: 4, Pages: 480-492, First published: 31 July 2019, DOI: (10.1002/ana.25563)

AI to Detect ICH

- AI algorithms have been reported to detect ICH on routine head CTs
- The use of AI to predict hematoma expansion in patients at high risk is innovative
- Morphology of hematoma on CT (e.g., blend sign) is a feasible target for deep learning techniques using neural networks

Figure: Deep Generative Classifier for CTs



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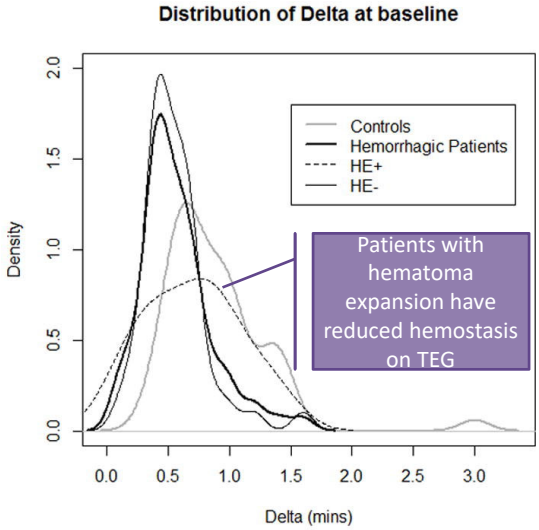
Thromboelastography Predicts Subsequent Hematoma Expansion

- Patients with hematoma expansion (HE) have less coagulation
- FXa inhibitor rivaroxaban leads to increased R, K, and delta.



Stroke. 2014 Mar; 45(3): 683–688.
Published online 2014 Jan 14. doi: 10.1161/STROKEAHA.113.003826

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Platelet Activity Predicts Subsequent Hematoma Expansion and Functional Outcomes

These patients were measured substantially later than in FASTEST

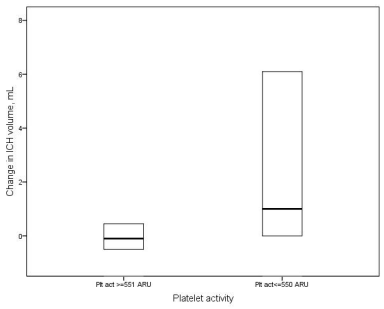
First CT within 6 hours:

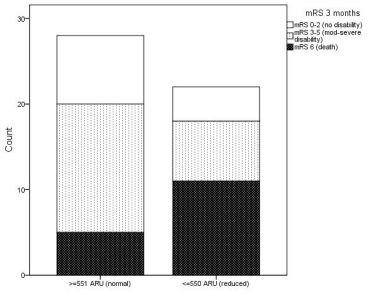
1.4 [0.05 to 8.45] vs. -0.2 [-0.5 to 0.4] mL, P=0.047

Similar results for presentation within 12h

Functional outcome at 3 months associated with less platelet activity (P=0.02)

Mortality at 3 months, 488 [453-612] vs. 633 [493-653] (P=0.009).





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Stroke 2009 Jul;40(7):2398-401. doi: 10.1161/STROKEAHA.109.550939

PHENOM Outcomes

Overall aim: Precise identify patients with acute ICH likely to benefit from acute hemostatic interventions

- **Primary Aim:** Determine the accuracy of an AI algorithm to identify patients most likely to have hematoma expansion from the diagnostic CT to a follow-up CT
- **Primary Outcome:** Hematoma expansion (change from baseline to follow-up), which will be the dependent variable for both the AI algorithm (**Aim 1**) and biomarkers of hemostasis (**Aim 2**).
- **Secondary Aims/Outcomes:**
  - Explore if an AI algorithm is predictive of the efficacy of F7 in FASTEST.
  - Predict hematoma expansion from biomarkers of hemostasis (platelet activity <= 550 aspirin reaction units; abnormal R, K, or alpha angle on thromboelastogram)
  - Explore if biomarkers of hemostasis predict efficacy of F7 in FASTEST
  - Explore if a combination of AI and biomarkers of hemostasis is superior to either alone for predicting hematoma expansion.

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Clinical, Scientific, and Public Health Impact

This study will improve clinical care by identifying the patients most likely to benefit from F7, a potent treatment that has thrombotic adverse effects.[4] Precise patient selection would allow treatment of the patients who are highly likely to have hematoma expansion and are likely to benefit from treatment.

This study will advance scientific knowledge

- AI could obviate the need to wait to obtain additional history (precisely documenting a last known normal), and could be available at off-hours (similar to automated selection algorithms for acute ischemic stroke).
- Biomarkers of hemostasis could improve our ability to identify subclinical coagulopathy (e.g., reduced platelet activity or delayed clot formation in the absence of bleeding visible on physical examination) and its effect on hematoma expansion.

This study will improve public health by advancing a treatment for the most deadly form of stroke, ICH. Precisely identifying the patients most likely to benefit from treatment would provide a compelling reason to improve ICH diagnosis, triage, and transport, as the advent of tPA and endovascular interventions have spurred the development of stroke centers.

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Additional Data Sources for Neuro-Imaging

Substantial data are available from FASTEST and other ICH trials

- Several completed studies have neuroimaging data, total N = 4805.
  - Enrolled from 2 – 8 h

Inclusion varies with aim (tentative):

- For efficacy of Factor VII, could derive in FAST trials and test in FASTEST
- For prediction of hematoma expansion without treatment, use placebo patients from FAST II, FAST III, TICH-2, and all from FAST-MAG.
- Will reconcile as appropriate (e.g., 2h window)

Trial	N
FAST II	399
FAST III	841
TICH – 2 • Within 2h • Within 4h	2,325 222 1,355
FAST-MAG	380
FASTEST	860

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Statistical Analysis for Biomarkers of Hemostasis

N=430 in Placebo for FASTEST

- Participating sites will upload biomarkers of hemostasis obtained as routine care
- We assumed the SD will be similar to the placebo group in the previous FAST trials of F7 in acute ICH (SD = 17.5). (Conservative)
- A sample size of 106 in each hemostasis group (i.e. 212 placebo patients) will have 80% power to detect a difference in means difference of 6 mL assuming that the standard deviation is 17.5 using a two group t-test with a 0.05 one-sided significance level.
- A sample size of 135 in each hemostasis group (270 placebo patients) would be needed for a 0.05 **two-sided** significance level.
- If the normality assumption is violated, we will perform these tests via Wilcoxon Rank Sum (Mann-Whitney) test.

- **Feasibility assessment needed to estimate likely N and associated cost.**

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Strengths/Limitations

Strengths

- Builds upon FASTEST, about to start recruitment
- Leverages neuroimaging data that will be centrally uploaded per routine
- Leverages biomarker data obtained routinely
  - No evidence this could unblind groups. Natural history is that patients with ICH have normalization of biomarkers of hemostasis with no treatment.

Limitations

- Limited to FASTEST patients and completed acute trials with a short time from symptom onset to diagnostic CT
- Could include registry studies with acute time to enrollment, e.g., PRESTO, Northwestern, and other registries
- Depend upon performance of biomarkers of hemostasis at participating sites

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PHENOM Impact

- Automated detection of patients most likely to have hematoma expansion could improve patient selection
  - A future algorithm could be made widely available and point of care, diffusing impact throughout the US and worldwide
- Patient selection with biomarkers of hemostasis could improve patient selection
- In future protocols, hemostatic treatment could be…
  - Administered to patients most likely to benefit, even within confines of narrow time window
  - Forgone for patients unlikely to benefit

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