Types of stroke vary in etiology

- Large-artery atherosclerosis: 38%
- Cardioembolism: 29%
- Lacunar: 36%
- Other: 8%
- Stroke of other determined etiology: 9%
- Stroke of undetermined etiology: 9%

TOAST classification of ischemic stroke¹
1) Large-artery atherosclerosis
2) Cardioembolism
3) Small-vessel occlusion (lacunar)
4) Stroke of other determined etiology
5) Stroke of undetermined etiology
High mortality with Large Vessel Occlusion

Despite stroke treatments like tPA and mechanical thrombectomy, why are there still bad outcomes in large vessel acute ischemic stroke?

Identical age, gender, co-morbidities, time from onset to revascularization, and success of revascularization

ARTERIAL COLLATERALS!
Extent of collaterogenesis varies greatly among mouse strains, and greatly influences infarct volume.

RABEP-2: Rab GTPase–Effector Binding Protein-2

Chromosome 7: Determinant of collateral extent-1 (Dce1) locus contains 28 protein-coding genes. RABEP-2: highest priority candidate of those 28 genes. SNP (rs33080487) substitutes an adenine for a guanine resulting in arginine to glutamine (R298Q) substitution and poor collaterals. Variants of Rabep2 alter collaterogenesis during embryogenesis, but have no effect on angiogenesis. Rabep2 deficiency alters endosome trafficking known to be involved in VEGF-A→VEGFR2 signaling required for collaterogenesis.

Geisinger MyCode is a voluntary, health system-wide exome sequencing program. Patients enrolled in MyCode can be informed of genetic predisposition that may influence the prognosis of potential stroke/cardiovascular disease.

How can this impact clinical practice?
Methods

Geisinger

- Reviewed acute ischemic stroke patients retrospectively from 10/2009 and 12/2016
  - All patients participated in the exome sequencing program (MyCode)
  - Initially had 1,728 patients from stroke registry and retained 94.2%.
- Used TOAST guidelines to classify the etiology of the ischemic event.
  - Used radiology studies, TEE, and hypercoagulable tests.
- Extracted risk factors from patient charts that could influence stroke.
- Determined the region of infarction through radiology reports and symptoms.
- Calculated NIH Stroke Scores, ASPECT scores, and Modified Rankin Scale.

Data collection from Geisinger MyCode
Results

Cardioembolic stroke is the most common etiology with greatest severity based on NIHSS
Part I: Large Vessel Occlusion (LVO) Prediction Scale

LVO Stroke

Patients with LVO stroke (cardioembolic, large-artery atherosclerosis, stroke of other/undetermined etiology) may meet criteria for mechanical thrombectomy.

Earlier detection of LVO stroke with elements of PMH

- Early identification of LVO stroke is then critical for transferring patients to comprehensive stroke centers for appropriate care.

- Other prediction scales (PASS, VAN, LAMS, RACE) have been produced to detect LVO stroke, but do not consider easily obtainable PMH information.

- Our study found that NIHSS, current smoking status, presence of intracranial atherosclerotic disease and extracranial atherosclerotic disease, as well as Type 2 Diabetes Mellitus (T2DM) are independently associated with anterior circulation LVO stroke.
History of current smoking, carotid stenosis, intracranial atherosclerosis, and T2DM associated with anterior circulation LVO stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>Coefficient</th>
<th>Prediction model</th>
<th>NIHSS model</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS (per point)</td>
<td>1.155 (1.098-1.217)</td>
<td>0.064</td>
<td>3</td>
<td>-2</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.064 (1.001-1.132)</td>
<td>0.060</td>
<td>2</td>
<td>-2</td>
</tr>
<tr>
<td>Carotid stenosis</td>
<td>1.000 (0.999-1.002)</td>
<td>0.000</td>
<td>1</td>
<td>-1</td>
</tr>
<tr>
<td>Intracranial atherosclerosis</td>
<td>1.000 (1.000-1.000)</td>
<td>0.000</td>
<td>1</td>
<td>-1</td>
</tr>
<tr>
<td>Diabetes mellitus type 2</td>
<td>1.000 (1.000-1.000)</td>
<td>0.000</td>
<td>1</td>
<td>-1</td>
</tr>
</tbody>
</table>

Prehospital score less accurately predicts LVO stroke than prediction model, but better than NIHSS alone.

Derivation cohort AUC - 0.780 (95% CI 0.760-0.804)
Validation cohort AUC - 0.770 (95% CI 0.745-0.795)

Example utilizations of the predictive model

The presence of T2DM, absence of extracranial carotid and intracranial atherosclerotic stenosis, and a low NIHSS score in non-smokers yielded a prediction score of ≤ 5, resulting in a negative predictive value of > 95%.

In contrast, a NIHSS of ≥ 10 in the smoking, non-diabetic stroke patients also suffering from extracranial carotid and intracranial atherosclerotic stenosis yielded a score of ≥ 24, resulting in a positive predictive value of > 87%.
Conclusions/Next Steps

- While atherosclerotic disease may not be known until cerebrovascular imaging has been obtained, PMH elements like T2DM and smoking history can be easily obtained.
- T2DM and smoking history are components that can supplement the NIHSS as a pre-hospital score.
- Patients identified with these PHM can be triaged as having LVO stroke earlier, and subsequently assessed for mechanical thrombectomy.
- Further investigation needed to confirm efficacy of the above components in detecting LVO stroke.

Part II

Matrix Gla protein polymorphism rs1800801 is associated with recurrence of ischemic stroke.
Matrix Gla Protein

- Expressed in a variety of tissues: Heart, lungs, kidneys, skin and arterial vessel walls.
- Chondrocytes, vascular smooth muscle cells, endothelial cells, and fibroblasts secrete these cells.
- Function is to inhibit calcification of vascular endothelium and bone.
- In mice, −/− Vitamin K dependent Matrix-Gla protein (GMP) leads to vascular calcifications and ultimately vascular rupture.

Matrix Gla Protein

Leon J. Schurgers, Jouni Uitto, and Chris P. Reutelingsperger, 2013

MGP SNP rs1800801 is associated with recurrent ischemic stroke within 1 year in a Spanish cohort, not North American.
- "G" allele was the high risk for recurrent ischemic stroke, not the "A" allele.
- GRECOS Score = (1.85 \times \text{Age} \geq 71) + (2 \times \text{inclusion TIA}) + (3.6 \times \text{AMI/ANGINA}) + (2.26 \times \text{rs1800801(G allele)})
What about the Northeast/Central Pennsylvania region?

Variables included in the predictive model

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Genotype</th>
<th>Recurrent strokes</th>
<th>No recurrent strokes</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1000801</td>
<td>GG (n = 422)</td>
<td>22/425 (5.2%)</td>
<td>404/425 (94.8%)</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>GA (n = 361)</td>
<td>39/558 (7.0%)</td>
<td>407/558 (92.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AA (n = 348)</td>
<td>18/410 (4.3%)</td>
<td>322/410 (95.7%)</td>
<td></td>
</tr>
</tbody>
</table>

Subgroup analysis between AA Vs. GA genotypes suggests the AA genotype is at higher risk for recurrent ischemic stroke within 1 year (OR = 2.062, 95% CI 1.013 – 3.937, p = 0.029).

AA genotype has the highest risk
Improved model with Gla SNP, but not significant

With SNP rs1800801: AUC of 0.744 (95% CI 0.717 – 0.770)
Without SNP rs1800801: AUC of 0.740 (95% CI 0.712 – 0.766)

How do our results compare to others?

- The “A” allele is high risk for recurrence Vs. “G” allele in GRECOS
- GRECOS did not find an association between the Gla SNP and recurrence of ischemic stroke in a North American population.
- AA genotype was associated with increased ischemic atherothrombotic stroke in Ukrainian females.  
- In a meta-analysis by Sheng et al., the A allele in the rs1800801 SNP is associated with vascular calcification and atherosclerotic disease in Caucasians, but not Asians.

Take home message/Next Steps

- “A” allele in rs1800801 SNP is significantly associated with recurrence of ischemic stroke within 1 year.
- Inclusion of rs1800801 SNP into predictive models for recurrent ischemic stroke within 1 year is marginally beneficial.
- We will need to expand our participant racial demographics to see if the “A” allele is high risk in non-caucasian populations.
- Conduct larger association studies with 100,000+ patients in order to compare multiple SNPs.
  - Our study with 1,700 patients is not large enough to conduct multiple comparisons.
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References