

# Genetically-Mediated Serious Skin Rash

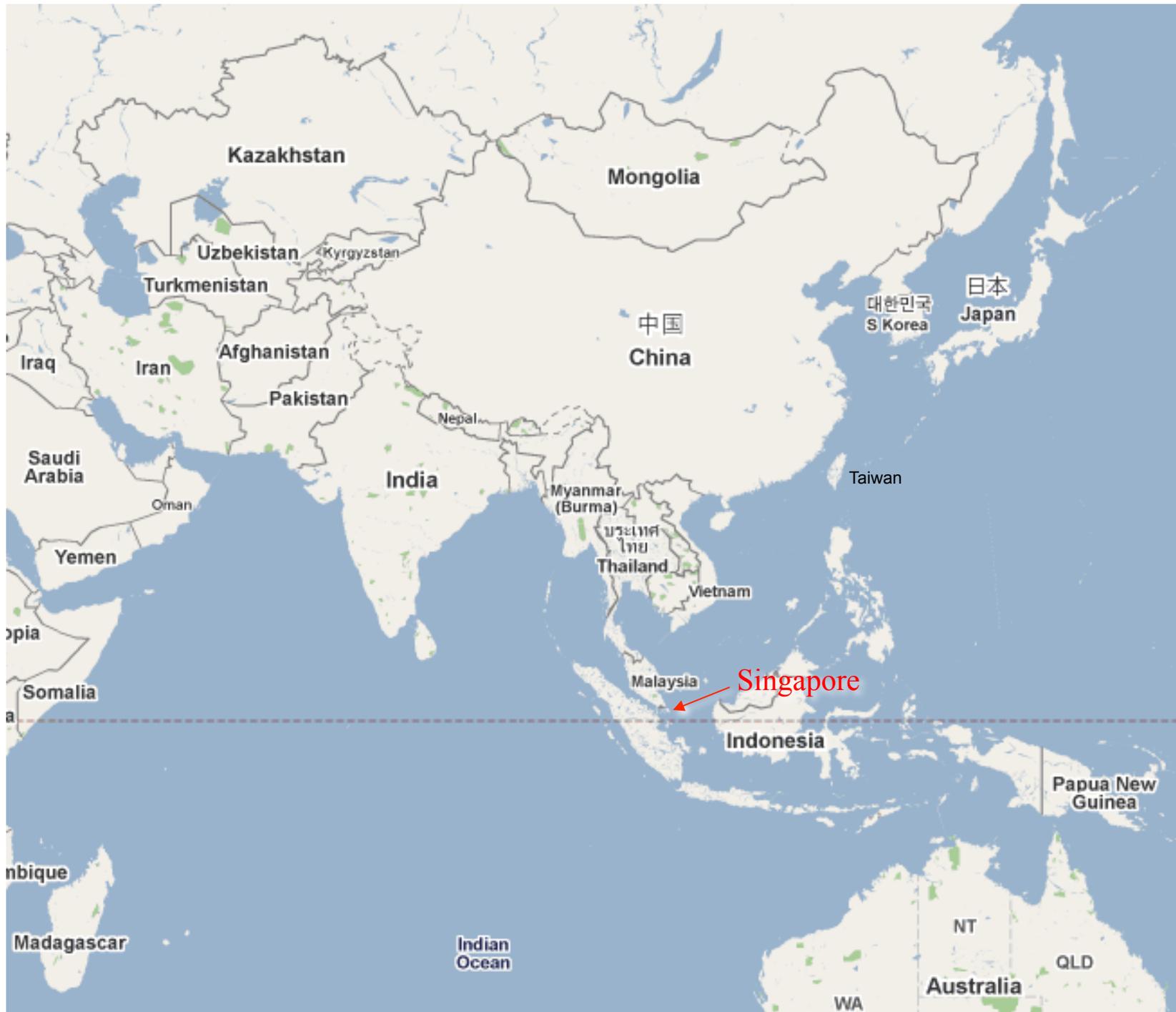
*Singapore Health Sciences Authority Experience*

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**For the HSA Pharmacogenetics Team**

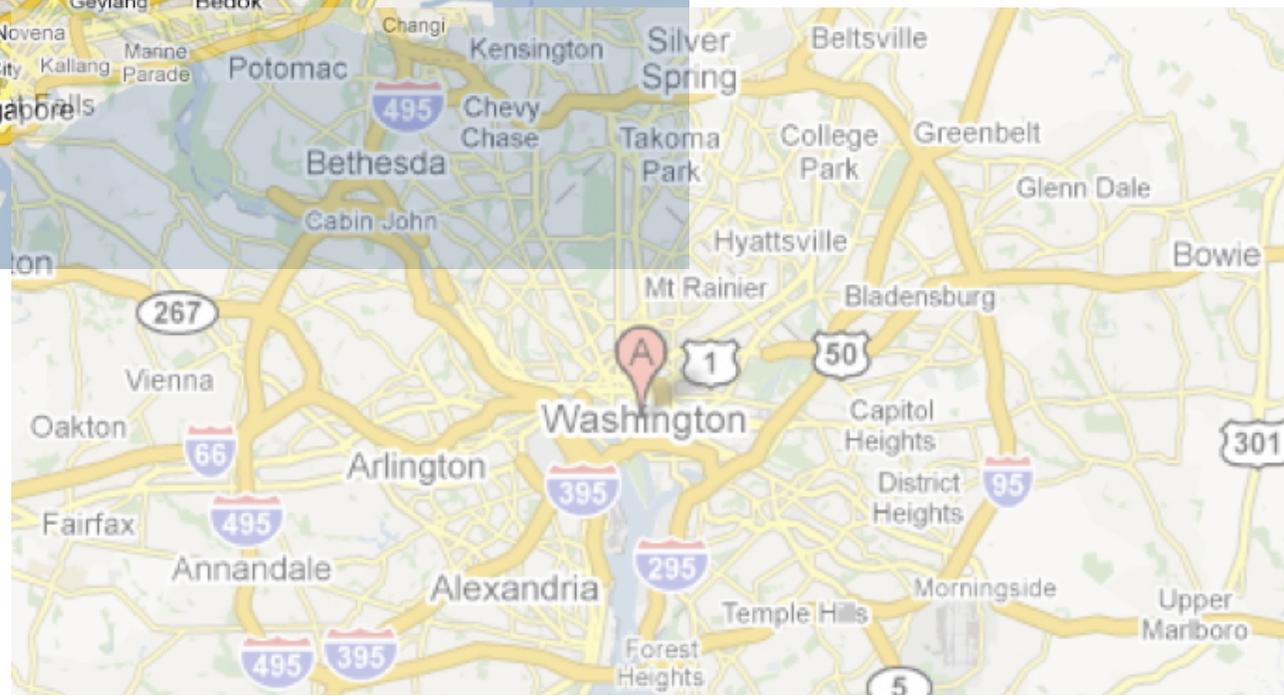
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# Singapore and Washington DC

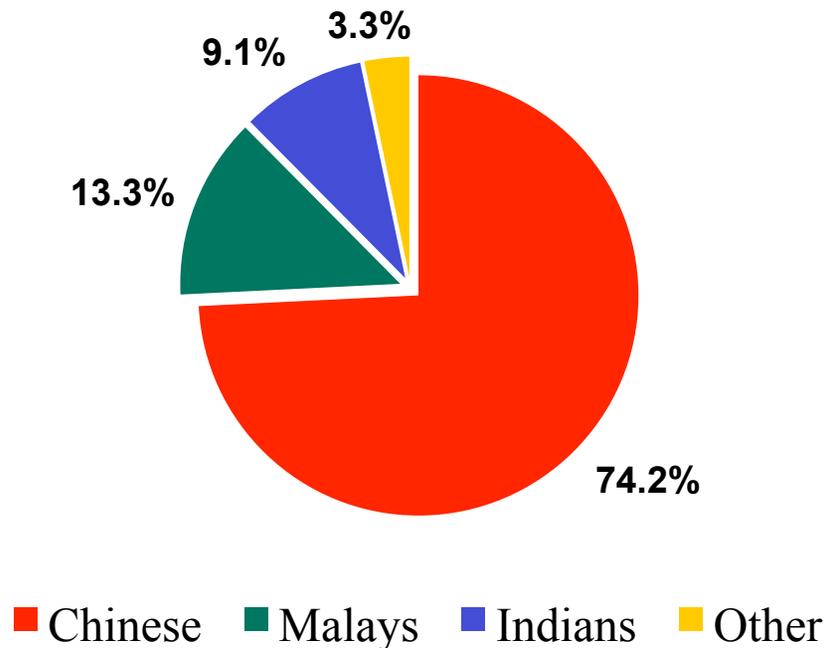


Land Area - 277 sq mi.



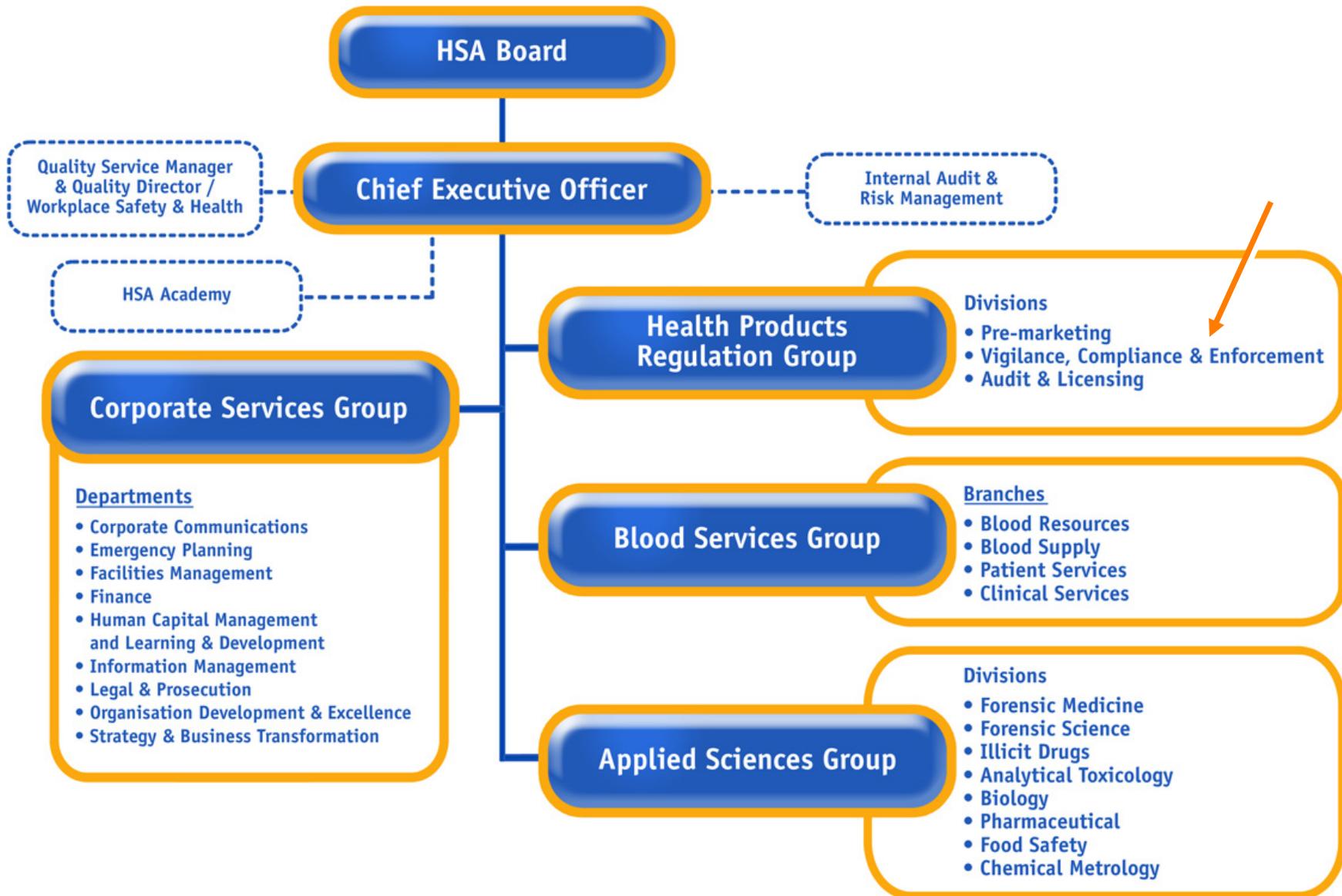
# Singapore Demographics

- Population – 5.47 million (June 2014)
  - 3.87 million citizens and permanent residents
  - 1.6 million foreign workers and other non-residents
- Ethnic composition of citizens & PRs



health care system

# Health Sciences Authority



## Top 10 System Organ Class/ Body system disorder (1/1/2014 to 12/31/2014)

Top	System organ class	No. of reports	% of total no. of ADR terms quoted
1	Skin And Appendages Disorders	12,228	52.3
2	Body As A Whole - General Disorders	4,192	17.9
3	Respiratory System Disorders	1,459	6.2
4	Centr & Periph Nervous System Disorders	1,220	5.2
5	Gastrointestinal System Disorders	1,213	5.2
6	Urinary System Disorders	825	3.5
7	Musculo-Skeletal System Disorders	312	1.3
8	Vascular (Extracardiac) Disorders	310	1.3
9	Heart rate and Rhythm Disorders	252	1.1
10	Metabolic And Nutritional Disorders	219	0.9

- **Launched in 2008**
- **Objectives**
  - Develop regulatory expertise in pharmacogenetics
  - Establish collaborative network with healthcare professionals and research institutions
  - Build infrastructure to collect & store DNA samples and clinical data of patients experiencing serious ADRs and drug tolerant controls
- **Regulatory Outcome**
  - Update drug package inserts
  - Make recommendations to healthcare professionals based on local data

# Drug Class (Oct 2014)

Drug Class	Number of SJS/TEN Cases
Antiepileptics (CBZ, phenytoin, lamotrigine)	20* (* 1 case of phenytoin / piperacillin & tazobactam)
Antibiotics	16
Allopurinol	7
Others (eg. Paracetamol, NSAIDs, COX-2 inhibitors)	16
<b>Total</b>	<b>59</b>

# CBZ - HLA Genotyping in S'pore

As of 27 Feb 2013

	CBZ	Cases (n=13)	Controls (n=26)	Odds Ratio (OR)
<b>HLA-B*1502</b>	Positive	13	3	<b>181</b> (8.7 to 3785) $p=6.9 \times 10^{-8}$
	Negative	0	23	

**Sensitivity=**  
**13/13 = 100%**

**Specificity=**  
**23/26 = 88.5%**

- Data from HSA's study supports strong association between CBZ-induced SJS/ TEN and HLA-B\*1502

(The Pharmacogenomics Journal 2014; 14: 316-321)

# CBZ Cost-Effectiveness Study

To Genotype or not to Genotype?

- **Population of interest:**
  - Newly diagnosed adult epilepsy patients in Singapore for whom CBZ/ Phenytoin (PHT) is considered appropriate treatment
- **3 strategies were compared:**
  - Status quo: no genotyping and prescribe CBZ/PHT to all new patients as first line treatment
  - Genotype and prescribe CBZ/PHT to those who test negative and valproate for those who test positive
  - No genotyping and prescribe valproate to all patients

# Prevalence of HLA-B\*1502

	Frequency of Carriers
<b>Singapore Chinese</b> <sup>1, 2</sup>	1 in 8
<b>Singapore Malays</b> <sup>1, 2</sup>	1 in 5
<b>Singapore Indians</b> <sup>1</sup>	1 in 25
<b>Caucasians</b> <sup>1</sup>	1 in 500
<b>Japanese</b> <sup>1</sup>	≤1 in 1000

<sup>1</sup> Allele frequencies.net

<sup>2</sup> Singapore Immunology Network

# CBZ Cost-Effectiveness Study

Population	ICER (\$S/QALY) when genotyping cost at \$205
<b>Singapore population (ethnicity weighted)</b>	<b>S\$31,120</b>
Singapore Chinese	S\$38,620
Singapore Malays	S\$ 8,430
Singapore Indians	S\$123,000

A commonly accepted cost-effectiveness threshold:  
USD\$50,000/QALY ~SGD65,000/QALY

Neurology 2012; 79: 1259-1267

## End 2012

- Analysed findings from study and consulted with neurologists, psychiatrists, dentists, primary care drs, dermatologists

## 2013

- MOH and HSA jointly convened an expert panel to formulate local recommendations for HLA-B\*1502 testing
- Centralised HLA-B\*1502 testing laboratory
- Dear Healthcare Professional Letter, jointly issued by MOH and HSA
- Strengthened package inserts of carbamazepine-containing medicines
- 75% subsidy for genotyping test for low-income patients

# Final Recommendations

- Genotyping for the HLA-B\*1502 allele prior to the initiation of CBZ in new patients of Asian ancestry is considered the **standard of care** by MOH
- The package insert of CBZ strengthened to **highly recommend** the testing of this genetic variant in this group of patients
- Genotyping is **not required** in patients who have been taking CBZ for  $\geq 3$  months without adverse reactions

# Final Recommendations

- CBZ should not be prescribed before knowing HLA-B\*1502 test results
- Treatment alternatives (excluding phenytoin) are recommended for patients who have tested positive for HLA-B\*1502
- Preliminary data have shown a suspected association between this genetic marker and phenytoin-induced SJS/TEN, although the effect size is not as large

# Final Recommendations

- Some Asian patients positive for HLA-B\*1502 and treated with CBZ will not develop SJS/TEN and patients negative for HLA-B\*1502 can still develop SJS/TEN
- The role of other factors in the development of SJS/TEN such as drug dose, compliance, concomitant medications, co-morbidities and level of dermatologic monitoring have not been studied
- Genetic testing should not substitute for appropriate clinical vigilance and patient management

# CBZ-induced SJS Cases

- 2003 – 2012: 15 cases on avg. per year
- 2013 before making testing std of care: 4 cases
- After making testing std of care: 0 cases

# Learning Points

- Importance of engaging multiple stakeholders, especially clinicians, pre- and post- “standard of care” letter
- Importance of lowering cost and turnaround time of genotyping test
- C/E analysis to inform decisions on subsidy for genotyping test

# Acknowledgements

- All participating clinicians & coordinators from Sg Gen Hosp, Nat'l Univ Hosp, Changi Gen Hosp
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- Duke-NUS Graduate Medical School
- Singapore Biobank/ NUHS Tissue Repository
- Pharmacogenetics Expert Panel
- Pharmacogenetics Team at HSA

