Success Stories of Local Cost Effectiveness Studies

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Outline

- How do we measure success
- Examples
- Concluding comments

How do we measure success

- Partnerships
  - With MOH/HSA, Students, Clinicians
- Grants and contracts
- Publications
  - We have lots but that is only one measure of success (and not a great one)
- Press coverage
  - Nice but not a great measure either
- Impact
  - Evidence that our studies are making a difference
  - Policy changes (or lack there of)

Examples

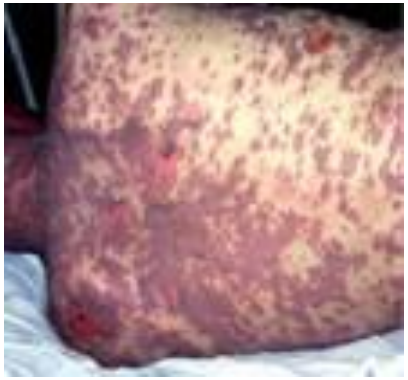
1. Cost-effectiveness of HLA-B*1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore, Dong, D., Sung, C., & Finkelstein, E.A. (2012). Neurology, 79(12),1259-1267.
2. Cost-effectiveness analysis of genotyping for HLA-B*5801 and an enhanced safety program in gout patients starting allopurinol in Singapore, Dong D., Tan-Koi W.C., Gim G.T., Finkelstein E.A., Sung C. (2015). Pharmacogenomics. 2015 Nov;16(16):1781-93.
3. Incremental cost-effectiveness analysis of gestational diabetes mellitus screening strategies in Singapore, Chen, P.Y., Finkelstein, E.A., Ng, M.J., Yap, F., Yeo, G.S.H., Rajadurai, V.S., Chong, Y.S., et al. (2015). Asia-Pacific Journal of Public Health. 2015 Oct 28.

Example 1

Cost-effectiveness of HLA-B*1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore, Dong, D., Sung, C., & Finkelstein, E.A. (2012). Neurology, 79(12),1259-1267.

Cost-effectiveness of HLA-B*1502 testing for newly diagnosed epilepsy patients

- **Epilepsy**
  - A common neurological disorder (incidence~ 0.05% per year)
- **Treatment**
  - Older Anti-epileptics
    - **Carbamazepine (CBZ), phenytoin (PHT)** – fairly inexpensive (cost several hundred dollars per year) and generally effective
    - Valproate (VPA) – similar effectiveness but more expensive (2x)
  - Newer Anti-epileptics
    - Topiramate (TPM), Levetiracetam (LEV), lamotrigine (LTG), and others – at least as effective and much more expensive (up to 100x)
- **CBZ and PHT may cause potentially life-threatening side effects SJS and TEN**



Cost-effectiveness of HLA-B*1502 testing for newly diagnosed epilepsy patients

- HLA-B*1502 has been identified as the genetic risk factor for SJS/TEN (Odds Ratio=1,357) and is common among some Asian groups
- This finding raises the question of whether to genotype for HLA-B*1502 in Singapore prior to prescribing CBZ
- With a Duke-NUS PhD student and collaborators from HSA, we conducted a cost-effectiveness analysis to evaluate the benefits and costs testing for newly diagnosed epilepsy patients.

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HSA Health Sciences Authority

Research Question: Should HLA-B*1502 testing be used routinely in clinical care for newly diagnosed epilepsy patients?

Cost-effectiveness of HLA-B*1502 testing for newly diagnosed epilepsy patients

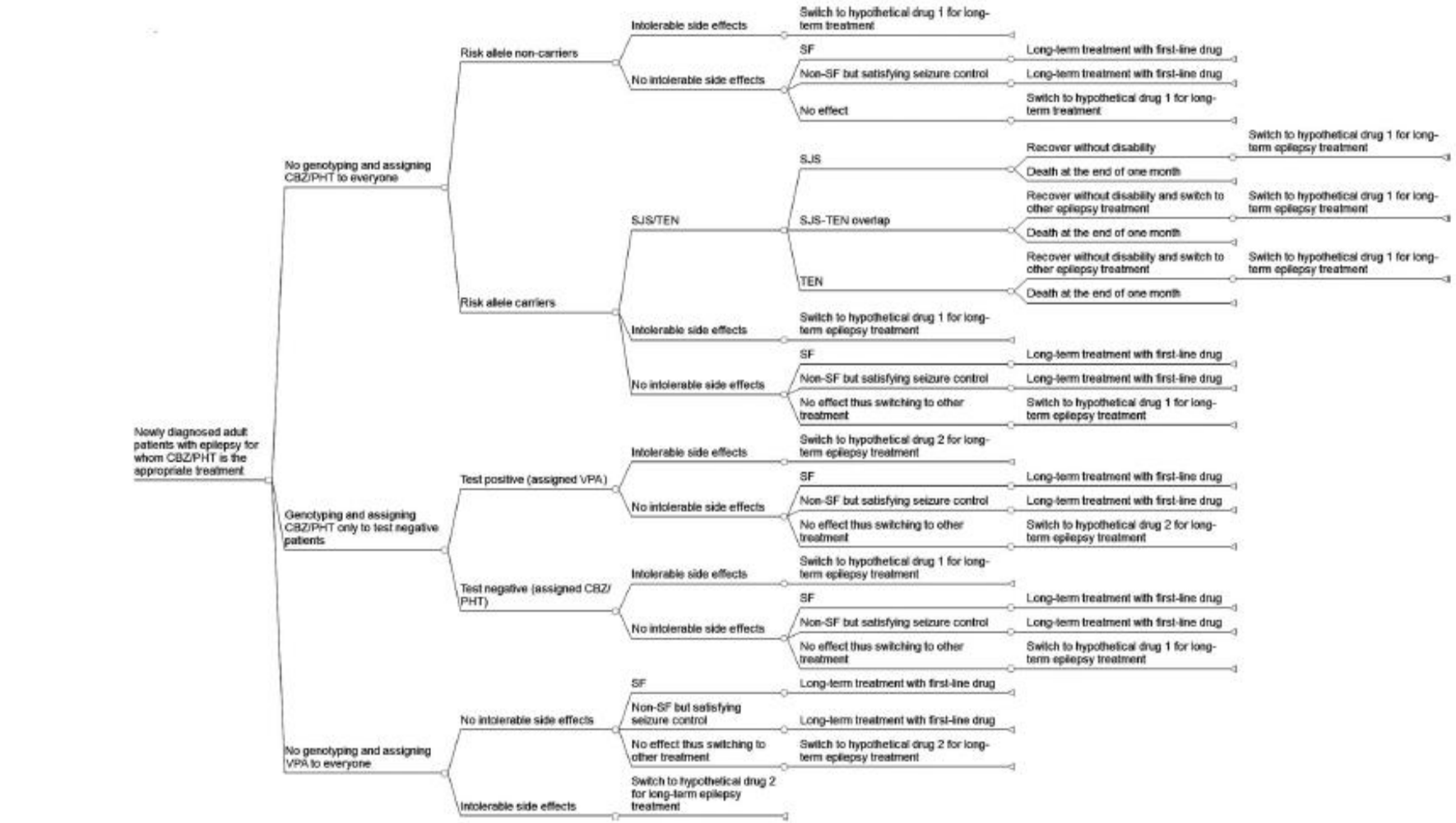
Pros

- Reduce mortality and morbidity resulting from SJS/TEN
- Avoid high medical cost for SJS/TEN treatment

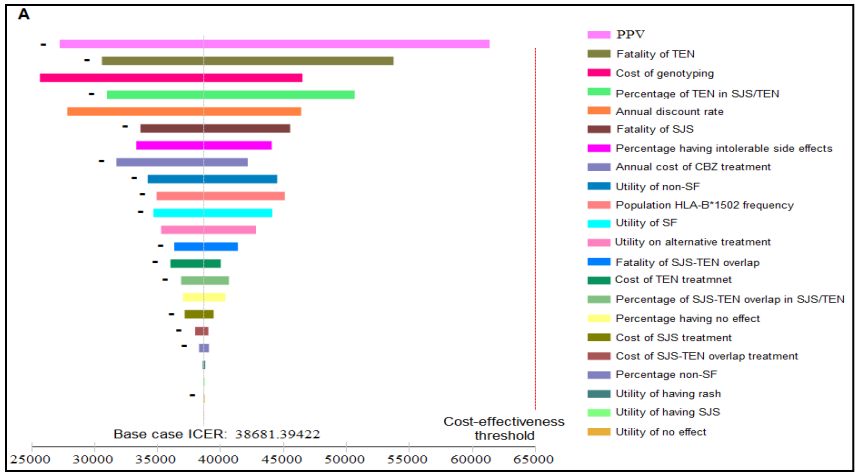
Cons

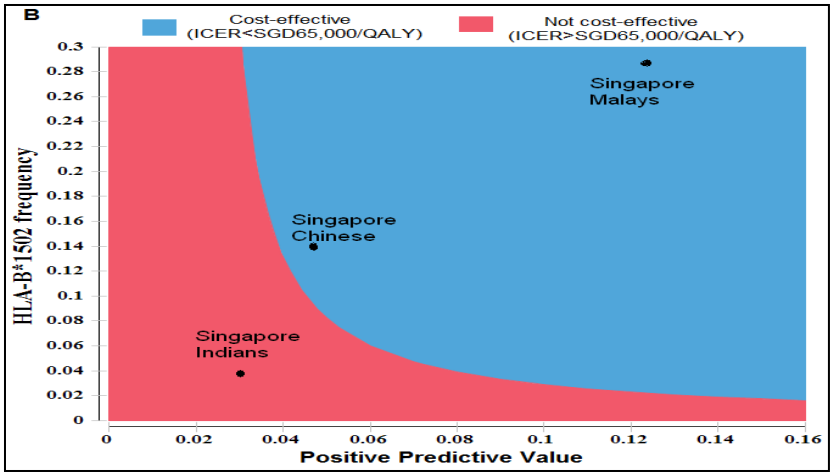
- Genotyping costs $ (SGD205)
- Expensive alternative drug (>2x cost of CBZ) elevates long-term treatment cost
- Low population HLA-B*1502 frequency (14.87%) and low PPV(5.96%) suggests payoff is low

Decision Tree



Cost-effectiveness of HLA-B*1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore





- We found HLA-B*1502 testing to be highly cost-effective for Singapore Chinese and Malay patients (but not Indians) based on established guidelines for cost effectiveness.

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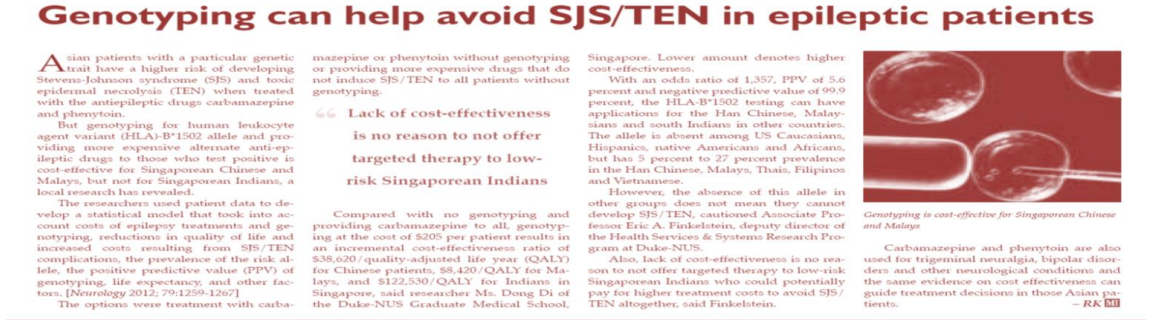
Impact

- In April 2013, MOH made an announcement that HLA-B*1502 genotyping prior to the initiation of carbamazepine therapy in new patients of Asian ancestry was the new standard of care.
- HSA, together with MOH, issued a Dear Healthcare Professional Letter to communicate the new recommendations.
- 75% of the test cost subsidized for low-income patients
- Several hospitals now offer the test with a turnover time of 2-4 working days
- No SJS adverse event reports related to carbamazepine have been received since the letter was issues.



Genotyping can help avoid SJS/TEN in epileptic patients

Asian patients with a particular genetic trait have a higher risk of developing Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) when treated with the antiepileptic drugs carbamazepine and phenytoin.

But genotyping for human leukocyte agent variant (HLA)-B*1502 allele and providing more expensive alternate anti-epileptic drugs to those who test positive is cost-effective for Singaporean Chinese and Malays, but not for Singaporean Indians, a local research has revealed.

The researchers used patient data to develop a statistical model that took into account costs of epilepsy treatments and genotyping, reductions in quality of life and increased costs resulting from SJS/TEN complications, the prevalence of the risk allele, the positive predictive value (PPV) of genotyping, life expectancy, and other factors. [*Neurology* 2012; 79:1259-1267]

The options were treatment with carbamazepine or phenytoin without genotyping or providing more expensive drugs that do not induce SJS/TEN to all patients without genotyping.

> Lack of cost-effectiveness is no reason to not offer targeted therapy to low-risk Singaporean Indians

Compared with no genotyping and providing carbamazepine to all, genotyping at the cost of $205 per patient results in an incremental cost-effectiveness ratio of $38,620/quality-adjusted life year (QALY) for Chinese patients, $8,420/QALY for Malays, and $122,530/QALY for Indians in Singapore, said researcher Ms. Dong Di of the Duke-NUS Graduate Medical School, Singapore. Lower amount denotes higher cost-effectiveness.

With an odds ratio of 1,357, PPV of 5.6 percent and negative predictive value of 99.9 percent, the HLA-B*1502 testing can have applications for the Han Chinese, Malaysians and south Indians in other countries. The allele is absent among US Caucasians, Hispanics, native Americans and Africans, but has 5 percent to 27 percent prevalence in the Han Chinese, Malays, Thais, Filipinos and Vietnamese.

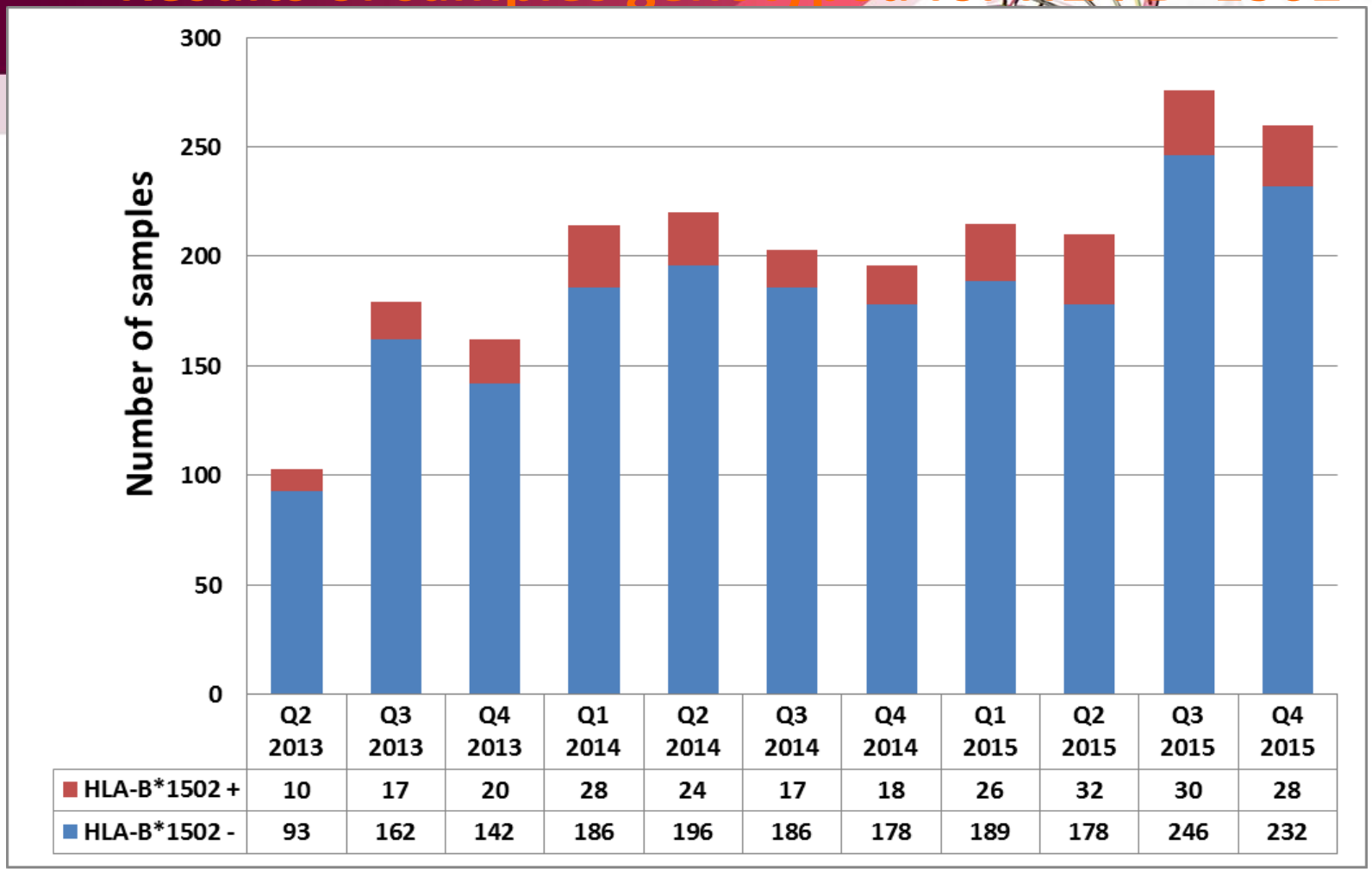
However, the absence of this allele in other groups does not mean they cannot develop SJS/TEN, cautioned Associate Professor Eric A. Finkelstein, deputy director of the Health Services & Systems Research Program at Duke-NUS.

Also, lack of cost-effectiveness is no reason to not offer targeted therapy to low-risk Singaporean Indians who could potentially pay for higher treatment costs to avoid SJS/TEN altogether, said Finkelstein.

Genotyping is cost-effective for Singaporean Chinese and Malays

Carbamazepine and phenytoin are also used for trigeminal neuralgia, bipolar disorders and other neurological conditions and the same evidence on cost effectiveness can guide treatment decisions in those Asian patients. – RK MT

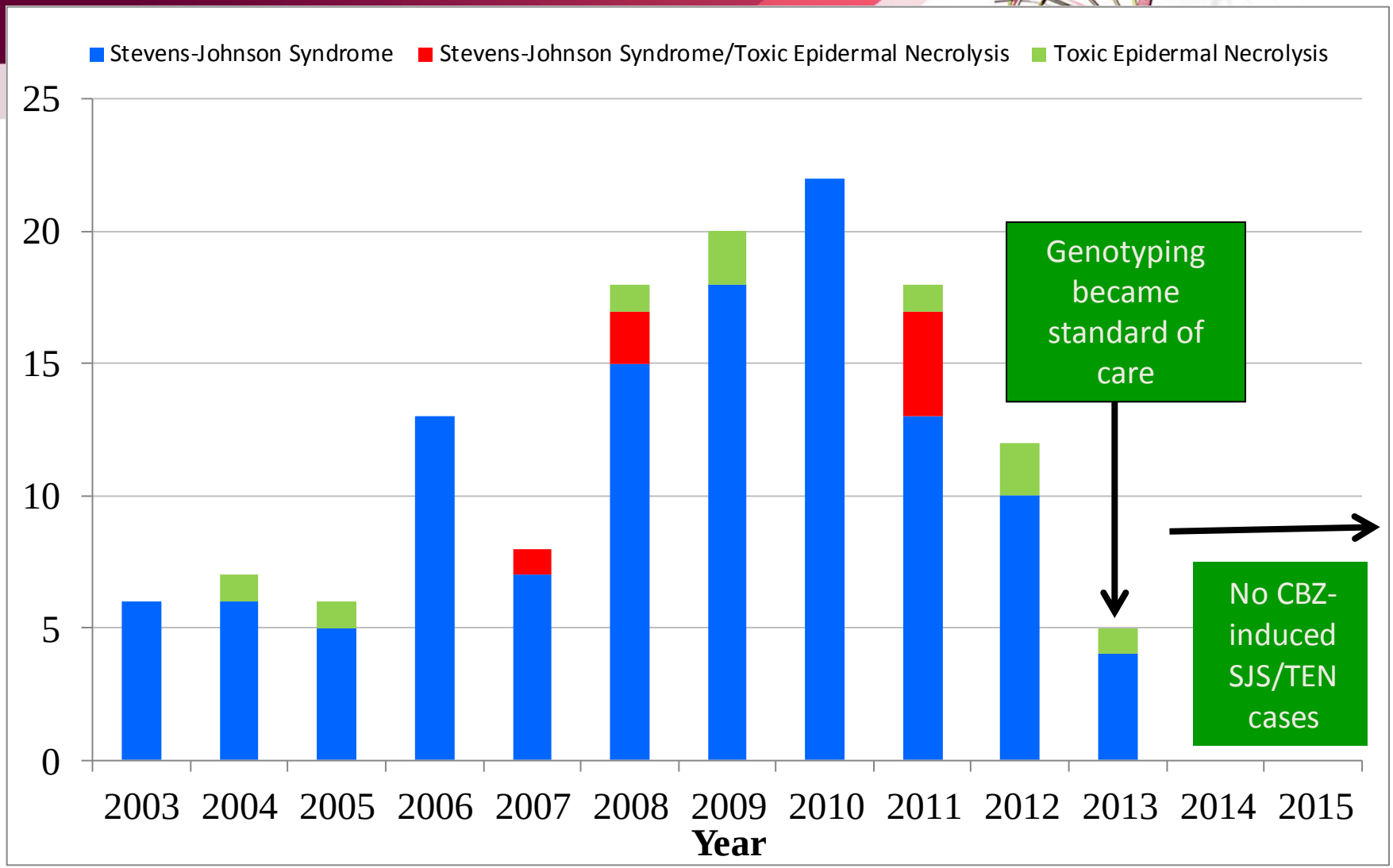
Results of samples genotyped for HLA-*B**1502



	Q2 2013	Q3 2013	Q4 2013	Q1 2014	Q2 2014	Q3 2014	Q4 2014	Q1 2015	Q2 2015	Q3 2015	Q4 2015
HLA-B*1502 +	10	17	20	28	24	17	18	26	32	30	28
HLA-B*1502 -	93	162	142	186	196	186	178	189	178	246	232

As of 31 Dec 2015, 2244 samples have been genotyped, of which **11.2% tested positive** for HLA-B*1502

CBZ-induced SJS/TEN cases

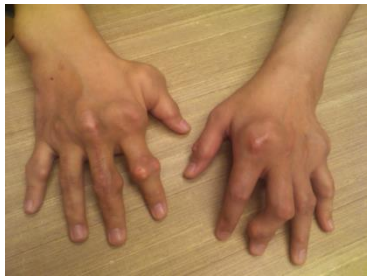
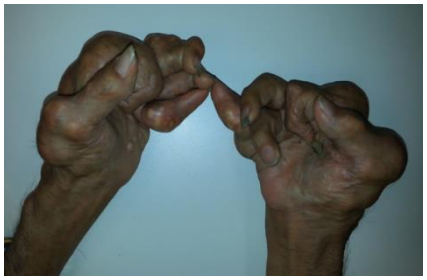
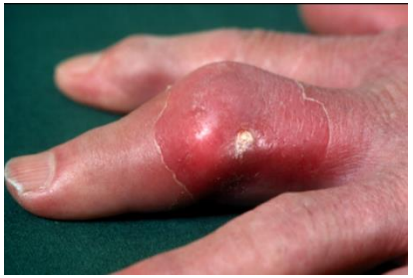
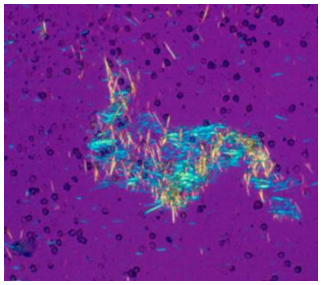


Example 2

Cost-effectiveness analysis of genotyping for HLA-B*5801 and an enhanced safety program in gout patients starting allopurinol in Singapore, Dong D., Tan-Koi W.C., Gim G.T., Finkelstein E.A., Sung C. (2015). Pharmacogenomics. 2015 Nov;16(16):1781-93.

Cost-effectiveness of HLA-B*5801 testing for chronic gout patients

- **Gout is the most common inflammatory arthritis among men.**
  - Prevalence: 2.6% - 8% (Lawrence, 2008)
  - Deposition of uric acid crystals
  - Severe pain, joint damage, and loss of physical function

- **Allopurinol is the first-line urate lowering therapy (ULT) for chronic gout management.**
  - Effective and relatively inexpensive
  - Can also cause SJS/TEN

Cost-effectiveness of HLA-B*5801 testing for chronic gout patients

- Though genetic association between HLA-B*5801 allele and allopurinol-induced SJS has been demonstrated, the predictive power of HLA-B*5801 test in Singapore population is low, and the alternative gout treatments may be inferior in efficacy and are more costly.
- With a Duke-NUS PhD student and collaborators from HSA, NUH, and NUS, we conducted a cost-effectiveness analysis to evaluate the benefit and cost of applying HLA-B*5801 testing and/or a safety monitoring program among gout patients initiating allopurinol

Research Question: Should HLA-B*5801 testing and/or safety monitoring be used routinely in clinical care for newly diagnosed gout patients?

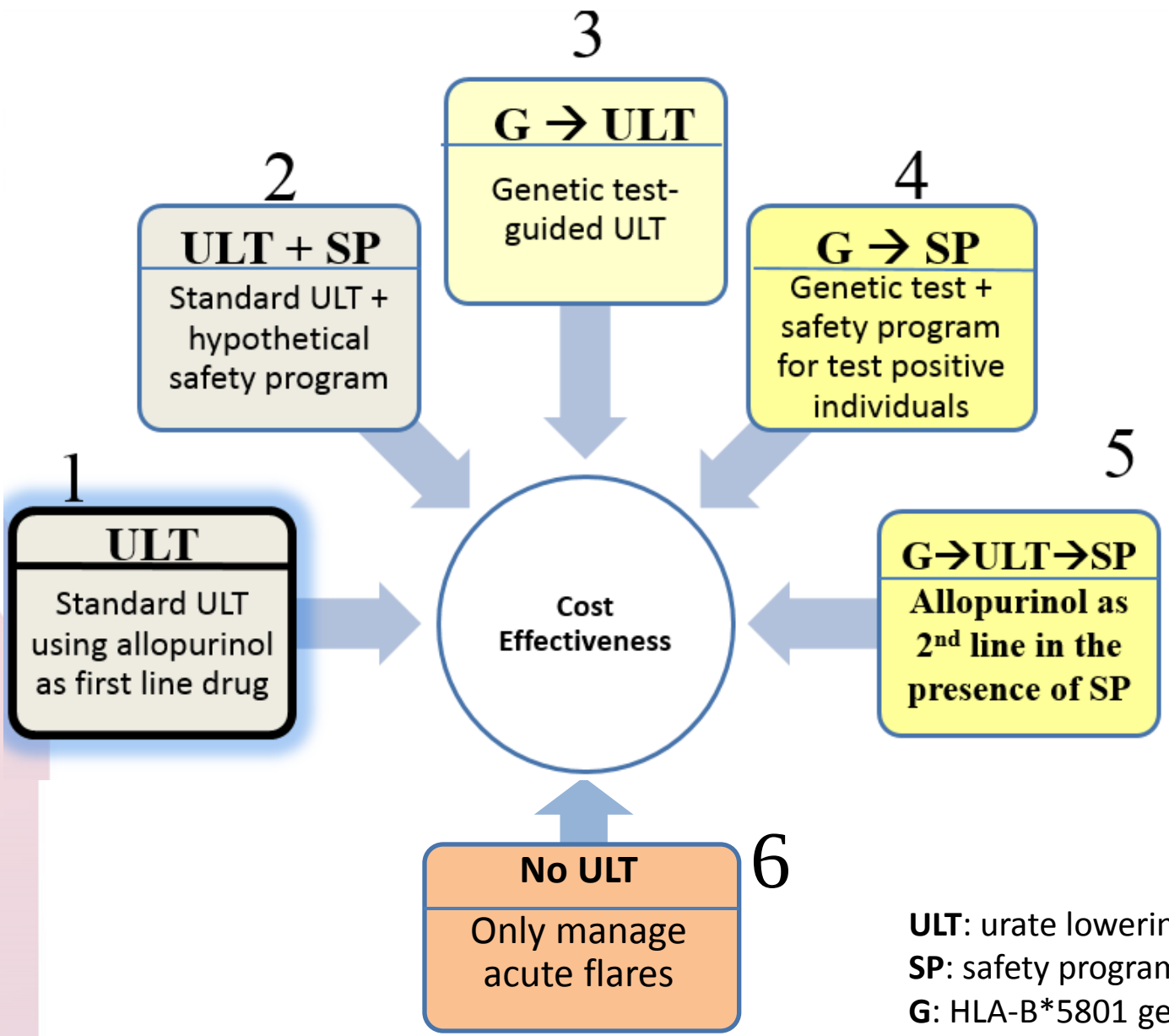
Alternative to genetic testing?

- **Safety monitoring**

- Early withdrawal of allopurinol
  - better prognosis
  - lower mortality of SJS/TEN

    odds ratio= 0.69 for each day of early withdrawal (Garcia-Doval,2000)
  - No structured safety program documented

AIM: Compare the 30-year cost-effectiveness of 6 strategies of chronic gout management from the Singapore health system perspective



ULT: urate lowering therapy
SP: safety program
G: HLA-B*5801 genetic testing

Results

1. **Allopurinol treatment, without genetic testing, despite the risk of inducing life-threatening SJS/TEN, is the preferred strategy for Singapore from C/E perspective.**

2. **Genetic testing-guided drug selection is not preferred from cost-effectiveness perspective.**

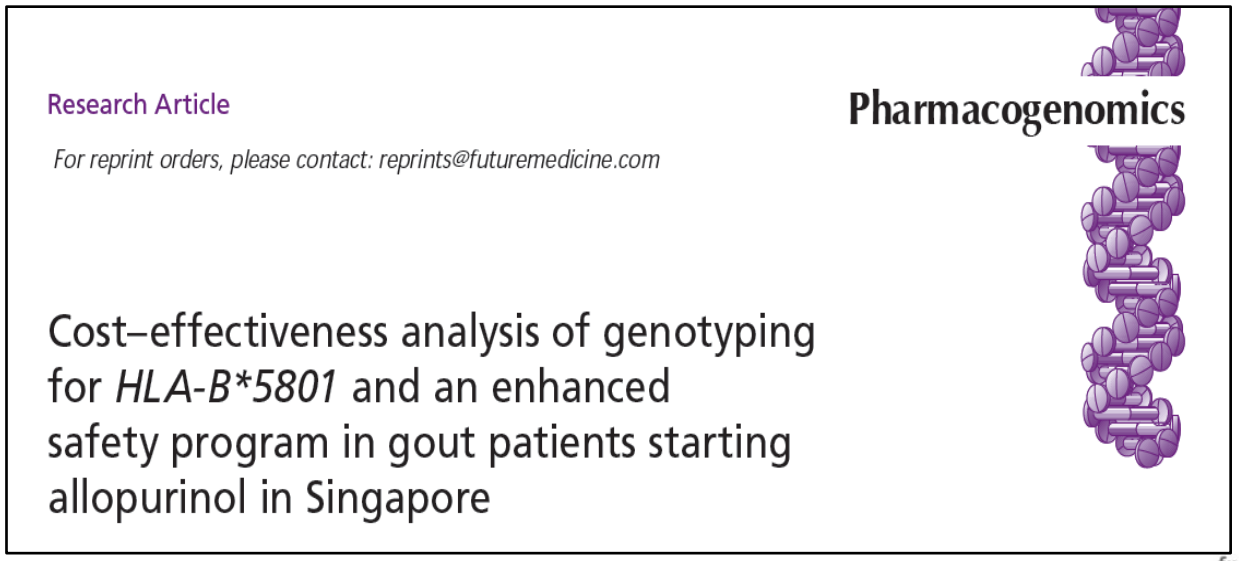
   - Compared to allopurinol, it has higher cost, but paradoxically gives lower QALYs.
   - Alternatives to allopurinol are limited. If avoiding allopurinol, some test positive patients will receive no urate lowering therapy, and have poor gout management in the long term.
   - At the **population level**, the long term risks of forgoing allopurinol treatment (in 18.5% of population) is higher than the benefits from preventing SJS (in 0.2% of population).

Results

3. **Allopurinol+ Safety program can be cost-effective compared with standard allopurinol if:**
   - Safety program can reduce SJS/TEN ***mortality*** by 47%, or
   - **Cost** of safety program drops below $40, or
   - **In high risk groups of patients** (where the incidence of allopurinol-induced SJS/TEN is higher than 0.32%)
4. **Allopurinol as 2nd line for test positive patients who fail probenecid, in the presence of safety program**
   - **Currently not cost-effective**
   - **Will be cost-effective** when testing **costs** less than **$90**.

Impact

- The Health Science Authority (HSA) has plans to issue a Dear Health Care Professional Letter (DHCPL) to provide advice regarding genotyping prior to use of allopurinol in Singapore.
- **Despite lack of cost-effectiveness,** HSA identified a lab that will do HLA-B*580 testing, in part, because we show (in another study) that some people are willing to pay a high price for piece of mind



Comparing the two studies

- Treatments guided by genetic testing that can predict ADRs are not always cost-effective, even though ADR risk is reduced.
- Testing is unlikely to be cost-effective when:
  - Positive predictive power is low
  - Alternative drugs are limited
  - Alternative drugs are inferior in efficacy, or very expensive
- In general this is my take-away for precision medicines
  - Sometimes cost effectives, sometimes not

Example 3

Incremental cost-effectiveness analysis of gestational diabetes mellitus screening strategies in Singapore, Chen, P.Y., Finkelstein, E.A., Ng, M.J., Yap, F., Yeo, G.S.H., Rajadurai, V.S., Chong, Y.S., et al. (2015). Asia-Pacific Journal of Public Health. 2015 Oct 28.

Incremental cost-effectiveness analysis of gestational diabetes mellitus (GDM) screening strategies in Singapore

KK Women's and Children's Hospital
SingHealth

- Prevalence of GDM in Singapore has increased due to higher rates of obesity and advancing maternal age
- GDM is associated with higher rates of maternal and fetal morbidity.
- Singapore does not routinely screen for GDM
- In collaboration with and a third year Duke-NUS medical student, KK Hospital and members of the Gusto (birth cohort) study team we conducted a cost-effectiveness analysis of gestational diabetes screening strategies in Singapore.

Research Question: Is it cost-effective to universally screen all pregnant women for GDM?

- We show DGM screening to be highly cost effective

Impact

- Practice change: KKH & SGH will be offering GDM screening to all pregnant patients at 24 to 28 weeks gestation from 1 January 2016 as pilot project.

| WEDNESDAY, NOVEMBER 18, 2015 | THE STRAITS TIMES |

Diabetes screening for expectant mums

KKH, SGH to offer service for gestational diabetes from Jan as part of a 6-month trial

Seow Bei Yi

From January next year, all expectant mothers at KK Women's and Children's Hospital (KKH) and Singapore General Hospital will be offered screenings for gestational diabetes – a temporary condition that occurs during pregnancy.

On average, KKH sees around 12,000 births in a year.

As part of a six-month trial, the screenings will be offered to women at 24 to 28 weeks of pregnancy, when symptoms tend to appear.

KKH currently offers screenings mainly to pregnant women identified as high-risk. They include those with a high body mass index, first-degree relatives with diabetes, or those aged 35 and above.

But according to a study published by KKH and the Duke-NUS Graduate Medical School last month, the current approach of targeted screening fails to identify more than 60 per cent of mothers with mild diabetes.

The new trial aims to enable earlier detection and intervention.

Around one in 10 pregnant women develops gestational diabetes, said Professor Tan Kok Hian, head of perinatal audit and epidemiology unit at KKH.

This is based on data from a cohort of some 924 pregnant women who took part in the long-term study, Growing Up in Singapore Towards Healthy Outcomes. All of them were tested – not just the women identified as "high-risk".

They are screened using an oral glucose tolerance test, where two blood samples are taken, one before consuming a flavoured sweet drink, and another two hours after the drink. Both samples are tested to determine the level of glucose in the patient's blood.

The test costs about $20 for patients with subsidies, and about $40 for those without.

Mothers diagnosed with gestational diabetes go through counselling to help them monitor and manage their condition. This may be done through dietary control or prescription of insulin.

"Medical intervention for patients with gestational diabetes reduces complication rates by as much as 40 per cent," said Prof Tan.

Gestational diabetes can lead to health risks.

Babies have a higher chance of weighing more than 4kg at birth, and mothers may suffer obstructed labour.

During pregnancy, mothers may develop high blood pressure or go into pre-term labour, when symptoms of labour occur before 37 weeks of pregnancy.

This could lead to premature birth.

Mothers also have a higher chance of developing Type 2 diabetes after giving birth.

Corporate communications manager Lillian Lee has often been underweight, so it came as a surprise when she was diagnosed with gestational diabetes.

"I had to control my diet, otherwise my baby could have grown quite big," said the 40-year-old, who was first screened for the condition in 2012.

byseow@sph.com.sg

Concluding Comments

- There is much potential for high quality CEA studies to help guide decision making in health care
- But CEA studies are not designed to identify cost saving interventions (nor should they be).
  - Purpose is to identify good value for money
- CEA studies are tough to fund via competitive grants
  - Other mechanisms should be considered
- Expectation is that demand for high quality CEA studies will continue to increase
  - We need to create infrastructure to meet that demand
- CEA is just one piece of evidence, and often only part of a compelling HTA story

QUESTIONS?