Making Medicines Personal: Is It All In Your Genes?

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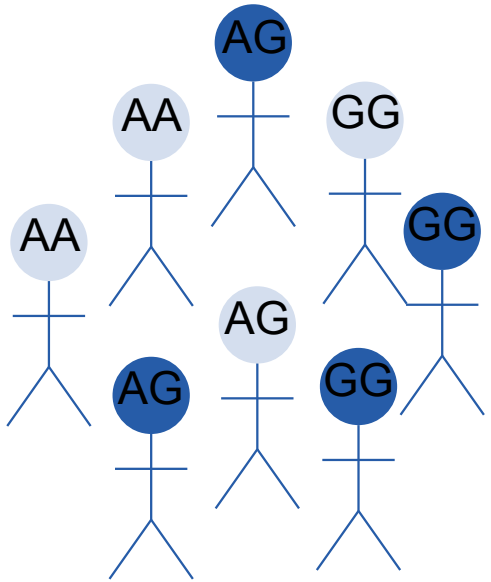
Personalised medicine: using genetic information

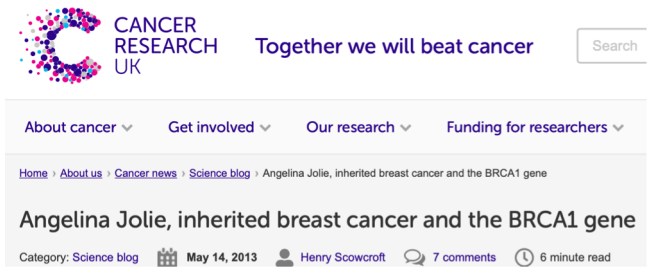
Any two people share >99% of their DNA, the remaining <1% makes us unique

How can we use genetic information to understand variation in disease and stratify patients?



Genetic variants associated with disease can help with prevention, diagnosis and treatment

Genetic variants in the *BRCA1* and *BRCA2* genes are associated with increased risk of breast and ovarian cancer



Genetic variants are associated with response to warfarin

Narrow therapeutic index and difficulty in predicting individual dose requirements

Variants in *CYP2C9* (enzyme that metabolized warfarin) and *VKORC1* (enzyme that is inhibited by warfarin) can affect starting dose

Genetic variants are associated with response to warfarin

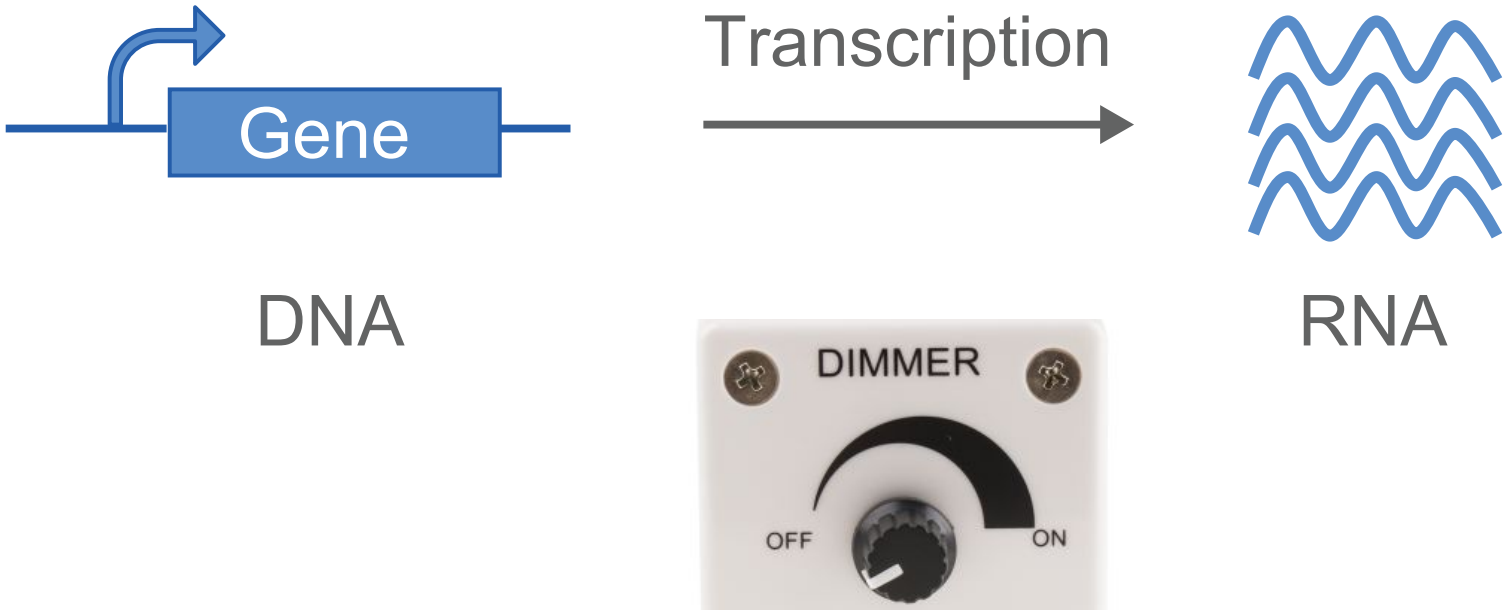
Narrow therapeutic index and difficulty in predicting individual dose requirements

Variants in CYP2C9 (enzyme that metabolized warfarin) and VKORC1 (enzyme that is inhibited by warfarin) can affect starting dose

For many complex diseases it remains challenging to determine which genetic variants are responsible for variation in disease status and response to treatments

Using gene expression to understand variation across disease cohorts

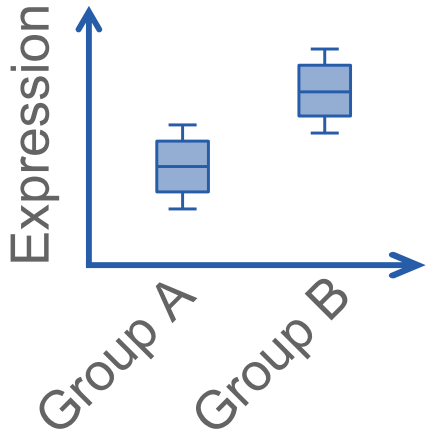
Gene expression is like a dimmer switch on a light



Using gene expression to understand variation across disease cohorts

Gene expression captures information about the current environmental stresses on the body

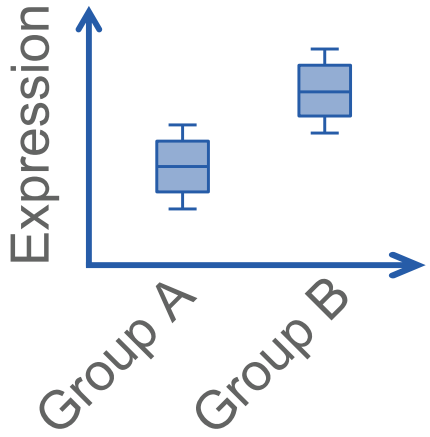
Differential expression



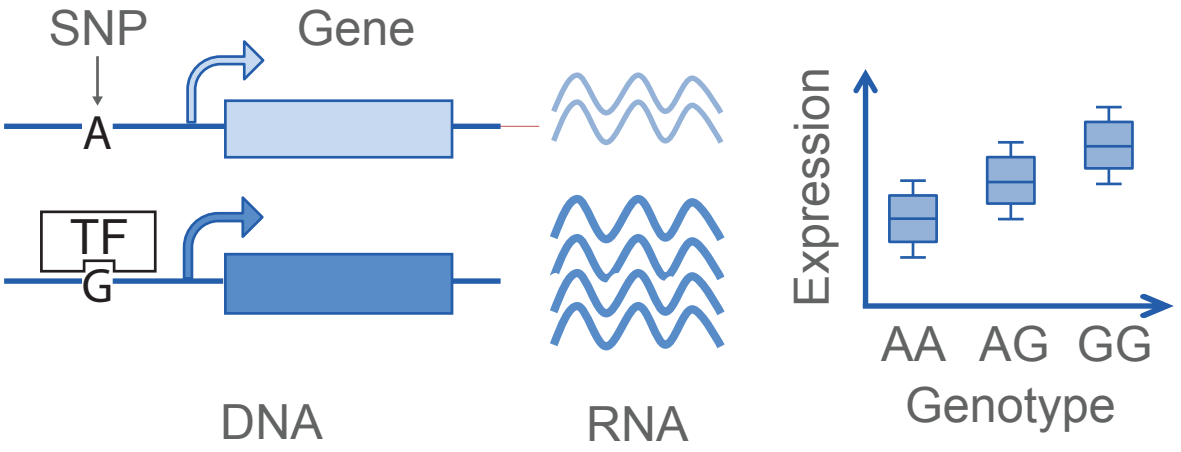
Using gene expression to understand variation across disease cohorts

Gene expression captures information about the current environmental stresses on the body and someone's genome

Differential expression

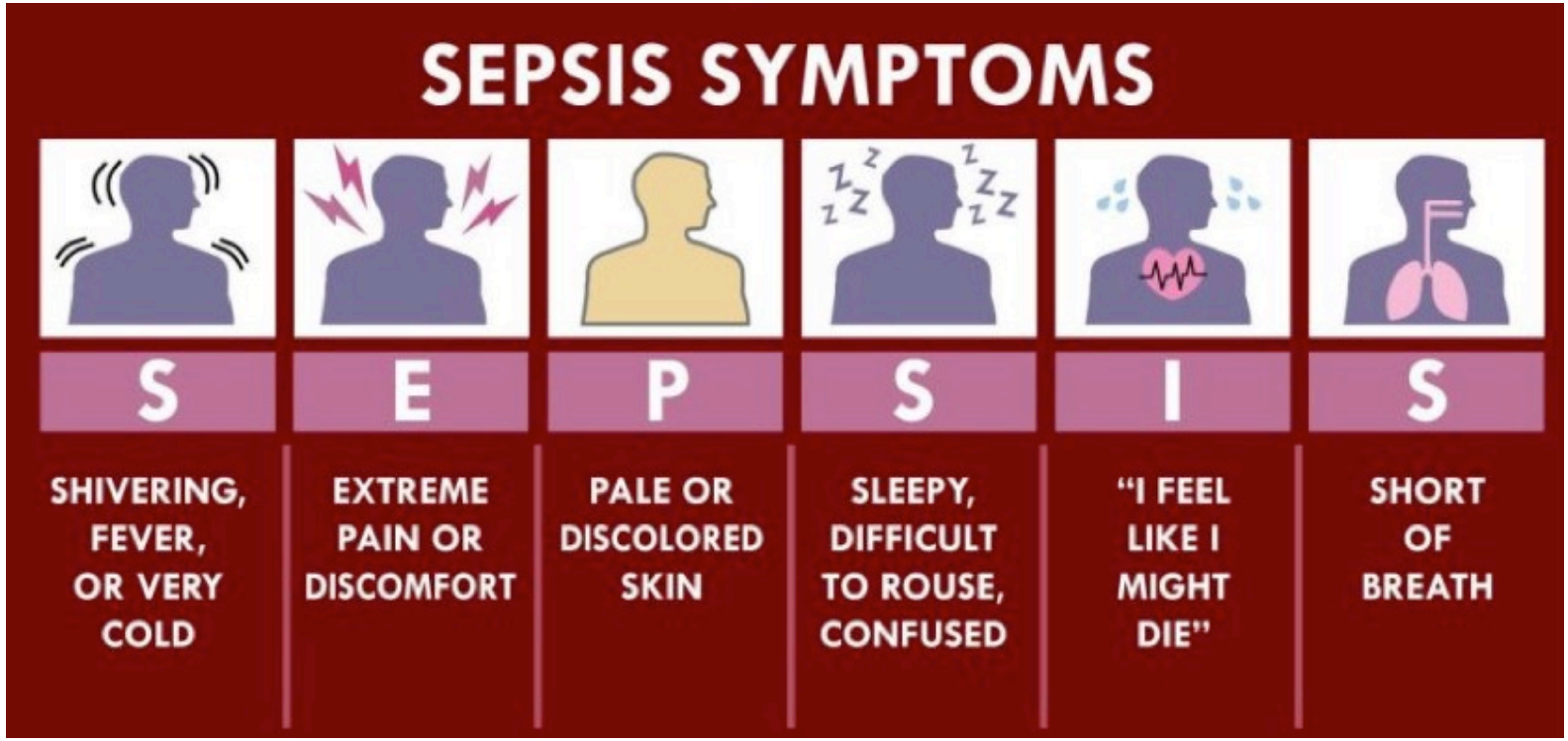


Expression quantitative trait locus (eQTL)



Sepsis

A life-threatening condition that occurs when the body's immune system responding to an infection injures it's own tissues and organs



Sepsis is challenging to diagnose and treat

- Anyone can develop it
- It can be caused by a chest infection, abdomen problem or an infected cut or bite
- Worldwide, 1/3 of people with sepsis die
- No reliable diagnostic marker

Treatments

- Antibiotics and organ support but none that target host immune response
- Substantial variation in response

Genomic Advances in Sepsis (GAinS) study

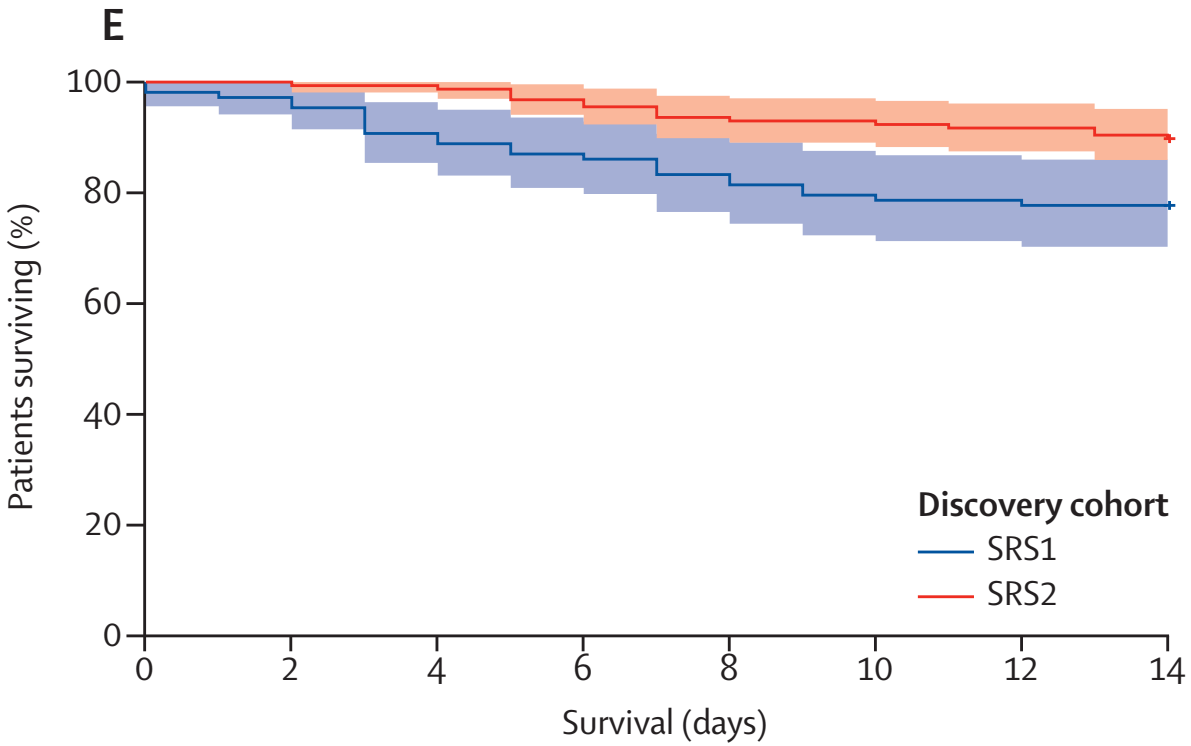
>1,000 sepsis patients recruited from Intensive Care Units around the UK

Blood collected to measure gene expression across the genome

Cohort stratified into two groups:
Sepsis Response Signature (SRS) groups

www.ukccggains.com

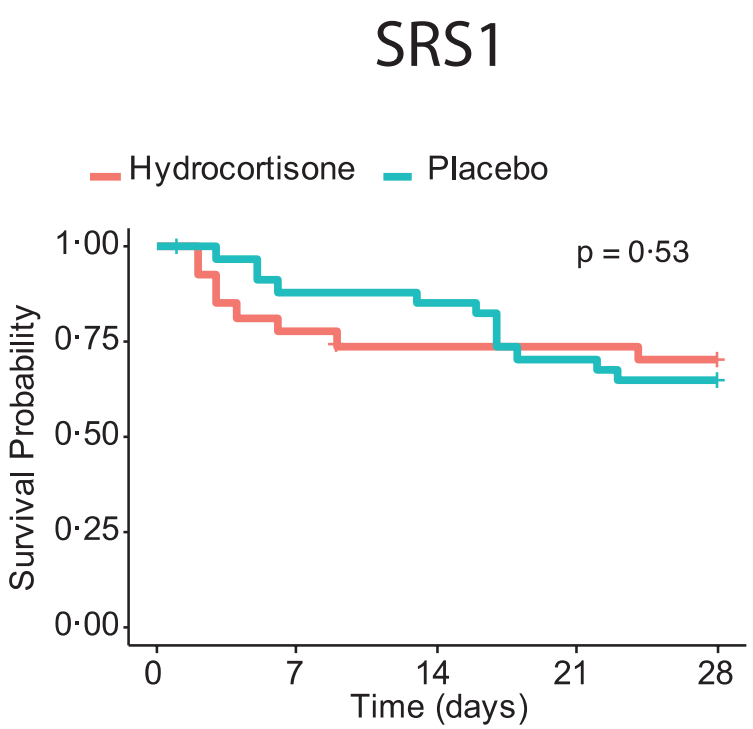
SRS1 (immunosuppressed) group associated with early mortality



Davenport et al. *Lancet Respiratory Medicine* 2016

SRS group membership can affect response to treatment

VANISH trial: placebo vs hydrocortisone



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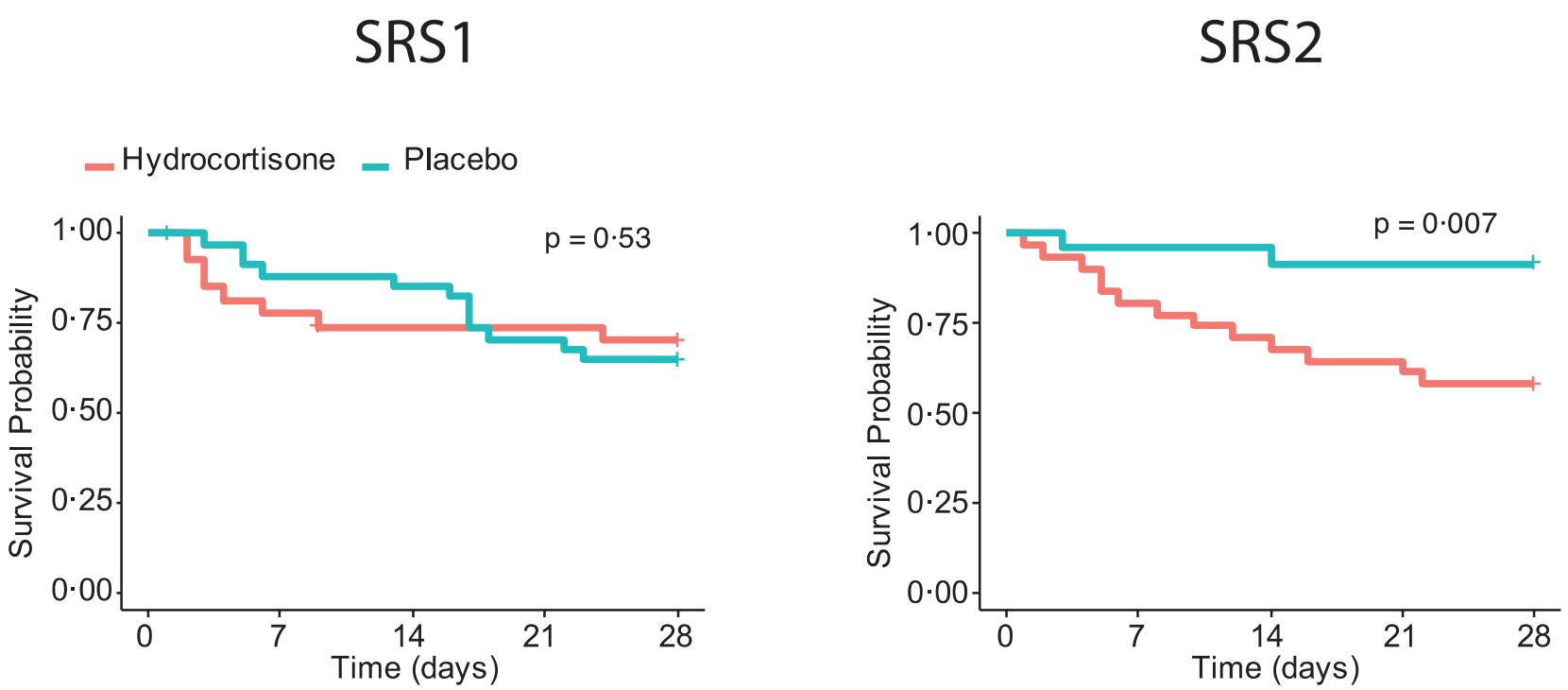


Detecting SRS groups at an earlier time point

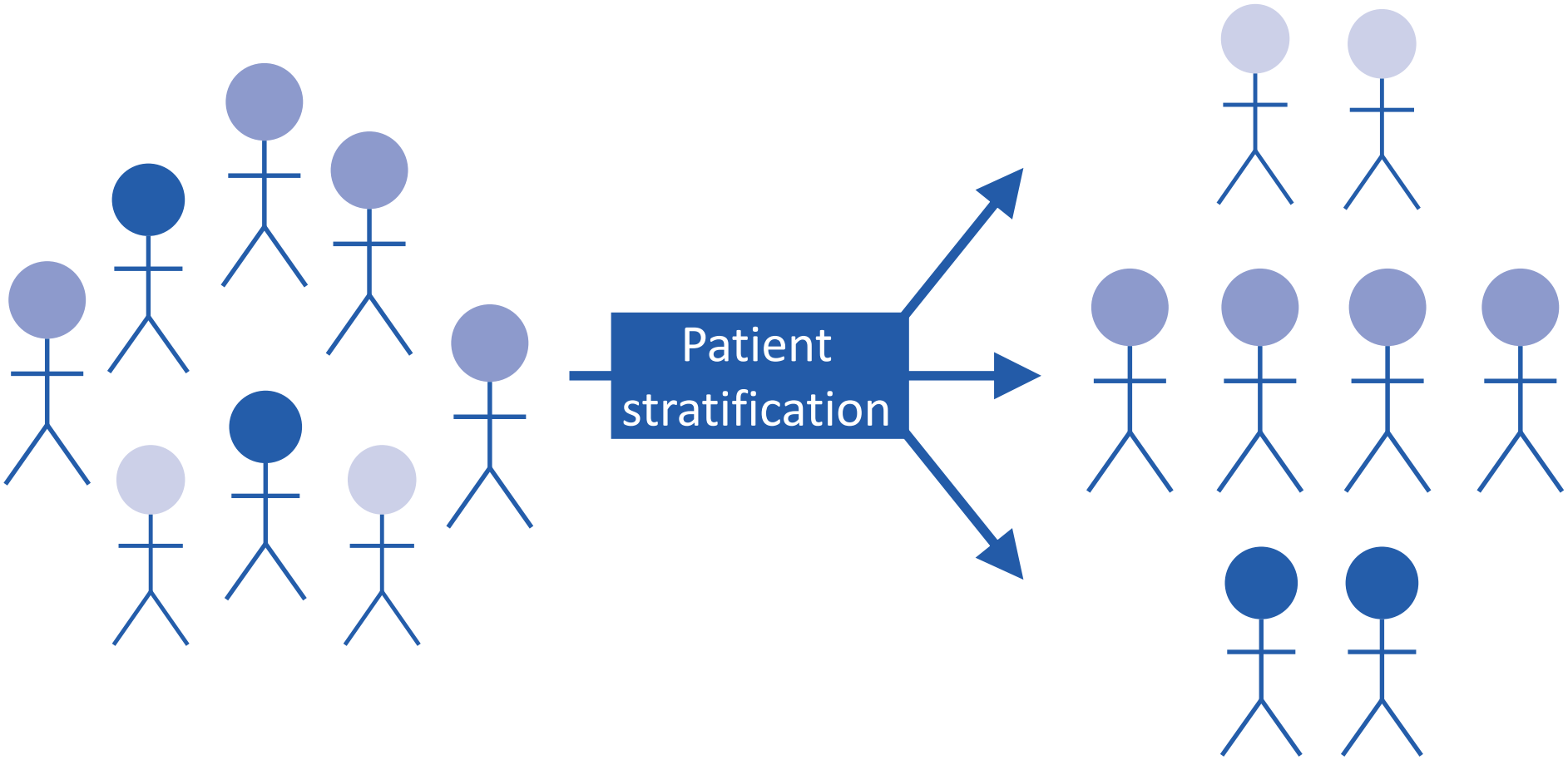
Bioresource in Adult Infectious Disease

Adult patients with suspected infection presenting to the emergency room

Gene expression data for 1,800 patients

Can we identify those most likely to develop sepsis to improve diagnosis and treatment?

Ultimate goal:
Delivering the right drug to the right person at the right time



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The patients

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