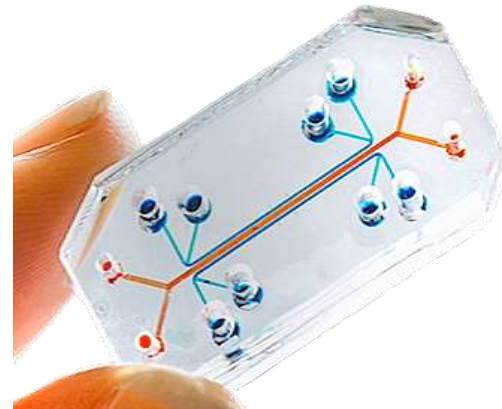


Developing 3D cell culture systems to combat human pathogens & disease



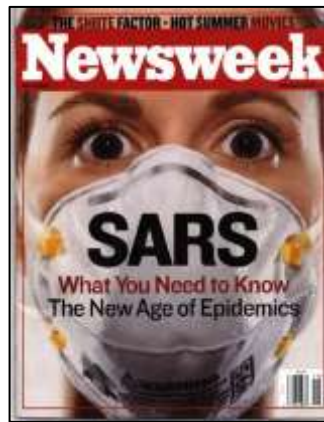
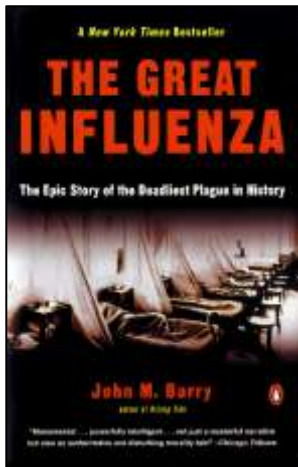
Dr Elizabeth Pharo

CSIRO Australian Animal Health Laboratory (AAHL)

Probing Biosystems Future Science Platform

Outline

- **CSIRO *Probing Biosystems* Future Science Platform**
- **Human 3D cell culture models**
 - Lung: respiratory viruses
 - Skin: chronic wound healing, new biomaterials, biosensing
- **Challenges**



CSIRO Probing Biosystems Future Science Platform



Organ-on-a-chip

- *Disease mechanisms*
- *Biomarker development*
- *High throughput drug screening*

Respiratory & Vascular

- *Mechanisms of viral infection*
- *Improved antiviral delivery*

3D Tissue Models

- *Wound healing / infection control*

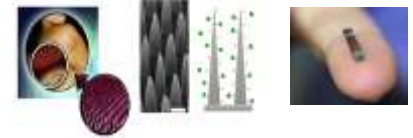
Brain – Functioning Blood Brain Barrier

Gut organoid



Point-of-care diagnostics

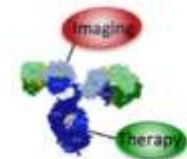
- *Blood biomarkers*
- *Saliva (premature ageing)*
- *Breath (asthma, air quality)*
- *Nanochannels (virus detection)*



Wearable & implantable biosensors

- *Diagnostics*
- *Real-time monitoring*
- *Drug administration*

Health surveillance & Biosecurity



Precision nanomedicine

- *Targeted drug delivery*



3D lung models to fight emerging respiratory viruses



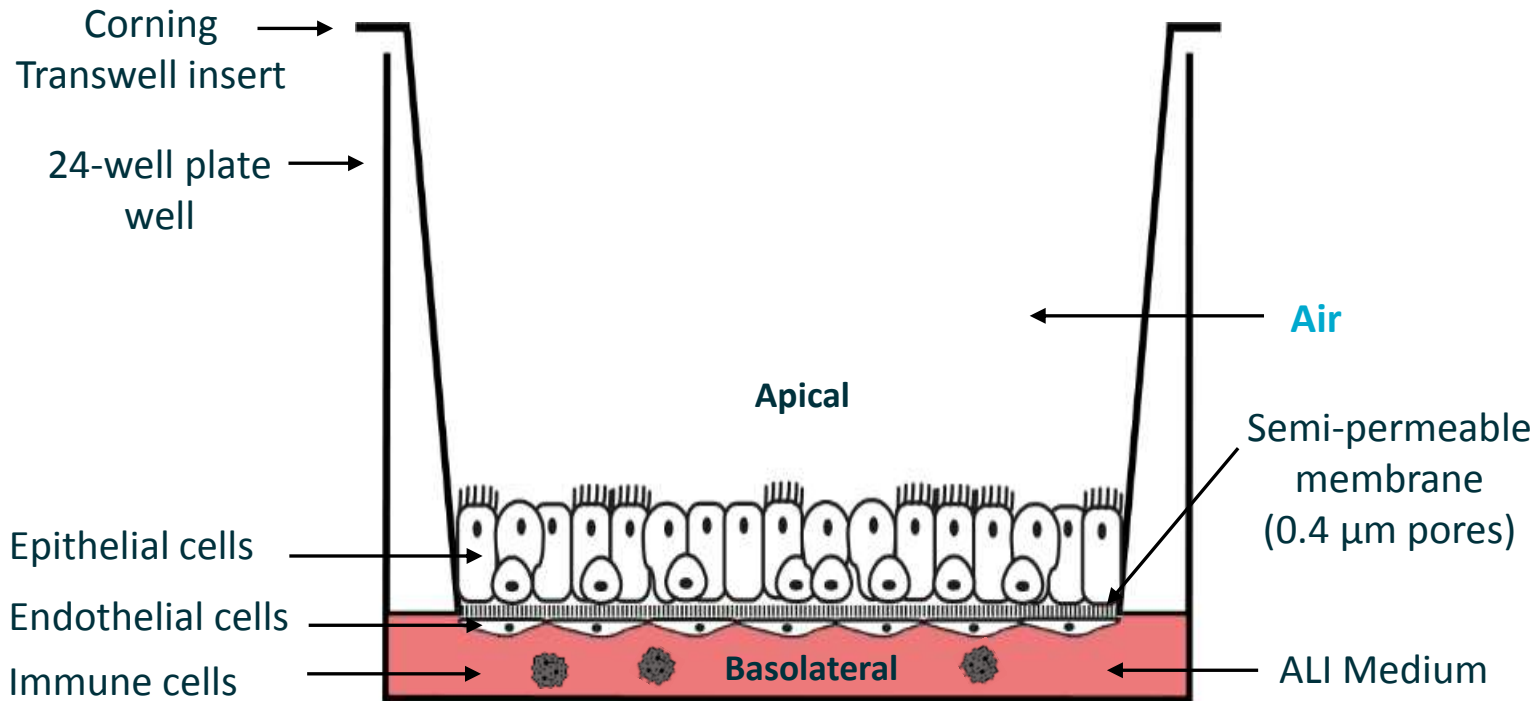
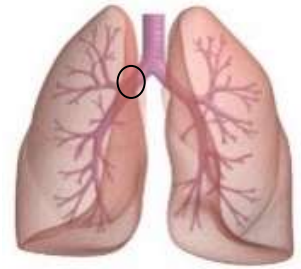
Respiratory viruses are airborne and highly contagious

- **We are vulnerable to pandemics and seasonal flu**
 - **Human cost**
 - Spanish flu (H1N1) 1918: >50-100 million deaths
 - SARS: 774 deaths, MERS: 449 deaths
 - **Economic cost**
 - Next flu pandemic: US \$3 trillion¹
- **Poor diagnostics**
- **No therapeutics or vaccines**
- **Animal models costly, not always representative of the response in humans, long lead-time**
- **New disease models needed**

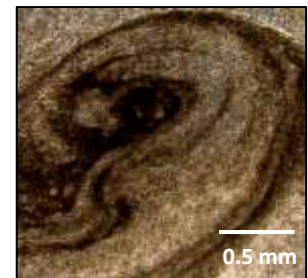
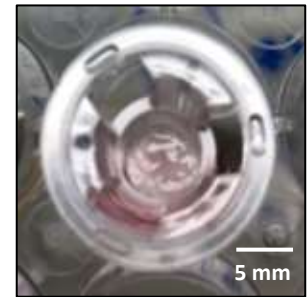


Mimicking the human lung³

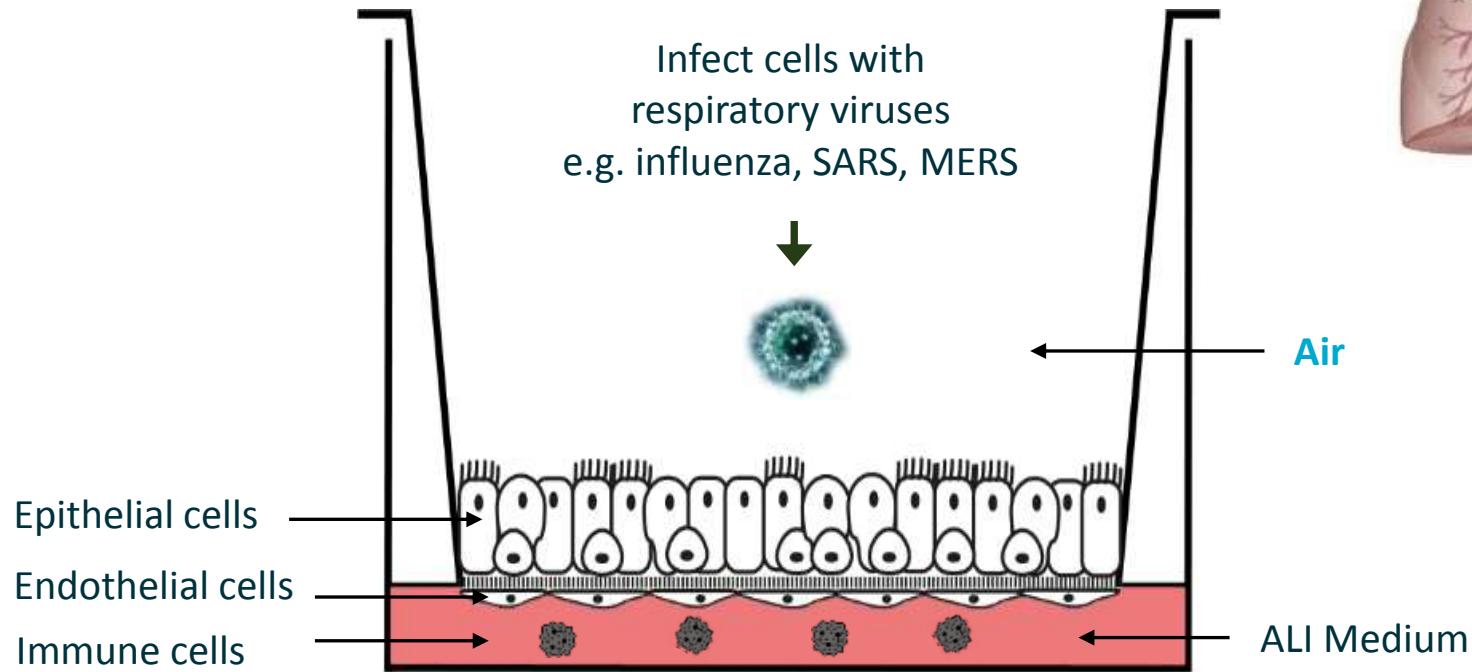
- **Primary lung epithelial and endothelial cells co-cultured on Transwells at the air liquid interface (ALI)**
 - Epithelial cells differentiate 21-27 days post-airlift to form ciliated, goblet (mucus-producing), club and basal cells



Mucus secretion



Respiratory virus challenge

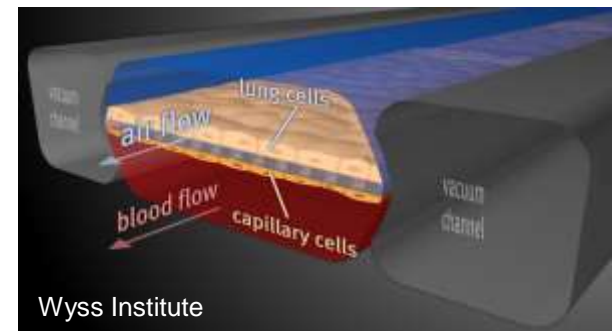
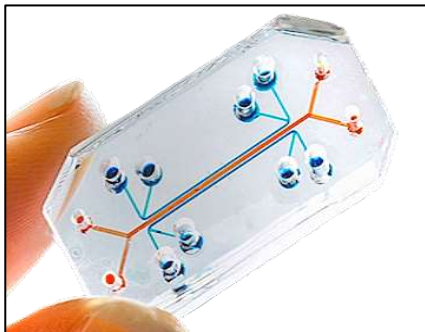


Characterise host-pathogen response
e.g. cytokines, barrier integrity, cell viability, etc.

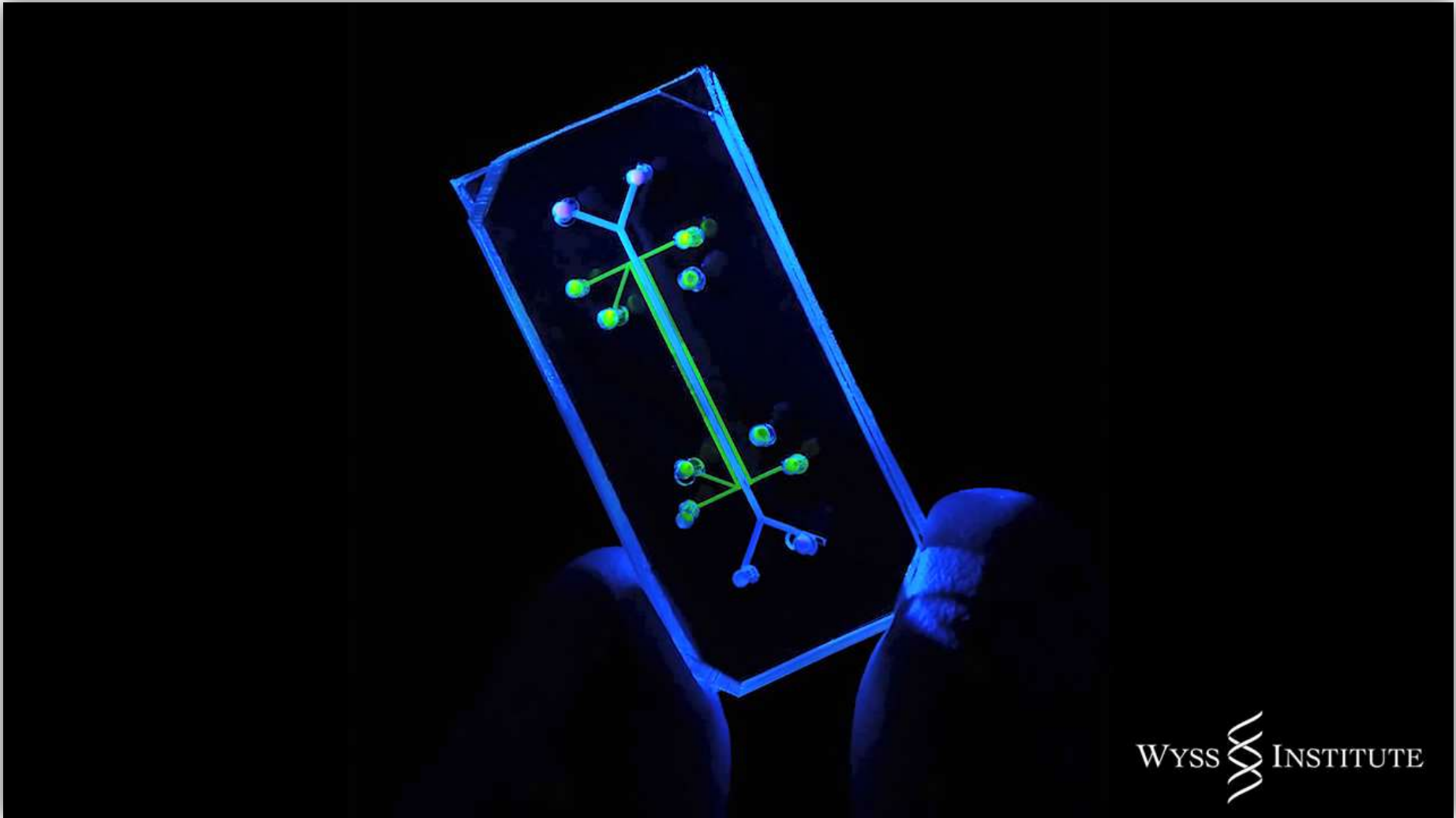
Test antiviral compounds

The next step: human lung-on-a-chip

- **3D microfluidic perfusion device to mimic blood flow**
 - More physiologically relevant system
 - Directional flow of nutrients, mechanical stress (breathing)
- **Identify new disease biomarkers**
- **Fast fail therapeutic candidates**
- **Minimise use of animal models, saving time and money**
- **Rapid response during a pandemic**
- **Test bacteria, nanoparticles, chemicals, toxicity**



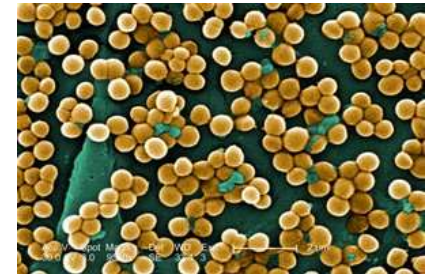
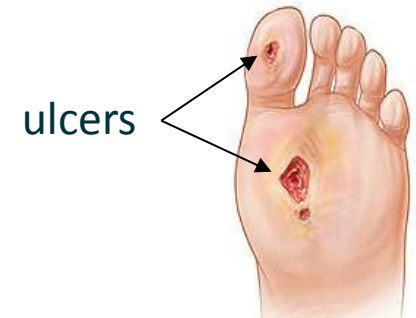
Human lung-on-a-chip



3D and 4D skin cell culture systems

Chronic wounds are a huge cost to Australia

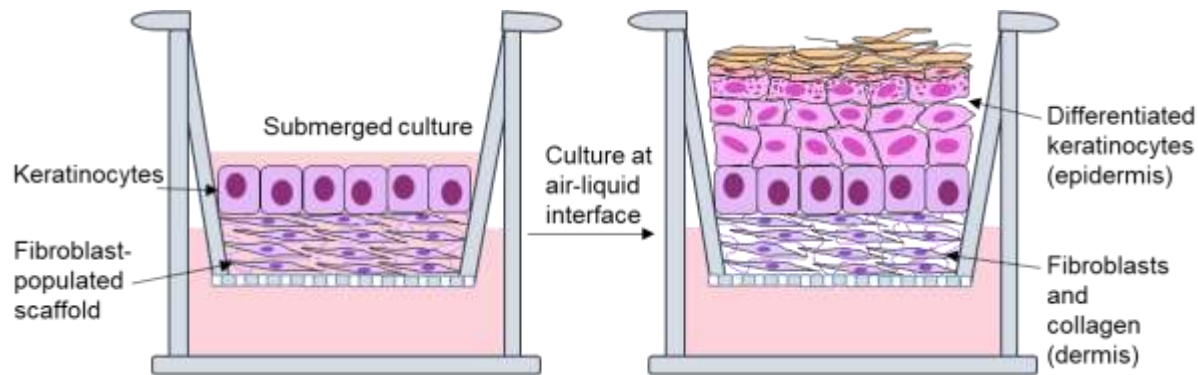
- \$3 billion cost to healthcare system p.a.⁴
- Over 400,000 people affected at any time⁴
 - Associated with diabetes, elderly, immune suppression, severe burns
 - Increased risk of bacterial infection, e.g. *E. coli*, *S. aureus*, *P. aeruginosa*
 - Amputation in severe cases
- **Create human skin models to study infection and inflammation**
- **New biomaterials**
- **Drug and gene delivery systems**



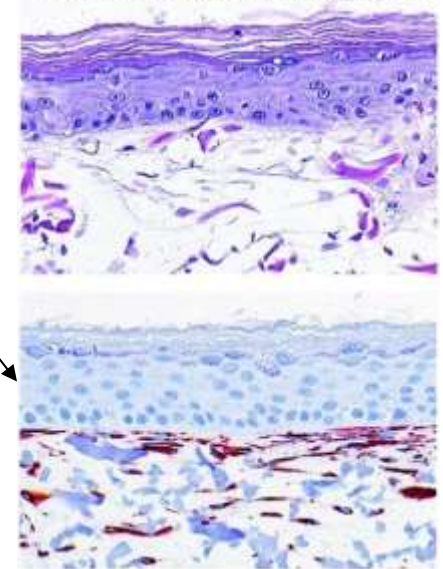
3D Skin Culture

- **Creation of human skin using the Transwell system**

- Keratinocytes differentiated at the air liquid interface (ALI) (epidermis)
- Fibroblasts and collagen scaffold (dermis)
- ‘Wound’ skin culture by slicing or burning
- Immune cells and bacteria added to simulate infection and inflammation
- Test drugs and gene delivery systems



Cell line human skin equivalent



4D Cell culture systems

Combine 3D models with biosensing and reporting

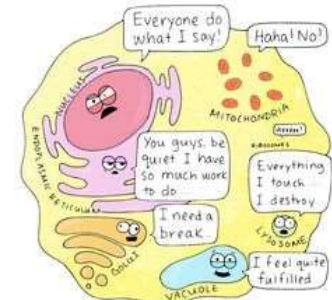
Microfluidic device



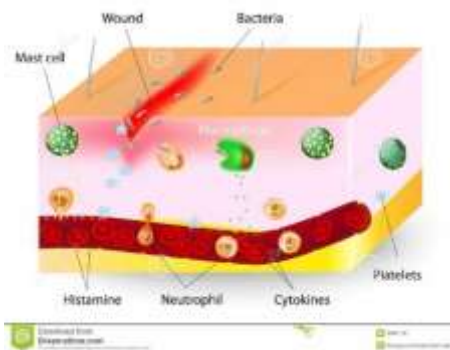
Biosensing



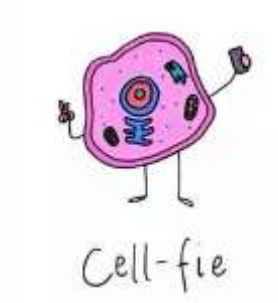
Real-time functional readouts



3D cell culture system



Cell imaging



If organelles could talk
Beatrix the Biologist



Advanced disease models
New medical devices

Challenges

Physiologically relevant models

- **Reliable, reproducible, scalable**
- **Cell source is critical**
 - Human primary cells / induced pluripotent stem (iPS) cells
- **Model complexity**
 - Tissue structure (matrix scaffold) / appropriate cell types and numbers
- **Sensors and real-time reporting**
- **2D monoculture systems still useful**
- **Animal models needed for comparison**

Summary

3D cell culture & organ-on-a-chip models

- Multiple applications
- Complex disease models
- Personalised medicine
- Sensors and functional readouts for real-time patient monitoring
- Advanced healthcare devices to improve patient outcome

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