The Regulatory Challenges of Innovative Therapies/Diagnostics in Precision Medicine

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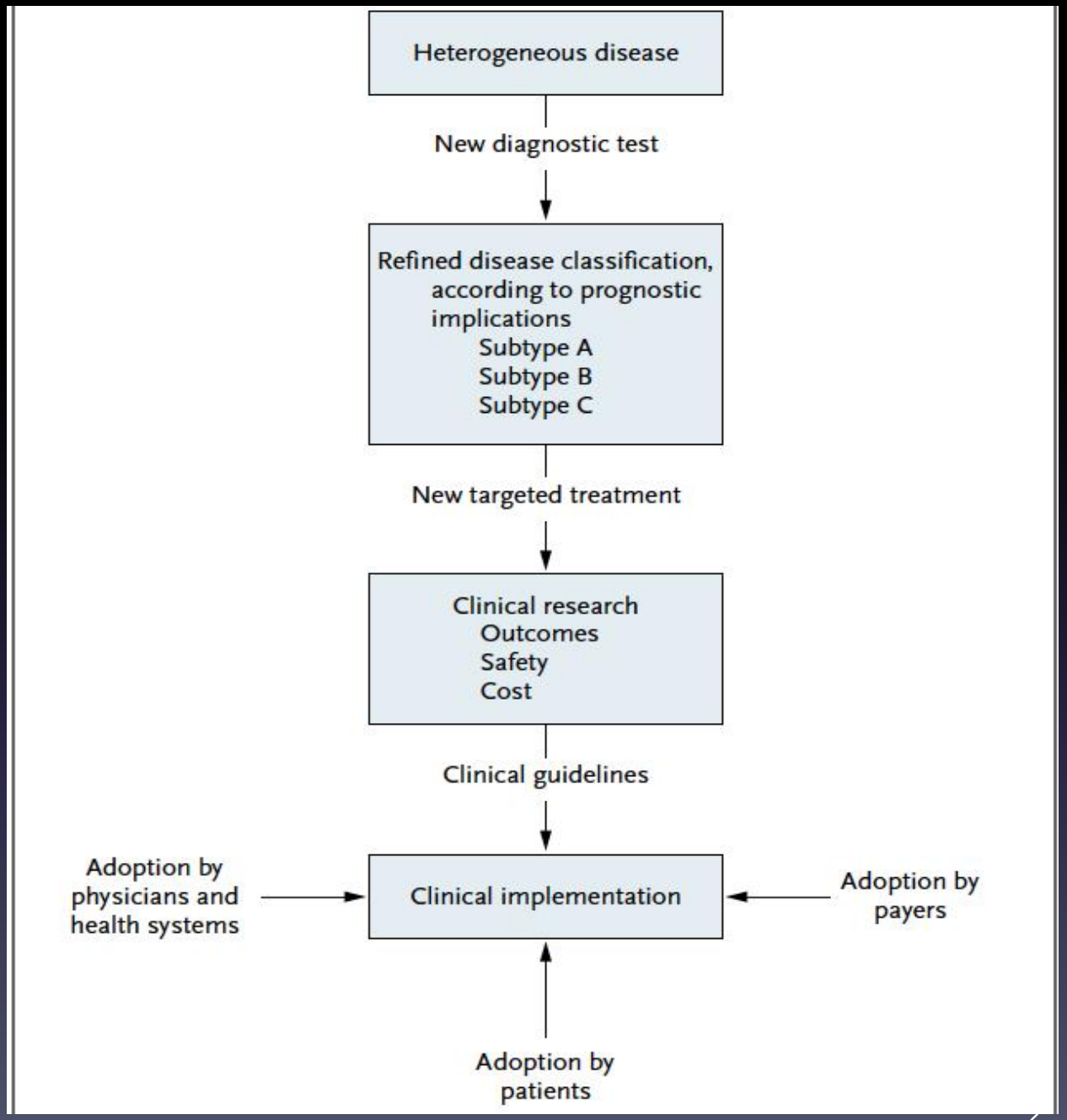
Scope of precision medicine



Innovation in Precision Med

- Combination of biomarker (genomic and other “omics”) tests with
  - new investigational drugs or unapproved drugs
  - Off-label uses of approved drugs
- New diagnostic biomarker tests, or off-label uses
- Examples:
  - Cytochrome P-450 testing and SSRI prescriptions/Rituxan oncology drug + laboratory test identifying most responsive patients
  - Translational research in oncology therapies
    - POLARIS project in Singapore

What are innovative treatments?

- Uncontrolled, often single, interventions intended to manage or solve particular clinical problems.
- They are not undertaken in order to gain new knowledge beyond the needs of the patient
- Although their use may lead to new knowledge, this is secondary to their primary purpose of benefiting patients.
  - *Pang Ah San v. SMC* (2013) Singapore High Court of Three Judges
  - No explicit inclusion of diagnostic methods, but this is the case in New Zealand.

Singaporean encounters

- Cases at the Disciplinary Tribunal or High Court:
  - Regenerative medicine:
    - *SMC v. Martin Huang* (2009) - *Stem cell treatments for aesthetic treatments*
    - *SMC v. Wong Yoke Meng* (2010) - *Stem cell treatment for facial rejuvenation*
  - Medical devices:
    - *SMC v. Erwin Kay* (2010) - *Bioresonance therapy for addiction, allergies*
    - *Devathasan v SMC* (2010) High Court – "off-label" rTMS and ultrasound therapy
    - *Pang Ah San v SMC* (2014) High Court – new loop-PEG gastric tube invention
  - Off-label oncology drugs
    - *SMC v. Gerard Teoh* (2012) - *VELCADE-based targeted therapy for B-cell lymphoma*
    - *Physician had "close association" with pharmaceutical company selling the treatment*
  - Aesthetic medicine
    - *SMC v. Low Chai Ling* (2012) - *Various aesthetic procedures alleged to lack sufficient evidence base*.

The regulatory context of precision medicine in Singapore

Regulatory framework for pharmaceuticals

- Medicines Act, Revised Ed. 1985
  - Reg framework in transition to the Health Products Act 2007
  - Medicinal products à Therapeutic products
- Exceptions to registration: named-patient import licence
  - Guidelines for Approval to import an unregistered product (March 2011)
- Post-market pharmacovigilence
  - Adverse events and “environment scanning”

Devices, diagnostic tests

- Health Products Act (2007); Med Devices Regs (in force 2010)
  - Medical devices include in vitro diagnostics, but *not* laboratory developed tests
  - Registration requirement, 4 class risk-based evaluation
  - Exception for import on a named patient basis (special access route): Reg 8, MDR
- Private Hospitals and Medical Clinics Act (1980)
  - PHMC Regulations for Clinical Laboratories
  - Qualifications, Quality Control, Record keeping

Devices, diagnostic tests

- Professional guidelines
  - NMEC, Ethical Guidelines for Gene Technology (2001)
    - Part III - Principles and criteria for genetic test development
- In the pipeline:
  - Specific Licensing Terms and Conditions for Clinical Genetics Services (under internal review)

Professional standards

- SMC Ethical Code and Guidelines
- 4.1.4 Untested practices and clinical trials
  - A doctor shall treat patients according to generally accepted methods and use only licensed drugs for appropriate indications. A doctor shall not offer to patients, management plans or remedies that are not generally accepted by the profession, except in the context of a formal and approved clinical trial.

SMC Ethical Code and Guidelines

- It is not acceptable to experiment or authorise experiments or research which are not part of a formal clinical trial and which are not primarily part of treatment or in the best interest of the patient, or which could cause undue suffering or threat to the life of a patient.

“Generally accepted methods”

- *Pang Ah San v. SMC* [2013]
  - The requirement of general acceptance contains a scientific aspect, rather than a purely empirical issue [based purely on professional behaviour].
    - However, general professional acceptance over a substantial period of time is *prima facie* evidence of general acceptance.

“Generally accepted methods”

- Factors looked at in determining positive acceptance:
  - May be based on a range of activities
    - from anecdotal uncontrolled “experiences” of numerous practitioners to carefully conducted randomised controlled trials
  - Potential benefits and risks must approach a level of predictability acceptable to the medical community in general
    - Validated by reliable research methods, Firm basis of support from clinical community, Sufficient evidence of safety

The legitimacy of innovative treatments

Innovative treatments

- *Pang Ah San v SMC* [2013]
- Experimental or innovative treatments administered in the best interests of the patient are permissible.
  - Innovative treatments remain so when the *primary purpose is to benefit the patient*
    - May be given as one-off therapy before conducting a clinical trial
  - Onus is on the doctor to demonstrate that therapy administered is in the best interests of the patient.
  - When in doubt, the HC suggests seeking approval of an IRB, if not impractical.

Innovative treatments

- When is innovative treatment justified?
  - HC quotes with approval the Helsinki Declaration, art 37:
    - Where proven interventions do not exist, or are ineffective
    - After seeking expert advice
    - With informed consent of the patient
    - If it is in the best interests of the patient, in order to offer hope of saving life, re-establishing health or alleviating suffering
    - Should subsequently be made object of research to evaluate safety and efficacy.

Innovative treatments

- *Devathasan v. SMC* [2010]
  - Recognised guidelines developed for off-label drug use:
    - (1) Better alternative to standard but ineffective therapy
    - (2) Sufficient *evidence base or experience [and scientific rationale]* to demonstrate safety and efficacy
    - (3) Intent is therapeutic objective, not research

Innovative therapy or Research?

- Critical to distinguish research from innovative therapy
  - Different regulatory regimes apply:
    - Key difference: the requirement of prospective external review
  - Misalignment of professional and patient interests
- How?
  - Research is activity where there is “a deviation between serving the best interests of the patient and interests in developing generalisable knowledge”.

Implications for Precision Med

- A statutory licensing body tends to provide greater clarity to the pathways of development and translation, and oversight of innovations, at least for threshold entry into clinical practice
  - Lack of clear thresholds or standards makes it difficult for clinicians to know when they are crossing the line
  - There will still be leakage – “off label” usage
- Innovative treatments are essentially exceptions to these regulatory processes and need to be managed carefully

Implications for Precision Med

- Model for regulation of innovative treatments needs more work
  - Ethics of innovative treatments needs work
    - Is it based on beneficence and autonomy
    - Or a balancing of those principles with public health interests
  - Clarity on peer review requirement needed
    - Level of rigour, independence, competency
    - IRBs? Hospital ethics committees? Specialty peers?
  - Need to develop institutional and specialty best practices
  - Better integration with statutory frameworks needed
    - E.g. notification requirements when innovative treatments are deployed

The End