11th China Health Technology Assessment Forum

# Adapting HTA to Meet the Challenges of Emerging Technologies

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# Some Emerging Technologies Challenge HTA

- Technologies used in rare ("orphan") or ultra-rare ("ultra-orphan") diseases
- Technologies that depend on real-world evidence to demonstrate effectiveness and safety
- Technologies that are cost-effective but have very high budget impact
- Genomic tests used in screening and diagnosis
- Genome editing technologies
- Technologies that have new mechanisms of action (e.g., use new biological pathways) with unknown long-term effects (e.g., viral vectors for certain gene therapies)
- Combination technologies, e.g., drug-diagnostic combinations and drug-device combinations
- Biosimilars (near-copies of biologic medical products, usually very large molecules, e.g., insulin, human growth hormone, interferons, monoclonal antibodies)
- Technologies that may be used one time to cure (permanently or temporarily) a disease but that have very high unit costs (e.g., US $500,000-$2,000,000 for a gene therapy)

# Technologies used in rare and ultra-rare diseases

# What Are the Main Challenges of HTA Involving Technologies for Rare Diseases? (1)

- In rare diseases, it is difficult to enroll enough patients into clinical trials to yield statistically significant findings
- Also, due to severity of many of these diseases, clinicians and patients want to rely on shorter-term interim/surrogate outcomes rather than long-term endpoints of mortality and morbidity
  - ➢ So, evidence base may be weak
- Traditionally, HTA agencies/organizations have used methods and criteria more suited to assessing technologies used in large populations
  - ➢ For example, evidence quality criteria, cost/QALY thresholds

# What Are the Main Challenges of HTA Involving Technologies for Rare Diseases? (2)

- Prices of new therapies for rare diseases tend to be high (or very high) as manufacturers seek to cover costs of development (which may be comparable to development costs of therapies for common conditions) and achieve acceptable return on investment across a much smaller patient population
  - ➢ So, it is more difficult to achieve generally acceptable thresholds of cost effectiveness
- Until recent years, many therapies for rare diseases were used so little that they were not high priorities for payers and HTA were
  - ➢ Even at relatively high cost per patient, their overall budget impact was small due to few patients

# What Are the Main Challenges of HTA Involving Technologies for Rare Diseases? (3)

- However, the very success of therapies for some orphan diseases has increased their budget impact substantially
  - More patients are treated; these patients live longer; these patients incur additional costs (of managing other diseases/conditions) that accompany longer lives
- National policies to encourage drug development for rare conditions are working, leading to more therapies
  - As a group, the increased number of therapies for rare conditions place competitive pressure on each other for limited budgets, attracting more HTA attention
- Patient advocacy is increasing and more sophisticated across more rare conditions
  - Increasing competition for attention of payers and HTA

# Highly specialised technologies guidance

Proposed highly specialised technology evaluations

Block scoping reports

Achieving and demonstrating compliance with NICE TA and HST guidance

Budget impact test

Highly specialised technology (HST) evaluations are recommendations on the use of new and existing highly specialised medicines and treatments within the NHS in England.

View guidance in development

## How we identify topics

We only consider drugs for very rare conditions. The majority of our topics are identified by the National Institute for Health Research Innovation Observatory. They aim to notify the Department of Health of key, new and emerging healthcare technologies that might need to be referred to NICE against the following timeframes:

### Cost recovery plans for appraisals

Plans for NICE to recover the costs of its appraisals through charges to the companies which make them, have been put on hold until the Government completes its life sciences strategy.

# Criteria for NICE Highly Specialised Technologies

All criteria are required:

- Target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS
- Target patient group is distinct for clinical reasons
- Condition is chronic and severely disabling
- Technology is expected to be used exclusively in the context of a highly specialised service
- Technology is likely to have a very high acquisition cost
- Technology has the potential for life long use
- Need for national commissioning of the technology is significant

Source: NICE. Interim process and methods of the Highly Specialised Technologies Programme: Updated to reflect 2017 changes. 2017.

# Why a different approach for rare conditions? (1)

"The [Highly Specialised Technology] guidance recognises the particular circumstances of these very rare conditions –the vulnerability of very small patient groups with limited treatment options, the nature and extent of the evidence, and the challenge for manufacturers in making a reasonable return on their investment because of the very small populations treated …."

Andrew Dillon, CEO, UK NICE

Source: Channel 4 Television Corporation (UK). Sir Andrew Dillon. NICE's Role in NHS Funding. 20 Feb 2015.

# Why a different approach for rare conditions? (2)

"…. In evaluating these drugs, NICE takes into account a greater range of criteria about the benefits and costs of highly specialised technologies than is the case with its appraisals of mainstream drugs and treatments. We do this because applying our standard approach to treatments for very small groups of patients would result in us always recommending against their use. This would be unfair."

Andrew Dillon, CEO, UK NICE

Source: Channel 4 Television Corporation. Sir Andrew Dillon. NICE's Role in NHS Funding. 20 Feb 2015.

# NICE HST: Weighting of QALYs for Technologies that Provide a Large Increase in QALYs

- UK NICE uses a cost-effectiveness threshold of approximately £20,000-30,000 per QALY gained for recommending acceptance of a new technology.
- In 2016, NICE proposed a cost-effectiveness threshold of £100,000 per QALY gained for HST technologies.
- That would enable more HST technologies to achieve an acceptable cost per QALY gained threshold.
- However, public comment indicated that even the higher threshold of £100,000 was not acceptable. So, NICE changed its approach.
- NICE now uses a method that gives more weight to QALYs for technologies that provide an increase of >10 QALYs in a patient's lifetime.
- "More QALYs" improves the cost per QALY ratio, making it easier to achieve the threshold of £100,000 per QALY gained.

# Weighting of QALYs in NICE HST

| Weighting of QALYs for Technologies with Large Increases in Lifetime QALYs | |
|---|---|
| Incremental QALYs gained (per patient, using lifetime horizon) | Weight of QALYs |
| ≤ 10 QALYs | 1 |
| 11-29 QALYs | >1 - <3 (using equal increments) |
| ≥30 QALYs | 3* |

Source: NICE. Interim process and methods of the Highly Specialised Technologies Programme: Updated to reflect 2017 changes. 2017.

# Weighting of QALYs in NICE HST

Example:

•A genetic therapy for a rare disease in a child costs an additional £6,000,000 over the child's lifetime and provides 30 QALYs gained. So:

- £6,000,000 ÷ 30 QALYs = £200,000 per QALY gained
- This is higher than the £100,000 threshold

•However, as 30 QALYs gained is greater than 10 QALYs gained, the weighting of 3 is used. So:

- £6,000,000 ÷ (30 X 3) QALYs = £66,667 per QALY gained
- This is below the £100,000 per QALY threshold

# NICE HST Budget Impact Test

As of April 1, 2017:

- Purpose is to assess the budget impact of a technology in the first 3 years of its use in the NHS.
- If the budget impact > £20million, in any of the first 3 years, National Health Service (NHS) England may engage in commercial discussions with the company.
- Purpose of these discussions is to **manage the impact** that paying for the technology would have on the rest of the NHS.

Source: NICE. Interim process and methods of the Highly Specialised Technologies Programme: Updated to reflect 2017 changes. 2017.

## NICE backs first ‘ultra-orphan’ drug Soliris

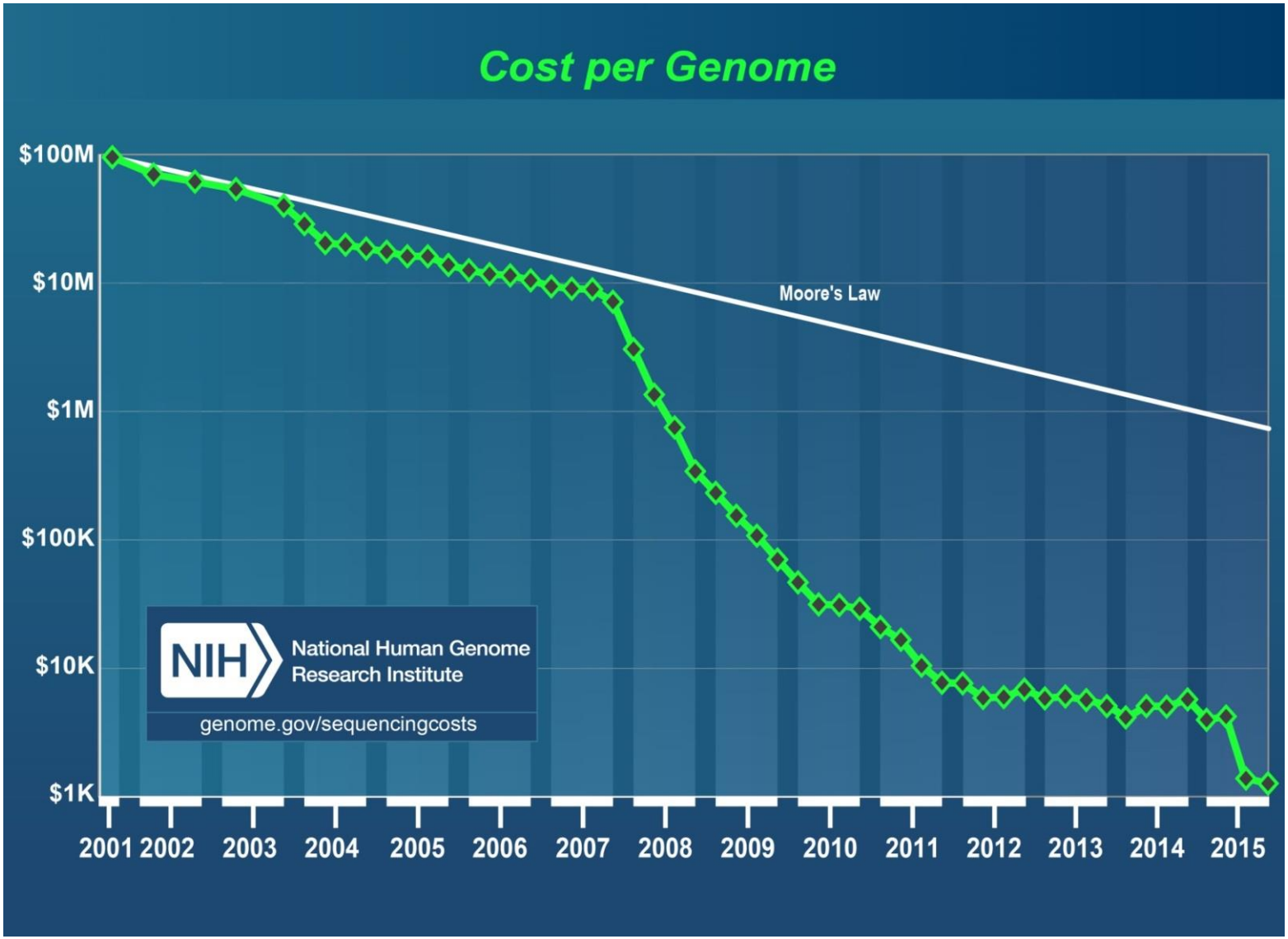
*Final guidance backs Alexion’s treatment for very rare blood clot condition*


Eculizumab (Soliris) for atypical hemolytic uremic syndrome (aHUS)

- This was the first NICE drug guidance under the HST programme for treatments for very rare conditions, where standard NICE assessments may be inappropriate.
- Special requirements include:  prescription from an expert center, data monitoring on dose and duration of treatment, national protocol for starting and stopping use, and research programme to evaluate starting, stopping, and dose adjustment.
- NICE chief executive said: “The committee accepted that eculizumab is a step change in the management of aHUS and can be considered a significant innovation for a disease with a high unmet clinical need.”

# Genomics and gene therapy (including very expensive “one-time cures”)

# Cost of Sequencing a Human-Sized Genome




Data from 2001-2015 represent costs of generating DNA sequence using first generation sequencing technology. Beginning January 2008, data represent costs of generating DNA sequence using 'second-generation' (or 'next-generation') sequencing platforms. The change in instruments represents the rapid evolution of DNA sequencing technologies that has occurred in recent years.

Source: Wetterstrand KA. DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP) Available at: www.genome.gov/sequencingcostsdata. Accessed 9.1.16.

The New York Times

# US Clears Breakthrough Gene Therapy for Childhood Leukemia

By THE ASSOCIATED PRESS AUG. 31, 2017, 6:52 A.M. E.D.T.

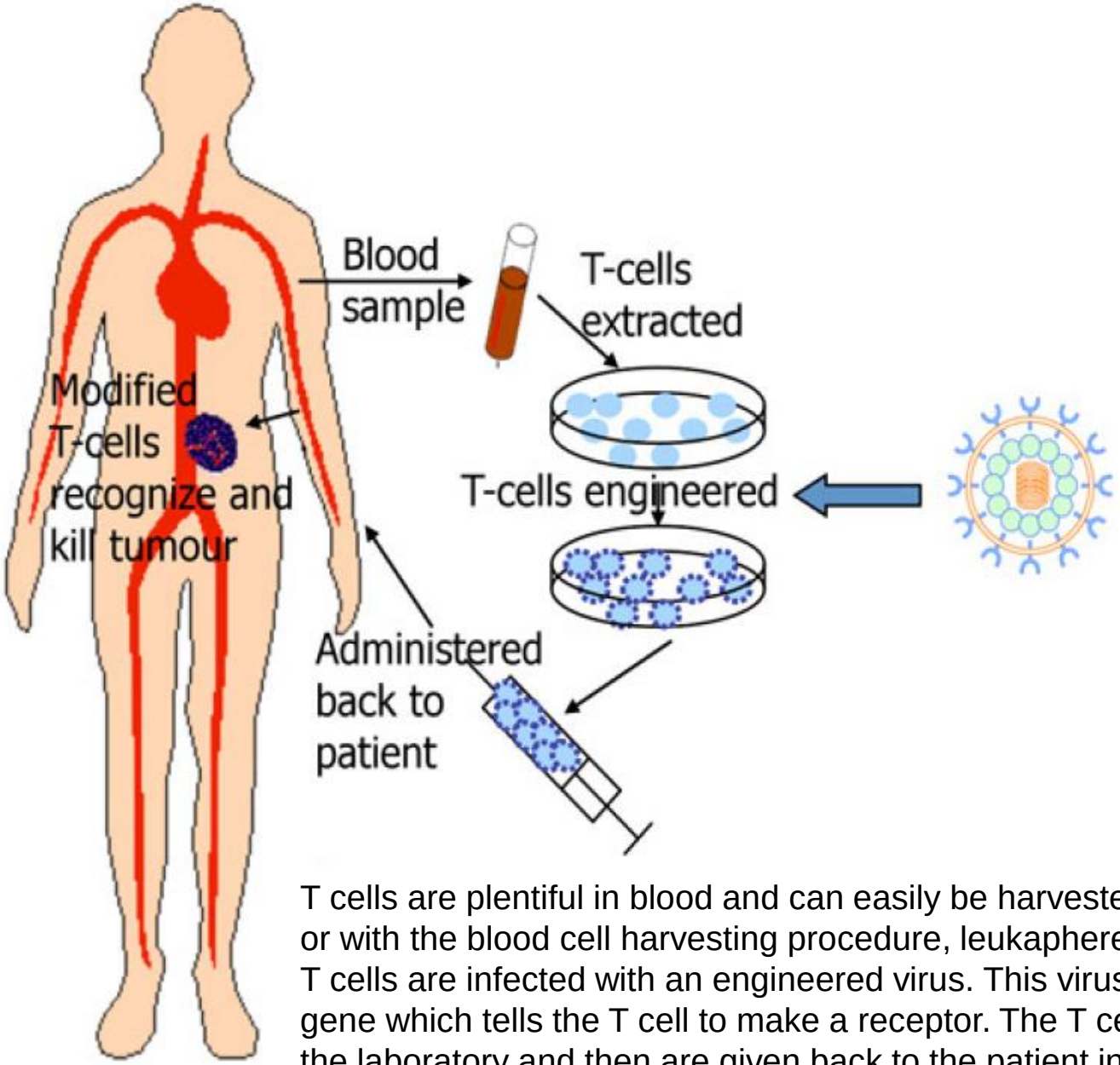
WASHINGTON — Opening a new era in cancer care, U.S. health officials have approved a breakthrough treatment that genetically engineers patients' own blood cells into an army of assassins to seek and destroy childhood leukemia.

The Food and Drug Administration said the approval on Wednesday was historic, the first gene therapy to hit the U.S. market. Made from scratch for every patient, it's one of a wave of "living drugs" under development to fight additional blood cancers and other tumors, too.

Novartis Pharmaceuticals set the price for its one-time infusion of so-called "CAR-T cells" at $475,000, but said there would be no charge for patients who didn't show a response within a month.

.... The $475,000 price tag doesn't include the cost of needed hospitalizations, travel to a certified hospital and other expenses.

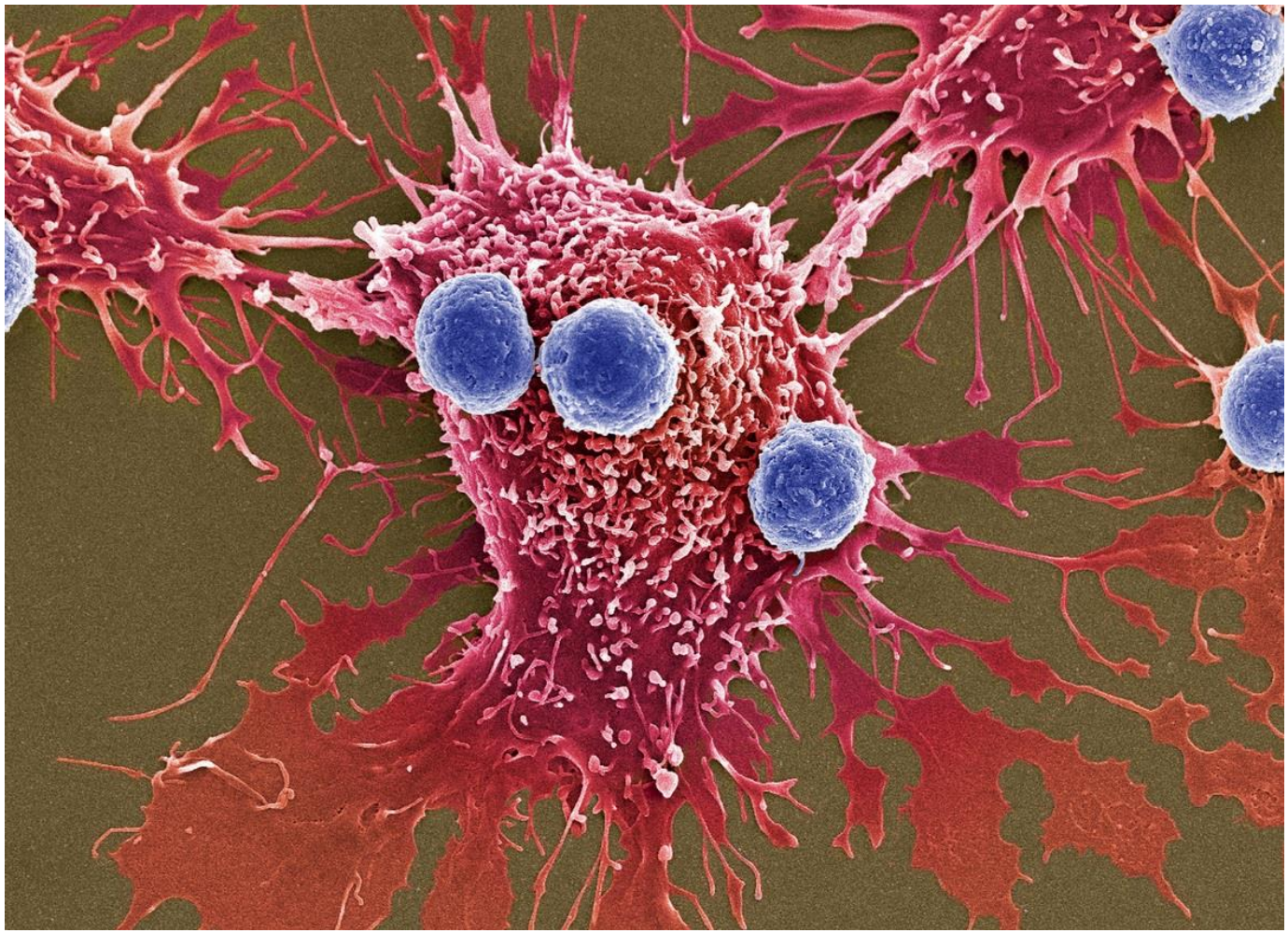
# CAR-T Cell Cancer Immunotherapy




T cells are plentiful in blood and can easily be harvested from either a blood sample or with the blood cell harvesting procedure, leukapheresis. In a specialized laboratory, T cells are infected with an engineered virus. This virus permanently introduces a new gene which tells the T cell to make a receptor. The T cells are grown for a few days in the laboratory and then are given back to the patient in an I.V. drip.

Source: The Stiliyan Petrov Foundation, UK.

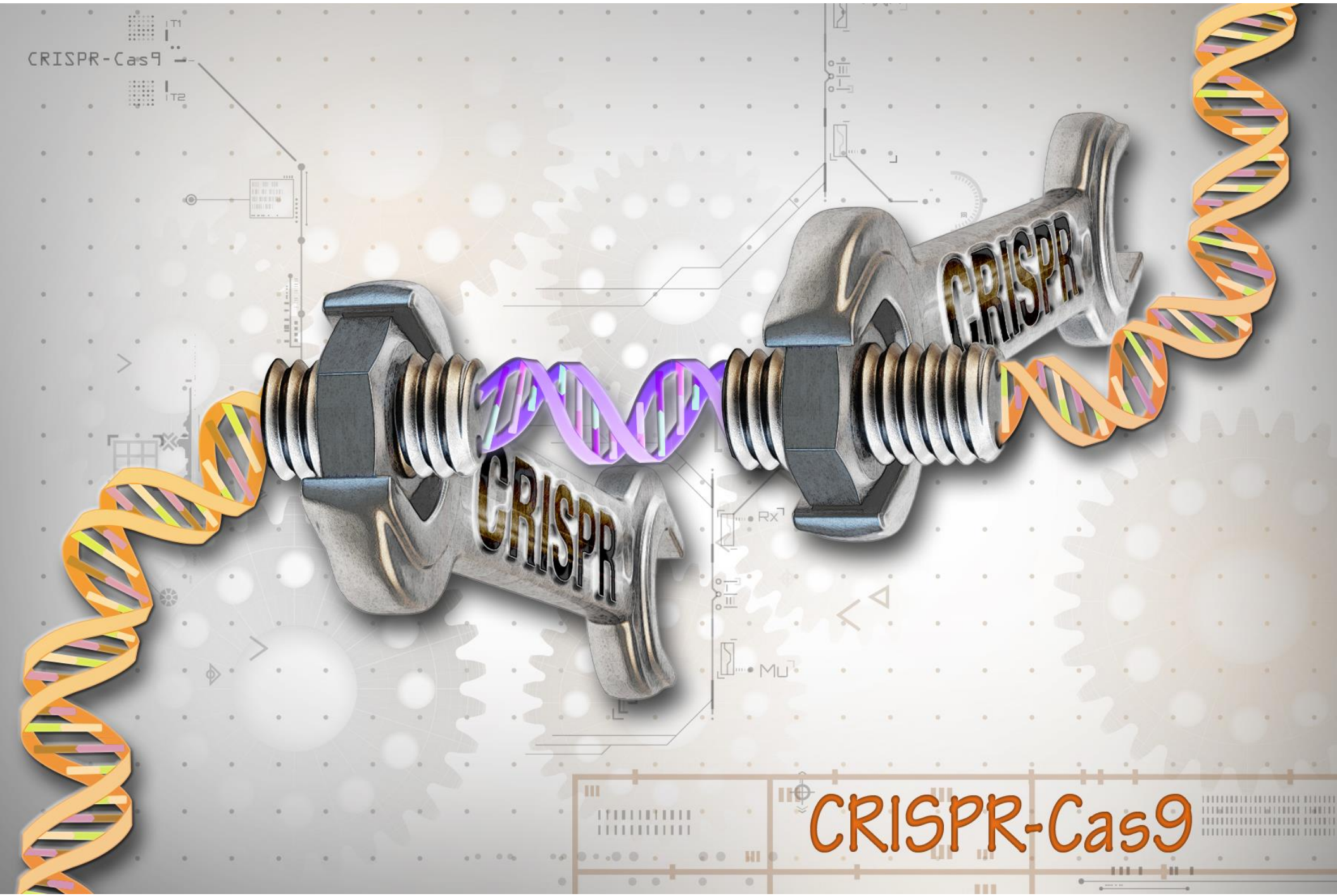
# CAR-T Cell Cancer Immunotherapy



A T cell recognizes a cancer cell and proceeds to kill it. The T cell will perforate the membrane lining the cancer cell and inject it with toxic proteins. Unlike usual cancer chemotherapies, T cells are living cells. T cells can reproduce themselves, and one T cell can kill many cancer cells. T cells can migrate through different tissues looking for disease and may survive for years to form an immune system's memory.



Sources: Photo: Steve Gschmeissner/Science Source. Text: The Stiliyan Petrov Foundation, UK.




CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats

Source: Ernesto del Aguila III, National Human Genome Research Institute

# CRISPR in Research …

- Genetically modifying crops (e.g., corn, tomatoes, cotton)
- Virus eradication (e.g., hepatitis C)
- Screening for cancer genes
- Genome engineering (including human germ cells)
- Potential corrections of genetic mutations: cystic fibrosis, sickle cell anemia, Huntington's disease
- Organ transplantation: gene editing of donor organs to reduce immune rejection in recipients
- Develop animal models for understanding human disease, drug testing
- Ethical and safety concerns, e.g., use in human embryo

CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats

# CRISPR Challenges for HTA

- Regulatory status unclear: Medical product (e.g., drug or biologic) or medical procedure? What agency/authority approves it for clinical use in humans?
- May be difficult to identify patients: rare or ultra-rare diseases; must also consider genotype and phenotype
- Evidence standards for CRISPR as a personalized genomic therapy unclear: N-of-1 trials? Groups of patients with similar therapies?
- Defining successful outcomes: Biomarkers? Mortality and morbidity? Will good outcomes be only temporary?
- Unknown longer-term outcomes and adverse events: costly, long-term follow-up (patient monitoring, phase IV studies, etc.) may be required
- New ethical, legal, social concerns
- Engagement of patients and the public on complex technical subject
- Cost-effectiveness (e.g., cost/QALY) of CRISPR therapies may exceed standard thresholds
- Payment: Even if cost-effective and acceptable budget impact, high one-time cost may require different payment approach

# Technologies that depend on real-world evidence to demonstrate effectiveness and safety

# When Can Real-World Evidence (RWE) Help to Address Limitations of Traditional RCTs?

- When patients respond differently to a technology (heterogeneity of treatment effects)
- Technologies that are approved via accelerated (fast) regulatory pathways (smaller sample sizes, fewer outcomes measured, shorter duration of study)
- Technologies intended for small (rare) patient populations
- Technologies with uncertain long-term outcomes and adverse events (safety)
- Technologies being used for “off-label” indications
- Technologies intended for special patient populations who may not be appropriate for randomization (e.g., children, pregnant women)
- When adherence in community populations is likely much lower than in RCT populations
- Technologies being reimbursed using “value-based” arrangements

# Real-World Evidence (RWE)

- Derived from real-world data (RWD) sources other than traditional RCTs
- Complements -- does not substitute for -- evidence from traditional RCTs
- Uses study designs and methods adapted for routine or community settings
- Informs determinations about effectiveness (vs. efficacy) and external validity (vs. internal validity)
- Re-balances relative importance:  RWE vs. traditional pre-marketing clinical trials for regulatory approval

# Sources of RWD

- Payment claims
- Electronic health records (EHRs)
- Registries (e.g., of health care utilization or outcomes of patients who received a particular health technology)
- Laboratory test results
- Molecular/genomic data
- Vital statistics (births, deaths, marriages, etc.)
- Patient-generated data (directly from patients, e.g., from personal phone, computer “apps,” social media)

➢ Also: Advanced, powerful computing can be used to link and analyze large sources of real-world data

# RWE Strengths and Weaknesses

Strengths, e.g.:

- Assess long-term and rare outcomes (effectiveness and safety)
- More heterogeneous population (external validity)
- Size may allow for subgroup analyses
- Less time required compared to clinical trials
- Less costly than clinical trials
- Assess many factors that might affect outcomes

Weaknesses, e.g.:

- Potential for various biases (e.g., patient selection bias)
- Potential for confounding (e.g., uncontrolled factors affecting outcomes)
- Data sources may be unreliable (poor quality)
- Data sources may be incomplete (missing data)
- May require complex design and analytical methods

# Drug-diagnostic combination technologies

# ARE PAYERS READY TO ASSESS THE COMBINED VALUE OF DRUGS WITH A COMPANION DIAGNOSTIC?

by Anick Dubois PhD and Marie-Pierre Dubé PhD

Targeted drugs that are tailored to biomarkers are most often developed or co-developed with a companion diagnostic to identify patients who are good responders. Such companion diagnostic (CDx)-drug-(Rx) pairs have gained substantial interest in the recent years. This market is currently worth approximately $42 billion and should be worth over $60 billion by 2019[1]. The oncology area leads the market (e.g. Herceptin, Erbitux, Vectibix, Gleevec, Iressa, Glotrif, Zelboraf, Xalkori, Mekinist, Tafinlar). Currently, 42% of all drugs and 73% of oncology drugs in development are targeted drugs[2]. In 2014, 20% of drug approvals in the United-States (US) were targeted drugs[3].

The high cost (average of $100,000 to $300,000 USD per year)[4] and rapid market expansion of CDx-Rx pairs has put pressure on Health Technology Assessment (HTA) bodies to conduct joint assessment and to provide reimbursement guidelines for CDx-Rx pairs. HTA bodies and payers have much experience in the assessment of drugs, but adding a test to the assessment of a drug is creating additional challenges. In particular, the establishment of a unique and clear approach for the assessment of CDx has been difficult. Consequently, guidance on the appraisal of the combined value of CDx-Rx pairs for decision-making is lacking.

# Evaluation Framework for Tests

- **Analytic validity**: how well a test detects (or measures) a property or trait it is intended to detect (e.g., a genotype)
- **Clinical validity**: how well a test detects or predicts a clinical condition (e.g., a phenotype)
- **Clinical utility**: extent to which a test result affects a decision that affects patient outcomes

Also may include:

- **Cost effectiveness**: gain in health outcomes per unit cost per patient
- **Budget impact**: impact of the test on the budget (overall costs) of a health system (or hospital) when used for the indicated patient population
- **Ethical, legal, social implications**: impact of the test on individuals, families, society (stigma, discrimination, lack of equity, etc.)

## BlueCross BlueShield Technology Evaluation Center (TEC) Evaluation Criteria

1.The technology must have final approval from the appropriate governmental regulatory bodies.

2.The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

3.The technology must improve the net health outcome.

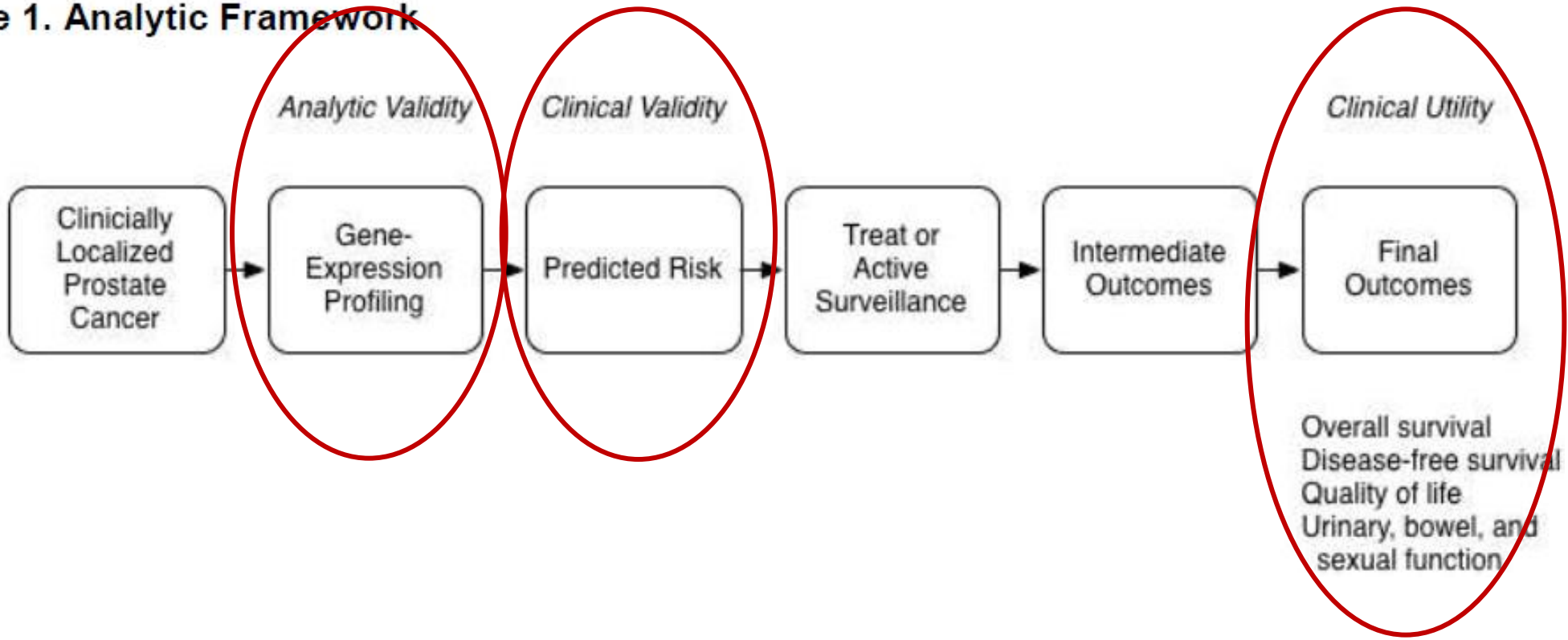
4.The technology must be as beneficial as any established alternatives

5.The improvement must be attainable outside the investigational settings.

**Gene Expression Analysis for Prostate Cancer Management – Jan. 2015**

What is the incremental value of gene expression testing compared with clinical criteria for discriminating men with aggressive cancer from those with indolent disease to guide treatment decisions that improve overall net health outcomes?

**Figure 1. Analytic Framework**



**Gene Expression Analysis for Prostate Cancer Management – Jan. 2015**

## Author Conclusions and Comment

Two RTPCR-based gene expressions tests -- Prolaris® and Oncotype Dx® Prostate -- are commercially available in the United States. We evaluated published evidence on their use in combination with current clinical criteria (Gleason score, PSA serum levels, clinical stage) to further stratify biopsy-diagnosed, localized prostate cancer according to expression levels of discrete sets of genes that, when overexpressed, are considered to reflect increased biological aggressiveness of a lesion. Such information would assist in initial clinical disease management, specifically to decide whether a patient should proceed to definitive therapy (i.e., surgery) or could safely proceed to active surveillance. Published evidence is sparse and insufficient to draw conclusions on the analytic validity, clinical validity, or clinical utility of Prolaris ®, and is insufficient to determine the clinical validity or utility of Oncotype Dx ® Prostate in patients under active surveillance program.

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