FIRST OF ITS KIND

Health Economic Impact Project
Analysis of regenerative medicine advanced therapy
This analysis includes a review of published academic literature, health technology assessments, and value frameworks related to the global health economic impact of cell and gene therapies. Performed by IQVIA on behalf of the ARM Foundation Health Economic Impact Working Group, the landscape analysis is the initial step in the Foundation’s broader Health Economic Impact Project, which will ultimately provide a framework to measure and forecast the effect that breakthrough and potentially curative therapies will have on national and global healthcare economies.
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Project Overview
RM/ATs face suboptimal consideration of value throughout development and lifecycle management

<table>
<thead>
<tr>
<th>Approval</th>
<th>Reimbursement</th>
<th>Launch</th>
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</thead>
<tbody>
<tr>
<td>Jan. 2010 – Oct. 2012 - Glybera approved after 4th review in EU</td>
<td>Nov. 2015 - Drop pursuit of FDA approval after request for additional study</td>
<td>x Only limited reimbursement available via specialized services (UK) or temporary funding mechanism (DE) despite inconclusive efficacy data and very small patient population</td>
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<tr>
<td>May 2015 - Strimvelis approved for use in EU</td>
<td>Nov. 2014 - Price set at €1.1M in Germany</td>
<td>✓ In EU, availability of long term clinical data, discounted price, and outcome based refund led to a favorable reimbursement status, yet cross-border complexities delayed adoption</td>
</tr>
<tr>
<td>Aug. 2016 - GSK opened negotiations at €1M but payers were successful at reducing the price</td>
<td>Launched at price of €1.1M</td>
<td>Launched at price of €594,000</td>
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</table>

*RM/AT therapies include cell and gene therapy products; excludes tissue engineered products
To reframe the economic argument, a RM/AT specific economic model is needed

**Project Objective:** Build RM/AT specific economic model and being to identify the benefit (cost impact) to the entire healthcare system (e.g. payers, patients, hospitals, etc.) associated with RM/ATs

**Project Approach**

1. **Regenerative Medicine Landscape Analysis**
   - Conduct detailed literature review of existing resources on RM/ATs economic impact
   - Conduct primary market research with KOLs to refine understanding of current RM/AT economic impact models
   - Synthesize findings and identify preliminary inputs for RM/AT economic impact model

2. **Economic Model Development and Validation**
   - Use inputs from Phase 1 to develop initial economic model
   - Validate economic model with relevant stakeholders (payers, providers, and patients / patient advocates) via primary market research
   - Review and revise economic model based on PMR and present findings to ARM Foundation

3. **Application of Model to Case Studies**
   - Leverage internal IQVIA databases to collect data for one existing and one pipeline regenerative medicine therapeutic as finalized inputs
   - Enter data into economic model to calculate overall current/ projected cost-savings associated with selected therapeutics when compared to the current SoC

**Key Deliverables**

- **Readout of current landscape of RM/ATs economic impact models**
- **Preliminary inputs for economic model**
- **Refined and robust economic model**
- **Further validation of model through calculation of net economic impact of regenerative medicine therapeutics across two case studies**
Executive Summary
Executive Summary

Key Findings

• There is a need for a more robust framework to demonstrate the value of RM/ATs stakeholders

• Our research across 52 publications uncovered additional economic considerations needed for a robust RM/AT framework:
  • HTA models identified societal burden during treatment and patient population size as inputs
  • Academics suggested to include innovative payment / contracting models, patient / caregiver non-medical and indirect medical costs, expanded time horizon, and mnf costs
  • Based on CAGT Center expertise, lifetime patient / caregiver non-medical costs, system-wide impact, and patient-centered endpoints should also be included

The Cell and Gene Therapy (CAGT) Center is now positioned to translate findings and insights from RM/AT economic framework landscape work into a white paper in collaboration with ARM Foundation team

Additional considerations from research:
1. Lack of RM/AT-specific evidence base
2. Need for real world evidence platform
RM/AT therapies are facing specific challenges to demonstrate value to stakeholders

**Patient / Caregiver**
- Patients face **high access barriers** due to enormous co-pays for RM/ATs and small number of accredited centers for treatment.

**Manufacturer**
- Difficult to **demonstrate clinical superiority** as small target patient populations make it difficult and expensive to conduct RCT, head-to-head studies.
- Difficult to **demonstrate short-term cost-effectiveness** vs. non-curative comparators.

**RM/AT Challenges**

**HTA / Payers**
- Payers **skeptical of long-term clinical efficacy** due to lack of statistically significant, head-to-head trials.
- RM/ATs often not cost-effective as payers typically prioritize short-term, direct impact; they do not completely capture long-term, indirect / non-medical benefits of RM/ATs.
- Payer 3-5 year budgetary cycles cannot handle high upfront cost of RM/ATs.

**Providers / Hospitals**
- Lack of uniform assessment of RM/ATs causes hospitals / providers to struggle to obtain reimbursement.
- Hospitals assume high financial risk of RM/ATs due to prolonged reimbursement timelines caused by payers struggling to absorb budget impact of RM/ATs.
RM/AT therapies have been unable to meet market expectations due to challenges in value determination

**Common challenges across RM/AT commercial success considerations include**

- Stakeholder skepticism of high upfront costs for RM/AT therapies with uncertain economic value
- Unclear models and inputs for economic assessments by regulators and payers
- Suboptimal patient access and reimbursement schemes compared to traditional therapies
- Unclear long-term therapy benefit of potentially curative therapies

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**Provenge**
Approved by FDA, but faced high scrutiny over lack of value for high cost and overall budget impact due to large patient pop.

**Imlygic**
Approved by FDA as it demonstrated clinical benefit, but failed to gain ODD

**MACI**
Mnf cut production costs to improve chances of success in US

**Kymriah**
Approved by FDA but high budget impact causing slow uptake

**Yescarta**
Approved by FDA but slow uptake due to reimbursement barriers

**Luxturna**
Approved by FDA and launched 3 payment/contracting schemes

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**Glybera**
Failed to achieve commercial success as mnf. did not guarantee clinical performance via P4P deal

**MACI**
Was able to demonstrate CE over SoC, but withdrew from EU market due to lack of sales

**Provenge**
Approved by EMA, but did not demonstrate CE to NICE and withdrew from market

**Imlygic**
Struggled to demonstrate CE to NICE, but eventually approved with large discount and P4P guarantee;

**Strimvelis**
Favorable reimbursement at discounted price, but cross-border manufacturing and administration delayed adoption
Most countries have leveraged traditional archetypes and frameworks that are not suitable for RM/ATs

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<th>Payer Archetypes</th>
<th>Pharmacoeconomic</th>
<th>Therapeutic Referencing</th>
<th>Willingness-to-pay</th>
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<td><strong>Definition of value:</strong></td>
<td>Value is considered in the context of utility that a treatment brings to stakeholders and/or the ability to implement that treatment with constrained resources</td>
<td>Value is considered as the therapeutic benefit that a product brings over the standard of care and/or other therapeutic alternatives</td>
<td>Value is influenced by the complex dynamics of competition on both the supply and demand side of the payer equation, reflecting both willingness and ability to pay</td>
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<tr>
<td><strong>Key test of value:</strong></td>
<td>• Cost-effectiveness (usually by ICER)</td>
<td>• Clinical benefit relative to comparator(s)</td>
<td>• Clinical and non-clinical benefit; unmet need, Cost / budget impact</td>
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<tr>
<td><strong>Issues for RM/ATs:</strong></td>
<td>• Difficult to meet current QALY thresholds due to small patient populations</td>
<td>• Challenging to compare clinical superiority and cost savings against non-curative comparator</td>
<td>• Difficult to justify non-clinical benefit to payers focused on clinical value, Fragmented systems make it difficult to pay upfront</td>
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With regulatory requirements varying across geographies for RM/AT therapies...

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<tr>
<th>Country</th>
<th>Clinical Evidence</th>
<th>Comparative Clinical Evidence</th>
<th>Cost Effectiveness Analysis</th>
<th>Budget Impact Assessment</th>
<th>Company Costing Information</th>
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<td>Red</td>
<td>*For products with ASMR rating I – III only</td>
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<td>Japan</td>
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<td>Red</td>
<td>*Starting in Oct 2016, CEA required for certain drug candidates</td>
<td>*Only if “cost-plus” pricing method is used</td>
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</table>

**Legend:**
- **Green:** Required evidence
- **Orange:** Optional / required only circumstantially
- **Red:** Not required

- **Pharmaco-economic**
- **Therapeutic Referencing**
- **Willingness-to-pay**
…there is substantial variation on which HTA bodies manufacturer’s pursue, and on HTA outcomes

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<tr>
<th>Therapy</th>
<th>Regulatory / HTA Agency</th>
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<td></td>
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<td>Luxturna</td>
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<td>Provenge</td>
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</table>

- **Green**: Approved / Favorable Assessment
- **Orange**: Approved / Favorable Assessment with Exceptions
- **Red**: Not approved / Unfavorable Assessment
- **Gray**: Not assessed by HTA or currently under review
The CAGT Center team conducted a literature review to identify existing and suggested economic considerations for RM/ATs. The literature review included HTA reports and appraisals, topical publications, and additional considerations. The HTA reports and appraisals were used to understand economic considerations in prior evaluations of existing RM/ATs by HTAs. The team identified literature that provided a broader perspective on economics related to RM/ATs. Academic insights on additional economic considerations that should be incorporated into existing valuation approaches were also considered. The CAGT Center team utilized findings from the literature review to generate additional economic considerations to more comprehensively capture the value of RM/ATs.
Although there is no specific valuation framework for RM/ATs, major agencies have conducted initial studies into their value.

- **NICE CAR-T Model**
- **ICER CAR-T White Paper**
- **NICE Appraisal T-VEC**
- **NICE Appraisal MACI**
- **CADTH Enviro. Scan**
- **ICER Luxturna Model**
- **ICER CAR-T Model**

Highlights significant clinical potential of gene therapies and recommendations for future consideration by stakeholders.

T-VEC failed to demonstrate cost-effectiveness until further evidence was submitted by mnf. and a discount was offered.

MACI demonstrated cost-effectiveness over surgical intervention, especially in patients with prior fracture.

CADTH determined there were no existing HTA frameworks specific to gene therapies.

Luxturna demonstrated cost-effectiveness when taking into consideration societal burden on patients and caregivers.

Kymriah and Yescarta were shown to be cost-effective when looking at lifetime horizon.

**NICE and ICER cost-effectiveness models begin to demonstrate importance of expanding economic inputs taken into consideration during evaluation of RM/ATs**
Emerging HTA models begin to demonstrate value by including a more comprehensive set of metrics on RM/AT economic impacts

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<td>Non-medical costs (during treatment)</td>
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</table>

Patient and caregiver inputs are less commonly considered than other considerations.
HTA white papers highlight additional considerations due to the absence of a RM/AT-specific HTA framework

CADTH Environmental Scan: Gene Therapy*

CADTH aimed to identify existing frameworks or HTA approaches to evaluating gene therapies

• NICE, GBA, and SBU believe that existing HTA framework is sufficient to assess gene therapies
• AHTA is planning to develop separate guidelines for evaluation of gene therapies

From its current research, CADTH concluded that gene therapies often fail to meet evidence and pricing requirements when limited comparator data, long-term data, and health budgets are restricted

ICER Gene Therapy White Paper

ICER provided recommendations for mnfs. to overcome likely reimbursement and access hurdles

• Offset high budget impact by presenting alternative payment strategies, such as pay for performance or amortization, to payers
• Robust registry studies to reduce uncertainty where RCTs are not possible
• Present evidence demonstrating how overall cost of therapy is linked to costs of development

ICER highlighted the need to incorporate novel elements into manufacturers’ strategy to clearly demonstrate value of gene therapies to payers

*CADTH paper still in progress, findings based on current draft
SBU: Swedish HTA, AHTA: Australian HTA
NICE appraisals for both T-VEC and MACI validate additional inputs taken into consideration for economic value assessment

**NICE Appraisal T-VEC (2016)**
- NICE agreed with the company’s inputs to determine cost-effectiveness:
  - Treatment costs
  - Administration costs
  - Routine care costs
  - On progression costs
  - BSC/palliative care costs
  - Terminal care costs
  - Adverse events

  Additional economic considerations including reduced anxiety for patients with visible skin tumors, and caregiver-related cost were not included in the cost-effectiveness model but were brought up during discussions

- NICE determined T-VEC clinically and cost-effective only after additional manufacturer submitted evidence, and implementation of a patient access scheme (PAS), further discounting, and a prior EMA agreement for additional post-marketing studies to address long-term safety

**NICE Appraisal of MACI (2017)**
- NICE used MACI’s budget impact analysis and ChondroCelect’s cost-effectiveness analysis for the appraisal:
  - Development costs*
  - Microfracture
  - First TKR (PKR or TKR)
  - Further TKR
  - Outpatient TKR
  - Rehabilitation
  - HrQoL and Adverse events

  Health-related quality of life improvements and adverse event disutility scores were considered, but demonstrated either no difference than standard of care, or did not demonstrate sufficient data

- NICE determined cost-effectiveness for roughly half of the eligible patient population but noted that QALY gain estimates for the full eligible population would likely be greater than £20,000.

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PSS=personal social services; TKR=total knee replacement; PKR=partial knee replacement

*Development costs include courier services and development of cell culture, cell harvesting procedures, ACI kit, staff time, and transporting the cells to and from the laboratory
A detailed review of current academic literature further identified new economic inputs that demonstrate value of RM/ATs (1/3)

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Selected literature was prioritized based on content relevance; a comprehensive list of literature sources reviewed can be found in the supplemental capture sheet.
A detailed review of current academic literature further identified new economic inputs that demonstrate value of RM/ATs (2/3)

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A detailed review of current academic literature further identified new economic inputs that demonstrate value of RM/ATs (3/3)

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Selected literature was prioritized based on content relevance; a comprehensive list of literature sources reviewed can be found in the supplemental capture sheet.

*Aggregate score is a composite score of suggestions across all 19 research reports.
Innovative payment models have been critical to help overcome HTA / payer uncertainties of high upfront costs

Payers skeptical of long-term efficacy of RM/ATs

- **Kymriah**
  - P4P contract with CMS

- **Imlygic**
  - P4P contract with NICE

- **Strimvelis**
  - P4P contract with AIFA

- **Luxturna**
  - P4P contract with Harvard Pilgrim and Express Scripts

Payers unable to absorb large budget impact of high-cost RM/ATs

- **Luxturna**
  - Annuity-based contracting model with CMS, with payments tied to outcomes

Manufacturers are guaranteeing clinical efficacy of their products through outcomes-based contracting agreements

Spark is reducing budget impact by allowing CMS to spread payment over several years

**Additional Considerations**

Although innovative contracting and payment models reduce payer skepticism and budget impact, issues remain:

- Lack of infrastructure to track patients and link clinical outcomes to claims
- Innovative payment models reduce immediate budget impact and/or spread risk but do not improve long-term sustainability
Real world evidence generation will play a key role in reducing stakeholder uncertainty over long-term clinical / safety of RM/ATs

### Historical Challenges

- Amgen did not provide sufficient clinical comparison evidence to differentiate Imlygic from current SoC comparator
- Glybera did not accurately establish natural progression of disease and chose an incorrect primary endpoint
- Provenge demonstrated significant benefit for OS but not PFS; Dendreon did not identify subpopulations where benefit may be greater to improve overall value story

### Historical Successes

- Kymriah leveraged RWE approaches to identify natural progression of disease and burden of illness in patients
- Kymriah compensated for a single-arm pivotal trial by leveraging RWE to highlight significant benefit to patients

### Application of RWE Strategies to RM/ATs

**Retrospective data analyses**

- Define historical treatment landscape, patient journey, burden, and generate data for SOC / comparators
- RWE will characterize how product will address disease burden and fulfill gaps in treatment, differentiating it from SoC

**Prospective observational studies (cohort)**

- Track safety and effectiveness before, during, and after treatment of patients
- Identify potential subpopulation benefits to differentiate pdt
- Demonstrate durability of effect and safety after launch

**Registry Studies**

- Continue to demonstrate real-world durability of effect / safety
- Capture outcomes to support innovative payment models / contracting agreements
- Identify potential subpopulations and follow-on indications
Internal CAGT Center expertise identified additional economic inputs and considerations to maximize RM/AT value to stakeholders

**Additional economic inputs**

**System-wide costs**
- Looking at loss of economic productivity due to chronic illness from a broader perspective, such as the government

**Lifetime non-medical costs**
- Lifetime transportation costs, loss of earnings, loss of education

**Patient-centered Endpoints**
- Premiums for new patient-centered endpoints into clinical value consideration

**Delayed reimbursement codes**
- Lack of reimbursement codes increases financial risk for hospitals / providers, with some unable to bear high costs of RM/ATs during interim before reimbursement is issued

**Stakeholder Engagement**
- Early engagement with payers to align on most meaningful clinical endpoints, real world evidence, pricing comparators to create most compelling value story
Inclusion of these additional economic considerations will allow HTAs / payers to better assess the net economic benefits of RM/ATs

<table>
<thead>
<tr>
<th>Inputs from HTA Models*</th>
<th>Inputs from Literature Review</th>
<th>Inputs from CAGT Center</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population size</strong></td>
<td><strong>Age of onset</strong></td>
<td><strong>Societal economic impact</strong></td>
</tr>
<tr>
<td>Small patient populations lead to higher prices to offset development costs</td>
<td>Younger patients will gain significantly larger value from curative treatments across all inputs</td>
<td>Costs to employers, government, etc. due to loss of productivity and chronic care</td>
</tr>
<tr>
<td><strong>Lifetime horizon</strong></td>
<td><strong>Additional value for curative nature</strong></td>
<td><strong>Patient centered endpoints</strong></td>
</tr>
<tr>
<td>Shifting focus from traditional short-term budgetary cycles to assess long-term cost-effectiveness</td>
<td>Modifying CE thresholds or budget impact considerations for curative therapies</td>
<td>Ascribing greater value to PCEs to better understand non-clinical / clinical benefit of RM/ATs for patients</td>
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<tr>
<td><strong>Patient indirect costs (during treatment)</strong></td>
<td><strong>Patient &amp; caregiver indirect medical costs (lifetime)</strong></td>
<td><strong>Patient &amp; caregiver non-medical costs (lifetime)</strong></td>
</tr>
<tr>
<td>Costs associated with loss of productivity</td>
<td>Costs associated with loss of productivity</td>
<td>Costs associated with transport, home care, counseling, etc.</td>
</tr>
<tr>
<td><strong>Patient &amp; caregiver non-medical costs (during treatment)</strong></td>
<td><strong>Real world evidence</strong></td>
<td></td>
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<tr>
<td>Costs associated with transport, home care, counseling, etc.</td>
<td>Valuing subpopulation data, indirect comparisons vs. SoC, follow-up data, etc. from RWE</td>
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<tr>
<td><strong>Innovative payment models / contracting</strong></td>
<td><strong>Innovative payment models / contracting</strong></td>
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<tr>
<td>Reducing payer uncertainty surrounding high cost / budget impact</td>
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</table>

Although these inputs will help uncover additional value of RM/ATs, they will require different levels of resource investment and involve different stakeholders across health systems

*These inputs are derived from assessments conducted by HTAs, however they are not currently included in most HTA / payer approaches

**Will not impact value of overall product, but will reduce budget impact and improve market access
Next Steps
Upon completion of secondary research the CAGT Center team is positioned to translate findings into a white paper.

**Secondary research findings from landscape development**

- **White paper detailing economic inputs for a novel valuation framework to capture complete value of RM/ATs to stakeholders**
  - White paper will inform greater RM/AT community of need for a novel RM/AT-specific valuation framework

- **Utilizing economic inputs from literature review to inform the development of RM/AT-specific database**
  - Database will allow RM/AT manufacturers to reference historical data and understand steps needed to successfully commercialize their products

- **Utilizing findings related to RM/AT evidence requirements to inform development of a real-world evidence platform**
  - Platform will help manufacturers understand real-world evidence strategies to reduce clinical and safety uncertainties related to their products

**Additional considerations**
The whitepaper will give a holistic view of the RM/AT landscape, and will culminate in recommendations for a new framework.

**IQVIA-ARM RM/AT Whitepaper**

- Executive summary
- Understanding of the cell and gene therapy
  - Current and future market
- Challenges and considerations for RM/AT value
  - Key gaps in RM/AT economic considerations
  - Recommendations for new inputs
  - Preliminary thinking around new economic model
- Implementation of new framework
  - Case study: value assessment of marketed RM/AT
  - Case study: value consideration of pipeline RM/AT
- Additional Considerations
- Conclusions

The whitepaper will introduce new economic considerations that should be taken into account by different stakeholders for value determination.
Prioritization of recommended inputs for RM/AT framework will take into account the variation in perceived product value.

<table>
<thead>
<tr>
<th>Factors Considered</th>
<th>Therapeutic benefit</th>
<th>Patient benefit</th>
<th>Cost effectiveness</th>
<th>Budget impact</th>
<th>Innovative characteristics</th>
<th>Availability of therapeutic alternatives</th>
<th>Equity considerations</th>
<th>Public health impact/Unmet need</th>
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<tbody>
<tr>
<td>Formal HTA / P&amp;R</td>
<td>NICE</td>
<td>G-BA</td>
<td>HAS</td>
<td>CIPM</td>
<td>AIFA</td>
<td>ORPH-VAL</td>
<td>ICER-ODA</td>
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Greater ease of implementation ✓  Lesser ease of implementation ~

ODA= Orphan Drug Assessment; ORPH-VAL = European Working Group for Value Assessment and Funding Processes in Rare Diseases.
The white paper will further explore strategies and implications of different approaches for manufacturers.

**Prioritization of inputs**

![Resource Investment vs. Likelihood of Success](image)

**Implications for White Paper**

- Highlight how curative nature of RM/ATs presents a unique challenge to approaching these inputs.
- Explore strategies to bring inputs into stakeholder consideration, using historical analogues facing similar challenges.
- Identify partners to engage in order to improve likelihood of success.
- Utilize tradeoff between resource investment and likelihood of success to prioritize inputs RM/AT manufacturers should target.

---

**Stakeholders will need to engage in various activities to improve uptake of a novel RM/AT valuation framework**

<table>
<thead>
<tr>
<th><strong>Patient / Caregiver</strong></th>
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<tbody>
<tr>
<td>• Patient advocacy groups will need to lobby payers and regulatory oversight agencies to incorporate patient and caregiver burden into RM/AT valuation process</td>
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<thead>
<tr>
<th><strong>Manufacturer</strong></th>
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<tr>
<td>• Need to invest in real world evidence generation strategies to strengthen clinical / safety data</td>
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<tr>
<td>• Develop mechanisms to utilize innovative payment models and contracting strategies</td>
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<tr>
<td>• Generate compelling value story that demonstrates development and operational risks and costs assumed by mnf</td>
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<thead>
<tr>
<th><strong>HTA / Payers</strong></th>
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<tbody>
<tr>
<td>• Pilot a uniform, novel valuation framework that takes into consideration RM/AT-specific economic considerations</td>
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<tr>
<td>• Develop data infrastructure to support innovative payment models and contracting strategies</td>
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<tr>
<td>• Initiate early dialogue with mnfs to shape clinical development of RM/ATs</td>
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<tr>
<th><strong>Providers / Hospitals</strong></th>
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<tr>
<td>• Engage public and private payers to create timely reimbursement plans for RM/ATs</td>
<td></td>
</tr>
<tr>
<td>• Work with mnfs to generate real world evidence to strengthen argument for RM/ATs</td>
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Detailed Findings
Emerging value considerations
As healthcare spending spans well beyond prescription drug costs, it will be important to understand impact across categories.

### U.S. Health Spending by Category (as of January 2017)

- Hospital care: 32.0%
- Physician and clinical services: 20.0%
- Other health spending: 15.0%
- Remaining personal health care: 11.0%
- Prescription drugs: 10.0%
- Physician and clinical services: 5.0%
- Dental services: 4.0%
- Home health care: 3.0%

### Health Spending Year-over-Year Growth for Selected Categories, January 2017 vs. January 2016

- **Hospital care**:
  - January 2017: 6.0%
  - January 2016: 5.0%
- **Physician and clinical services**:
  - January 2017: 6.0%
  - January 2016: 5.0%
- **Prescription drugs**:
  - January 2017: 4.0%
  - January 2016: 3.0%
- **Nursing home care**:
  - January 2017: 8.0%
  - January 2016: 7.0%
- **Home health care**:
  - January 2017: 7.0%
  - January 2016: 6.0%
- **Dental services**:
  - January 2017: 4.0%
  - January 2016: 3.0%

Source: Altarum monthly national health spending estimates; Center for Sustainable Health spending, Altarum Institute Spending Brief #17-03, January 2017 data
Major existing models have started to take a more holistic approach in assessing value, and have overlap in their economic inputs

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<thead>
<tr>
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<tbody>
<tr>
<td><strong>Inputs</strong></td>
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<td>Cost of acquisition</td>
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<td><strong>Outputs</strong></td>
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<td>Cost vs. benefit</td>
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</table>
Using hypothetical CAR-Ts, NICE developed the first model to determine if their valuation framework was still valid for RM/ATs

**Approach**

- NICE developed a model to understand how hypothetical CAR-Ts would perform with their typical CE framework
- Created two hypothetical TPPs:
  - CAR-T as a bridge to HSCT treatment (~350k GBP, 7.5 QALY)
  - CAR-T is used with curative intent (~500k GBP, 10 QALY)
- Tested outcomes under three hypothetical evidence sets:
  - 60-80 patients with 10 month follow-up
  - 60-80 patients with 5 year follow-up
  - 120-140 patients with 5 year follow-up

**Economic Considerations**

- The model took into account:
  - HSCT costs
  - Adverse events costs
  - Treatment administration and monitoring costs
  - Patient follow-up costs (e.g. ongoing care and rehabilitation)
  - Short-term HRQoL (defined by relapse or remission)
  - Long-term HRQoL (defined by development of comorbidities)

**Conclusions**

- For the curative intent base case with minimum evidence set, assessments were borderline or favorable only when either given a discount of 10% with lifetime leasing, reducing cost to same price as bridging to HSCT (~350k GBP), or a combination of these strategies
  - Increased maturity of evidence had a significant impact by reducing uncertainty, and may facilitate traditional payments strategies
- NICE conclusions: (1) NICE appraisal methods are still applicable to CGTs, (2) quantifying and presenting clinical outcomes and decision uncertainty is a key factor in the assessment outcome, (3) Where evidence is immature but there is potential for substantial patient benefits, innovative payment methodologies will need to be developed to reduce budget impact and share risk
NICE developed a model to investigate the cost-effectiveness of ACI treatments compared to microfracture

**Approach**
- NICE developed a Markov model to understand how autologous chondrocyte transplantation (e.g. MACI) compared to microfracture (surgical alternative)
- Utilized two cases for analysis:
  - **Base case**: patient starting age of 33, lifetime horizon, procedure conducted as day case, and based on existing clinical evidence
  - **Sensitivity analysis**: patient starting age of 45 (increased likelihood of knee replacements), with varied time horizon, and based on potentially improved clinical evidence for ACIs

**Economic Considerations**
- The model took into account:
  - Cost of procedure / treatment
  - Cost of knee replacement
  - Utility (QoL based on patient-reported surveys of patient health)
  - Mortality

**Conclusions**
- For the base case, the models determined that there was a 14k GBP/QALY gained through MACI vs. microfracture
- In patients who have previously had knee repair, the assessment determined 22k GBP/QALY gained vs. microfracture
- In patients who have not had previous knee repair surgery, the assessment determined 8k GBP/QALY gained vs. microfracture
- NICE recommended use of MACI, but limited use to patients (1) who have not had previous knee repair (2) have minimal osteoarthritic damage to the knee (3) articular cartilage defects over 2 cm³
ICER developed a model to understand the cost-benefit profile of two approved CAR-Ts against the SoC in the US

**Approach**
- Created a model to determine CE of Kymriah and Yescarta vs. SoC (clofarabine and chemotherapy)
- Utilized a two part model consisting of a short-term decision tree and long-term patient survival model
- Patient survival, quality-adjusted survival, and health care costs from payer perspective were estimated across the lifetime horizon
- Base case took only the payer perspective (e.g. direct medical costs), but productivity loss was considered in a scenario analysis

**Economic Considerations**
- Economic inputs considered by the model:
  - Treatment acquisition costs
  - Hospital mark-up costs
  - Healthcare utilization costs (e.g. administration/monitoring)
  - Adverse event costs
  - Lost productivity during inpatient and administered treatments

**Conclusions**
- Base case: assuming outcomes-based contracting, the CE of each therapy fell below the commonly cited thresholds of $50-150k/QALY
- CAR-Ts were not CE when looking at a short time horizon but with a longer time horizon (7 years for Kymriah, 24 years for Yescarta), both fell below the $150k/QALY threshold
- Kymriah would have acceptable budget impact if it achieves $50-150k/QALY; Yescarta would do the same if it meets $50k/QALY threshold
- Societal case, considering loss of productivity during treatment, did not improve CE Ratio
ICER developed a model demonstrating significance of including indirect costs when evaluating cost effectiveness of Luxturna

Approach

- Created a model to determine **CE of Luxturna vs. SoC** (physician visits and supportive care)
- Utilized a Markov model with a population mirroring Luxturna’s trial population
- Investigated two scenarios: (1) **base case** was the US payer perspective, which only includes direct medical costs and (2) **modified societal perspective** included direct and indirect costs
- Due to lack of QoL data, authors had to utilize outdated data from studies of other retinal disease populations, potentially biasing the study results

Economic Considerations

- Cost of drug and surgery
- Adverse events
- Direct cost of medical care
- Direct cost of ophthalmic-related depression
- Direct cost of ophthalmic-related trauma
- Indirect cost of education
- Indirect costs of productivity loss
- Direct non-medical costs for caregivers, transportation, and nursing home care

Conclusions

- Authors concluded that in the **base case**, due to the **high cost** of the Luxturna, it is **not cost-effective** compared to SoC
- Taking the **modified societal perspective**, however, authors concluded that Luxturna is **cost-effective for younger populations** when taking into consideration indirect costs
- Study suggested that in order to **achieve a $100k/QALY** threshold from the **base case**, Spark would need to reduce cost from $850k/patient to $153k for patients (15 y.o.) and $348k for patients (3 y.o.)
- Utilizing the **modified societal perspective**, Spark would need to reduce cost to $363k for patients (15 y.o.) and $756k for patients (3 y.o.)
HTAs released white papers to explore approaches towards RM/ATs and their associated challenges

**ICER Gene Therapy White Paper**

**Key challenges**

- **Small patient population** and serious / progressive symptoms of patients raise [ethical](#) and [financial](#) barriers to RCTs and generating robust clinical evidence for decision-makers

- It is **challenging** to assess the value of potential “cures” as **limited data** make it **difficult** to **guarantee** long-term efficacy / safety

- If **curative** effect is assumed, **traditional QALY** valuation may justify **immense prices**, raising **affordability issues** under existing payment models

**Mechanisms to address affordability**

- Most promising strategies include **outcomes-based agreements**, **reinsurance**, and forms of **amortization**

**Recommendations**

- Report details multiple **recommendations for mnfs.** (e.g. engaging in early dialogue with payers and patient groups) and **payers** (gaining a better understanding of RM/ATs and creating a classification system)

**CADTH Environmental Scan: Gene Therapy**

Understand regulatory / HTA definition of gene therapy

- Widespread variation in definition of gene therapies, such as the **EMA** groups gene therapies with cell therapies under **ATMP** designation but **FDA** believes gene therapies fall under umbrella of **regenerative medicinal therapy**

Identify HTA guidelines / frameworks specific to gene therapy

- Literature results and survey **did not identify any HTA guidelines specific to gene therapies**

- **NICE**, **GBA**, and **SBU** believe that **existing HTA framework is sufficient** to assess gene therapies

- **AHTA** is planning to **develop separate guidelines** for evaluation of gene therapies

Study regulatory and reimbursement decisions for gene therapies

- **Recent regulatory approvals** of Strimvelis, Yescarta, and Luxturna, suggest that mnfs. are improving their ability to **compensate** for uncertainties underlying clinical data

*CADTH research in progress, results from draft report

**SBU**: Swedish HTA, **AHTA**: Australian HTA
Detailed Findings
RM/AT Approvals and
Reimbursement Decisions
Experience from previous approvals suggests increased evidence requirement to justify high prices associated with RM/ATs

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<th>NICE</th>
<th>IQWiG / GBA</th>
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<td>Yescarta</td>
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<td>Approved / FV Assessment with Exceptions</td>
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<tr>
<td>Luxturna</td>
<td></td>
<td>Not assessed by HTA or currently under review</td>
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<tr>
<td>Provenge</td>
<td></td>
<td>Not approved / UFV Assessment</td>
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</tbody>
</table>
Glybera was approved by EMA but failed to demonstrate differentiating clinical evidence to HTAs

**Regulatory Review**

In Europe, Glybera was assessed through a collaboration of the CHMP and CAT groups

- Committee members were concerned if the data was robust enough to justify a novel biomarker in the presence of inconclusive clinical evidence, which warranted further data either pre-authorization (CHMP) or post-market (CAT)

- Glybera was eventually approved in 2012 “under exceptional circumstances” with post-approval data supplementation mandated and due to unmet clinical need of patients

In the US, FDA asked UniQure to conduct further trials in 2015, so the company gave up seeking FDA approval

**HTA Review**

HAS cited concerns about the clinical evidence for the primary endpoint, its transient efficacy, and uncertainties about short/long-term safety

- HAS concluded that the actual benefit of Glybera does not warrant its reimbursement by the national health insurance

Glybera was evaluated by AMNOG

- GBA concluded that its clinical evidence did not warrant “additional benefit”, so it was granted “unquantifiable additional benefit” due to its orphan drug designation

Direct hospital/payer negotiations were used for the single patient treated so far, with the price being set at 900k Euros

**Key Learnings**

- Glybera highlighted the importance of using the natural history of the disease (e.g. patient registries) to inform clinical trial design

- Late assessment of the natural history of the disease, led investigators to conclude that serum triglycerides (primary efficacy endpoint) were too variable in these patients to be a useful endpoint and the ongoing clinical development program would need to be modified

- Lack of available patients underpowered clinical trials and prevented statistically significant findings, emphasizing the importance of incorporating rigorous patient follow-up programs to demonstrate long-term efficacy and safety

- Investors noted uniQure lacked the knowledge to successfully navigate the complex reimbursement process for advanced therapies

CHMP: Committee for Medicinal Products for Human Use, CAT: Committee for Advanced Therapies
Strimvelis presented long-term follow-up data that led to approval by EMA and HTAs, but revenue is limited by small patient population

**Regulatory Review**

- CHMP endorsed the CAT conclusion on the benefit risk balance and Strimvelis gained market authorization in 2016
- As ADA-SCID affects an estimated 15 children per year in the EU, the drug was designated an orphan medicinal product
- Clinically, the benefit/risk balance was deemed as positive due to strong efficacy and safety data (18 children treated with Strimvelis had 100% survival rate 7 years after treatment)
- EMA recommends Strimvelis for patients who suffer from ADA-SCID and have no suitable stem cell donor available, on the condition that the mnf. submit interim registry reports / studies every two years for 15 year follow-up period

**HTA Review**

- AIFA agreed to reimburse Strimvelis at a price of 594k Euros due to its strong safety and efficacy data and cost-effectiveness
  - Strimvelis is offered at a significantly lower cost compared to the SoC (long-term enzyme replacement therapy)
  - Mnf. supplemented cost offset with a P4P scheme, where they will pay back in the case of treatment failure
- NICE determined a favorable appraisal of Strimvelis in cases where no stem cell donors are available
  - Strimvelis improves OS compared with SCT and reduces risk of post-treatment GvHD, demonstrated clinical efficacy
  - Strimvelis also significantly improves QoL for patients

**Key Learnings**

- Although sales of Strimvelis will remain limited due to the small patient population, it provides a successful case study of commercialization of a gene therapy
- Mnf. was able to demonstrate cost-effectiveness over the chronic SoC treatment, which justified its high price tag
- Seven year follow-up data on patients, at time of submission, made a compelling case for long-term efficacy and safety, despite the small trial patient population

ADA-SCID: adenosine deaminase deficiency – severe combined immunodeficiency, SoC: standard of care, P4P: pay for performance, OS: overall survival, SCT: stem cell transplant, QoL: quality of life
Provenge failed to demonstrate value in the EU, but was approved by the FDA due to its marginal improvement in clinical efficacy over SoC

**Regulatory Review**

- Provenge was granted marketing authorization by the EMA in Q4 2013 after demonstrating adequate safety and efficacy data to CAT and CHMP
  - In 2015, Dendreon officially withdrew Provenge from the EU market due to poor commercial performance

- FDA did not approve Provenge in 2007, but approved it in 2010 after further evidence was provided by the mfn.
  - CMS announced it would cover Provenge after a national review, a process that is typically reserved for complex or potentially controversial coverage decisions, that concluded there is “moderate” evidence Provenge will help patients

**HTA Review**

- NICE rejected Provenge after concluding that the treatment was not cost-effective
  - Provenge demonstrated an average improvement of 4 months in overall survival for prostate cancer patients, but did not demonstrate the ability to delay the progression of the disease like available treatments
  - NICE concluded that the clinical benefit provided by Provenge did not warrant the 50,000 GBP price tag

**Key Learnings**

- Provenge was forced to withdraw from the EU market for commercial reasons
  - Provenge was unable to provide sufficient evidence to justify its high cost, suggesting Dendreon needed to generate additional evidence to demonstrate the value of Provenge

- In the US, CMS faced the challenge of a high cost drug with a large patient population
  - CMS opted to conduct a national coverage analysis to further understand budget impact and eventually decided to cover Provenge
  - CMS skepticism highlighted the need for innovative contracting / payment models
Imlygic gained FDA and EMA approval, but failed to impress HTAs as clinical benefit did not warrant cost increase over SoC

**Regulatory Review**

- **EMA approved** Imlygic in 2015 on the basis of its Ph III trial
  - CHMP and CAT determined that the drug was well-tolerated by patients and its benefits outweigh its risks
- **FDA also approved** Imlygic in 2015 on the basis of its Ph III pivotal trial demonstrated a significant improvement in the durable response rate for the patient population (primary endpoint)
  - Although FDA committee determined it had a favorable benefit risk ratio (23-1 vote), they were concerned about the OS and rejected accelerated approval

**HTA Review**

- In its initial guidance, NICE provided a negative recommendation
  - Skeptical of clinical evidence supporting OS outcomes compared to other treatment options and did not find it to be cost-effective
- AMG later provided further clinical evidence and agreed to a patient access scheme (list price discount) and further restricted label
- IQWiG concluded that the mfn. dossier contained no data suitable for assessment
- GBA disagreed on AMG’s comparator choice, as it is not an approved therapy for the indication; will likely receive “no quantifiable additional benefit”

**Key Learnings**

- Although Imlygic gained market authorization from the EMA and FDA, HTA frameworks / payers are less concerned about its novel mechanism and more focused on the overall outcomes
- AMG failed to produce compelling comparative, clinical evidence demonstrating a significant improvement in endpoints (e.g. OS) that are meaningful to payers
- AMG failed to anticipate how GBA would select a comparator for their drug, which led to a negative recommendation from the committee
  - Early dialogue with payers is critical to align on endpoints and other criteria that are most meaningful to payers
MACI failed to gain commercial success in the EU and is now seeking to target US market

Regulatory Review

Matrix-induced Autologous Chondrocyte Implantation (MACI) gained regulatory approval from the EMA in 2013 on the basis of its trial data, which demonstrated superior clinical outcomes to surgical intervention as well as a better safety profile.

- Vericel voluntarily withdrew MACI from the EMA in 2014 upon closure of its manufacturing site due to poor commercial success.

Vericel shifted its focus to the US market and MACI was approved by the FDA in 2016.

- Vericel also presented longer-term clinical trial data that included Summit knee function and pain scores.

HTA Review

Due to lack of RCT data, NICE assessment of ACI in 2000 recommended against use of ACI for routine care and only used in cases for ongoing clinical trials.

- Although in 2005 there were 4 RCTs for ACI, NICE reaffirmed its prior negative recommendation due to the short time frame of data collected through trials.

- In 2015, NICE revisited ACI and determined that long-term RCT data demonstrated superior clinical efficacy over traditional surgical intervention at a reasonable cost.

- Consequently, NICE recommends ACI with some restrictions on patient population.

Key Learnings

- While Vericel assumed that central approval from the EMA would give it almost exclusive access to the market, hospitals in Spain and Germany were allowed to continue producing ATMPs without EMA marketing authorization, severely eroding MACI’s target patient population.

- After withdrawing from the EU, Vericel shifted focus on the US market due to greater capacity of patients to pay privately, illustrating the magnitude of budget impact issues on commercialization in the EU.
Kymriah was approved by FDA due to its curative potential and also demonstrated cost-effectiveness in ICER model

**Regulatory Review**
- Novartis has filed for marketing authorization with the EMA (Q4 2017) and has been granted an accelerated assessment
- FDA approved Kymriah in Q3 of 2017 due to clinically significant remission within trial population after six month follow-up
  - Granted Priority Review & Breakthrough Therapy designations
  - Due to risks of CRS and neurological events, Kymriah was approved with REMS with ETASU as well as mandated post-marketing studies
  - Novartis has negotiated outcomes based contracting agreements with CMS, with the possibility of indication-specific pricing for indication expansion

**HTA Review**
- NICE built a hypothetical model to determine whether its framework could be applied to high-cost CAR-Ts
  - Determined that framework was still valid, but CGTs need to reduce uncertainties around clinical data to improve outcome
- ICER created robust model comparing Kymriah to SoC
  - Determined that at current price, Kymriah falls within acceptable cost-effectiveness thresholds
  - Also demonstrated that Kymriah’s cost-effectiveness significantly improved when looking at lifetime horizon rather than short term

**Key Learnings**
- Novartis demonstrated the ability to successfully commercialize a high-cost CGT with only short-term clinical data
  - Novartis engaged with CMS to enter in outcomes-based contracting to gain greater access to patients, highlighting the importance of innovative contracting in pricing potential and market access
  - Negotiated approval of separate J-Codes from CMS, which allows for indication-specific pricing, allowing Novartis to reduce price of Kymriah for certain target populations without suffering an overall reduction in ASP
- Currently, lack of a billing code from CMS has raised reimbursement issues, with hospitals negotiating on a case-by-case basis

**ALL**: acute lymphoblastic leukemia, **CRS**: cytokine release syndrome, **REMS**: risk evaluation and mitigation strategy, **ETASU**: elements to assure safe use, **ASP**: average sales price
Yescarta was approved by FDA and demonstrates cost-effectiveness over time, but faces reimbursement challenges from CMS

**Regulatory Review**

- Yescarta was **approved** by the **FDA** in Q4 2017
  - Committee members found the efficacy and safety results from its pivotal trial to demonstrate a favorable risk benefit ratio
  - FDA mandated a 15 year post-marketing registry that will include 1500 patients and a REMS program

- Yescarta has been granted **PRIME regulatory support** by the **EMA**, and is expected to be **approved by Q3 2018**

**HTA Review**

- **ICER** built a **model** to understand the cost-effectiveness of Yescarta vs. SoC
  - When **assuming outcomes-based contracting** is in place, Yescarta fell below commonly accepted cost-effectiveness thresholds
  - Yescarta was **not cost-effective** within a **short time horizon** and only became **cost-effective 24 years post-treatment**

**Key Learnings**

- Yescarta is facing very **slow uptake** as **waiting lists** for treatment are **growing**
  - Gilead **failed to secure a billing code** from CMS and faced **reimbursement issues** shortly after its launch due to Yescarta’s **high price tag** ($375,000), which is further **compounded by potential costs due to AEs**
  - Lack of a billing code forces **hospitals to bear the enormous costs** of treatment until CMS creates one, which has led to **significant access hurdles** for Yescarta’s target patient population as a **large number of them rely on Medicare**
- ICER model demonstrates **importance** of considering cost-effectiveness over **long-term horizon**

**PRIME**: Priority Medicines (EMA)
Luxturna was approved by FDA and is implementing innovative contracting / payment models to offset high budget impact

**Regulatory Review**

- **Luxturna was approved** by the FDA in Q4 2017 (ODD)
  - Committee deemed Luxturna has a **favorable risk benefit ratio** as trial demonstrated functional improvement (MLMT)
  - FDA requires long-term follow-up of trial patient population, voluntary patient registry, and routine pharmacovigilance
  - To reduce budget impact, Spark launched three new programs: (1) **Outcomes-based rebate** with long-term durability measure, (2) **Innovative contracting model** where SP purchases drug, (3) allowing **CMS to make payments over time**

- **Luxturna will be commercialized by Novartis in EU**

**Key Learnings**

- Spark **developed** its own **primary endpoint** (MLMT), to **demonstrate** the **functional improvement** caused by its drug to regulatory bodies
- In efforts to **offset large budget impact** of Luxturna’s high price, Spark **aggressively** offered different **innovative contracting and payment** options to payers
  - By **proactively** doing this, Spark has positioned itself to **lower access barriers** to patients from both commercial and government plans
- **ICER model** demonstrates the **importance** of taking **indirect societal costs** into consideration to **capture true value** of RM/ATs

**HTA Review**

- **ICER built a model to understand the cost-effectiveness of Luxturna vs. SoC**
  - In the base case (US payer perspective of direct costs), Luxturna was **not cost-effective** due to its **high cost** ($850,000)
  - When taking into account **indirect societal costs** (e.g. indirect productivity costs, non-medical nursing home costs) and looking at a **younger population**, Luxturna met **accepted cost-effectiveness thresholds**

OAD: orphan drug designation, MLMT: multi-luminance mobility testing
Payers are concerned about the long-term efficacy of RM/ATs, warranting a shift to innovative contracting agreements

**RM/ATs have the potential to save payers costs over the long-term horizon**

- However, payers are skeptical of the short-term clinical efficacy data used by mnfs. to predict long-term outcomes for patients

**Payers are shifting to value-based models to guarantee long-term outcomes from RM/ATs**

- Glybera faced severe access restrictions as its mnfs. did not guarantee outcomes for a $1M treatment
- Strimvelis (AIFA), Imlygic (NICE), Kymriah (CMS), and Luxturna (CMS, commercial) have all entered VBP contracting agreements (e.g. P4P) to lower access barriers

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**Value-Based Pricing Agreements**

- Higher price / reward based on actual product performance
- Lower price / reward based on actual product performance

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**VBP**: value-based pricing agreements, **P4P**: pay for performance,
Large budget impact from traditional one-time payment models, warrants further exploration of novel payment models for RM/ATs

Payers highlight key obstacles to innovative payment models

- US health system infrastructure will need to be modified as the current 12-month financial cycle does not capture long-term value of RM/ATs
- Payers are also concerned about “beneficiary churn”, on payment models that are greater than one year as patients may switch plans

However, payers acknowledge need for innovative payment models moving forward

- Payers believe that their health plans would not be able to absorb the high costs of RM/ATs
- They highlight the need for financing structures that capture the unique aspects of RM/ATs
Numerous innovative payment models have been proposed for reducing budget impact of RM/ATs (1/2)

<table>
<thead>
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<th>Type</th>
<th>Description</th>
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| Consumer Mortgage | • Healthcare loans are managed by financiers  
                          • Cost to patient is amortized over time plus interest  
                          • Payment can be linked to efficacy of therapy over time | • High interest rates for patients  
                          • Patients would have to pay both loan payments and healthcare premiums  
                          • Likely trigger government oversight |
| In-house        | • Healthcare loans managed by industry (e.g. mnf.)                           | • Additional investment needed by mnf.  
                          • High interest rates for patients |
| Hybrid Model    | • Partial coverage by payer (e.g. 50%) and rest of cost covered by patient (may link with consumer mortgage) | • Make coverage more attractive to payer by reducing budget impact and improving risk-benefit tradeoff |
| Rebate          | • Patients copays decrease over time correlated to clinical outcomes and patient adherence | • Need updated infrastructure to link outcomes with claims  
                          • May be difficult to scale to RM/AT needs |
| Amortization    | • Payer can pay mnf. over time  
                          • Payments can be linked to outcomes (VBP)  
                          • Payers and mnf. would need to agree on clinical milestones and timing | • Challenging to agree on and manage clinical milestones (e.g. stopping payments)  
                          • Spreads risk and reduces immediate budget impact but does not solve overall sustainability issues |
Numerous innovative payment models have been proposed for reducing budget impact of RM/ATs (2/2)

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| **Annuity (“lifetime leasing”)** | • Payer reimburses mnf. in pre-defined installments over a large, time span  
• Not always linked to list price  
• Payments are based solely on clinical efficacy, allowing mnf. to make more than list price if outcomes are greater than expected | • Challenging to agree on and manage clinical milestones (e.g. stopping payments)  
• Spreads risk and reduces immediate budget impact but does not solve overall sustainability issues |
| **Reinsurance**       | • Payers pool risk associated with high-cost RM/ATs  
• Could link outcomes to payments | • Impact on patient premiums is unclear  
• Short-term solution (stopgap) |
| **High Risk Pool**    | • Separate insurance pool for high risk patients requiring RM/ATs          | • Patient impact depend largely on definitions of which treatments are included in risk pool |
| **Stop Clause**       | • Spread costs over 2-3 years with stop clause if treatment is ineffective | • Reduce initial budget impact to payers by spreading payments |
| **Bond Mechanisms**   | • Government issues bonds to market investors  
• Linked to clinical outcomes and only for extremely high-cost therapies | • Effectiveness of therapy must be guaranteed  
• Extensive policy changes and negotiations with payers regarding set up and debt transfer |
Detailed Findings
Literature Review
A detailed analysis of the literature revealed additional economic considerations to uncover true value of RM/ATs (1/10)

<table>
<thead>
<tr>
<th>Title</th>
<th>Author</th>
<th>Year</th>
<th>High-level Summary</th>
<th>Economic Inputs</th>
</tr>
</thead>
</table>
| **Regeneration X: The Payer Perspective on Gene Therapy**            | Spoors et al.      | 2017 | • Payers are likely to point to the data uncertainties, safety, and upfront cost to either reduce the cost or restrict patient access to RM/ATs  
• Price of RM/ATs largely driven by potential cost savings, so the issues of affordability and who should bear the financial risk (risk sharing) arise  
• Three innovative payment models: Personal Contract Purchase Model, Regular Payment Model, Service Model                                                                                                         | Innovative payment / contracting models                                          |
| **Reimbursement of licensed cell and gene therapies across the major European healthcare markets** | Jorgensen et al.   | 2015 | • Cost effectiveness analyses are applied to RM/ATs, but only the UK has a defined QALY threshold that is methodically linked to the reimbursed price  
• It is important to demonstrate that the incremental benefit is proportionate to its incremental cost above SoC by accounting for differences in individual country frameworks and value drivers  
• Targeting small populations can also help reduce both payers’ budget impact concerns and the risk of reimbursement restrictions being imposed                                                                 | Patient Population  
• Lifetime horizon  
• Innovative payment/contracting models  
• Real world evidence                                                                                                                   |
A detailed analysis of the literature revealed additional economic considerations to uncover true value of RM/ATs (2/10)

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| **Advancing gene Therapies and Curative Health Care Through Value-Based Payment Reform** | Daniel et al.   | 2017 | • Co-authored by CEO of Spark Therapeutics and CEO of Bluebird Bio  
• As we shift from chronic to curative treatments, there is a need to adapt health care payments  
• Need to shift framework to capture long-term value and utilize novel strategies to counterbalance high upfront costs and uncertainty regarding variability and durability of outcomes | • Novel Framework  
• Patient Burden  
• Innovative payment/contracting models  
• Real world evidence |
| **Ensuring Patient Access to Regenerative and Advanced Therapies in Managed Care: How Do We Get There?** | Faulkner et al. | 2018 | • Stakeholder education will play a key role in the success of RM/ATs  
• RM/ATs need to demonstrate value beyond clinical superiority, but also the product’s uniqueness and other patient benefits  
• Current value frameworks are sufficient, but do not capture duration of RM/AT effects and curative nature  
• There is need for novel reimbursement models for RM/ATs | • Lifetime horizon  
• Patient Burden  
• Innovative payment/contracting models  
• Additional value for curative nature |
A detailed analysis of the literature revealed additional economic considerations to uncover true value of RM/ATs (3/10)

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| The Health Economics for Regenerative Medicine: How Payers Think and What That Means for Developers | McCabe et al. | 2016 | • HTAs should utilize a value-engineered translation (VET) process to inform the decision-making process  
• As such, HTAs have a different conceptualization of uncertainty compared to the analyses done by the FDA or EMA  
• VETs allow for uniform decisions based on key inputs such as operational / development costs and the patient population | • Patient Population  
• Innovative payment/contracting models  
• Development / operational costs |
| Concise Review: The High Cost of High Tech Medicine: Planning Ahead for Market Access | Driscoll et al. | 2017 | • Lessons from HSCT transplants demonstrate how reimbursement is focused on episode of care; the cost of acquisition can often consume the entire DRG for treatment  
• There is a need to reimburse based on the burden of disease over the lifetime  
• Even if a RM/AT is designated as the SoC for a TA, does not mean it will be reimbursed without complications  
• Mnfs need to be aware of hazards associated with planned site of care, coding structures, healthcare legislation, payer-driven utilization requirements, and payer mix associated with target patient population | • Patient Population  
• Innovative payment/contracting models |
A detailed analysis of the literature revealed additional economic considerations to uncover true value of RM/ATs (4/10)

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| Value-Engineered Translation for Regenerative Medicine: Meeting the Needs of Health Systems | Bubela et al.   | 2013 | • There is a need to adopt better economic modelling methods that will better link investment decisions to value-based criteria of health systems  
• Mnfs can no longer assume that technologies that make it to the market will be adopted and reimbursed  
• Mnfs must abandon traditional hypothesis-driven research and adopt value-of-information analyses, based on values expected by HTA authorities  
• Development of frameworks that incorporate patient inputs into the decision-making process | • Novel Framework  
• Patient Population  
• Patient Burden  
• Innovative payment/contracting models  
• Additional value for curative nature |
| Leveraging Real-World Evidence for Regenerative Medicine and Advanced Therapy Success Beyond the Regulator | Mihos et al.    | 2017 | • Clinical trials for RM/ATs are unable to capture total benefit to stakeholders  
• There is a need to utilize real world evidence approaches to generate these data for stakeholders  
• RWE studies can help mnfs bridge gap between rapidly getting to market vs. optimizing price and access  
• Need to understand the patient population and burden suffered over time to close gaps in value story | • Novel Framework  
• Patient Population  
• Patient Burden  
• Real world evidence |
A detailed analysis of the literature revealed additional economic considerations to uncover true value of RM/ATs (5/10)

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| Gene therapy: evidence, value and affordability in the US health care system | Hampson et al.   | 2017 | • Extra value should be ascribed to curative therapies  
• Elements of value to patients may not be captured in the traditional value assessment  
• Small patient populations mean that mnfs will seek higher prices beyond traditional QALY thresholds  
• Health budget impact will be high, but payers need to take into consideration long-term benefits in affordability as well as new payment models | • Novel Framework  
• Patient Population  
• Patient Burden  
• Innovative payment/contracting  
• Real world evidence |
| Innovative regenerative medicines in the EU: a better future in evidence? | Corbett et al.   | 2016 | • Despite the clinical promise of RM/ATs, they have been largely inaccessible to patients  
• Licensed products often impose immense budget impact burden, warranting development of alternative financing approaches  
• There is a need for more flexibility in the licensing and financing processes of RM/ATs to foster continued application of regenerative medicine within the clinic | • Novel Framework  
• Innovative payment/contracting |
A detailed analysis of the literature revealed additional economic considerations to uncover true value of RM/ATs (6/10)

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| Addressing Pressing Needs in the Development of Advanced Therapies   | Morrow et al.         | 2017 | • Only part of the overall direct mnf cost of these products is linked to the "sticker price"  
• Lack of price comparators results in little to no prior HTA data and lack of a clear reimbursement strategy  
• It is likely that current HTA frameworks cannot be applied to these novel ATMPs  
• Assessments should take into consideration value-engineered translation frameworks to uniformly understand unmet need and other relevant factors | • Novel Framework  
• Development / operational costs                                      |
| Advanced therapy medicinal products: current and future perspectives  | Hanna et al.          | 2016 | • Poor pricing and market access strategy for RM/ATs has led to minimal commercial success and HTA rejections  
• Health authorities are unprepared for the high budget impact associated with ATMPs and tend to deviate from their own established decision-making rules, applying exceptional rules and capping drug class expenditure  
• Due to the small patient population size, mnfs may end up with insufficient information to demonstrate value of their product; therefore post-launch real world evidence generation studies will be a critical activity | • Novel Framework  
• Real World Evidence                                                      |
A detailed analysis of the literature revealed additional economic considerations to uncover true value of RM/ATs (7/10)

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| Impressions from Market Access for Cell & Gene Therapies Congress  | Touchot et al.        | 2017 | • No additional funds are being directed to drug budgets and reimbursement will hinge on the increased quality of evidence requirements to demonstrate cost-effectiveness  
  • Payers recognize even highly cost-effective drugs may have high budget impact, but they are no closer to creating a reimbursement framework where value is realized over time (payer budget cycles are 3-5 years)  
  • NICE may looking into modifying the timeframe of evaluation; whereas in DE, the majority of all arrangements are simple rebate contracts  
  • There is clear evidence, suggesting that the system will have to change to be sustainable | Novel Framework  
  • Lifetime horizon  
  • Innovative payment/contracting  
  • Real World Evidence                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Annuity payments can increase patient access to innovative cell and  | Jorgensen et al.      | 2017 | • Full upfront payments at the time of treatment will significantly increase the barriers to patient access  
  • Innovative models, such as annuity-based payments with an outcomes-based pay-for-performance scheme, can reduce the uncertainties associated with ATMPs and increase patient access without exceeding budget impact threshold | Innovative payment/contracting                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
A detailed analysis of the literature revealed additional economic considerations to uncover true value of RM/ATs (8/10)

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</table>
| The path to successful commercialization of cell and gene therapies: empowering patient advocates | Abou-El-Enein et al.     | 2017 | • Patient advocacy groups (PAG) can serve a critical role in early assessment and shaping of pricing and reimbursement potential for RM/ATs  
• By mediating discussions between mnfs and payers, PAGs can spur the development of novel reimbursement approaches  
• PAGs can also lobby to demonstrate value of patient perspectives (e.g. PROs) to reimbursement agencies | • Novel Framework  
• Patient Burden                                                                                      |
| After Glybera’s withdrawal, what’s next for gene therapy?            | Senior                   | 2017 | • Spark Therapeutics believes that payment should be based on number of years the treatment modifies a disease, which can be accomplished by innovative payment models  
• HTAs will struggle to quantify value for most indications; however, in cases such as Hemophilia, it is clear that a curative therapy can offset need for infusions and lead to substantial cost savings  
• Payers will need to understand how to value these “one-time cures” and mnfs will need to demonstrate long-term data | • Additional value for curative nature                                                              |
A detailed analysis of the literature revealed additional economic considerations to uncover true value of RM/ATs (9/10)

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<th>Author</th>
<th>Year</th>
<th>High-level Summary</th>
<th>Economic Inputs</th>
</tr>
</thead>
</table>
| Gene-Therapy, The Way Forward In Europe – The Payer Perspective | Poschen et al. | 2017 | • Secondary research conducted by authors revealed that among European HTA agencies, only Italian payers believe they have the infrastructure ready to handle RM/ATs  
 • It was clear that manufacturers and other stakeholders would need to invest heavily in improving payers’ understanding of the unique, curative value of RM/ATs to improve outcomes of future launches | • Novel Framework  
 • Additional value for curative nature |
| Translation and Reimbursement: The Twin Challenges for Cell and Gene Therapies Reflections of an Ex-Regulator | Gopalan | 2016 | • Complexity of RM/AT manufacturing processes, due to regulations for strict quality control, impose a high cost burden on mnfs  
 • Mnfs need to generate real world evidence for HTAs in order to improve reimbursement potential  
 • The development of unique pathways, such as PRIME, facilitate the development of RM/ATs: regulatory agencies should continue to create programs that recognize the innovative mechanism of RM/ATs | • Development / operational costs  
 • Additional value for curative nature  
 • Real world evidence |
A detailed analysis of the literature revealed additional economic considerations to uncover true value of RM/ATs (10/10)

<table>
<thead>
<tr>
<th>Title</th>
<th>Author</th>
<th>Year</th>
<th>High-level Summary</th>
</tr>
</thead>
</table>
| The 3Rs of Cell Therapy | Caplan et al.   | 2016 | • Due to the **high cost of manufacturing** RM/ATs will **continue to be high cost products** into the foreseeable future; it is likely that only large pharmaceutical companies can sustain the initial net negative revenue; however, by **demonstrating proof of concept** it is likely the development of economies of scale will **bring down development costs**
• There is still an **issue** of how should **mnfs be compensated** for a **curative product**; recognizing the **value of RM/ATs is created and captured over time** has led to **innovative payment / contracting models**
• The **field should look creatively for new economic and regulatory evaluation mechanisms** that can accelerate bringing these potentially revolutionary treatments to patients |

**Economic Inputs**

- Novel Framework
- Additional value for curative nature
- Innovative payment/contracting
Appendix
HTA Evidence Requirements
Pharmacoeconomic countries rely primarily on cost-effectiveness analyses that limit RM/AT QALY thresholds

**Inputs**
- Product and comparator clinical data
- Drug price (and other costs)

**Analysis**
- HEOR modeling of drug effectiveness (QALYs)
- \[ \text{ICER} = \frac{(C_1 - C_0)}{(E_1 - E_0)} \]

**Output (UK example)**
- ICER
  - 30,000 GBP: Not cost-effective (though may still be recommended given additional factors)
  - 20,000 GBP: May be cost-effective (recommendation contingent upon additional factors)
  - Cost-effective (generally results in recommendation)

**Key challenges for RM/AT therapies:**
- RM/AT therapies are reliant on historic QALY thresholds for non-curative therapies
- The comprehensive benefit of curative therapies including non-clinical and societal costs does not fit the current QALY framework
Price is generally an output of the therapeutic referencing process, where RM/ATs lack precedence.

Key challenges for RM/AT therapies:
- Lack of clinical comparator data and precedence make it difficult for RM/ATs to be compared against current SOCs
- High price differential against current standard of care makes it difficult to compare curative therapies to annualized benefits
Willingness-to-pay countries are characterized by many payers and free pricing resulting in hesitation to cover RM/AT costs

**United States**

**Private Payers**
- Free drug pricing
- P&R process focuses on formulary inclusion, reimbursement status (via tiering), and utilization management controls
- Highly fragmented decision-making given pluralistic payer system
- AMCP dossier format is most typically used as means of evidence submission
- Health technology assessment not formally used, but third party value frameworks (e.g. ICER) are growing in influence

**China**

**Cash Market**
- Drug coverage is relatively limited in scope; for biologics China is still generally a cash market
- Pricing controls for most drugs have been dropped
- Aside from drugs deemed essential, the NRDL (national drug list) requires two years on the market before a new drug will be included for reimbursement
- Provincial drug lists are more commonly the first point of access for patented drugs
- HTA not yet adopted in China

**Key challenges for RM/AT therapies:**
- Fragmented U.S. system makes it challenging for stakeholders to accept one-time or financed payments for a lifetime benefit
- No specific guidance on pricing in regulatory decision leads to restricted or non-reimbursed drugs after approval
The key decisions for US P&T committees are formulary inclusion, placement and imposition of UM restrictions

Though no single decision-making frameworks exist, the following can be generally assumed:

- Inclusion on formulary is commonly a decision based on medical need. Thus, evidence surrounding clinical benefit are most relevant to initial decision to approve a drug for reimbursement.

- Formulary positioning, however, is more often driven by financial considerations, including budget impact, contracting, and in some cases, cost-effectiveness (though usually with focus on near-term benefits rather than long-term).

- For drugs with a high anticipated budget impact, utilization management may be employed to restrict overall usage and mitigate potential budget issues.

- Individual stakeholder decision criteria varies; drug budget managers may not value cost offsets, while a medical budget manager would.

- Contracting commonly used as a means of gaining/protecting formulary position and/or avoiding utilization management controls such as prior authorization or step edit.

### Most plans follow a 3, 4 or 5-tier formulary structure

<table>
<thead>
<tr>
<th>Tier</th>
<th>Description</th>
<th>Avg. Copay / Coinsurance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Generic</td>
<td>$10</td>
</tr>
<tr>
<td>2</td>
<td>Preferred Brand</td>
<td>$30</td>
</tr>
<tr>
<td>3</td>
<td>Non-preferred brand</td>
<td>$50</td>
</tr>
<tr>
<td>4</td>
<td>Specialty (or preferred specialty in 5-tier plans)</td>
<td>$80 / ~32%</td>
</tr>
<tr>
<td>5</td>
<td>Non-preferred specialty</td>
<td>Variable</td>
</tr>
</tbody>
</table>

Source: Kaiser, 2012
Canada employs a combination of cost-effectiveness analysis and reference-based price controls

The PMPRB sets the maximum allowable price (MAPP) for new drugs using a two step process:

1. Classification of drug (at PMPRB’s discretion):

2. Application of reference tests based on classification:

- **MIPC**
  - Median International Price Comparison Test
  - Price shall not exceed the median price of France, Germany, Italy, Sweden, Switzerland, the United Kingdom and the United States

- **TCC**
  - Therapeutic Class Comparison Test
  - The National Average Transaction Price and the Market-Specific Average Transaction Prices for each class of customer shall not exceed the price of comparator drug products

- **HIPC**
  - Highest International Price Comparison Test
  - Regardless of classification, the price shall never exceed the highest of prices in France, Germany, Italy, Sweden, Switzerland, the United Kingdom and the United States

Concurrently, CADTH conducts cost-effectiveness evaluation for new drugs:

- CADTH conducts separate cost-effectiveness assessments for oncology drugs (through pCODR) and all other drugs (through CDR).

- No explicit ICER threshold exists in Canada; however, OECD research indicates that positive recommendations generally showed an ICER at or below CAD 80,000, while negative recommendations had ICERs ranging from CAD 31,000 to 137,000. This suggests that while cost effectiveness plays a role in evaluation, other criteria – including overall clinical benefit, alignment with patient values, and feasibility of adoption into the health system – are also significant contributors to recommendation decisions.
Technology assessment in UK relies most heavily on cost-effectiveness, but other factors are considered

NICE recommendations are primarily but not exclusively driven by cost per Quality Adjusted Life Year (QALY) analysis. The nominal QALY threshold publicized by NICE is 20,000 – 30,000 GBP per QALY. However, above 20,000 GBP, additional factors may be considered, including:

- The degree of certainty around the ICER. In particular, the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented.
- Whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured, and may therefore misrepresent the health utility gained.
- The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure.
- Whether the technology meets the criteria for special consideration as a 'life-extending treatment at the end of life' (which can have an upper limit around 50,000 GBP)
- Aspects that relate to non-health objectives of the NHS.

Under the voluntary Pharmaceutical Price Regulation Scheme, participating manufacturers agree to repay excess return on capital to the NHS under an agreed method of calculation. This acts as an indirect control on price.

In addition, two different mechanisms aimed at better reflecting value as part of the 2009 Pharmaceutical Price Regulation Scheme can result in recommendations of otherwise costly drugs:

- **Flexible Pricing** – where a scheme member can apply for an increase or decrease to a product's original list price in light of new evidence or a different indication being developed.
- **Patient Access Schemes** – which can facilitate patient access to a medicine where NICE's assessment of value, on the current evidence base, is unlikely to support the list price. These can include simple discounting, rebates, stock supplied at zero cost, dose capping and outcome-based schemes.
G-BA assesses added therapeutic benefit of a new drug; incremental benefit enables potential for price premium

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
<th>Pricing / reimbursement Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Major added benefit</td>
<td><strong>Incremental therapeutic benefit:</strong> Qualify for price negotiations and may obtain a price premium over the appropriate therapeutic comparator</td>
</tr>
<tr>
<td>2</td>
<td>Considerable added benefit</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Minor added benefit</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Non-quantifiable added benefit</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>No added benefit proven</td>
<td>Price referenced vs. current standard of care/drug</td>
</tr>
<tr>
<td>6</td>
<td>Less than comparator</td>
<td>GKV-SB will stipulate a deduction</td>
</tr>
</tbody>
</table>

GVK-SB negotiating criteria:
- G-BA rating
- Cost of comparable drugs (internal referencing)
- Price of drug in other EU countries (external referencing)
- Expected annual sales

Negotiated price generally reflects a discount to the manufacturer’s listed price, but a premium against comparators

If added benefit is proven, negotiations will follow

Reference pricing based on a three-tiered system:
- Pharmaceuticals with identical active ingredients
- Pharmaceuticals with pharmacologically and therapeutically comparable active ingredients, particularly with chemically related substances
- Pharmaceuticals with therapeutically comparable effect, particularly combinations of pharmaceuticals

Manufacturers are not required to lower price to meet reference prices, but if they do not, patients are expected to cover the difference

If no added benefit is proven, price referencing is implemented

G-BA may or may not accept IQWiG’s assessment in the process of determining clinical benefit
ASMR and SMR ratings, set by CT, are key drivers of pricing and reimbursement outcomes

The level of improvement of clinical benefit, the so-called ASMR (Amélioration de service médicale rendu). An ASMR is only provided for new registrations or extension of indication reports.

<table>
<thead>
<tr>
<th>ASMR Category</th>
<th>Description</th>
<th>General Price Expectation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASMR I</td>
<td>New therapeutic area, reduction of mortality</td>
<td>European Price, not lower than lowest price observed in Germany, Spain, Italy and UK for first five years of listing</td>
</tr>
<tr>
<td>ASMR II</td>
<td>Important improvement in therapeutic efficacy and/or with important reduction of side-effects</td>
<td>Price will also be subject to CEESP review of cost-effectiveness</td>
</tr>
<tr>
<td>ASMR III</td>
<td>Modest improvement in therapeutic efficacy and/or with reduction of side-effects</td>
<td>Price may be higher than comparators by ~5%-15%</td>
</tr>
<tr>
<td>ASMR IV</td>
<td>Very minor improvement</td>
<td>Reimbursement only if price is lower than comparators</td>
</tr>
<tr>
<td>ASMR V</td>
<td>No improvement</td>
<td></td>
</tr>
</tbody>
</table>

The Transparency Committee will recommend an SMR (Service médicale rendu) based on the product’s medical benefit to determine the reimbursement level. For renewal reports only the SMR is provided.

<table>
<thead>
<tr>
<th>SMR Category</th>
<th>Reimbursement rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant</td>
<td>65%</td>
</tr>
<tr>
<td>Moderate</td>
<td>30%</td>
</tr>
<tr>
<td>Weak</td>
<td>15%</td>
</tr>
<tr>
<td>Insufficient</td>
<td>Not listed</td>
</tr>
</tbody>
</table>

*Products for chronic diseases (on HAS ‘ALD’ list), including oncology products, are always reimbursed at 100%.

Additional controls which may be used in France include:

- **Volume Targets** – where an agreement will be made to penalize a manufacturer in the form of rebate or price reduction if utilization exceeds the expected amount.
- **Price-Performance Agreements** – though not yet used widely, recent information suggests CEESP and CEPS may be moving in the direction of controlling payment based on achievement of metrics or pay-back schemes for non-responding patients.
Explicit considerations by CIPM are mostly focused around drug cost and price referencing

- CIPM explicitly evaluates a number of factors in pricing, including:
  - The cost of manufacturing and R&D
  - Cost per day compared with equivalent products in Spain
  - Sales forecasts, expected impact on the National Health System (SNS; Sistema Nacional de Salud) budget
  - Product's price in other low-cost European countries (particularly France and Italy)

- Inclusion of Therapeutic Positioning Report in the process implies that therapeutic value and efficacy over comparators are considered in the process, but no explicit rationale for how this information is used is provided

- Reimbursement rates are set based on setting of use and severity (chronicity) of disease:

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Reimbursement Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital drugs</td>
<td>100%</td>
</tr>
<tr>
<td>Pharmaceuticals for chronic illnesses</td>
<td>90%</td>
</tr>
<tr>
<td>Most other prescription pharmaceuticals</td>
<td>60%</td>
</tr>
</tbody>
</table>
Appendix
Value Frameworks
Limitations in the current frameworks restrict each one’s individual applicability as a starting point for an RM/AT framework

- NHB scores are not comparable for multiple treatments
- Various issues in methodology (e.g., nearly impossible to gain or lose points for toxicity)
- The type of clinical outcomes available (OS vs. RR, for example) has a dramatic effect on the final score
- Simplified scoring system (1-5) narrows the degree of distinction between drugs
- Limited information on scoring procedures (qual. vs quant.)
- Overweighting of trial design compared to the other frameworks / value tools
- No universally recommended price for each drug; utility depends on customization
- No procedures in place to add new drugs or adjust existing drugs
- Only lists ~3 drugs per each indication; difficult to compare head-to-head
- Budget impact limited to no more than (an arbitrary value of) $904 million annually
- ICER methods rely on a QALY benchmark; difficult to determine lifetime QALY for curative therapies
- Economic benefits such as improvements in worker productivity are not taken into consideration
The ASCO framework is a simplified tool for patients which compares outcomes and costs.

The ASCO Value Framework

- Designed to guide patient/oncologist joint decision making
- Two separate frameworks: Advanced and Adjuvant treatments
- Long-term goal of adaption into a mobile app for simplified public use
- Compares new, high-cost treatments to standard of care or placebo

Clinical Benefit

Toxicity

Bonus Points

Net Health Benefit Score

Outcomes from NDA Clinical Trials
ASCO Score Calculation (Advanced Setting)

Points are earned through comparison of certain outcome metrics to the standard of care or a placebo.
NCCN Evidence Blocks™ provides a visual summary of different therapies for one indication

- Evidence Blocks are released by indication, and include all recommended treatment regimens
- Intended for use/inclusion with popular NCCN Clinical Practice Guidelines
- Evidence Blocks for Multiple Myeloma and CML were released in October 2015
- Treatments are scored 1-5 in five different categories; mix of qualitative and quantitative analysis
NCCN Evidence Blocks™ provides a visual summary of different therapies for one indication

Evidence Block for Velcade®+Revlimid®+dexamethasone as first-line Multiple Myeloma therapy (non-transplant):

<table>
<thead>
<tr>
<th>Efficacy of Regimen (E)</th>
<th>Safety of Regimen (S)</th>
<th>Quality of Evidence (Q)</th>
<th>Consistency of Evidence (C)</th>
<th>Affordability of Regimen (A)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E = 4/5</strong> Very Effective:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sometimes provides long-term survival advantage or has curative potential</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>S = 3/5</strong> Mildly Toxic:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild toxicity that interferes with activities of daily living is common</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Q = 4/5** Good Quality:
Several well-designed randomized trials

**C = 4/5** Mainly Consistent:
Multiple trials with some variability in outcome

**A = 1/5** Very Expensive

MSKCC’s DrugAbacus allows patients assess drug value based on customizable needs

- **Patient-specific tool**: limited application for Pharma or payers
- **Modifiable sliders** can adjust emphasis levels for QALY, toxicity, burden of disease, etc.
- Compares actual drug prices to “Abacus prices” (i.e., how much a drug should cost)
- **Includes 54 oncology drugs** introduced to the market since 2001
- There is not necessarily a “standard” output; Abacus is dependent on customization
ICER’s Framework calculates “value-based price benchmarks”

- Serves as a way to categorize and integrate various conceptual elements into judgments of two different aspects of value, called “care value” and “provisional health system value” to calculate a “value-based price benchmark” for each new therapy reviewed as part of its new drug assessment program.

- **Care Value**: determined by looking at four elements: comparative clinical effectiveness, incremental costs per outcomes achieved, other benefits or disadvantages, and contextual considerations. Represents the long-term perspective, at the individual patient level, on patient benefits and the incremental costs to achieve those benefits.

- **Provisional “Health System Value”**: represents a judgment integrating consideration of the long-term care value of a new intervention with an analysis of its potential short-term budget impact if utilization is unmanaged.
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The ARM Foundation for Cell and Gene Medicine is an independent, 501(c)(3) non-profit organization dedicated to providing education and research that will accelerate patient access to safe, efficacious and potentially curative therapies. Its programs engage, educate and empower patients, caregivers, industry leaders and other stakeholders to help advance the science and benefits of gene therapy, gene editing, cell therapy, tissue-engineering and organ regeneration. By increasing understanding and acceptance of these transformative technologies, the Foundation hopes to involve more people in the clinical trial process and therefore help expedite the development of life-saving therapies. To learn more, visit http://www.thearmfoundation.org.

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