Next Generation Therapies and related Life Sciences topics
## Contents

1. Overview of Deloitte’s Next Generation Therapy Practice
2. Overview of Next Generation Therapies
3. Gene Therapy
4. Challenges of Commercializing Gene Therapy
5. Gene Editing
6. Regenerative Medicine
7. Supply Chain/Commercialization
8. Appendix 1: Next Generation Therapies Deloitte Case Studies
9. Appendix 2: Deloitte’s Life Sciences M&A Opportunities
Overview of Next Generation Therapies
Evolution to Next Generation Therapies
We are moving toward an ability to cure and heal rather than merely ameliorating symptoms

Polyclonal & Monoclonal Antibodies
Plasma & Recombinant Proteins
Small Molecules & Infectious Disease Vaccines

Increasing Complexity of Therapeutic Intervention

Regulatory/Reimbursement
Supply Chain/Commercialization
AI/Bioinformatics

Modify Gene Expression
- Antisense
- RNAi/siRNA
- Aptamers
- Ribozymes
- Exon Skipping

Gene Correction
- Gene Therapy with Viral Vectors
- Gene Therapy with Other Vectors
- Gene Editing (Meganucleases, ZFN, TALENS, CRISPR)

Regenerative Medicine
- Autologous & Allogenic Cells
- Stem Cell Therapy
- Mitochondrial Transfer
- Tissue Engineering
What Makes Next Generation Therapies Different?
Next gen therapies alter the healthcare ecosystem

Discovery Pathway
- Internal R&D
- New Drug Application (NDA)

Regulatory Approval Pathway
- BLA/Orphan Indications
- Prior Authorization & Clinical Protocols

Reimbursement Mechanisms
- Formulary & Tenders
- Biological Batch Systems

Manufacturing Process
- Chemical Synthesis
- Specialty & Hospital Pharmacy w/ Batch COI & COC

Distribution Channels
- Retail Pharmacy w/Batch COI & COC
- Clinics & Hospitals

Therapy Delivery
- Outpatient
- Field Sales Force to High Prescribers

Commercial Focus
- Specialty Sales Forces and P&T Committees
- Conferences & Peer Reviewed Articles

Market Engagement
- DTC/DTP Advertising, Samples & Coupons
- EHR & REM/RMPs

Real World Evidence Capture
- Rx Data & Adverse Event Reports

Next Generation Therapies
- Translational Medicine at AMC
- Ultra Orphan & Accelerated Programs
- Value Based Billing & Individual Approvals
- Individual Product Production
- Direct Shipment w/ Product COI & COC
- Certified & Trained Institutions
- Medical Affairs Led Team Engaging Institution
- Multiple Stakeholders through on-line portals
- Long-Term Patient Registry

© 2019. For information, contact Deloitte Touche Tohmatsu Limited.
Multiple cell & gene therapies have been approved and are on-market
A timeline showing approvals of such therapies in the US and/or EU highlights
the recent growth in activity in this space

* Products only have EU approvals
Revenues of Currently Approved Next Generation Therapies
Analysts anticipate a ~$9 Billion market for 48 approved products in the next 6 years

**WW Sales of Next Generation Therapies (USD $MM)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Gene Expression</th>
<th>Gene Correction</th>
<th>Regenerative Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>$1,739</td>
<td>867</td>
<td>1,509</td>
</tr>
<tr>
<td>2018E</td>
<td>$3,263</td>
<td>487</td>
<td>2,152</td>
</tr>
<tr>
<td>2019E</td>
<td>$4,472</td>
<td>585</td>
<td>2,790</td>
</tr>
<tr>
<td>2020E</td>
<td>$5,676</td>
<td>679</td>
<td>3,363</td>
</tr>
<tr>
<td>2021E</td>
<td>$6,742</td>
<td>780</td>
<td>3,847</td>
</tr>
<tr>
<td>2022E</td>
<td>$7,549</td>
<td>889</td>
<td>4,235</td>
</tr>
<tr>
<td>2023E</td>
<td>$8,335</td>
<td>1,009</td>
<td></td>
</tr>
<tr>
<td>2024E</td>
<td>$8,955</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Number of Approved and Marketed Next Generation Therapies**

- Total = 48
- Gene Expression: 6%
- Gene correction: 17%
- Regenerative Medicine: 77%

Source: Evaluate Pharma Analyst Consensus Projections; Annual Reports, Product websites and Deloitte Analysis
Note: Gendicine and Oncarine are only sold in China with combined sales of USD ~$8 Million in 2017 are not included in revenue projections; Glybera was pulled from the market in 2017 and is not included.

© 2019. For information, contact Deloitte Touche Tohmatsu Limited.
In the last three years, acquisitions worth over USD $100 Billion have demonstrated the market value of these new technologies.

**M&A in Next Generation Therapies***
(USD $ Billion)

These 3 Acquisitions Accounted for more than USD $29.6 Billion

- Gilead
- Kite
- Novartis AveXis
- Takeda
- Tigenix
- Merck
- Viralytics
- Celgene
- Juno
- BMS
- Celgene
- Roche**
- Spark
- Boehringer
- ViraTherapeutics
- PTC
- Agilis
- Merck
- Viralytics
- Allergan
- LifeCell (Tissue Matrices)
- Gilead Cell Design
- Novartis AveXis

Dec-16 | Oct-17 | Dec-17 | Jan-18 | Jan-18 | Feb-18 | Apr-18 | Jul-18 | Sep-18 | Jan-19 | Feb-19 | Other | Total

10 Deals

113.2
## Major Licensing Deals in the Last 3+ Years (USD $ Millions)

<table>
<thead>
<tr>
<th>Date Announced</th>
<th>Buyer</th>
<th>Licensee</th>
<th>Therapeutic Area</th>
<th>Upfront Payments</th>
<th>Total Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct-18</td>
<td>J&amp;J</td>
<td>Arrowhead</td>
<td>RNAi for Hepatitis B</td>
<td>$235</td>
<td>$3,700</td>
</tr>
<tr>
<td>Aug-18</td>
<td>Pfizer</td>
<td>BioNTech</td>
<td>mRNA flu vaccine</td>
<td>$120</td>
<td>$425</td>
</tr>
<tr>
<td>Apr-18</td>
<td>Eli Lilly</td>
<td>Sigilon</td>
<td>Cell Therapy for Type 1 diabetes</td>
<td>$63</td>
<td>$473</td>
</tr>
<tr>
<td>Feb-18</td>
<td>Abbvie</td>
<td>Voyager</td>
<td>AAV Vectors for GT for Alzheimer's</td>
<td>$69</td>
<td>$1,119</td>
</tr>
<tr>
<td>Feb-18</td>
<td>Gilead</td>
<td>Sangamo</td>
<td>ZFN for Cancer Drug Development</td>
<td>$150</td>
<td>$3,000</td>
</tr>
<tr>
<td>Jan-18</td>
<td>Novartis</td>
<td>Spark</td>
<td>Marketing Luxturna in Europe</td>
<td>$105</td>
<td>$170</td>
</tr>
<tr>
<td>Dec-17</td>
<td>J&amp;J</td>
<td>Legend</td>
<td>BCMA-targeting CAR-T for Multiple Myeloma</td>
<td>$350</td>
<td>--</td>
</tr>
<tr>
<td>May-17</td>
<td>Pfizer</td>
<td>Sangamo</td>
<td>ZFN for Hemophilia A</td>
<td>$70</td>
<td>$545</td>
</tr>
<tr>
<td>Feb-16</td>
<td>Baxalta/Shire</td>
<td>Precision Bioscience</td>
<td>Allogenic CAR-T using Arcus Platform</td>
<td>$105</td>
<td>$1,700</td>
</tr>
<tr>
<td>Dec-15</td>
<td>Bayer</td>
<td>CRISPR</td>
<td>Form JV (Casebia) to develop CRISPR therapies</td>
<td>$300</td>
<td>$335</td>
</tr>
<tr>
<td>Mar-15</td>
<td>Merck Serono</td>
<td>Intrexon</td>
<td>CAR-T with non-viral vector</td>
<td>$115</td>
<td>$941</td>
</tr>
</tbody>
</table>

**Total** $1,682 $12,408

---

**Source:** Alliance for Regenerative Medicine; Company Websites & Press Releases

**Note:** *Only upfront payments represented due to uncertainties about future milestone achievement and product sales to generate royalties*

© 2019. For information, contact Deloitte Touche Tohmatsu Limited.
Worldwide Growth in Next Generation Therapy Companies

On a global basis there has been 15% annual growth over the last 3 years with North America and Europe hosting ~80% of Next Generation companies.

Source: Alliance for Regenerative Medicine Annual Report
There is a significant opportunity in the China Market in the Next Generation Therapies Space

USA and China are the leaders in the development of cell therapies

A representation of clinical trials investigating cell therapies across major markets in the world

USA and China are the leaders in the development of cell therapies

Stem cell & CAR-T therapies represent the largest share of the global cellular therapy market

USA has the largest number of Stem cell therapies under investigation (300+) followed by EU (80+)

Data as of December 10, 2018
Note: The percentages indicate the proportion of studies for a certain intervention/therapy and the number inside the doughnut hole indicates the grand total of on-going studies registered on Clinicaltrials.gov

© 2019. For information, contact Deloitte Touche Tohmatsu Limited.
Deloitte’s Experience with Next Generation Therapies

Over the last 3 years Deloitte has completed over 20 engagement with clients which span the entire patient journey and industry value chain.

### Next Generation Therapies Patient Journey

1. **Referral**
   - Physician initial assessment and referral to treatment center

2. **Enrollment**
   - Confirm patient eligibility
   - Patient consent

3. **Evaluation**
   - Patient education
   - Genetic eligibility

4. **Treatment**
   - Supportive care

5. **Post-Treatment Evaluation**
   - Observation
   - Outpatient/inpatient care

6. **Long-term Follow Up**
   - Community Physician Monitoring
   - Patient registries

#### Value Chain Element

<table>
<thead>
<tr>
<th>Research &amp; Development</th>
<th>Supply Chain</th>
<th>Commercial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Representative Projects</strong></td>
<td><strong>Order to Cash optimization</strong></td>
<td><strong>Pricing &amp; Market Access for CAR-T</strong></td>
</tr>
<tr>
<td>Identification of new viral vectors acquisition targets for gene therapy</td>
<td>Chain of Identity (COI) analysis for European launch</td>
<td>Development of stakeholder portal for launch of CAR-T</td>
</tr>
<tr>
<td>Risk analysis &amp; mitigation strategy for Phase I clinical trials</td>
<td>Supply chain assessment and playbook definition</td>
<td>Customer experience workshops for product launch</td>
</tr>
</tbody>
</table>

© 2019. For information, contact Deloitte Touche Tohmatsu Limited.
Pharma and biotech companies continue to invest heavily to build their NextGen product portfolio
Gene Therapy

Gene Therapy

Modify Gene Expression
- Antisense
- RNAi/siRNA
- Aptamers
- Ribozymes
- Exon Skipping

Gene Correction
- Gene Therapy with Viral Vectors
- Gene Therapy with Other Vectors
- Gene Editing (Meganucleases, ZFN, TALENS, CRISPR)

Regenerative Medicine
- Autologous & Allogenic Cells
- Stem Cell Therapy
- Mitochondrial Transfer
- Tissue Engineering

Supply Chain/Commercialization

Regulatory/Reimbursement

AI/Bioinformatics
A Primer on Molecular Biology
We will use several terms which must be defined

**Cell: Building Block of Life**

- There are an estimated 37.2 trillion cells in the human body.
- Cells are replaced at a rate of millions per second except for few types such as the central nervous system, lens and oocyte cells which last for a lifetime.

**Central Dogma of Molecular Biology**

- **DNA:** DeoxyriboNucleic Acid
  - Carrier of genetic information in the nucleus of the cell.
  - Made of four chemical building blocks (nucleotides--ATCG) which form a double helix.
  - ~3 billion base pairs (A-T, C-G) make up the human genome.
  - Human DNA is tightly wound into 23 pairs of chromosomes.
  - Genes are sequences of DNA ranging from 200 base pairs to 2 million which provide instructions for making proteins.
  - There are between 20,000 and 25,000 human genes of which only 1% are different between individuals.

- **RNA:** RiboNucleic Acid
  - Copies genetic information from the DNA by binding to unzipped DNA.
  - Is a single helix made of four nucleotides (AGCU) and ~15 Million strands of RNA in a cell.
  - RNAs shuttle between the nucleus and rest of cell.
  - RNA is critical in regulating protein synthesis and RNA & DNA repair.

- **Protein**
  - Building blocks of the structure and do the work of cells.
  - Composed of 23 amino acids whose sequence is determined by RNA.
  - Proteins catalyze chemical reactions which impact DNA, RNA and other proteins.
Gene Therapy Approaches

All gene therapies insert engineered DNA/RNA into living cells to make or modify new proteins.
Gene Therapy Technology Platforms
There are multiple platform technologies which are being utilized

**Maturity of Platform Technologies**

**More Mature**
*Platforms Used with Current Drugs*

- **AAV** (adeno associated viruses)
  vectors support production of protein, leading to therapeutic effect, without permanently altering the patient’s DNA

- **Lentiviral** vectors are retroviruses used to introduce a functional copy of a gene to the patient’s extracted hematopoietic stem cells with longer term therapeutic effect

**Less Mature**
*Platforms with Drugs in Clinical Trials*

- **CRISPR** (Clustered Regularly Interspaced Short Palindromic Repeats)
  is a gene editing tool originally discovered as a RNA-based bacterial defense mechanism designed to eliminate foreign DNA from invading bacteriophages and plasmids

- **ZFNs** (Zinc Finger Nucleases) and **TALENs** (Transcription Activator-Like Effector Nucleases)
  Gene editing tools to remove a gene or insert a therapeutic gene into the genome in a targeted fashion
# Approved and Marketed Gene Therapies

12 of the 14 products approved across the US, EU and China are still available

## In Vivo

<table>
<thead>
<tr>
<th>Name (Company)</th>
<th>Date Approved</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gendicine (Benda Pharma)</td>
<td>Oct 2003*</td>
<td>Adenovirus with the p53 tumor-suppressor gene for head &amp; neck cancer</td>
</tr>
<tr>
<td>Oncorine (Shanghai Sunway Biotech)</td>
<td>Nov 2005*</td>
<td>Oncolytic recombinant adenovirus for nasopharyngeal cancer with chemotherapy</td>
</tr>
<tr>
<td>Glybera (uniQure)</td>
<td>Nov 2012**</td>
<td>AAV1 treatment for lipoprotein lipase deficiency</td>
</tr>
<tr>
<td>Kynamro (Kastle)</td>
<td>Jan 2013***</td>
<td>Antisense oligomer which treats homozygous familial hypercholesterolemia</td>
</tr>
<tr>
<td>Imlygic (Amgen)</td>
<td>Nov 2015</td>
<td>HSV-1 Virus to treat melanoma lesions</td>
</tr>
<tr>
<td>Exondys 51 (Sarepta)</td>
<td>Sep 2016***</td>
<td>Anti-sense oligomer for exon skipping to treat Duchenne Muscular Dystrophy (DMD)</td>
</tr>
<tr>
<td>Spinraza (Biogen/Ionis)</td>
<td>Dec 2016</td>
<td>Anti-sense oligomer for alternate gene splicing for Spinal Muscular Atrophy (SMA)</td>
</tr>
<tr>
<td>Luxturna (Spark)</td>
<td>Mar 2018</td>
<td>AAV2 treatment for RP caused by RP165 gene</td>
</tr>
<tr>
<td>Onpattro (Alnylam)</td>
<td>Aug 2018</td>
<td>RNAi drug to treat adult hereditary transthyretin amyloidosis</td>
</tr>
</tbody>
</table>

## Ex Vivo

<table>
<thead>
<tr>
<th>Name (Company)</th>
<th>Date Approved</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provenge (Dendreon)</td>
<td>Apr 2010***</td>
<td>Dendritic cells extracted and viral transfection with a recombinant fusion protein and then reinfused to treat metastatic prostate cancer</td>
</tr>
<tr>
<td>Strimvelis (GSK/Orchard)</td>
<td>May 2016**</td>
<td>Bone Marrow cells are extracted and transfected with a gamma retrovirus to treat Adenosine Deaminase Severe Combined Immunodeficiency deficiency (ADA-SCID)</td>
</tr>
<tr>
<td>Zalmoxis (MolMed)</td>
<td>Aug 2016**</td>
<td>Adjunct treatment for Graft vs Host Disease (GvHD) in bone marrow transplants with “suicide switch”. Retrovirus gene insertion into donor T- cells infused to patient</td>
</tr>
<tr>
<td>Kymriah (Novartis)</td>
<td>Aug 2017</td>
<td>Patient’s T-cells are extracted and CAR targeting CD19 inserted using lentivirus for reinfusion for pALL &amp; DLBCL</td>
</tr>
<tr>
<td>Yescarta (Kite/Gilead)</td>
<td>Oct 2017</td>
<td>Patient’s T-cells are extracted and CAR targeting CD19 inserted using retrovirus for reinfusion for DLBCL</td>
</tr>
</tbody>
</table>

*Only approved in China  **Only Approved in the EU  ***Only Approved in the US

Notes: Kynamro was withdrawn from US in May 2018 before Kastle Therapeutics bankruptcy; Glyberra was withdrawn from the EU in October 2017

Sources: EvaluatePharma and company websites

© 2019. For information, contact Deloitte Touche Tohmatsu Limited.
Approved In Vivo Gene Therapies Sales
Currently approved and on-market in vivo gene therapies have ~ USD $1B in sales and are projected to be a ~USD $4B market

WW Sales of In Vivo Gene Therapy Drugs (USD $MM)

<table>
<thead>
<tr>
<th>Name (Developer)</th>
<th>Approval Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinraza (Biogen/Ionis)</td>
<td>Dec 2016</td>
<td>Gene splicing antisense for SMA</td>
</tr>
<tr>
<td>Exondys 51 (Sarepta)</td>
<td>Sep 2016</td>
<td>Exon skipping antisense for DMD</td>
</tr>
<tr>
<td>Imlygic (Amgen)</td>
<td>Nov 2015</td>
<td>HSV-1 Virus to treat melanoma lesions</td>
</tr>
<tr>
<td>Onpattro (Alnylam)</td>
<td>Aug 2018</td>
<td>RNAi drug to treat adult hereditary transthyretin amyloidosis</td>
</tr>
<tr>
<td>Luxturna (Spark)</td>
<td>Mar 2018</td>
<td>AAV2 treatment for RP caused by RP165 gene</td>
</tr>
</tbody>
</table>

Notes: Glybera (Uniqure) was pulled from the market in 2016 so is not included; Gendicine and Oncorine are only sold in China with combined sales of USD ~$8 Million in 2017 are not included in analysis Source: Evaluate Pharma for Consensus Equity Analyst Projections; company websites
Current approved and on-market ex vivo gene therapies have ~USD $350 million in sales with projections to achieve ~USD $3.9 billion.

Sales of Ex Vivo Gene Therapy Drugs (USD $MM)

<table>
<thead>
<tr>
<th>Name</th>
<th>Approval Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yescarta (Kite/Gilead)</td>
<td>Oct 2017</td>
<td>Patient’s T-cells are extracted and CAR targeting CD19 inserted using retrovirus for reinfusion for DLBCL</td>
</tr>
<tr>
<td>Kymriah (Novartis)</td>
<td>Aug 2017</td>
<td>Patient’s T-cells are extracted and CAR targeting CD19 inserted using lentivirus for reinfusion for pALL &amp; DLBCL</td>
</tr>
<tr>
<td>Zalmoxis (MolMed)</td>
<td>Aug 2016</td>
<td>Retrovirus gene insertion into donor T-cells infused to patient for GvHD in BMT</td>
</tr>
<tr>
<td>Provenge (Dendreon)</td>
<td>Apr 2010</td>
<td>Dendritic cells extracted and viral transfection with a recombinant fusion protein. Cells reinfused to treat metastatic prostate cancer</td>
</tr>
</tbody>
</table>

Notes: Strimvelis transferred to Orchard Therapeutics on June 2018 and had sales of $3.2MM in 2017 and $2MM in 2018. Future sales are uncertain and have not been included. Source: Evaluate Pharma for Consensus Equity Analyst Projections; company websites.
Future of Gene Therapies

Expectations are for ~40 new gene therapies to be approved in the U.S. alone

By 2022
39 products
 +/- 4

Jan 2017 Gene Therapy Pipeline in US & EU

539 Preclinical
142 Phase 1
213 Phase 2
31 Phase 3
7 In Review/Approved

Oncology
Orphan
Ultra Orphan
Other TA
I don’t know if their [MIT] estimates [~40 approved gene therapy drugs by 2022] are right or wrong. But I know that directionally, these predictions are correct. Just this past year we saw the first three approvals of gene therapies: two cell-based gene therapies for blood cancers, and a directly administered gene therapy to address a form of hereditary retinal dystrophy. The promise is very much becoming a reality. These recent product approvals represent just the tip of the iceberg.

Scott Gottlieb FDA Commissioner
Bio 2018, June 7, 2018
Chimeric Antigen Receptor T-cells (CAR-T) for Gene Therapy

The approval and launches of Kymriah and Yescarta have led to significant press coverage and buzz for the entire field of gene therapy.
CAR-T & TCR Approaches for Gene Therapy

The most mature approaches either target surface tumor antigens (CAR-T) or attack internal tumor cancer proteins as they migrate to the surface (TCR).

**New Types of Immune Cells using CAR Approach**

- Tumor Infiltrating Lymphocytes (CAR-TIL)
- Natural Killer T-Cells (CAR-NKT)
- Natural Killer Cells (CAR-NK)
- T-cell Receptor Fusion Complex (TRUK)

- Gamma Delta T-Cells (CAR-γδ)
- Cytostatic T-Cells (CAR-CTL)
- Cytokine Induced Killer Cells (CAR-CIK)

Source: National Cancer Institute; Wells Fargo Securities Conference, Nov. 2017

© 2019. For information, contact Deloitte Touche Tohmatsu Limited.
Proliferation of CAR-T/TCR Candidates in Development

Of the ~200 drugs in development, 13 are projected to generate an additional USD $5B+ above Kymriah and Yescarta revenues by 2024

Projected Sales of CAR-T/TCR Drugs
(USD $MM)

Source: EvaluatePharma Consensus Forecasts; Wells Fargo Securities Conference, Nov. 2017
Gene Therapy in the Context of Immuno-Oncology

Gene therapy will continue to be a complementary approach to monoclonal antibody based checkpoint inhibitors.

Immuno-Oncology (I-O) Approaches

- **Blocking T-Cell Checkpoint Pathways**
  - Targets: CTLA-4, PD-1, PD-L1/2
  - Anti-CTLA-4, Anti-PD-1

- **Promoting T-cell Costimulatory Receptor Signaling**
  - Targets: CSF1, OX-40, CD19, CD137/4-1BB, GITR

- **Potentiating Immune-Cell Effector Function**
  - Targets: IDO, TGF-β

- **Adoptive T cell**
  - Targets: CD19
  - Reverse engineering T cells to recognize tumor cells

- **Immunizing the Function of Innate Immune Cells**
  - Targets: NK, Macrophage, Dendritic Cells

- **Yervoy (CTLA-4)**
- **Opdivo (PD-1)**
- **Keytruda (PD-1)**
- **Tecentriq (PD-L1)**
- **Bavencio (PD-L1)**
- **Imfinzi (PD-L1)**
- **Arzerra (CD-20)**
- **Campath (CD-52)**
- **Rituxan (CD-20)**
- **Kymriah (CD19)**
- **Yescarta (CD19)**

Source: *Immunotherapy and Novel Combinations in Oncology: Current Landscape, Challenges, and Opportunities*

© 2019. For information, contact Deloitte Touche Tohmatsu Limited.
Challenges of Commercializing Gene Therapy
Lessons Learned from Gene Therapy Commercialization

Early gene therapy products struggled with product uptake

Gene Therapy Products Launched
(Bubble size is Cost of Course of Therapy in USD $000’s)

- The total cost of care matters; not just the drug price for determining reimbursement
- Establishing treatment networks requires balancing patient reach vs. cost to serve
- Being prepared to offer value based pricing (e.g. rebates, performance guarantees, long payment terms) is essential at first launch
- Identifying and capturing the potential patient pools for ultra orphan indications requires working with healthcare providers and hospitals

Source: Company Press Releases

© 2019. For information, contact Deloitte Touche Tohmatsu Limited.
## Approaches to Reimbursement for Gene Therapies

Prices for gene therapies have set new records; requiring innovative pricing models to obtain reimbursement and coverage

<table>
<thead>
<tr>
<th>Brand</th>
<th>Company</th>
<th>Indication</th>
<th>Price</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glybera</td>
<td>uniQure</td>
<td>Lipoprotein in lipase deficiency patients who have acute and chronic pancreatitis attacks</td>
<td>$1M+</td>
<td>• First gene therapy approved in Europe; however, none of the price setting markets provided access. HTA groups in Germany and France concluded that the benefit is insufficient to justify reimbursement.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• UniQure decided not to renew marketing authorization in Europe and abandoned plans for commercializing in the US</td>
</tr>
<tr>
<td>Strimvelis</td>
<td>gsk</td>
<td>ADA-SCID or “bubble boy syndrome”</td>
<td>$714,000 (£594,000)</td>
<td>• Extremely rare condition affecting ~15 patients per year in Europe</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Faced reimbursement and payment hurdles – despite the money back guarantee and pay-for-performance pricing model, GSK struggled to make Strimvelis a commercial success</td>
</tr>
<tr>
<td>Kymriah</td>
<td>NOVARTIS</td>
<td>B-cell precursor ALL for patients &lt;25 years</td>
<td>$475,000 ALL, $373,000 DLBCL</td>
<td>• First CAR-T therapy approved in the US</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• R/R ALL Outcomes-based reimbursement model – fully payment only if the patients respond to therapy 30 days after initiating treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• R/R DLBCL does not offer any outcomes-based concessions</td>
</tr>
<tr>
<td>Yescarta</td>
<td>Kite</td>
<td>Relapsed/refractory large B-cell lymphoma, including DLBCL</td>
<td>$373,000 DLBCL</td>
<td>• 2nd CAR-T therapy approved in the US for a much larger patient population</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Has a boxed warning for Cytokine Release Syndrome (CRS) and neurologic toxicities, thus part of a REMS program</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• CMS &amp; some private insurers lack billing codes for CAR-T treatments</td>
</tr>
<tr>
<td>Luxturna</td>
<td>Spark</td>
<td>Confirmed biallelic RPE65 mutation-associated retinal dystrophy</td>
<td>$850,000 or $425,000/eye</td>
<td>• Three innovative programs to improve access: 1. Outcomes-based rebate linked to short- and long-term efficacy; 2. Installment payment option negotiated with CMS with greater rebates tied to clinical outcomes; 3. Agreement with commercial payers for alternative contracting to “buy and bill”</td>
</tr>
<tr>
<td>Zolgensma</td>
<td></td>
<td></td>
<td>$2.125M</td>
<td></td>
</tr>
</tbody>
</table>

Source: Defined Health—Advanced Therapeutic Webinar, August 2018

© 2019. For information, contact Deloitte Touche Tohmatsu Limited.
Challenges to Therapeutic Commercialization of Gene Therapy

**Medical/Hospital**
- Rare genetic diseases require a testing infrastructure to identify patients
- Long-term patient follow-up and registry maintenance (10-15 years)

**Technical/Scientific**
- Off-target edits
- Immunogenicity
- Delivering the gene editing machinery to the cell nucleus
- Ensuring genetic changes continue for new generations of cells
- Addressing diseases which are the result of multiple genes

**Commercial**
- Uncertainty about IP ownership for CRISPR
- Obtaining reimbursement for high cost of therapy
  - Logistics/Supply Chain Issues for autologous therapies
  - As CRISPR brings down the cost of discovering new therapies--will this lead to a flood of similar therapeutic solutions

**Ethical/Moral**
- Potential religious issues with altering human genetics
- Should there be a uniform patient informed consent process regardless of where the therapy is developed?
- Going beyond treating diseases to selecting for specific human traits
Gene Editing

- Gene Editing
- Regenerative Medicine
  - Autologous & Allogenic Cells
  - Stem Cell Therapy
  - Mitochondrial Transfer
  - Tissue Engineering

- Modify Gene Expression
  - Antisense
  - RNAi/siRNA
  - Aptamers
  - Ribozymes
  - Exon Skipping

- Gene Correction
  - Gene Therapy with Viral Vectors
  - Gene Therapy with Other Vectors
  - Gene Editing (Meganucleases, ZFN, TALENS, CRISPR)

- Supply Chain/Commercialization
  - AI/Bioinformatics

- Regulatory/Reimbursement
Gene Editing has captured the popular imagination as the next major scientific breakthrough

Clustered Regularly Interspaced Short Palindromic Repeats-CRISPR associated protein 9 (CRISPR-Cas9) has received the most buzz

CRISPR-Cas9 has multiple applications spanning animal health, agriculture and industrial production, but the ability to “edit” human genes to cure disease and select traits has received the most press.
How Does CRISPR-Cas9 Work?

Cas9 protein was discovered in bacteria to combat viruses and uses guide RNA (gRNA) to identify viral DNA targets to disable.

By swapping out different gRNAs, researchers can target specific regions of DNA to modify.

The Cas9 protein breaks both strands of DNA at the specific target point.

**Repair/Replace a Gene**

**DNA to insert**

**Gene inserted**

**DNA repaired with inserted gene**

**Gene knocked out**

**DNA repaired**


© 2019. For information, contact Deloitte Touche Tohmatsu Limited.
Alternatives to CRISPR-Cas9 for Gene Editing

TALENs, Zinc Finger Nucleases, Meganucleases and Homologous Recombination are all alternatives to CRISPR-Cas9

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Homologous Recombination</td>
<td>Meganucleases</td>
<td>Zinc Finger Nucleases (ZFNs)</td>
<td>Transcription Activator-Like Effector Nucleases (TALENs)</td>
<td>Clustered Regularly Interspaced Short Palindromic Repeats nucleases (CRISPR)</td>
</tr>
</tbody>
</table>

Homologous Recombination

Adeno-associated virus (AAV)

Nuclease Based Gene Editing

Source: BCG, Homology Medicines Website,
There an estimated ~10,000 genetic disorders cause by single gene mutation

<table>
<thead>
<tr>
<th>Common Single Mutation Disorders</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalassaemia</td>
<td>Absence and/or errors in gene responsible for production of haemoglobin, an oxygen carrying protein present in the red blood cells</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>Genetic mutation which causes the entire blood cell to change shape under stressed conditions</td>
</tr>
<tr>
<td>Haemophilia</td>
<td>A hereditary bleeding disorder with partial or total lack of an essential blood clotting factor. It results in excessive bleeding and often spontaneous internal bleeding</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>A genetic disorder that affects the respiratory, digestive and reproductive systems involving the production of abnormally thick mucus linings in the lungs and can lead to fatal lung infections. The disease can also result in various obstructions of the pancreas, hindering digestion.</td>
</tr>
<tr>
<td>Tay Sachs Disease</td>
<td>A fatal genetic disorder in which harmful quantities of a fatty substance called Ganglioside GM2 accumulate in the nerve cells in the brain. It is caused by a decrease in the functioning of the Hexosaminidase A enzyme</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>A genetic mutation which varies considerably in severity among patients. Fragile X syndrome is the most common cause of inherited mental retardation.</td>
</tr>
<tr>
<td>Huntington’s Disease</td>
<td>A degenerative brain disorder, which affects the ability to walk, talk, think, and reason. This disease begins between ages 30-45, and every individual with the gene for the disease will eventually develop the disease</td>
</tr>
</tbody>
</table>

Source: WHO Genomic Resource Center
Publicly Traded Gene Editing Companies

Market capitalization far outpaces revenue and all companies are unprofitable

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Market Cap (USD $MM)</th>
<th>2017 Revenue (USD $MM)</th>
<th>2017 Net Income (USD $MM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRISPR Therapeutics AG (CRSP)</td>
<td>2.5</td>
<td></td>
<td>($25)</td>
</tr>
<tr>
<td>Editas Medical (EDIT)</td>
<td>1.6</td>
<td></td>
<td>($100)</td>
</tr>
<tr>
<td>Intellia Therapeutics (NTLA)</td>
<td>1.0</td>
<td></td>
<td>($75)</td>
</tr>
<tr>
<td>Cellectis SA (CLLS)</td>
<td>1.2</td>
<td></td>
<td>($50)</td>
</tr>
<tr>
<td>Sangamo Therapeutics (SGMO)</td>
<td>1.6</td>
<td></td>
<td>($25)</td>
</tr>
<tr>
<td>Precision Biosciences (Private)</td>
<td>0.2</td>
<td></td>
<td>($100)</td>
</tr>
<tr>
<td>Homology Medicine (FIXX)</td>
<td>0.7</td>
<td></td>
<td>($50)</td>
</tr>
<tr>
<td>Precision Biosciences (Private)</td>
<td>0.2</td>
<td></td>
<td>($100)</td>
</tr>
</tbody>
</table>

Source: Company 10-K reports; Company Press Releases; Market Capitalization calculated as of 12 May 2018

© 2019. For information, contact Deloitte Touche Tohmatsu Limited.
Venture Capital Investment in Gene Editing Companies
In the last five years ~USD $1.4 Billion invested in gene editing start-ups

Venture Capital Investment in Human Therapeutic Gene Editing (USD $Millions)

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Investment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>$52</td>
</tr>
<tr>
<td>2014</td>
<td>$86</td>
</tr>
<tr>
<td>2015</td>
<td>$365</td>
</tr>
<tr>
<td>2016</td>
<td>$607</td>
</tr>
<tr>
<td>2017</td>
<td>$273</td>
</tr>
</tbody>
</table>

Total=$1,382 MM

Current Clinical Trials Utilizing Gene Editing Technologies

China dominates for CRISPR trials but the U.S. and Europe are the most preferred destinations for the majority of gene editing patients.

<table>
<thead>
<tr>
<th>U.S. and Western Europe</th>
<th>Trials</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crispr</td>
<td>3</td>
<td>65</td>
</tr>
<tr>
<td>Talens</td>
<td>5</td>
<td>478</td>
</tr>
<tr>
<td>ZFN</td>
<td>10</td>
<td>132</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Peoples Republic of China</th>
<th>Trials</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crispr</td>
<td>10.5</td>
<td>361</td>
</tr>
<tr>
<td>Talens</td>
<td>1.5</td>
<td>70</td>
</tr>
<tr>
<td>ZFN</td>
<td>1</td>
<td>20</td>
</tr>
</tbody>
</table>

**Crispr**
- Sickle Cell Disease 7
- Multiple Myeloma 58

**Zinc Fingers**
- Hemophilia B 12
- HIV 79
- MPS I 7
- MPS II 9
- β-thalassemia 9
- ALL 210

**Talens**
- BPDCN 20
- ALL 240
- AML 156

**Zinc Fingers**
- HPV 20
- Bladder Cancer 20
- Lung Cancer 15
- Prostate Cancer 20
- Kidney Cancer 20
- Cervical Cancer 30

© 2019. For information, contact Deloitte Touche Tohmatsu Limited.
Clinical Trials Utilizing Gene Editing Technology
The next few years will continue the growth of products reaching human clinical trials

<table>
<thead>
<tr>
<th>Company</th>
<th>Compound</th>
<th>Indication</th>
<th>Milestone</th>
<th>Timing</th>
<th>Collaborators</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRISPR Therapeutics AG</td>
<td>CTX001</td>
<td>β-thalassemia (Europe)</td>
<td>Phase 1/2</td>
<td>2018Q1</td>
<td>Vertex</td>
</tr>
<tr>
<td></td>
<td>CTX001</td>
<td>Sickle Cell Disease</td>
<td>IND Filing</td>
<td>2018H1</td>
<td>Vertex</td>
</tr>
<tr>
<td></td>
<td>CTX101</td>
<td>CD-19 Cancers</td>
<td>IND Filing</td>
<td>YE2018</td>
<td></td>
</tr>
<tr>
<td>Intellia Therapeutics</td>
<td>ATTR</td>
<td>Liver Disease (transthyretin amyloidosis)</td>
<td>IND Filing</td>
<td>YE2018</td>
<td>Regeneron Pharmaceuticals</td>
</tr>
<tr>
<td>Editas Medicine</td>
<td>EDIT-101</td>
<td>Ophthalmology - Leber congenital amaurosis</td>
<td>IND Filing</td>
<td>2018H1</td>
<td></td>
</tr>
<tr>
<td>Homology Medicines</td>
<td>sHMI-102</td>
<td>Metabolic--Adult Phenylketonuria (PKU)</td>
<td>IND Filing</td>
<td>YE2018</td>
<td></td>
</tr>
<tr>
<td>Logic Biotherapeutics</td>
<td>LB-001</td>
<td>Pediatric metabolic disease methylmalonic acidemia (MMA)</td>
<td>IND Filing</td>
<td>YE2018</td>
<td></td>
</tr>
<tr>
<td>Bioverativ/Sanofi</td>
<td>BIVV003</td>
<td>Sickle Cell Disease</td>
<td>IND Filing</td>
<td>May-18</td>
<td>Sangamo Therapeutics</td>
</tr>
<tr>
<td>Cellectis</td>
<td>UCART22</td>
<td>Allogenic B-Cell Acute lymphoblastic leukemia (B-ALL) with CD-22</td>
<td>IND Filing</td>
<td>May-18</td>
<td></td>
</tr>
</tbody>
</table>

On average drugs which enter Phase 1 take 5-8 years to reach FDA approval but gene editing drugs with accelerated approvals are moving faster

Source: Company Websites

© 2019. For information, contact Deloitte Touche Tohmatsu Limited.
Diagnostic Applications of Gene Editing

New Cas proteins have opened the door to create highly sensitive assays for viral infectious diseases

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Baltimore Virus Classification</th>
<th>New CAS Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Double stranded DNA viruses (e.g. Adenoviruses, Herpesviruses, Poxviruses)</td>
<td><strong>New Cas Protein (Cpf1/Cas12a)</strong></td>
</tr>
<tr>
<td></td>
<td>Single stranded DNA viruses (Sense) (e.g. Parvoviruses)</td>
<td>Discovered in bacterium <em>Francisella novicida</em> which allows editing of both double strand DNA targets and single strand DNA</td>
</tr>
<tr>
<td></td>
<td>Double Stranded RNA Virus (e.g. Reoviruses)</td>
<td><strong>New Cas Protein (Cas13)</strong></td>
</tr>
<tr>
<td></td>
<td>Single Stranded RNA Virus (sense) (e.g. Picornaviruses, Togaviruses)</td>
<td>Discovered in <em>Prevotella</em> sp. and can be programmed to bind to a target RNA for a specific cut and then continues cutting multiple RNA</td>
</tr>
<tr>
<td></td>
<td>Single Stranded RNA Virus (antisense) (e.g. Rhabdoviruses)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single Stranded RNA-RT Viruses with DNA intermediate (e.g. Retroviruses)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Double Stranded DNA-RT Viruses with RNA intermediate (e.g. Hepadnaviruses)</td>
<td></td>
</tr>
</tbody>
</table>
Diagnostic Proofs of Concept using Gene Editing
Academics have shown success using gene editing for Dx applications

<table>
<thead>
<tr>
<th>Dx Techniques</th>
<th>Technique Description</th>
<th>Initial Academic Proof of Concepts</th>
</tr>
</thead>
<tbody>
<tr>
<td>DETECTR (DNA Endonuclease Targeted CRISPR Trans Reporter) developed by Howard Hughes Medical Institute and UC Berkeley</td>
<td>DETECTR demonstrated ability to detect HPV16 and HPV18 which cause 70% of cervical cancer. Out of 25 human samples from UCSF for HPV16, DETECTR made the right call for all of the samples. For HPV18, DETECTR got it right for 23 of 25 samples.</td>
<td></td>
</tr>
<tr>
<td>SHERLOCK (Specific High-Sensitivity Enzymatic Reporter UnLOCKing) developed by MIT/Broad Institute which uses Cas13 and synthetic RNA armed with reporter beacons to identify presence of target with high sensitivity and specificity</td>
<td>SHERLOCK demonstrated ability to distinguish multiple related viruses (Zika, dengue, West Nile, &amp; yellow fever) from one another. The method had high sensitivity (attomolar level—two molecules in $10^{18}$) and requires no specialized equipment which results in a low Cost of reagents (USD 0.61 per test). Reagents can be lyophilized making them cold chain independent</td>
<td></td>
</tr>
</tbody>
</table>

Diagnostic Companies Leveraging CRISPR

Mammoth Bioscience is one of the first but not the only gene editing Dx companies

- Raised USD $23.1 MM from venture capital investors in last 12 months
- Produces a Point of Care test for home use based on filter paper strips and a smartphone using DETECTR

“CRISPR on a Chip”

- Cas12a makes frayed cuts to DNA which allows tumor mutations to be replicated in human DNA outside the body
- Christiana Care Health System has demonstrated replicating sequenced tumor mutations from lung cancer and melanoma to DNA plasmids outside the cell where different drugs can be tested
- Novellus Dx licensed technology and expects to launch WW in 2018

Depletion of Abundant Sequences by Hybridization (DASH)

- CRISPR-Cas9 is used to delete the more abundant wild type DNA sequences of KRAS found in tumor samples while leaving intact the commonly mutated KRAS. The remaining tumor DNA is amplified using a Polymerase Chain Reaction (PCR) which enhances amplification of rare variants which drive cancer development

Source: Atkinson AE, Nerenz CE, Seger YR, Tsongalis GJ “CRISPR Gets Clinical”, Medical Lab Management March 2018 - Vol. 7 No. 2 - Page #10
Regenerative Medicine

- **Regenerative Medicine**
  - Autologous & Allogenic Cells
  - Stem Cell Therapy
  - Mitochondrial Transfer
  - Tissue Engineering

- **Gene Correction**
  - Gene Therapy with Viral Vectors
  - Gene Therapy with Other Vectors
  - Gene Editing (Meganucleases, ZFN, TALENS, CRISPR)

- **Modify Gene Expression**
  - Antisense
  - RNAi/siRNA
  - Aptamers
  - Ribozymes
  - Exon Skipping

- **AI/Bioinformatics**

- **Supply Chain/Commercialization**

- **Regulatory/Reimbursement**
Regenerative medicine relies upon the ability to grow new cells to replace damaged ones.

**Technologies Underpinning Regenerative Medicine**

**Development of Stems Cells**

- **Embryonic Stem Cells**
  - Totipotent: Able to differentiate into any type of cell in the body. Found in blastocysts during very early embryo development (1-5 days).
  - Embryonic at 5 days; can renew themselves indefinitely.

- **Induced Pluripotent Stem Cells (iPSCs)**
  - Are reprogrammed adult stem cells found throughout the body (bone marrow, skin, cord blood, fat, lung, neurons, mammarys, and baby teeth) which can be turned back into pluripotent cells and make new types of cells.

- **Endoderm Pluripotent Stem Cells**
  - Endoderm (internal layer): Lung cells (alveolar cell), Thyroid cells, Digestive cells (pancreatic cell).

- **Mesoderm Pluripotent Stem Cells**
  - Mesoderm (middle layer): Cardiac muscle cells, Skeletal muscle cells, Tubule cells of the kidney, Red blood cells, Smooth muscle cells (in gut).

- **Ectoderm Pluripotent Stem Cells**
  - Ectoderm (external layer): Skin cells of epidermis, Neuron on brain, Pigment cells.
The majority of unique approved products have been in Asia.

Markets Where Currently Marketed Regenerative Medicine Products Initially Approved (N=37)

- U.S.
  - Epicel
  - MACI (Carticel)
  - Omnigraft
  - Cardiocel
  - Vascucel
  - Aurix
  - Transcyte
  - Apligraf
  - Dermagraft
  - Gintuit
  - HPC Cord Blood*

- EU
  - Spherox
  - ReNovoCell
  - ReGenerCell
  - Vogenix-FG

- South Korea
  - Ossron
  - Hyalograft 3D
  - Holoderm
  - Kaloderm
  - Queencell

- Japan
  - Cupistem
  - Cellgram-AMI
  - Cartistem
  - Neuronata-R
  - HeartSheet
  - Temcell

- India
  - Stempeucel

Note: *Due to FDA regulation Cord Blood Products are required to have a BLA filed by each processing site. There are 8 approved BLAs for Cord Blood in the U.S.
### Cost of Approved Regenerative Therapies

Regenerative therapies have a significant range in costs

<table>
<thead>
<tr>
<th>Category</th>
<th>Product Name</th>
<th>Description</th>
<th>Cost per Therapy (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound Care</td>
<td>Apligraf</td>
<td>Skin substitute with a dermal layer of human cells (fibroblasts) in a bovine type I collagen and cornified epidermal layer of human keratinocytes. Indicated for the treatment of chronic venous leg ulcers and diabetic foot ulcers</td>
<td>$1500 - $2500</td>
</tr>
<tr>
<td></td>
<td>Dermagraft</td>
<td>Dermal substitute made from human cells (fibroblasts), placed on a dissolvable mesh material and used in wound closure of diabetic foot ulcers</td>
<td>$1700</td>
</tr>
<tr>
<td></td>
<td>Epicel</td>
<td>Permanent skin replacement grown from autologous keratinocytes which are co-cultured with irradiated murine cells to form cultured epidermal autografts (CEA). Indicated for treatment of deep dermal or full thickness burns</td>
<td>$6000 - $10,000 per 1% of body surface</td>
</tr>
<tr>
<td>Cartilage Replacement</td>
<td>MACI (Carticel)</td>
<td>Autologous cellularized scaffold indicated for the repair of single or multiple symptomatic, full-thickness cartilage defects of the knee with or without bone involvement</td>
<td>$15,000 - $35,000</td>
</tr>
<tr>
<td></td>
<td>Cartistem</td>
<td>Allogeneic human umbilical cord blood-derived mesenchymal stem cells indicated for the treatment of knee cartilage defects such as traumatic articular cartilage, degenerative arthritis and rheumatoid arthritis.</td>
<td>$19,000 - $21,000</td>
</tr>
<tr>
<td></td>
<td>Spherox</td>
<td>Spheroids of human autologous chondrocytes for use in cartilage defects</td>
<td>$9,500 - $12,000 per treatment</td>
</tr>
<tr>
<td>Heart Conditions</td>
<td>HeartSheet</td>
<td>Skeletal myoblast sheets for treating heart failure made by culturing skeletal myoblasts contained in patients thigh muscle tissue and then transplanting the sheets onto the surface of the patient’s heart.</td>
<td>$122,000</td>
</tr>
<tr>
<td></td>
<td>Cellgram-AMI</td>
<td>Autologous bone marrow-derived mesenchymal stem cell injection for treatment of acute myocardial infarction</td>
<td>$19,000 per treatment</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>Holoclor</td>
<td>Autologous cultures of limbal stem cells which regenerates a functional corneal epithelium allowing recovery of visual acuity. Indicated for the treatment of moderate to severe ocular burns</td>
<td>$100,000</td>
</tr>
<tr>
<td>IV Cell Therapy</td>
<td>Temcell (Prochymal)</td>
<td>Allogeneic mesenchymal stem cell for the treatment of acute radiation injury, chronic obstructive pulmonary disease, Crohn’s disease, graft-versus-host disease, Type I diabetes and myocardial infarction</td>
<td>$170,000 - $200,000</td>
</tr>
</tbody>
</table>

Sources: [www.bioinformant.com](http://www.bioinformant.com)
Supply Chain/Commercialization

Regulatory/Reimbursement

Supply Chain/Commercialization

AI/Bioinformatics

Modify Gene Expression
- Antisense
- RNAi/siRNA
- Aptamers
- Ribozymes
- Exon Skipping

Gene Correction
- Gene Therapy with Viral Vectors
- Gene Therapy with Other Vectors
- Gene Editing (Meganucleases, ZFN, TALENS, CRISPR)

Regenerative Medicine
- Autologous & Allogenic Cells
- Stem Cell Therapy
- Mitochondrial Transfer
- Tissue Engineering
NextGen therapies are of two types – gene and cell therapies

**Gene Therapy**
- One healthy donor
- One tissue source
- Master cell bank
- Several batches cell product
- Treatment of several patients

**Cell Therapy**
- Allogenic
  - One patient
  - One tissue source
  - One batch of cell product
  - Treatment of one patient
- Autologous
  - One patient
  - One tissue source
  - One batch of cell product
  - Treatment of one patient

*Source: Research Gate publication ([link](#))
**Source: Apceth MSC platform ([link](#))
There is a step change increase in the complexity to manufacture and deliver of cell & gene therapies

The patient is a both a supplier of raw material and “bioreactor” for effective delivery of cell and gene therapy

Supply Chain and Manufacturing are stretched to include multiple stakeholders including patients and clinicians
Cell and Gene therapy supply chain is enabled by specialized services from raw input suppliers and global CDMOs.

**Raw Input Suppliers**
- Equipment (e.g., centrifuge, flowcytometer)
- Raw materials (e.g., reagents, media)

**CDMOs**
- Day 0 Processing
- Vectors
- Drug Product
Cell and Gene Therapy CDMOs require a highly specialized set of capabilities

<table>
<thead>
<tr>
<th>Vector Manufacture</th>
<th>Day 0 Processing</th>
<th>Drug Product Manufacture</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proprietary technology</strong></td>
<td><strong>Process Execution</strong></td>
<td><strong>Process Development</strong></td>
</tr>
<tr>
<td>• Vector design</td>
<td>• Cell characterization, cell selection/enrichment</td>
<td>• Cell culture and transduction</td>
</tr>
<tr>
<td>• Assay development and validation</td>
<td>• Critical control point analysis</td>
<td>• Process validation</td>
</tr>
<tr>
<td>• Cell line and medium optimization</td>
<td>• Process analysis laboratory</td>
<td>• COI/COC management</td>
</tr>
<tr>
<td><strong>GMP Manufacturing</strong></td>
<td><strong>Product Storage and Logistics</strong></td>
<td><strong>GMP Manufacturing</strong></td>
</tr>
<tr>
<td>• Process optimization and scale-up</td>
<td>• Cold/Cryo storage</td>
<td>• GMP-certified manufacturing</td>
</tr>
<tr>
<td>• Stability testing</td>
<td>• COI/COC management</td>
<td>• Clean rooms and GMP suites</td>
</tr>
<tr>
<td>• Formulation and lyophilization</td>
<td>• Robust supply chain and courier network</td>
<td>• Clinical-grade manufacturing</td>
</tr>
<tr>
<td>• Aseptic fill and finish</td>
<td></td>
<td>• Sterile fill/finish</td>
</tr>
<tr>
<td><strong>Storage and distribution</strong></td>
<td><strong>Regulatory Compliance</strong></td>
<td><strong>Quality Control</strong></td>
</tr>
<tr>
<td>• Product storage</td>
<td>• Registration with regional regulatory bodies</td>
<td>• In-Process QA &amp; QC</td>
</tr>
<tr>
<td>• Distribution network</td>
<td>• Periodic audits and manufacturing facility certification</td>
<td>• Final product release &amp; stability testing</td>
</tr>
<tr>
<td></td>
<td>• Periodic staff training program</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Product Storage and Logistics</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cryogenic storage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Temperature controlled packaging for shipping</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• COI/COC management</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Regulatory Compliance</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Registration with regional regulatory bodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Periodic audits and manufacturing facility certification</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Periodic staff training program</td>
</tr>
</tbody>
</table>
Manufacturing and process development for **cell and gene therapies** is growing rapidly . . . making the **CDMO market** a hot target for roll-ups & acquisitions

**Sustained growth driven by new approvals**
- FDA expects 200 cell & gene therapy IND applications each year by 2020 and **15 - 20 approvals each year by 2025**
- A key distinction of cell & gene therapies is that they are being granted accelerated approvals with smaller clinical trials resulting in therapies entering the market with the completion of only Phase I/II

**Emergence of new players and capabilities in the market**
- Existing players are expanding their services and making huge investments to develop specialized capabilities
- In addition to cell therapy capabilities, many facilities provide APIs, vector manufacturing and other biologics production services

**Consolidations and partnerships among industry players**
- Two of the largest M&A deals ever in the CDMO industry were seen in 2017 – 2018:
  - Lonza’s acquisition of Capsugel for $5.5B
  - Thermo Fisher’s takeover of Patheon for $7.2B

**Manufacturing capacity crunch is resulting in a backlog for CDMOs**
- There is a wide gap between the **market demand and the supply capacity** on the end of vector and cell manufacturers
- Current **wait time averages more than 15 months** for CMOs to start cell and gene therapy projects

**Short-shelf life and highly-coordinated distribution network increases complexity**
- Novel cell and gene therapies require advanced capabilities in decentralized locations for a faster turnaround of therapeutic product, including cell scheduling and planning, manufacturing capacity collaboration and timely transport
- Establishment and maintenance of chain of identity and chain of custody in a regulatory-compliant manner requires robust systems and processing, and trained personnel
There has been a surge in M&A activity with many cell therapy manufacturers investing to bolster their market presence.
Recent deals from the European market illustrate the pace of activity.

<table>
<thead>
<tr>
<th>Buyer</th>
<th>Target</th>
<th>Overall Capacity</th>
<th>Capabilities</th>
<th>Employee #</th>
<th>Net Transaction Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Novartis International AG</td>
<td>CELLforCURE SASU</td>
<td>3600m² CMO &amp; manufacturing facility</td>
<td>CMO capabilities, Distribution services, Other capabilities</td>
<td>2300</td>
<td>N/A</td>
</tr>
<tr>
<td>2 Hitachi Chemical Advanced Therapeutics Solutions, LLC</td>
<td>Apceth Biopharma GmbH</td>
<td>2 GMP/BSL2 production facilities incl. 600 m² cleanroom area</td>
<td>CMO capabilities, Product tech platforms</td>
<td>36</td>
<td>$86.7 M</td>
</tr>
<tr>
<td>3 Orgenesis Inc.</td>
<td>Hemogenyx-Cell SA</td>
<td>N/A</td>
<td>Product tech platforms</td>
<td>12</td>
<td>N/A</td>
</tr>
<tr>
<td>4 Roche Holding AG</td>
<td>Tusk Therapeutics Ltd</td>
<td>N/A</td>
<td>Product tech platforms</td>
<td>25</td>
<td>$745 M</td>
</tr>
<tr>
<td>5 The Invus Group, LLC</td>
<td>BioNTech AG</td>
<td>GMP facility (10 independent cleanroom suites)</td>
<td>CMO capabilities, Product tech platforms</td>
<td>850</td>
<td>N/A</td>
</tr>
<tr>
<td>6 Thermo Fisher (CN) Luxembourg S.a.r.l</td>
<td>Patheon N.V.</td>
<td>22 facilities not incl. corporate offices</td>
<td>CMO capabilities, Product tech platforms, Distribution services</td>
<td>9000</td>
<td>$7.2 B</td>
</tr>
<tr>
<td>7 JSR Corporation; CMIC Holding</td>
<td>KBI Biopharma Inc.</td>
<td>4 facilities</td>
<td>CMO capabilities, Product tech platforms, Other capabilities</td>
<td>600+</td>
<td>$100 M</td>
</tr>
<tr>
<td>8 Catalent Pharma Solutions, Inc.</td>
<td>Cook Pharmica LLC</td>
<td>2 GMP production facilities</td>
<td>CMO capabilities, Product tech platforms, Distribution services</td>
<td>750</td>
<td>$950 M</td>
</tr>
</tbody>
</table>
There are many cell and gene therapy CDMOs across the globe with a concentration in the US and UK.

Several CDMOs offer a range of services across the cell and gene therapy value chain.

<table>
<thead>
<tr>
<th>Country</th>
<th>CDMOs</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>Aldevron, VGXI Inc, MassBiologics, Paragon Bioservices (Catalent), Brammer Bio (Thermo Fisher), KBI Biopharma (JSR Corporation; CMIC Holding), Gravitas Biomanufacturing, Cognate Bioservices, FUJIFILM Cellular Dynamics, Hitachi Chemical Advanced Therapeutics Solutions, LLC</td>
</tr>
<tr>
<td>Canada</td>
<td>C3i, CCRM</td>
</tr>
<tr>
<td>UK</td>
<td>Cobra Biosciences, The Clinical Trial Company, Advent Bioservices Ltd, Catapult Cell &amp; Gene Therapy, Cellular Therapeutics Ltd., Oxford Biomedica, Roslin Cell Therapies</td>
</tr>
<tr>
<td>Belgium</td>
<td>Eurogentec, MasTHERCell</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Batavia, Esperite, Lonza Netherlands B.V</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Lonza, Finvector</td>
</tr>
<tr>
<td>Germany</td>
<td>Cellex Cell Professionals, Angel Biotechnology PLC, Apeoth Biopharm (Hitachi), CARAT (CARs for Advanced Therapies), BioNTech (Invus), Fraunhofer Gesellschaft</td>
</tr>
<tr>
<td>Italy</td>
<td>Anemocyte, Molmed</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Lonza, Finvector</td>
</tr>
<tr>
<td>Spain</td>
<td>3P Biopharmaceuticals, Praxis, Pharmaceutical, Histocell SL</td>
</tr>
<tr>
<td>France</td>
<td>Novasep, Yposkesi, Bio Elpida CELLforCURE (Novartis)</td>
</tr>
<tr>
<td>Japan</td>
<td>AGC Asahi Glass, Medinet Co. Ltd., Niko Cell Innovation Co., Takara Bio</td>
</tr>
<tr>
<td>South Korea</td>
<td>CureCell</td>
</tr>
<tr>
<td>China</td>
<td>WuXi AppTec, CryxGen</td>
</tr>
<tr>
<td>Singapore</td>
<td>Cell Therapies Pty Ltd, Q-Gen Cell Therapeutics</td>
</tr>
<tr>
<td>Australia</td>
<td>Cell Therapies Pty Ltd, Q-Gen Cell Therapeutics</td>
</tr>
</tbody>
</table>

Companies that provide more than one of the above services

ILLUSTRATIVE: Representative footprint, not exhaustive.
Specialized manufacturing equipment in cell and gene therapies is distinct from other biologics manufacturing.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Equipment required</th>
<th>Illustrative vendor(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apheresis wash and cell separation</td>
<td>Cell separation system (e.g., Sepax)</td>
<td>Biosafe, GE Healthcare</td>
</tr>
<tr>
<td>Cell selection or enrichment</td>
<td>Cell separator (e.g., CliniMACS, Dynamag)</td>
<td>Miltenyi Biotec, Thermo Fisher Scientific</td>
</tr>
<tr>
<td>Cell thawing</td>
<td>Incubators or dry thawers (e.g., CytoTherm)</td>
<td>Thermo Fisher Scientific</td>
</tr>
<tr>
<td>Transduction</td>
<td>Centrifuge for spinoculation (e.g., Sepax devices)</td>
<td>Biosafe, Thermo Fisher Scientific</td>
</tr>
<tr>
<td>Cell expansion</td>
<td>Bioreactor, CO₂ incubator, static culture bags (e.g., Xuri, Wave bioreactor)</td>
<td>GE Healthcare</td>
</tr>
<tr>
<td>Cell harvest</td>
<td>Centrifuge and de-beading device (e.g., CliniMACS, Dynamag)</td>
<td>Miltenyi Biotec, Thermo Fisher Scientific</td>
</tr>
<tr>
<td>Cell cryopreservation</td>
<td>Controlled rate freezer (e.g., VIA freeze)</td>
<td>GE Healthcare</td>
</tr>
<tr>
<td>Cell characterization</td>
<td>Flow cytometer, cell counter, viability analyzer (e.g., FACSCalibur, Cellometer K2)</td>
<td>BD Biosciences, Thermo Fisher Scientific</td>
</tr>
</tbody>
</table>

In addition to such equipment, cell manufacturing also requires a number of reagents (e.g., growth media) and consumables (e.g., cell bags).
Drug developers and existing CDMOs face a number of challenges working together

Cell and gene therapies CDMOs are grappling with being oversubscribed

1. Manufacturing capacity crunch is resulting in a backlog for CDMOs
   - There is a wide gap between the market demand and the supply capacity on the end of vector and cell manufacturers
   - Current wait time averages more than 15 months for CMOs to start cell and gene therapy projects
   - There is a general lack of industry or institutional knowledge about how, when, or where companies would want to establish commercial manufacturing operations of products currently in development, thereby making forecasting a major challenge

2. Short-shelf life and highly-coordinated distribution network increases complexity
   - The supply chain network requires close coordination between multiple stakeholders across organizations and geographies for cell scheduling and planning, manufacturing capacity collaboration and timely transport of cellular products
   - Establishment and maintenance of chain of identify and chain of custody during the entire manufacturing process in a regulatory-compliant manner requires robust systems, processing and trained personnel

3. Communication and information flow between entities is yet to be streamlined
   - CDMOs have expressed frustrations over the lack of consistent and frequent communication with client companies
   - Collection and sharing of manufacturing data between entities requires establishment of customized communication portals, and training of CDMO personnel for its optimal usage
   - Navigating the complexities in the financial and product supply chain between the various entities requires establishment of a robust model within the organizations
AI/Bio-informatics

Regulatory/Reimbursement

Supply Chain/Commercialization

AI/Bioinformatics

Modify Gene Expression
- Antisense
- RNAi/siRNA
- Aptamers
- Ribozymes
- Exon Skipping

Gene Correction
- Gene Therapy with Viral Vectors
- Gene Therapy with Other Vectors
- Gene Editing (Meganucleases, ZFN, TALENs, CRISPR)

Regenerative Medicine
- Autologous & Allogenic Cells
- Stem Cell Therapy
- Mitochondrial Transfer
- Tissue Engineering
Explosion of Data in Healthcare

Healthcare like many other sectors of the economy is grappling with the profusion of data and evidence.
Decoding the Human Genome adds Exponentially to Healthcare Data

The Human Genome Project jumpstarted DNA sequencing which provides one of the most insightful but dense data sets available in healthcare.

Genome Sequencing Overview

Data Storage Requirements for Whole Genome Sequencing

1 Petabyte = 1 \times 10^{15} \text{ Bytes}

(2 Petabytes = all U.S research libraries)

Storage Requirements for a Single Genome:
- 4 MB for an abbreviated version (Powerpoint file)
- 100 GB for a complete version (Laptop Hard Drive)

Source: National Human Genome Research Initiative (NHGRI); Mike Orcutt “Bases to Bytes” MIT Technology Review, April 25, 2012
Sequencing entire populations driven by cost declines and sequencing capacity availability.

**Cost of Whole Genome Sequencing ($) and Genomes Completed**

Sources: Deloitte Analysis; GenBank and Whole Genome Shotgun Statistics from NCBI; International Society of Genetic Genealogy; Antonio Regalado, 2017 was the year consumer DNA testing blew up” MIT Technology Review, February 12, 2018; illumine Website, Broad Institute; Nature “Genomes by the Thousands” October 28, 2010
Data is Behind Delivering Effective Patient Care

Healthcare is increasingly becoming a data industry and delivering better patient outcomes requires new capabilities in data mining and analytics.

### Levels of Data Involved in Patient Care

- Molecular pathways
- **Genome**
- Gene Expression
- Epigenome
- Metabolome
- **Phenotypic Data (EHR)**
- Microbiome

Currently, genomic and phenotypic data are the most widely integrated into clinical care delivery.

### Strategic Implications

- Current focus on genomics will expand
- Solution implications include agility to integrate data, model new data and reference sets, and capture clinical associations and annotations
- Increased use of advanced analytics to enable clinically interpretable and actionable insights with implications on resource planning and information governance
- Stewardship of the Data still unclear. Diversity of business models will increase around controlled data collaboration as new layers of data come online

Developing the necessary data and analytics infrastructure through direct investment, commercial solutions, and strategic partnerships has become a new source of competitive advantage.

Challenges in Using Data in Healthcare

Turning data into clinical insights which impacts clinical outcomes is complex

- Create reports & dashboards
- Select visualization tools (e.g. Qlik, Spotfire, Tableau)
- Develop external interfaces and policies with external collaborators

- Find appropriate sources of data with insight potential and clinical annotation (e.g. EHR, claims, social media, imaging, clinical trials, genomic)
- Obtain permission to utilize data
- Navigate national data privacy requirements

- Handle structured and unstructured data
- Obtain storage capacity and determine modality (e.g. public cloud, private cloud, private servers)

- Select analytic tools (e.g. SAS, R, MATLAB)
- Establish standard workflows and toolkits
- Determine level of self-service and experimentation allowed

- Determine data architecture & ontology
- Create data governance framework
- Develop data cleansing approaches
- Develop data curation standards
## Multitude of New Healthcare Data Players

While many players started with data aggregation, they are now pushing to provide insights from the data.

### Industry Trends Today

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>[DNA]</td>
<td>The emergence of competencies in data management and analytics is moving beyond Academic Medical Centers</td>
</tr>
<tr>
<td>[Person]</td>
<td>Empowerment of individuals around their data</td>
</tr>
<tr>
<td>[Graph]</td>
<td>Increasing life sciences’ interest in investments on Real World Evidence, with interest moving beyond R&amp;D</td>
</tr>
<tr>
<td>[Piggy Bank]</td>
<td>Life Sciences companies are changing buying habits for RWD from blockbuster deals to targeted cohorts</td>
</tr>
<tr>
<td>[Graph]</td>
<td>As RWE has matured past the proof-of-concept stage, life sciences organizations are seeking insights (unique data + data sciences) over data-as-a-product</td>
</tr>
</tbody>
</table>

### Key Players Today

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="allofus.png" alt="All of Us Research Program" /></td>
<td><img src="cota.png" alt="COTA" /></td>
<td><img src="edico.png" alt="edico genome" /></td>
</tr>
<tr>
<td><img src="foundation.png" alt="Foundation Medicine" /></td>
<td><img src="guardant.png" alt="Guardant Health" /></td>
<td><img src="healthverity.png" alt="Healthverity" /></td>
</tr>
<tr>
<td><img src="om1.png" alt="OM1" /></td>
<td><img src="optum.png" alt="Optum" /></td>
<td><img src="projectgenie.png" alt="Project Genie" /></td>
</tr>
<tr>
<td><img src="tempus.png" alt="Tempus" /></td>
<td><img src="trimet.png" alt="TriNetX" /></td>
<td><img src="vector.png" alt="Vector Oncology" /></td>
</tr>
</tbody>
</table>

© 2019. For information, contact Deloitte Touche Tohmatsu Limited.
Leading players have differentiated strategies to gain access to data

<table>
<thead>
<tr>
<th>Prominent Competitors</th>
<th>Key Differentiator</th>
<th>Funding</th>
<th>Number of Employees</th>
<th>Patient Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>M2GEN</td>
<td>Richest data set tuned for R&amp;D</td>
<td>$100 Million</td>
<td>11-50</td>
<td>~7,000</td>
</tr>
<tr>
<td>TEMPUS</td>
<td>CLIA Sequencing and Impactful Analytics</td>
<td>$210 Million</td>
<td>251-500</td>
<td>1 Million with clinical data, of those 50,000 with NGS data</td>
</tr>
<tr>
<td>flatiron</td>
<td>EMR Asset</td>
<td>$313 Million</td>
<td>251-500</td>
<td>~2 Million</td>
</tr>
<tr>
<td>Foundation Medicine</td>
<td>CLIA Sequencing</td>
<td>$97 Million</td>
<td>251-500</td>
<td>4 Million globally; &gt;180,000 profiled patients</td>
</tr>
<tr>
<td>Verily</td>
<td>Innovative Use of Capital</td>
<td>$800 Million</td>
<td>11-50</td>
<td>10,000</td>
</tr>
<tr>
<td>Syapse</td>
<td>Support of molecular tumor board workflow</td>
<td>$70 Million</td>
<td>51-100</td>
<td>~1 Million</td>
</tr>
<tr>
<td>COTA</td>
<td>Value Based Contracting</td>
<td>$65 Million</td>
<td>200-250</td>
<td>~1 Million</td>
</tr>
<tr>
<td>Project Genie</td>
<td>Focus on Provider Member Research</td>
<td>$5 Million</td>
<td>1-10</td>
<td>39,000 (aimed to expand to &lt;100,000 by 2022)</td>
</tr>
<tr>
<td>TriNetX</td>
<td>Clinical Trial Design and Matching</td>
<td>Undisclosed</td>
<td>11-50</td>
<td>40 Million</td>
</tr>
<tr>
<td>Vector Oncology</td>
<td>Next Generation Registries</td>
<td>Undisclosed</td>
<td>51-100</td>
<td>1.5 Million</td>
</tr>
</tbody>
</table>
Movement toward Richer and Curated Data
Investments have enabled Data companies to increase the value of their data increased the shift upward and to the right.

Key Takeaway
Major players in this space are now curating data for over 1 million patients. The richness of the data varies depending on the source of data. Some companies have access to clinical and molecular data and some have access to clinical data only.

LEGEND
Richness of Data
Breadth, variety, and volume of data collected and offered
Maturity of Data Source
Proven ability to generate meaningful evidence from the data
Database Size (Patients)

*Syapse Oncology is a private instance and the size of the dataset depends on the number of patients in the provider practice.

© 2019. For information, contact Deloitte Touche Tohmatsu Limited.
Tempus forms relationship with Mayo Clinic, adding to their provider agreement portfolio including Rush University and UPenn.

Roche acquires Flatiron Health for $1.9 BB.

Tempus raises $80 MM is latest round of funding, totaling $210 MM to date on a $1.1 B valuation.

Illumina acquires Edico Genomics for $100 MM.

Roche acquires Foundation Medicine for $2.4 B.

GxlaosSmithKline announces $300 MM equity investment in 23andMe.

Tempus value prop resonates with providers (CLIA + curated data + analytics).

Roche expands on “own the pipeline” strategy in RWE.

Tempus story resonates with investors.

Potential step towards clinical interpretation.

Big pharma getting closer to the patient – builds on 2016 GSK / Apple efforts.

In the last 12 months, healthcare data players have been valued in the Billions, and will continue to be an acquisition focus.

Financing and M&A for Data Companies

August 2017

January

February

March

May

June

July

August 2018

© 2019. For information, contact Deloitte Touche Tohmatsu Limited.
### Additional Entrants in the Race for healthcare data

While traditional Healthcare players have access to longitudinal patient records, non-traditional Healthcare players possess an extensive repository of rich data sets on individuals, e.g. Facebook had 1.86B monthly active users in 2016 generating a multitude of data points.

<table>
<thead>
<tr>
<th>Traditional Healthcare Players</th>
<th>Non-traditional Healthcare Players</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Info Tech (HIT)</td>
<td>Frightful Five</td>
</tr>
<tr>
<td>Medtech</td>
<td>Big Tech</td>
</tr>
<tr>
<td>Cerner (88M Patient Lives)</td>
<td>Google (300M Patient Lives)</td>
</tr>
<tr>
<td>athenahealth (~40M Patient Lives)</td>
<td>Apple</td>
</tr>
<tr>
<td>Allscripts (190M Patient Lives)</td>
<td>Microsoft</td>
</tr>
<tr>
<td>Epic</td>
<td>facebook</td>
</tr>
<tr>
<td>PHILIPS</td>
<td>CISCO</td>
</tr>
<tr>
<td>SAMSUNG</td>
<td>UCSF</td>
</tr>
<tr>
<td>GE imagination at work</td>
<td>SAP</td>
</tr>
</tbody>
</table>
### Frightful five health data platforms

The Frightful Five, are making bold moves into the health data ecosystem by building platforms, making substantial investments and expanding partnerships.

<table>
<thead>
<tr>
<th>Platforms</th>
<th>Investments</th>
<th>Partnerships</th>
<th>Market signals</th>
</tr>
</thead>
</table>
| Google Health, Google Fit, Google Baseline Study, Genomics Cloud, Google Glass, DeepMind, Android | Google Ventures – 34 total healthcare investments, Dexcom, Sanofi, Biogen | Abbvie, Novartis, J&J, Mayo Clinic, AMA, Augmedix | • Google-owner Alphabet’s Verily Life Sciences along with Sanofi is investing $500 million in a diabetes joint venture to develop better ways for Type 2 diabetes patients to manage their day-to-day health conditions.  
• Google DeepMind is using machine learning technology to support medical research and care delivery in UK. |
| iOS, App Store, iWatch, Apple Pay, HealthKit, ResearchKit, CareKit, iTunes | Gliimpse | Mayo Clinic, Epic, IBM, InstaMed, Deloitte Consulting | • Apples introduced a slew of health-focused software development kits - HealthKit, ResearchKit and CareKit – that are designed to make it easier for mobile developers and consumers to pull together disparate health information in one place and create innovative apps. |
| HealthVault, MS Health, MS Band | WebMD, Caradigm, Sentillion | HealthCatalyst, Dartmouth-Hitchcock, UPMC | • Microsoft’s new initiative Healthcare NExT aims to capture new opportunities to apply AI to healthcare, such as the Microsoft AI in Health Partner Alliance, an expanding group of partners focused on advancing health technology. |
| AWS, Marketplace, Echo/Alexa, Fire, Kindle | Illumina, Bristol-Meyers Squibb, Cleveland Clinic, Deloitte’s ConvergeHEALTH, Syapse, Ericsson | | • Amazon provides up to $100 million in venture capital funding to companies that build new Alexa skills or integrate Alexa into their physical devices or apps. Alexa is being leveraged by app developers, such as Healthtap’s Dr. AI to help diagnose health conditions of its users. |
| Facebook, Support Groups | Moves, Chan Zuckerberg Biohub | University of Michigan Genes for Good, Partners Health Care Medication Adherence, Free Basics/Social Blood | • Facebook’s Mark Zuckerberg and his wife, Priscilla Chan invested $600 million for a new research facility called the Chan Zuckerberg Biohub in San Francisco, which aims to cure, prevent and manage disease, and accelerate medical research. |
## Frightful five health data platforms

The Frightful Five, are making bold moves into the health data ecosystem by building platforms, making substantial investments and expanding partnerships.

<table>
<thead>
<tr>
<th>Platforms</th>
<th>Investments</th>
<th>Partnerships</th>
<th>Market signals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medtech</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Samsung</strong></td>
<td>SAMI, SIMAND</td>
<td>eCaring</td>
<td>Partners Healthcare, Cigna, American Well</td>
</tr>
<tr>
<td><strong>Philips</strong></td>
<td>HealthSuite Data Platform (HSDP)</td>
<td>Wellcentive</td>
<td>AWS, Salesforce, ClearDATA, Banner Health</td>
</tr>
<tr>
<td><strong>GE Health Cloud Services built on Predix Industrial Cloud</strong></td>
<td>Camden Group, API Healthcare</td>
<td>Boston Children’s Hospital, UC San Francisco</td>
<td>IBM Watson Health and the FDA are working on a research initiative to explore blockchain’s potential for sharing owner-mediated data sources, including information from EHRs, IoT devices, and precision medicine data sources</td>
</tr>
<tr>
<td><strong>Big Tech</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IBM</strong></td>
<td>IBM Watson</td>
<td>Modernizing Medicine, Explorlys, Phytel, Merge, Truven</td>
<td>J&amp;J, Epic, Mayo, Medtronics, NY Genome Center</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SAP</strong></td>
<td>Connected Health Platform, Health Engagement, Medical Research Insights, SAP HANA</td>
<td>ASCO/CancerLinQ, Castlight Health, Dharma Platform, StartUp Health</td>
<td></td>
</tr>
<tr>
<td><strong>Salesforce</strong></td>
<td>Salesforce Health Cloud</td>
<td>Zebra Medical Vision, Evariant</td>
<td>Philips, McKesson, Accenture, Deloitte Consulting, PwC</td>
</tr>
</tbody>
</table>
Deloitte Involvement in Data Transformation Efforts

Deloitte has been intimately involved in the digitization of biology and healthcare across all sectors.

**2011-2013**
- Mayo
- Moffitt
- Inova
- Geisinger
- 4 provider PM models
- TCGA at AACR 2011
- Crizotinib Approval

**2014**
- Novel trial design (NCI MATCH, I-SPY2)
- Shift in Oncology standard of care

**2015**
- Roche acquires Flatiron for $1.9B
- Kymriah Approval

**2016**
- Apple Health App in iOS 11.3

**2017**
- Deloitte / Vineti Partnership

**2018**
- PM Business Cases
- PM Sustainability

**Provider**
- PM Strategies
- City of Hope IUSM
- UKHC VCU

**Pharma**
- RWE POCs
- RWE Strategies
- RWE Informatics
- ML/AI/POCs
- Numerous pharma

**Other Life Sciences**
- Aggregators: Strategies
- MTB Vendors Emerge
- Aggregators: Supply
- Aggregators: Demand
- Crohn’s & Colitis Foundation Medicine
- Illumina
- M2Gen
- ORIEN: COH, Huntsman, CINJ
- M2Gen

**Aggregators:**
- Supply
- Demand

**Strategies**
- CAR-T
- Liquid Biopsy
- Value Based Contracting

© 2019. For information, contact Deloitte Touche Tohmatsu Limited.
Deloitte refers to one or more of Deloitte Touche Tohmatsu Limited, a UK private company limited by guarantee ("DTTL"), its network of member firms, and their related entities. DTTL and each of its member firms are legally separate and independent entities. DTTL (also referred to as "Deloitte Global") does not provide services to clients. Please see www.deloitte.com/about for a more detailed description of DTTL and its member firms.

Deloitte provides audit, consulting, financial advisory, risk management, tax and related services to public and private clients spanning multiple industries. With a globally connected network of member firms in more than 150 countries, Deloitte brings world-class capabilities and high-quality service to clients, delivering the insights they need to address their most complex business challenges. Deloitte's more than 200,000 professionals are committed to becoming the standard of excellence.

This publication is for internal distribution and use only among personnel of Deloitte Touche Tohmatsu Limited, its member firms, and their related entities (collectively, the "Deloitte Network"). None of the Deloitte Network shall be responsible for any loss whatsoever sustained by any person who relies on this publication.