Gene Therapies – A Global Sector Overview -- NYAS Workshop - 10 Oct 2019

Sector Overview

Janet Lambert, CEO, Alliance for Regenerative Medicine

Alliance for Regenerative Medicine

ge²p² global
governance, ethics, evidence, policy, practice

The New York Academy of Sciences

Sangamo THERAPEUTICS

About ARM

- **International advocacy organization**
  - Dedicated to realizing the promise of safe and effective regenerative medicines for patients around the world
  - Cell and gene therapy, tissue engineering
- **340+ members**
  - Small and large companies, non-profit research institutions, patient organizations, and other sector stakeholders
  - Across 25 countries
- **Priorities:**
  - Clear, predictable, and harmonized **regulatory** pathways
  - Enabling market access and value-based **reimbursement** policies
  - Addressing industrialization and **manufacturing** hurdles
  - Conducting key stakeholder outreach, **communication**, and education
  - Facilitating sustainable access to **capital**

Alliance *for* Regenerative Medicine

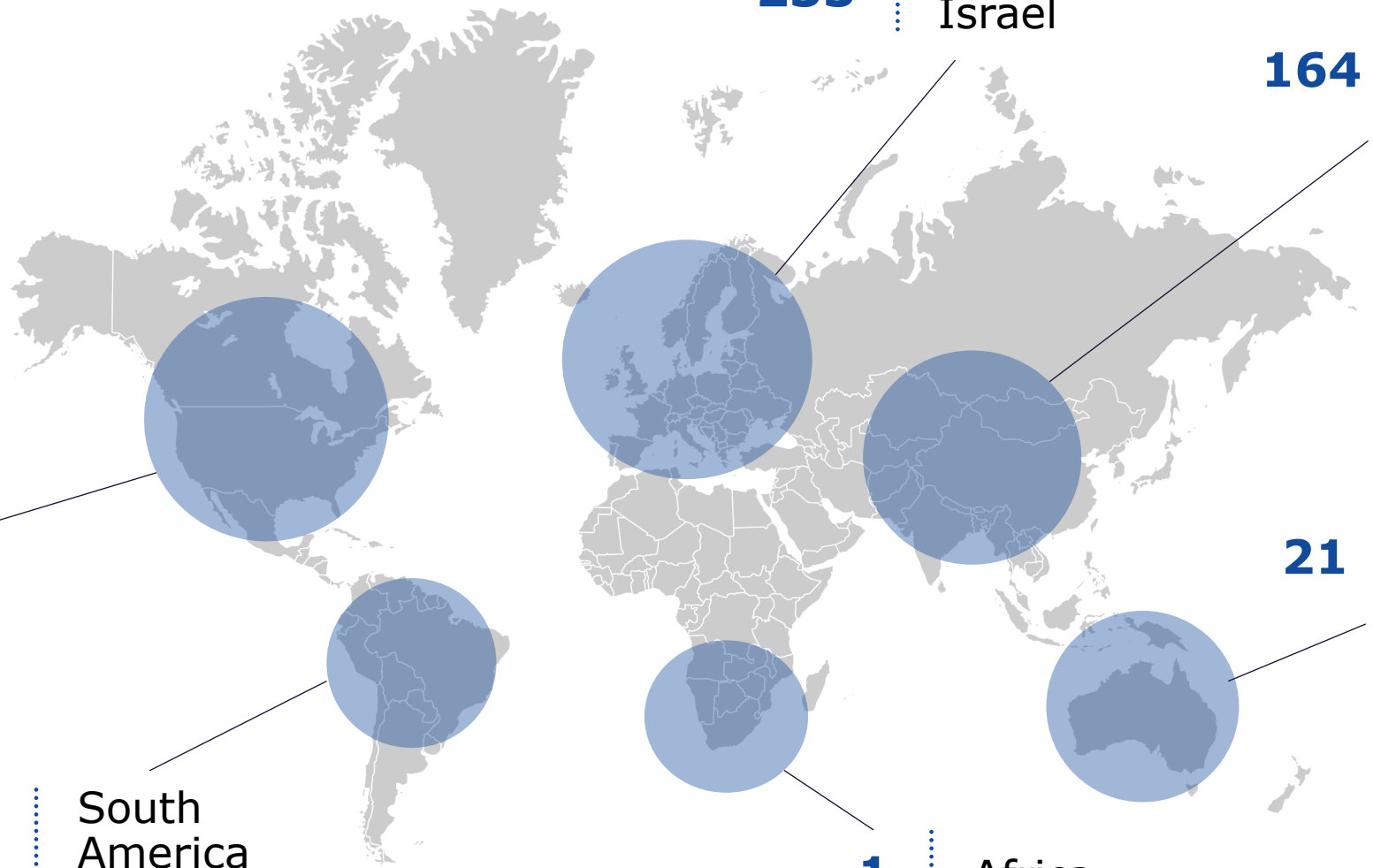
Select ARM Members

Alliance for Regenerative Medicine

Gene Therapy	Cell Therapy	Tissue Engineering	Research Orgs	Foundations, NPOs, + Patient Orgs
• AGTC • Amicus Tx • Atara Bio • Audentes Tx • AVROBIO • Axovant • BioMarin • Sanofi / Bioverativ • bluebird bio • Celgene • Caribou Bio • Casebia • CRISPR Tx • Editas Medicine • Flexion • GSK • Homology • Intellia Tx • LogicBio • Novartis / AveXis • Pfizer • Precision Bio • Orchard Tx • Oxford BioMedica • REGENXBIO • Sangamo Tx • Sarepta • Spark Tx • Ultragenyx	• Adaptimmune • Akron Biotech • Atara Bio • Athersys • Autolus • BlueRock Tx • CDI/Fujifilm • Celgene • Cell Medica • EMD Millipore • Fate Tx • Gamida Cell • GE Healthcare • Gilead / Kite • GSK • Iovance • J&J • Kiadis Pharma • Magenta Tx • MolMed • Mustang Bio • Novadip Bio • PCT/Hitachi • ReNeuron Group • Takeda Pharma • Thermo Fisher • Tmunity Tx • ViaCyte	• Aspect Biosystems • AxoGen • Avery Tx • Bone Tx • DiscGenics • Mesoblast • MiMedx Group • Miromatrix • Novadip Bio • Organovo • Orthocell • Pluristem Tx • PolarityTE • Skingenix • StemBioSys • TERMIS - Americas • VERIGRAFT • Videregen	• Tulane University • Gates Center for RM • Baylor College of Medicine • MSK • UMass Med School • City of Hope • Ludwig Boltzmann Institute • UC Irvine • Universidad de los Andes • Abramson Cancer Center (UPenn) • REMEDI • Sanford Stem Cell Clinical Center • Cornell University • Institut Clayton de la Recherche • Johns Hopkins Translational Tissue Engineering Center • Northwestern University Comprehensive Transplant Center • UCSD Stem Cell Program	• Cell and Gene Therapy Catapult • ISSCR • Missouri Cures • Fondazione Telethon • National Stem Cell Foundation • The Michael J. Fox Foundation • American Association of Tissue Banks • Be the Match Biotherapies • BioBridge Global • New York Blood Center • GE2P2 Global Foundation • AABB • Fred Hutch Cancer Research Center • National Disease Research Interchange • Neural Stem Cell Institute • Texas Heart Institute • Unite 2 Fight Paralysis • Fraunhofer Institute • New York Stem Cell Foundation • GCT and Connected Health Initiative • FARA • Gift of Life Marrow Registry • Nebraska Coalition for Lifesaving Cures • Alpha-1 Foundation • Global Genes • Stop ALD Foundation • EveryLife Foundation • Cleveland Clinic • ESGCT • ASGCT • Fight Colorectal Cancer • ISCT • National Multiple Sclerosis Society • EB Research Partnership • Prevent Cancer Foundation

Current Global Sector Landscape

953+
Regenerative Medicine Companies Worldwide, including Gene and Cell Therapies, and Tissue Engineering Therapeutic Developers



233 Europe & Israel

164 Asia

521 North America

21 Oceania
Australia, New Zealand, Marshall Islands

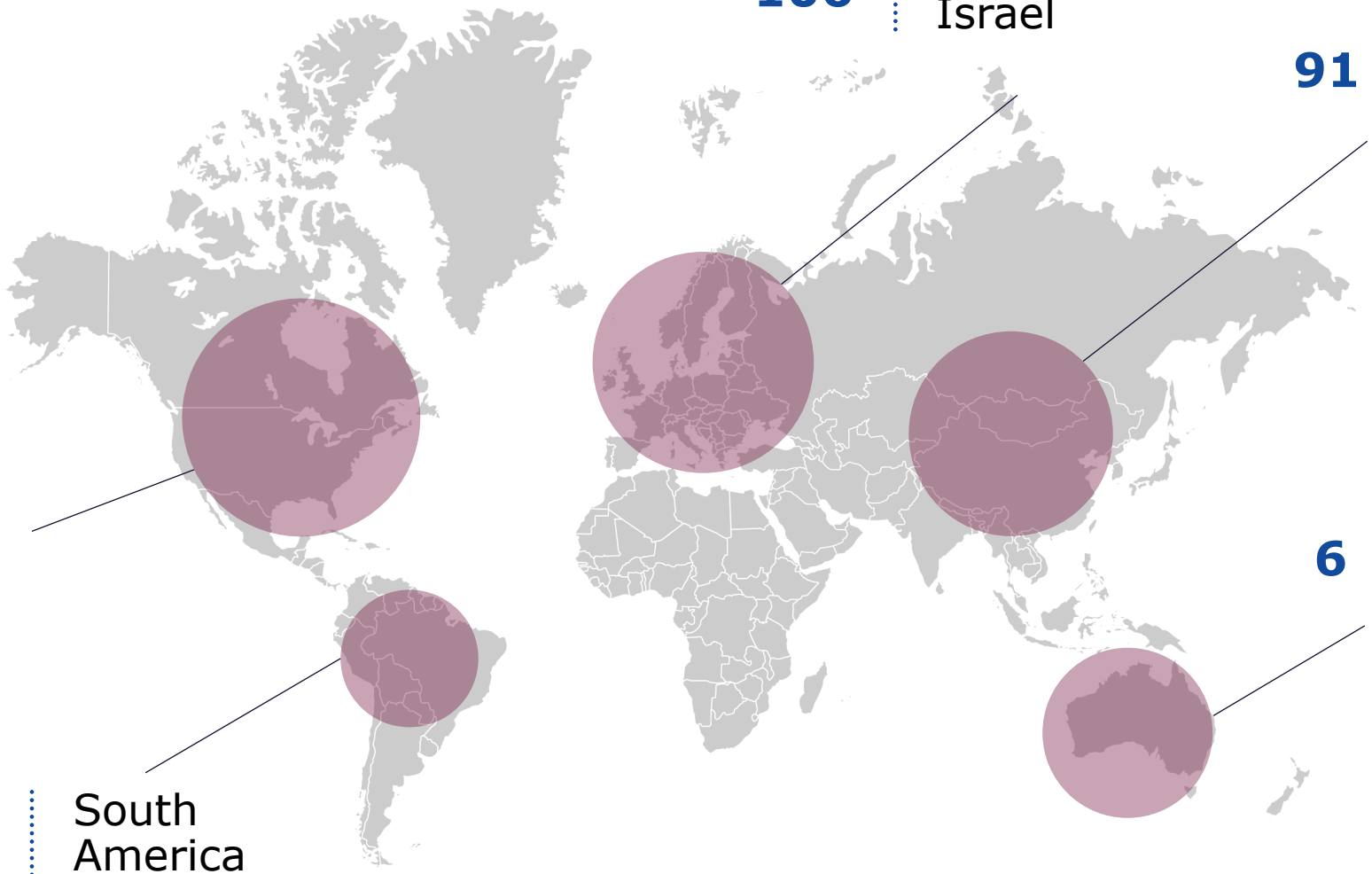
13 South America

1 Africa

Source data provided by: informa

Current Global Sector Landscape

454+
Gene Therapy & Gene-based Medicine Companies Worldwide



106 Europe & Israel

91 Asia

249 North America

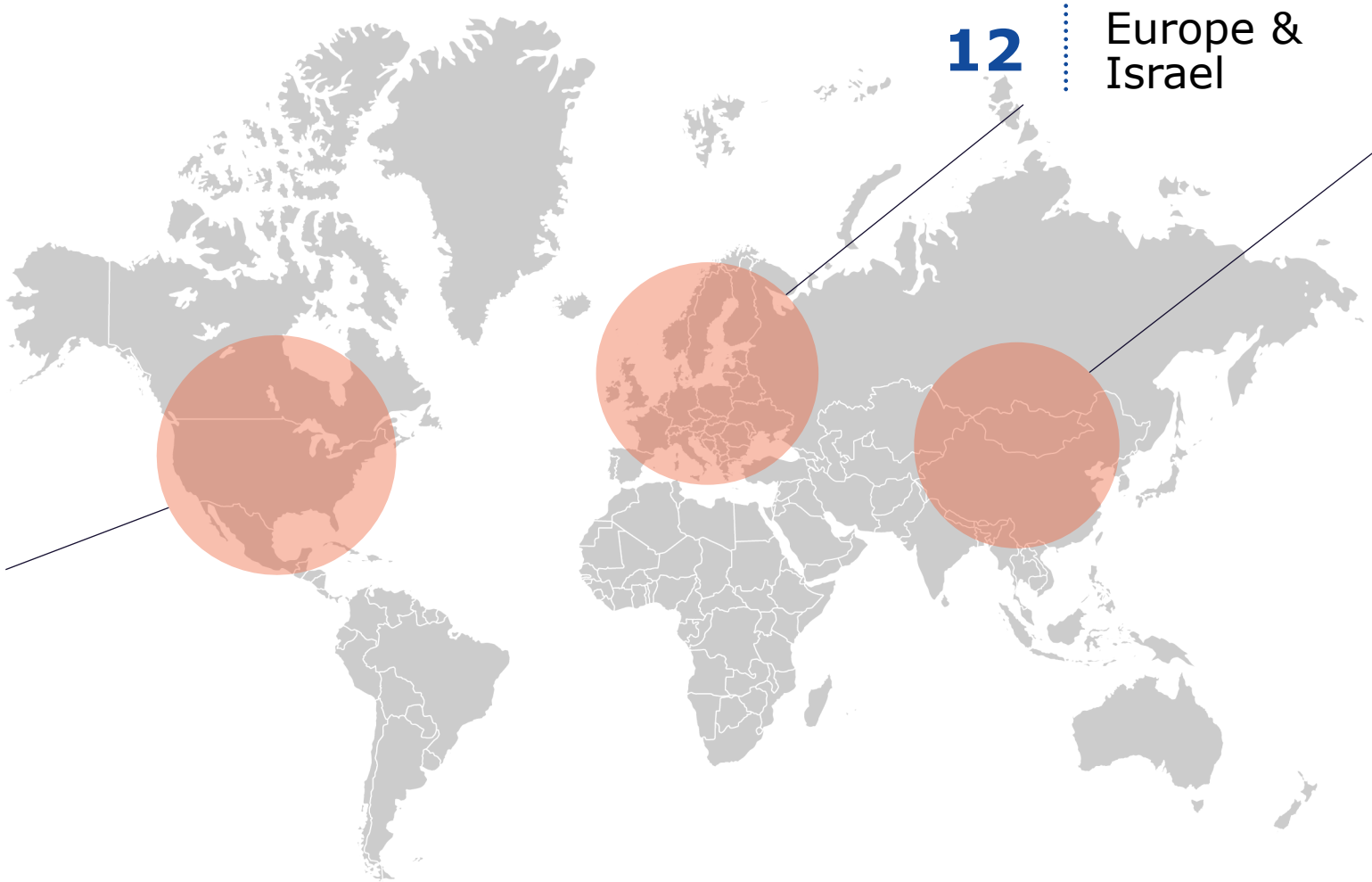
6 Oceania
Australia, New Zealand, Marshall Islands

2 South America

Source data provided by: informa

Current Global Sector Landscape

57+
Gene Therapy & Gene-based Medicine Companies Active in Gene Editing



Source data provided by: informa

Major Therapeutic Platforms & Enabling Technologies

- **Viral vectors:** retroviruses, adenoviruses, herpes simplex, vaccinia, and adeno-associated virus (AAV)
- **Non-viral vectors:** nanoparticles, nanospheres, transposons, electroporation, and others
- **Genetically modified cell therapies:** chimeric antigen receptors (CAR) T cell therapies, T cell receptor (TCR) therapies, natural killer (NK) cell therapies, tumor infiltrating lymphocytes (TILs), marrow derived lymphocytes (MILs), gammadelta T cells, and dendritic vaccines.
- **Genome editing:** meganucleases, homing endonucleases; zinc finger nucleases (ZFNs); transcription activator-like effector-based nucleases (TALEN); nucleases such as Cas9 and Cas12a that derive from the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR/Cas); homologous recombination of adeno-associated virus (AAV)-derived sequences.
- **Next-gen expression constructs:** novel capsids; innovative regulatory elements, including synthetic promoters that enable specificity, strength, and improve capacity; inducible elements to regulate gene expression temporally or in response to external stimuli: molecular kill switches to improve safety; etc.

Clinical Environment

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Patient Impact of Recently Approved Products

Therapy Name	Product Developer	Response
Kymriah	Novartis	• **40%** of patients with R/R DLBCL treated experienced a complete response • **60%** of patients with R/R B-Cell ALL treated experienced a complete response
Yescarta	Kite Pharma, a Gilead company	• **58%** of patients with R/R B-Cell NHL treated experienced a complete response
LUXTURNA	Spark Therapeutics	• **55%** of patients treated showed an improvement of 2+ light levels darker after treatment
Zolgensma	AveXis / Novartis	• **93%** of patients SMA Type 1 treated were alive without permanent ventilation at 24 months post-treatment
Zynteglo	bluebird bio	• **75%** of patients with TDT without β0/β0 genotype treated achieved transfusion independence

Select Anticipated Near-Term Approvals (Global)

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Gene Therapy

Zolgensma (AveXis / Novartis)
- Spinal muscular atrophy type 1
- Decision expected: mid 2019 (EU & Japan)

GT-AADC (PTC Therapeutics)
- AADC deficiency
- Expects to file: late 2019 (US)

Zynteglo (bluebird bio)
- Beta thalassemia
- Expects to file: 2019 (US)

Valrox (BioMarin)
- Hemophilia A
- Expects to file: Q4 2019 (US & EU)

GS010 (GenSight Biologics)
- Leber hereditary optic neuropathy
- Expects to file: H2 2020 (US & EU)

AT132 (Audentes Therapeutics)
- X-linked myotubular myopathy
- Expects to file: H2 2020 (US)

OTL-101 (Orchard Therapeutics)
- ADA-SCID
- Expects to file: 2020 (US)

OTL-200 (Orchard Therapeutics)
- Metachromatic leukodystrophy
- Expects to file: 2020 (US & EU)

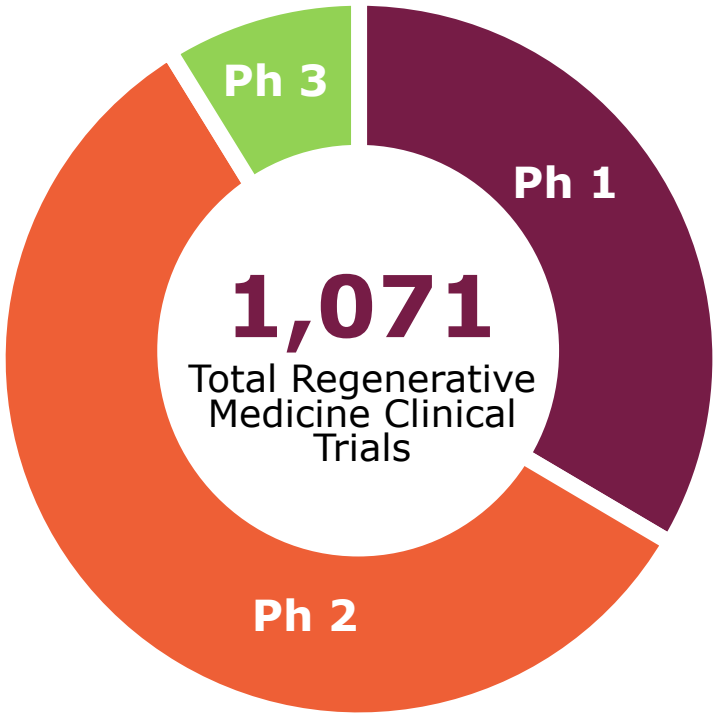
Gene-Modified Cell Therapy

liso-cel (Celgene)
- Diffuse large B-cell lymphoma (DLBCL)
- Expects to file: Q4 2019 (US)

ide-cel (bluebird bio / Celgene)
- Multiple myeloma
- Expects to file: 1H 2020 (US)

P-BCMA-101 (Poseida Therapeutics)
- Multiple myeloma
- Expects to file: 2020 (US)

Regenerative Medicine Clinical Trials by Phase and Technology Type



Phase 1: 366
across all tech types and indications

Gene Therapy: 117
Gene-Modified Cell Therapy: 199
Cell Therapy: 44
Tissue Engineering: 6

Phase 2: 609
across all tech types and indications

Gene Therapy: 227
Gene-Modified Cell Therapy: 205
Cell Therapy: 154
Tissue Engineering: 23

Phase 3: 96
across all tech types and indications

Gene Therapy: 32
Gene-Modified Cell Therapy: 16
Cell Therapy: 31
Tissue Engineering: 17

Source data provided by: informa

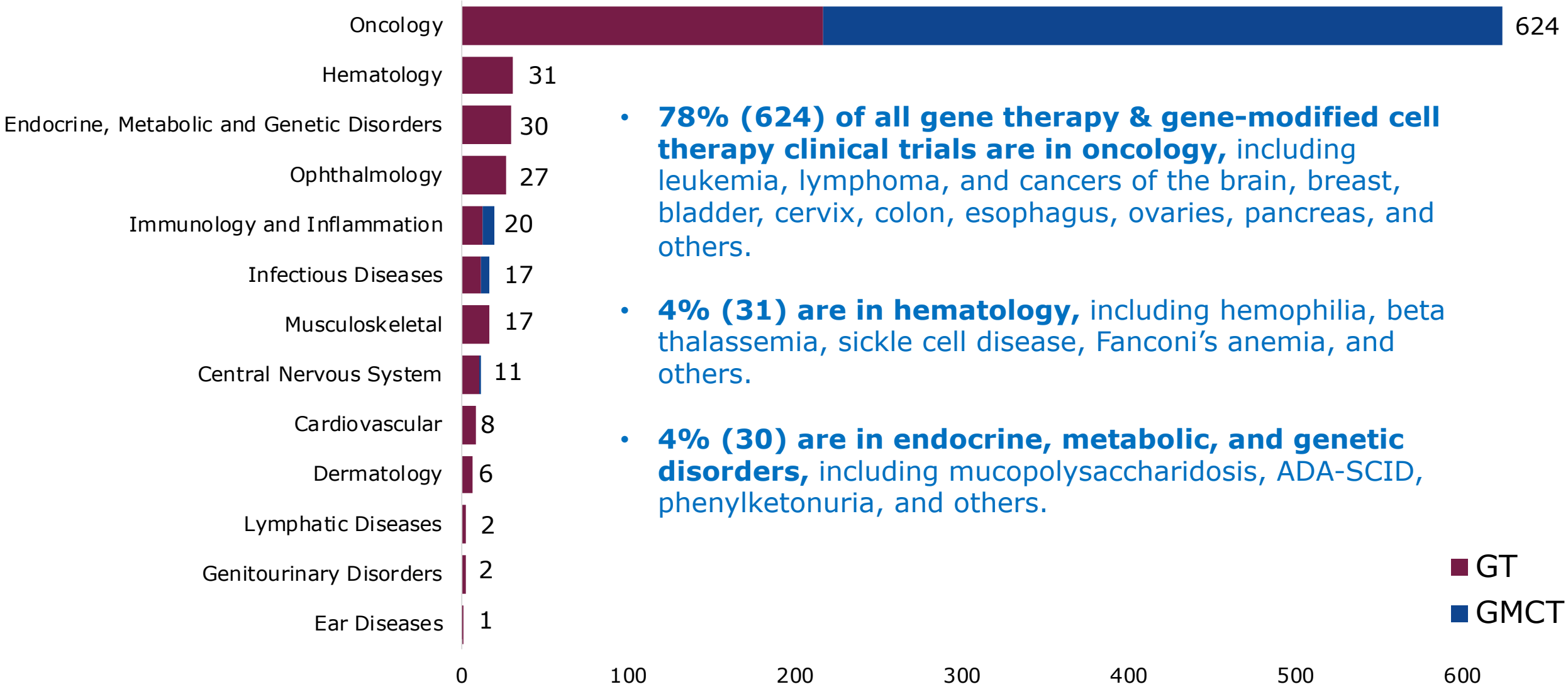
Anticipated Approvals 2025

*"We anticipate that by 2020 we will be receiving **more than 200 INDs per year**, building upon our total of more than 800 active cell-based or directly administered gene therapy INDs currently on file with the FDA. And by 2025, we predict that the FDA will be approving **10 to 20 cell and gene therapy products a year** based on an assessment of the current pipeline and the clinical success rates of these products."*

-- CBER Director Peter Marks, January 2019

Gene Therapy & Gene-Modified Cell Therapy Clinical Trials by Therapeutic Area

N = 796



- **78% (624) of all gene therapy & gene-modified cell therapy clinical trials are in oncology,** including leukemia, lymphoma, and cancers of the brain, breast, bladder, cervix, colon, esophagus, ovaries, pancreas, and others.
- **4% (31) are in hematology,** including hemophilia, beta thalassemia, sickle cell disease, Fanconi's anemia, and others.
- **4% (30) are in endocrine, metabolic, and genetic disorders,** including mucopolysaccharidosis, ADA-SCID, phenylketonuria, and others.

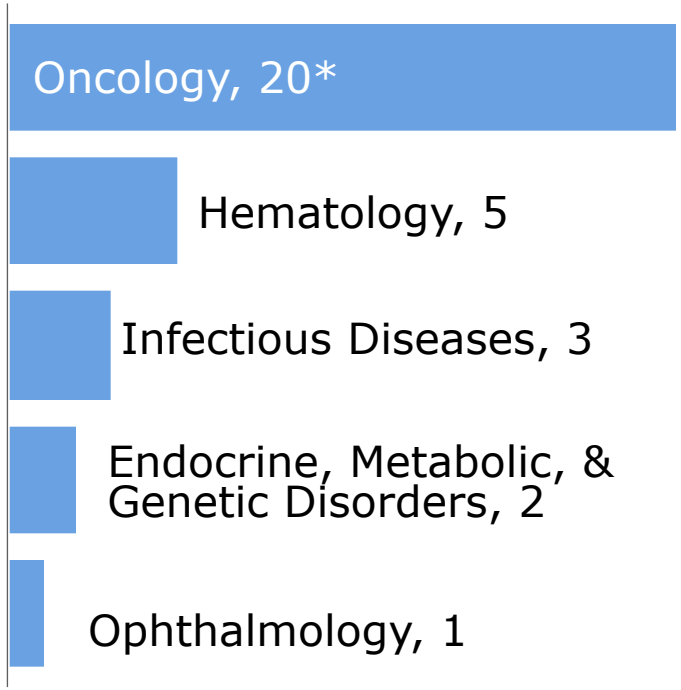
Source data provided by: informa

Clinical Pipeline for Gene Edited Therapies

There are currently 31 active, ongoing clinical trials involving gene editing

- 45% are Phase 1 and 55% are Phase 1/2.
- 85% are *ex vivo* and 15% are *in vivo*.
- The technologies used in these trials include:
  - CRISPR/cas9 (52%)
  - ZFN (29%)
  - TALEN (16%)
  - Other (6%)

Clinical Trials by Indication



Source data provided by: informa

** All clinical trials active in oncology are in gene-edited cell therapies (CAR-Ts, TCRs)*

Genome Editing Clinical Trials by Country

31 Active Trials in Genome Editing Worldwide*

20 **North America**

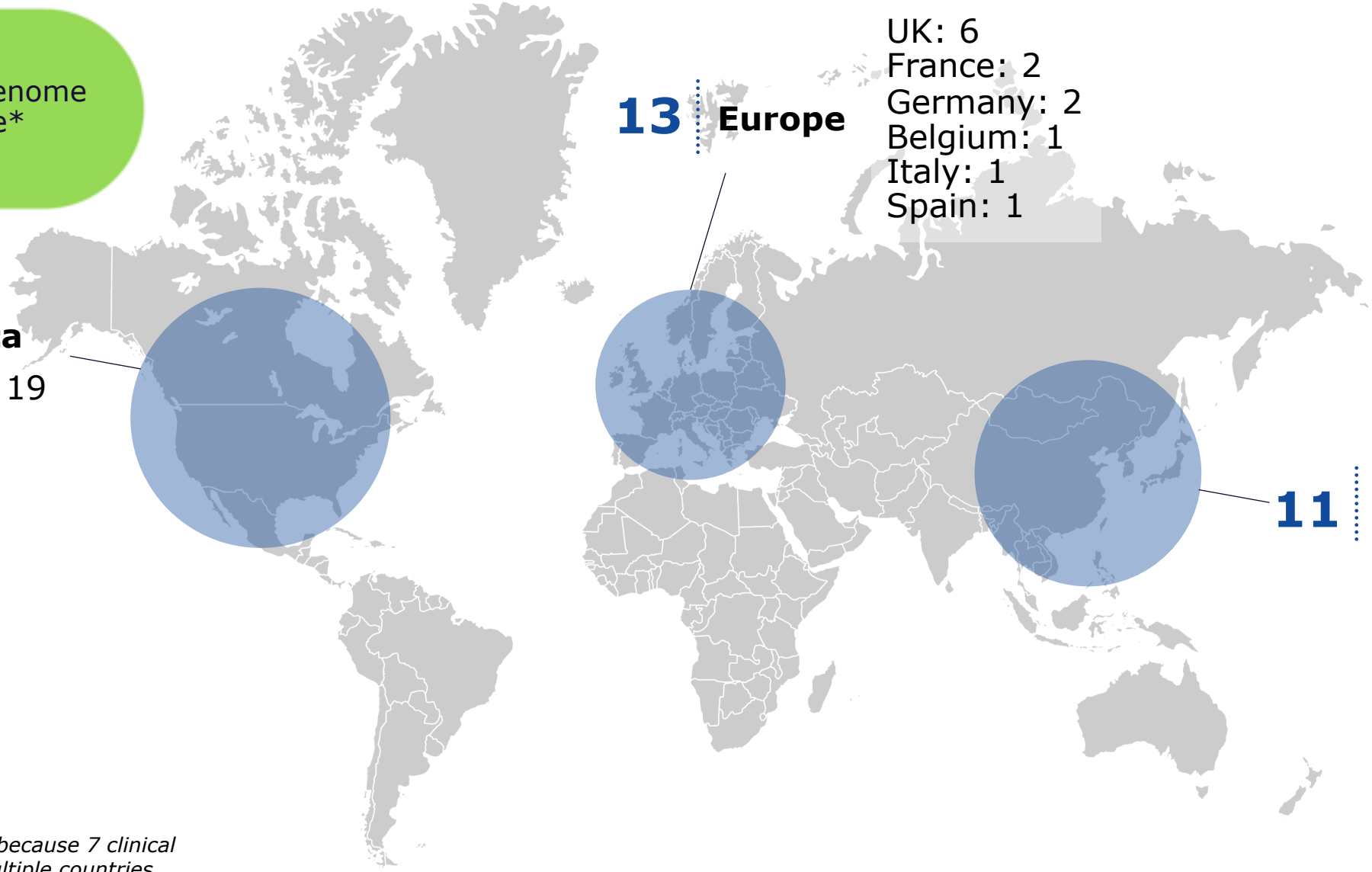
United States: 19
Canada: 1

13 **Europe**

UK: 6
France: 2
Germany: 2
Belgium: 1
Italy: 1
Spain: 1

11 **Asia**

China: 10
Japan: 1



** The country figures add up to 44 because 7 clinical trials have active clinical sites in multiple countries.*

Capital Formation

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Total Global Financings Year-to-Date

YTD 2019 financings calculated as of September 20, 2019

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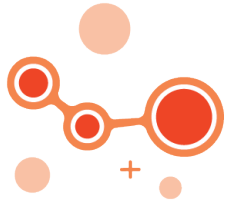
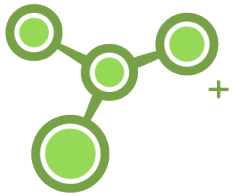
Total Global Financings

$7.5B
YTD 2019



Gene-Based Therapies

$5.7B
YTD 2019



Gene Editing

$858M
YTD 2019

Source data provided by: informa

Select Gene Therapy Corporate Partnerships & Public Financings YTD 2019

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Corporate Partnerships: (Upfront Payments)

- Vertex signs $175M upfront agreement with CRISPR Tx – June 6 *
- Neurocrine Bio and Voyager Tx sign $115M upfront agreement – January 29
- Janssen signs $100M upfront agreement with MeiraGTx – January 31
- Astellas signs $80M upfront agreement with Frequency Therapeutics – July 17
- Vivet Therapeutics and Pfizer enter into $51M upfront agreement – March 20

Private Placements & Venture Financings:

- AskBio secures $235M in financing – April 11
- Maze Tx raises $191M in venture funding – February 28
- Poseida raises $142M in Series C – April 22 *
- Beam Tx secures $135M in Series A – March 6 *
- Passage Bio raises $115.5M in Series A – February 15
- Nkarta raises $114M in Series B – September 4
- Passage Bio raises $110M in Series B – September 4
- Encoded Tx raises $104M in Series C – June 26
- Gracell Biotech raises $85M in Series B – February 25
- Adicet Bio raises $80M in Series B – October 3

Public Offerings: (IPOs & Follow-Ons)

- uniQure raises $225M in follow-on offering – September 4
- Fate Tx raises $173M in follow-on offering – September 18 *
- Sangamo raises $145M in follow-on offering – April 8 *
- Precision Bio raises $145M in IPO – April 1 *
- Homology raises $144M in follow-on offering – April 12 *
- AVROBIO raises $138M in follow-on offering – July 19
- Orchard Tx raises $128M in follow-on offering – June 3
- Prevail Tx raises $125M in IPO – June 24
- Autolus raises $115.9M in follow-on offering – April 15
- Krystal Bio raises $115M in follow-on offering – June 24

** Financings by companies active in gene editing marked with an asterisk*

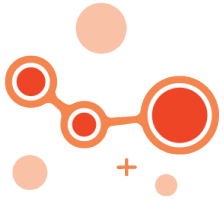
Policy & Advocacy

Alliance *for* Regenerative Medicine

Gene Therapy Policy Issues

Regulatory Issues

CMC requirements; draft guidance; European repository of regulatory requirements; Hospital exemption

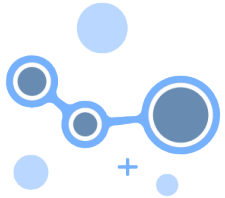


Market Access

Adapting value assessments to one time/durable/curative therapies; enabling payment over time and outcome based contracts

Clinical Trials

NIH ended duplicative review of gene therapy trials; GMO requirement harmonization; trial design



Gene Editing

ARM Published Therapeutic Developers Statement of Principles; WHO expert group; NAS

ARM Gene Editing Positions

- ARM has consistently supported the therapeutic use of somatic cell gene editing
    - Potential to provide important, perhaps life-saving, treatments for patients
    - Sole development focus of ARM members; operating with oversight of regulatory bodies
- ARM has consistently opposed gene editing of germline cells for the purpose of human implantation or in a clinical setting
- ARM positions on germline gene editing (from 2015) have been shared via press releases available at www.alliancerm.org/press-releases. Positions have also been shared with the U.S. Senate and the National Academies of Science.

ARM Gene Editing Task Force

- The ARM GETF is comprised of companies actively developing gene editing therapies or associated platform technologies

- All ARM members sign a code of conduct as a condition of membership
  - A commitment to regulatory oversight to protect patient safety
  - Agreement not to commercialize products in regions without well established regulations

- In light of recent events, ARM's GETF has developed a Therapeutic Developers' Statement of Principles
  - Public statement of companies' position on the ethical use of gene editing
  - Contribute to the international dialogue

Therapeutic Developers' Statement of Principles

- We endorse investigation of therapeutic applications of **somatic cell gene editing**, under the oversight of national or regional regulatory bodies
- We support the use of **gene editing standards** to facilitate the development of safe and effective therapies (e.g. the NIST Genome Editing Consortium)
- We support the continued **evolution of national and regional regulatory frameworks** governing the development of somatic cell gene editing technologies
- Unless and until ethical and potential safety questions with respect to germline gene editing are adequately addressed, **we do not support or condone germline gene editing in human clinical trials** or for human implantation
- We believe that these are international concerns and support discussion of therapeutic gene editing issues on a **global stage**

Therapeutic Developers' Statement of Principles

Alliance for Regenerative Medicine

Signatories:

- Audentes Therapeutics
- bluebird bio
- BlueRock Therapeutics
- Caribou Biosciences
- Casebia Therapeutics
- CRISPR Therapeutics
- Editas Medicine
- Homology Medicines
- Intellia Therapeutics
- LogicBio Therapeutics
- Pfizer Inc.
- Precision Biosciences
- Sangamo Therapeutics
- Tmunity Therapeutics

Released 27 August, 2019

The Statement of Principles remains open for additional ARM Member signatures
The full Statement is available at www.alliancerm.org

W.H.O. Opportunities

Alliance for Regenerative Medicine

- Articulate a globally-relevant set of ethical norms for gene editing
- Work in partnership with the scientific community, journal editors, regulators, and others to promote ethical gene editing research
- Develop mechanisms for communities to identify and report unethical and inappropriate research
- Track and regularly report on global gene editing clinical developments and research – in collaboration with relevant scientific societies and other stakeholders
- Convene/Support an ongoing multi stakeholder international dialogue on germline gene editing
- Underscore the distinction between somatic and germline work

Considerations for Gene Editing Registries

- Clarity of purpose and primary use case
- Provide appropriate transparency without casting doubts on somatic cell gene editing
- Registry relationship to new or existing regulatory requirements
- Avoid duplication and inconsistency with existing registries
- Ensure registry makes clear whether the therapy/investigation is approved, subject of a current marketing application, under the auspices of a regulatory agency or under an approved IRB (with specifics)
- Ensure the registry is not used for promotion/validation of an inappropriate/unethical research or product development program
- Sufficient resources for effective screening, management

Overcoming Manufacturing Barriers

Alliance for Regenerative Medicine

- Member workshop on comparability in cell & gene therapy development, with USP & global regulators
- *In Vivo* publication on manufacturing challenges in cell and gene therapy in June, and co-hosted a follow-up webinar in September
- Finalizing a comprehensive framework document -- A-Gene -- covering development, manufacture, regulatory submission, and lifecycle of gene therapies
  - Expected release in early 2020
  - Content is currently being drafted for A-Cell, a similar project focusing on cell therapies

A-Gene participants include:

Adicet Bio
AUDENTES
AVROBIO
BIOMARIN
bluebirdbio
brammer bio
CardinalHealth
CATAPULT Cell and Gene Therapy
ERA consulting
flexion
gsk
Hitachi Chemical
HOMOLOGY Medicines, Inc.
Hybrid Concepts INTERNATIONAL
Lentigen Technology Inc.
Lonza
Oxford Biomedica
Pfizer
REGENXBIO
Sangamo THERAPEUTICS
SAREPTA THERAPEUTICS
Takeda
Skyland Analytics
SOLID BIOSCIENCES
STANDARDS COORDINATING BODY
ultragenyx pharmaceutical
usp
VCLS Voisin Consulting Life Sciences
Voyager THERAPEUTICS

For More

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Visit **www.alliancerm.org** to access additional resources, including:

- Quarterly sector data reports
- Upcoming near-term clinical trial milestones & data readouts
- Access to slides, graphics, and figures from ARM presentations
- Our weekly sector newsletter, a robust round-up of business, clinical, scientific, and policy news in the sector
- Commentary from experts in the field

Thank You!

Alliance for Regenerative Medicine