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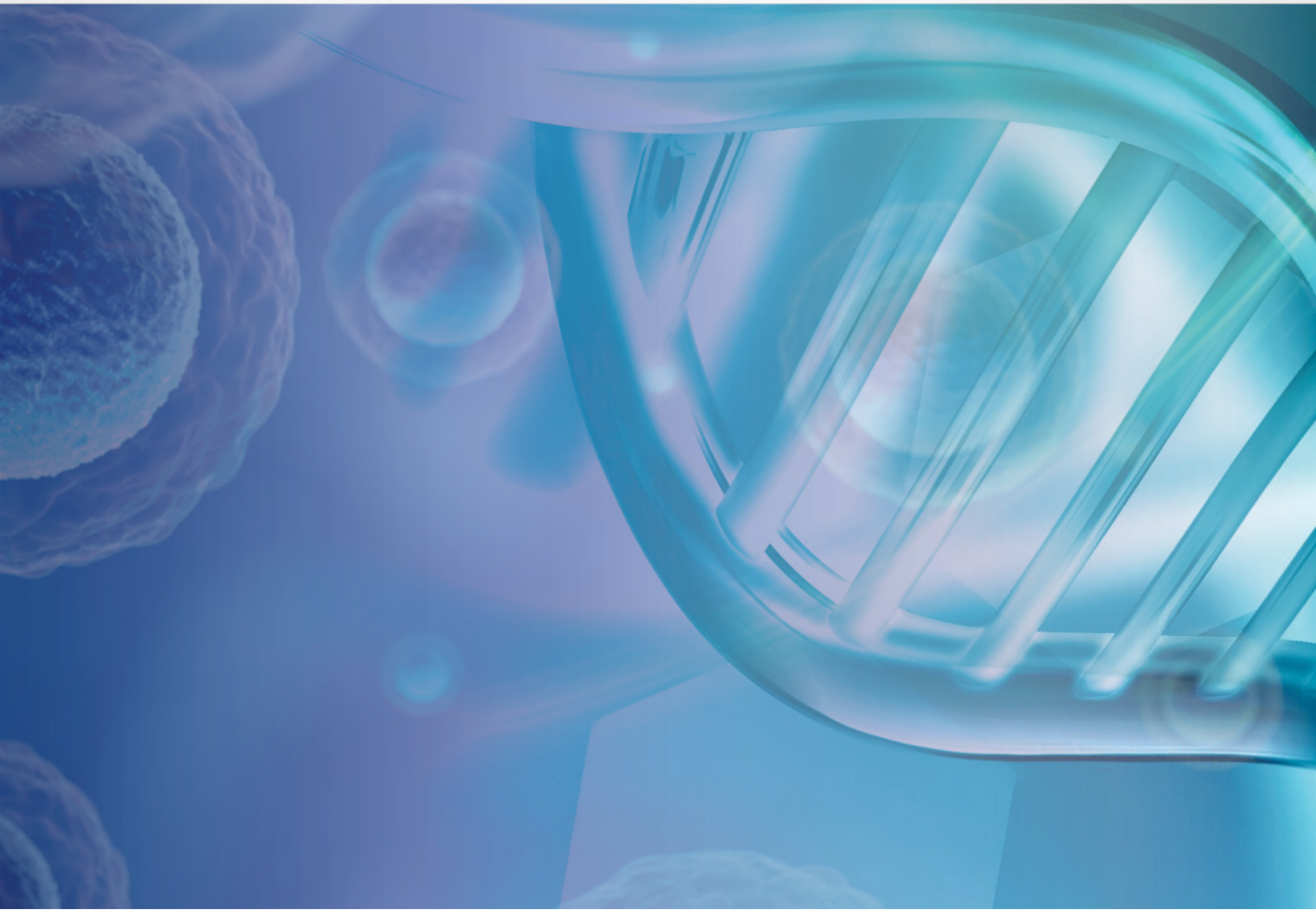
EMERGING TECHNOLOGIES AND THERAPEUTICS REPORT



LANDSCAPE REVIEW AND EVIDENCE MAP OF GENE THERAPY, PART II

Chimeric Antigen Receptor- T cell (CAR-T), Autologous Cell, Antisense, RNA Interference (RNAi), Zinc Finger Nuclease (ZFN), Genetically Modified Oncolytic Herpes Virus

Landscape Review and Evidence Map of Gene Therapy, Part II: Chimeric Antigen Receptor- T cell (CAR-T), Autologous Cell, Antisense, RNA Interference (RNAi), Zinc Finger Nuclease (ZFN), Genetically Modified Oncolytic Herpes Virus

Andrea Richardson, Eric Apaydin, Sangita Baxi, Jerry Vockley, Olamigoke Akinniranye, Rachel Ross, Jody Larkin, Aneesa Motala, Gulrez Azhar, and Susanne Hempel

RAND Corporation

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Revision [February 2020]
Since the completion of this report a gene therapy herein described as AVXS-101 has been approved by the FDA as Zolgensma therefore the report was revised in November 2019 to reflect that change.

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Executive Summary

Human gene therapy has evolved rapidly and may be poised to impact mainstream medicine. Gene therapy initially targeted incurable genetic diseases (eg, metabolic diseases) but is now most commonly used to treat select cancers. Given the increase in approved gene therapy approaches, the Patient-Centered Outcomes Research Institute (PCORI) commissioned a landscape review and evidence map. The purpose of this report is to better understand the evidence supporting currently approved gene therapies and those that may be available in the near term in the United States. This is the second of 2 reports and it focuses on chimeric antigen receptor T cell (CAR-T); autologous cell; zinc finger nuclease (ZFN); antisense; ribonucleic acid interference (RNAi); and oncolytic viral therapy replication-competent, attenuated derivative of herpes simplex virus type 1 therapies.

In November 2018, we reviewed scientific journal and gray literature to identify evaluations of therapies that meet the FDA's definition of gene therapy. Our overall aim was to provide a current view of the existing evidence on gene therapy and to identify gaps that need to be addressed for the field to move forward in the United States. We reviewed both completed and ongoing trials involving human participants, including controlled and uncontrolled trials. Ongoing trials are those that have completed recruitment but have not yet published results, whereas completed trials have published results. The literature results are documented in visualizations (ie, evidence maps) and comprehensive evidence tables.

We also conducted semistructured interviews with a diverse set of stakeholders to elicit feedback on challenges, hopes, and important issues related to gene therapy. We selected key informants capable of providing a range of perspectives, including patients or patient advocates, clinicians, payers/insurers, public policyHbA1maker representatives, and industry representatives.

The report describes the interventions, the context in which gene therapy is used, ongoing premarket and postmarket gene therapy studies, and current evidence for the use of gene therapy.

The FDA has approved 10 interventions that meet the definition of gene therapy, 8 of which are included in this report. In January 2013, the FDA approved Kynamro (Mipomersen sodium). Kynamro is based on antisense technology and is used to treat homozygous familial hypercholesterolemia. In 2015, the FDA approved Imlygic (Talimogene laherparepvec) to treat melanoma. Imlygic is a genetically modified oncolytic viral therapy replication-competent, attenuated derivative of herpes simplex virus type 1. The next 3 approved therapies used antisense technology to treat Duchenne muscular dystrophy (Eteplirsen, Exondys 51), spinal muscular atrophy (Spinraza, Nusinersen), and polyneuropathy of hereditary transthyretin amyloidosis (Tegsedi, Inotersen). In 2017, the FDA approved 2 CAR-T therapies. Yescarta (Axicabtagene ciloleucel) is used to treat relapsed or refractory large B-cell lymphoma and Kymriah (Tisagenlecleucel) treats children and young adults with refractory B-cell precursor acute lymphoblastic leukemia. In 2018, Kymriah gained additional approval to treat adult patients with relapsed or refractory large B-cell lymphoma. The FDA also approved an RNA interference drug, Patisiran (Onpattro, ALN-TTR02), in 2018 to treat hereditary transthyretin amyloidosis with polyneuropathy.

Our search of the gray literature identified 76 therapies that meet the FDA's definition of gene therapy and that have not yet been FDA approved but may be close to approval. A wide variety of modalities are being tested to treat patients. The most common type of therapy is based on adeno-associated virus. The identified therapies are being used to treat multiple disease types, including vision disorders (eg, choroidemia), muscular dystrophy (eg, Duchenne), blood disorders (eg, hemophilia), Sanfilippo syndrome, cancer, HIV, and Parkinson's disease.

In our literature search, we screened 3863 citations and assessed 1822 full-text publications for eligibility. We identified 302 complete studies and ongoing trials that evaluate gene therapy treatment

using antisense, autologous cell, CAR-T, genetically modified oncolytic viral therapy/herpes simplex virus type 1, RNAi, and ZFN technologies.

The indications in the identified completed and ongoing trials were cancer (60%), cardiovascular disease (11%), immune deficiency (11%), muscular conditions (6%), blood disorders (2%), neurodegenerative disorders (1%), inflammatory conditions (2%), ocular disorders (0.7%), respiratory conditions (0.3%), and other indications that were not easily categorized (eg, venous leg ulcer disease; 6%). Pharmaceutical companies claim that select gene therapies hold the potential to provide a one-time administration that will cure disease. Results from small trials are promising. However, true durability of treatment remains unclear from the current published results. Further, adverse events pose challenges to the use of gene therapy in patient care. Most existing gene therapy trials are based on either trials with multiple groups that were treated with different levels of the same therapy or single-arm trials. However, RCTs are increasingly being implemented in cancer, cardiovascular disease, and immune deficiency. Sample sizes remain relatively small across the studies, in part likely due to the rarity of the indications addressed by gene therapy. We observed larger sample sizes in the RCTs for the more common diseases, such as cardiovascular conditions, or for vaccine trials. Most studies evaluated safety and indicators of biodistribution, and relatively few studies tested clinical efficacy.

The potential and presumed advantages of gene therapies are first and foremost cures for previously incurable and fatal diseases. However, the potential disadvantages of gene therapies relative to current treatment practices include many unknowns that relate to (1) how clinically effective treatments are versus the risk for adverse outcomes, (2) how gene therapies will be implemented in health care systems where providers may be unfamiliar with requisite procedures and patients are not well informed about what gene therapies are, (3) the ethical implications of altering the genome, and (4) how patients and payers will pay for potentially expensive gene therapy. The most common types of published approaches among the eligible interventions for this report were antisense, autologous cell, and CAR-T. The ongoing trials show that there is an ongoing interest in CAR-T and, increasingly, RNAi gene therapy.

To address the gaps in knowledge that might support the use and approval of gene therapies, several areas of research may warrant future work. Suggested future research includes examining how Centers of Excellence may ensure that high-quality manufacturing processes and health care delivery standards are followed. In addition, patient registries with long-term follow-up will reduce the uncertainty about the durability of gene therapy effects. Other research could examine how training and education programs for providers and patients might improve provider familiarity with procedures and patient understanding of risks of unintended effects and how the therapy works. Lastly, microsimulation modeling of different scenarios of patient access and treatment efficacy may address the uncertainty about how gene therapy will impact disease.

Introduction of Report Series

The US Food and Drug Administration (FDA) defines gene therapy as products "that mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered microorganisms. The products may be used to modify cells *in vivo* or transferred to cells *ex vivo* prior to administration to the recipient."[1] Gene therapies operate by

- replacing a disease-causing gene with a healthy copy of the gene,
- inactivating a disease-causing gene that is not functioning properly, or
- introducing a new or modified gene into the body to help treat a disease.[1]

History of Gene Therapies

Human gene therapy evolved from bacterial and viral cell transformation studies.[2] Experimentation in humans started in the 1990s, when the FDA approved a gene therapy trial in 2 children with adenosine deaminase deficiency, a monogenic disease leading to severe immunodeficiency.[3] Some immune responses improved in this small study and the results suggested that the treatment may be safe and effective. Despite setbacks, gene therapy research has continued to expand and improve.

Gene therapy initially targeted relatively rare incurable genetic diseases (eg, metabolism diseases) but is now most commonly used to treat select cancers, including those that are inherited and not inherited. Today, cancer composes 65% of indications addressed by current gene therapy clinical trials, followed by monogenic diseases (11%), infectious diseases (7%), and cardiovascular diseases (7%).[4] The FDA has approved 16 products that are either cellular products or gene therapies: cord blood products (50%), autologous or allogenic cellular products (25%), and disease-specific therapies (25%).[5] Nine of the products meet the criteria in the FDA's definition of a gene therapy as described above and they employ multiple intervention modalities to treat specific cancers and vision loss.

Aim of the Report

Given the increase in approved gene therapy products and techniques, PCORI sought to better understand the evidence that exists for currently approved gene therapies and those that may be available in the near term (~5 years) in the United States. We also aimed to identify gaps that need to be addressed for the field to move forward. This report is the second report of a series that addresses the existing evidence on gene therapy and outlines evidence gaps.

Methodology Overview

Our methods are described in detail in Appendix A. Briefly, we conducted a landscape review of multiple data sources to cover critical aspects of current and future gene therapy approaches. Specifically, we describe the evidence base for FDA-approved gene therapies that are currently used to treat or cure conditions. In addition, we describe ongoing clinical trials testing applications that may be poised to gain FDA approval as well as the conditions that are relevant for future applications. The search strategy is documented in Appendix B. We applied, a priori, explicit inclusion and exclusion criteria, and the literature flow is shown in Appendix C. The FDA has approved gene therapies based on the results of single-arm trials when a life-threatening condition has no alternative treatment and its severity[6] justifies not performing controlled trials. Thus, we included in our literature review controlled and uncontrolled trials. The literature results are documented in a central figure and comprehensive evidence tables.

We also conducted interviews with stakeholders providing a variety of perspectives on gene therapies. We elicited feedback about challenges, hopes, and important issues related to gene therapy. We included patients or patient advocates, clinicians, payers, insurers, public policymaker and pharmaceutical industry representatives, and industry analysts. Through semistructured interviews, these key informants contributed to the development of our search strategy and the identification of interventions that may potentially be approved in the next 5 years. We also elicited perspectives on aspects of beneficial and harmful outcomes, important issues to patients, gene therapy-related challenges/gaps, hopes for future progress, and thoughts on how to move the field forward. More detail is documented in Appendix D. Interviewed key informants included the following:

Patient advocates

- Sharon Terry, president and chief executive officer, Genetic Alliance
- Ben Wakana, executive director, Patients for Affordable Drugs

Clinicians

- Flora Lum, MD, vice president of quality and data science, American Academy of Ophthalmology
- Cary Harding, MD, professor of molecular and medical genetics, Oregon Health & Science University

Insurers

- Geoff Crawford, MD, medical director, Anthem
- John Yao, MD, staff vice president, Anthem
- Naomi Aronson, MD, Executive Director, Technology Evaluation Center, Blue Shield of California

Public policymakers

- Katherine B. Szarama, presidential management fellow, Centers for Medicare & Medicaid Services

Industry and industry analysts

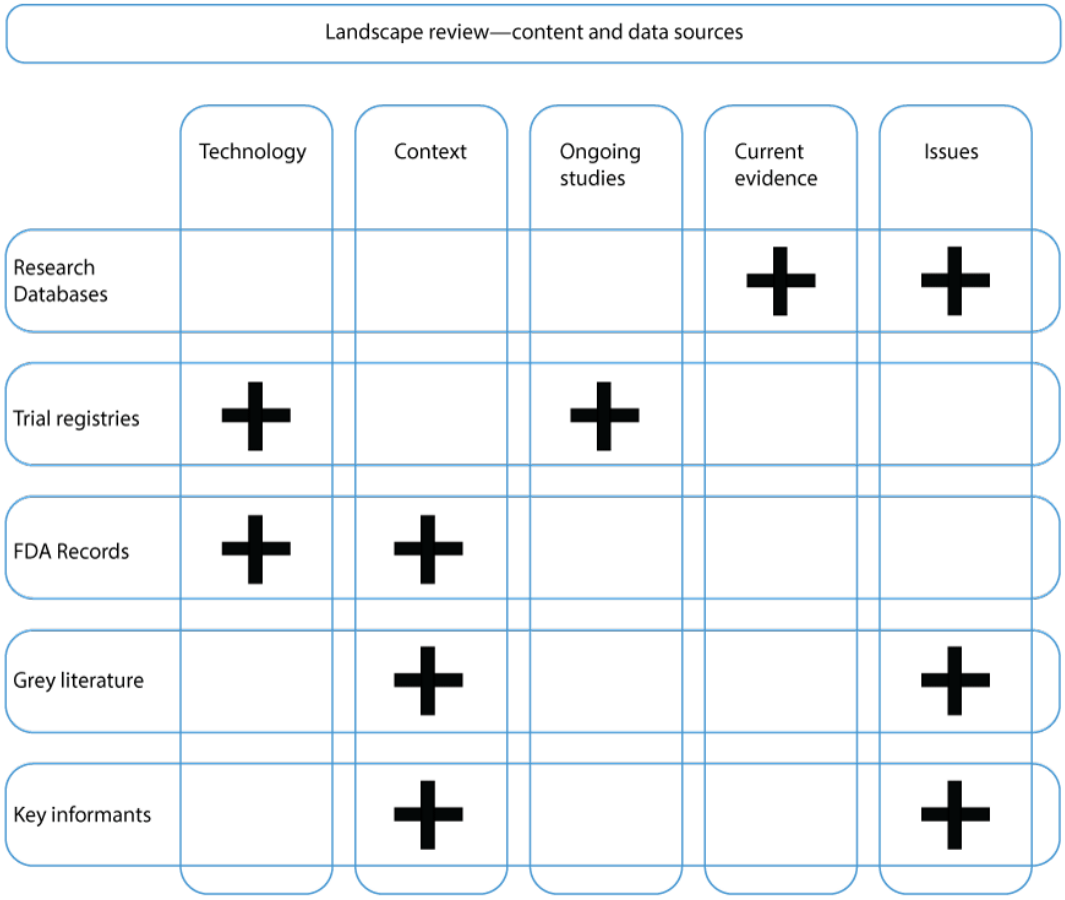
- Michael Ciarametaro, vice president of research, National Pharmaceutical Council
- Daryl Pritchard, PhD, senior vice president, Science Policy, Personalized Medicine Coalition

Data Sources

The report is based on peer reviewed literature, gray literature, and key informant interviews.

Figure 1 maps data sources to the report's content. It indicates which data sources we used to collect information on each content topic. For example, we used the information we gathered from the research databases to inform the content related to the types of studies, safety, and efficacy for each intervention. More details on the methodology can be found in Appendixes A and B.

Figure 1. Content and Data Sources



Organization of the Report Series and Organization of This Report

This is the second report on the evidence base for FDA-approved gene therapies that meet the definition for gene therapy. This report also covers interventions that are not yet approved but that we identified multiple times in our search for therapies in the research pipeline. In the first report, we focused on adenovirus; adeno-associated virus (AAV); and clustered regularly interspaced short palindromic repeats (CRISPR) gene therapy. In this report, we focus on chimeric antigen receptor T cell (CAR-T); autologous cell; zinc finger nuclease (ZFN); antisense; ribonucleic acid interference (RNAi); and oncolytic viral therapy replication-competent, attenuated derivative of herpes simplex virus type 1 therapies. Because the literature base across all of the above interventions is so large, we split the content into 2 reports. Due to increased interest in gene therapy and especially in CRISPR, we considered publication timing in our decision to split our review into 2 reports, with the first one focused on AAV, adenoviral, and CRISPR interventions.

The sheer number of studies spanning multiple interventions and conditions necessitates that the summaries provide only a broad overview. We do, however, point out specific issues when we or the key informants felt them to be especially relevant. For each report, the findings are organized by key questions:

Description of Interventions/Technologies

- 1a. What are the different types or modalities of the intervention that have been used in clinical practices and clinical research studies?

- 1b. What are potential/presumed advantages and disadvantages in contrast to current practices?
- 1c. What are the safety issues or expected adverse events?

Context in Which Gene Therapy Is Used

- 2a. What is the approval process and current approval/certification status for gene therapies?
- 2b. Are any additional accompanying resources or technologies required?
- 2c. What is the current state of adoption in practice and settings?
- 2d. What are the operator factors, such as training and staffing?

Ongoing Premarket and Postmarket Gene Therapy Studies

- 3a. What are indication/patient inclusion criteria in ongoing trials?
- 3b. What are the types of interventions in ongoing trials?
- 3c. What are the study designs/size in ongoing trials?
- 3d. What are the comparators in ongoing trials?
- 3e. What are the prior/concurrent treatments in ongoing trials?
- 3f. What is the length of follow-up in ongoing trials?
- 3g. What are the outcomes measured in ongoing trials?

Current Evidence for the Use of Gene Therapy

- 4a. What are the indication/patient inclusion criteria in published studies?
- 4b. What are the types of interventions in published studies?
- 4c. What are the study designs/size in published studies?
- 4d. What are the comparators in published studies?
- 4e. What are the prior/concurrent treatments in published studies?
- 4f. What is the length of follow-up in published studies?
- 4g. What are the outcomes measured in published studies?
- 4h. What are the adverse events in published studies?

Important Issues Raised by Gene Therapy

- 5a. What are the implications of the current level of adoption and future diffusion, given current level of evidence—efficacy/safety, ethical, disparity, resource allocation, and decision making?
- 5b. What are the key issues pertaining to decisional uncertainty?
- 5c. What are potential areas of research focus for PCORI and others?

Furthermore, for each report, the available evidence is documented in comprehensive evidence tables. The evidence tables list key characteristics for all included studies. We stratify the evidence by gene therapy type and by completed and published studies versus potential pipeline therapies in ongoing studies. We also provide an evidence map, a visualization of the evidence. Evidence maps are useful as signposts for health care practitioners, policymakers, and funding agencies. They are ideally suited to provide many different stakeholders with an overview of a broad research area.

Description of Interventions/Technologies

There are currently 16 FDA-approved cellular or gene therapies. Table 1 describes the 7 intervention types that meet the FDA's definition of gene therapy.

Table 1. Intervention Classes With FDA-approved Therapies

Intervention Type	Description
Adeno-associated virus vector	The virus infects patient cells to deliver a healthy copy of a gene so that it will be properly expressed, thereby curing the disease.
Antisense	Complementary messenger RNA binds to and silences a disease-causing gene.
Autologous cell	Recovered cells or tissue from a patient are reintroduced after they have been genetically modified.
CAR-T	This is a specific application of autologous cell therapy in which patients' T cells are removed, genetically modified to attack specific cancer cells, then infused back into the patient.
Genetically modified oncolytic viral therapy replication-competent, attenuated derivative of herpes simplex virus type 1	The virus infects and replicates in cancer cells to express protein (eg, granulocyte-macrophage colony-stimulating factor), which results in cell lysis and increased antitumor immunity.
RNAi	Double-stranded RNA degrades RNA that encodes disease-causing proteins.
ZFN	Engineered DNA-binding proteins that create double-strand breaks in DNA at specific targeted locations.

Abbreviation: CAR-T, chimeric antigen receptor T cell; RNAi, RNA interference; ZFN, Zinc finger nuclease

Table 2 lists the 10 currently approved gene therapies (as of November, 2019). The 8 approved therapies addressed in the current report are shaded. In January 2013, the FDA approved Kynamro (Mipomersen sodium), the first therapy within the scope of this report to be approved. Kynamro is based on antisense technology and is used to treat homozygous familial hypercholesterolemia. In 2015, the FDA approved Imlygic (Talimogene laherparepvec) to treat melanoma. Imlygic is a genetically modified oncolytic viral therapy replication-competent, attenuated derivative of herpes simplex virus type 1. The next 3 FDA-approved therapies use antisense technology to treat Duchenne muscular dystrophy (Eteplirsen, Exondys 51), spinal muscular atrophy (Spinraza, Nusinersen), and polyneuropathy of hereditary transthyretin amyloidosis (Tegsedi, Inotersen). Luxturna was the first AAV-based therapy approved in 2017 to treat biallelic RPE65 mutation-associated retinal dystrophy. Subsequently in 2017, the FDA approved 2 CAR-T therapies. Yescarta is used to treat adult patients with relapsed or refractory large B-cell lymphoma and Kymriah treats children and young adults with refractory B-cell precursor acute lymphoblastic leukemia. In 2018, Kymriah gained additional approval to treat adult patients with relapsed or refractory large B-cell lymphoma. The FDA also approved an RNA interference drug in 2018 to treat hereditary transthyretin amyloidosis with polyneuropathy.

A key aspect of gene therapies is their potential to cure disease with one application. For instance, CAR-T therapies Kymriah and Yescarta are not expected to need repeated procedures. However, enough follow-up of treated patients has not yet occurred to know if these treatments are truly curative because researchers need to follow patients for several more years and because the number of treated patients is small. Yescarta has been shown to have durable response after 15 months, as documented in the CAR-T evidence table in Appendix E.[7] Trial results also suggest Kymriah has a durable response after a median follow-up of 13 months; this trial is ongoing (see ongoing trials Table 6).[8] Most key informants discussed the need for longer-term studies spanning at least 10 years to assess durability.

Table 2. FDA-approved Therapies

Modality/Type of Intervention	Name (Brand Name if Applicable)	FDA Approval Date	Indication	Approval Date for Specific Indication	Are Repeat Procedures Expected?
Antisense	Kynamro (Mipomersen sodium)	1/29/13	Homozygous familial hypercholesterolemia	1/29/13	Yes
Genetically modified oncolytic viral therapy replication-competent, attenuated derivative of herpes simplex virus type 1	Imlygic (Talimogene laherparepvec)	10/27/15	Melanoma	10/27/15	Yes
Antisense	Eteplirsen (Exondys 51)	9/19/16	Duchenne muscular dystrophy	9/19/16	Yes
Antisense	Spinraza (Nusinersen)	12/23/16	Spinal muscular atrophy	12/23/16	Yes
Antisense	Tegsedi (Inotersen)	10/5/18	Polyneuropathy of hereditary transthyretin amyloidosis	10/5/18	Yes
Adeno-associated virus vector	Luxturna (Voretigene neparvovec)	12/19/17	Biallelic RPE65 mutation-associated retinal dystrophy	12/19/17	No
AAV	Zolgensma* (Onasemnogene abeparvovec-xioi)	5/24/19	Spinal muscular atrophy	5/24/19	No
CAR-T—CD19-directed genetically modified autologous T cell immunotherapy	Yescarta (Axicabtagene ciloleucel)	10/18/17	Relapsed or refractory large B-cell lymphoma	10/18/17	No
CAR-T—CD19-directed genetically modified autologous T-cell immunotherapy	Kymriah (Tisagenlecleucel)	8/30/17	Patients up to 25 years of age with refractory B-cell precursor acute lymphoblastic leukemia	8/30/17	No
			Adult patients with relapsed or refractory large B-cell lymphoma	5/1/18	No

Modality/Type of Intervention	Name (Brand Name if Applicable)	FDA Approval Date	Indication	Approval Date for Specific Indication	Are Repeat Procedures Expected?
RNAi, specifically: siRNA, formulated as lipid nanoparticles for delivery to hepatocytes	Patisiran (Onpattro, ALN-TTR02)	8/10/18	Hereditary transthyretin amyloidosis with polyneuropathy	8/10/18	Yes

Abbreviation: CAR-T, chimeric antigen receptor T cell; RNAi, RNA interference; siRNA, double-stranded small interfering ribonucleic acid
Notes: Shading indicates antisense, genetically modified oncolytic viral therapy replication-competent, attenuated derivative of herpes simplex virus type 1; CAR-T; or RNAi gene therapy. Status as of April 25, 2019.
*This table was updated on February 3, 2020 to reflect the approval of Zolgensma (formerly AVXS-101) for spinal muscular atrophy (approved on 5/24/19)

Table 3 lists the identified therapies that have not yet been approved but may be close to approval. To identify these therapies, we searched the gray literature, including a database maintained by the *Journal of Gene Medicine* and Pink Sheet of Pharma Intelligence (we provide more detail in Appendix B). We included therapies if we found multiple mentions of them in the gray literature regardless of whether studies were complete or still in progress. The table presents the intervention modality, name/brand, FDA designation, and indication associated with the therapies that have yet to be approved. The therapies addressed in the current report are shaded. The other therapies are addressed in report 1, except injectable retroviral replicating vector that encodes a prodrug activator enzyme, cytosine deaminase, and Wyeth strain vaccinia virus/ granulocyte-macrophage colony-stimulating factor expression because they were identified only once in our search for pipeline therapies (we provide more detail of our methods in Appendix A).

Table 3. Potential Pipeline Gene Therapies

Modality/Type of Intervention	Name (Brand Name if Applicable) of Intervention	Indication
Adeno-associated virus vector	A001 (AAV2/5-OPTIRPE65)	Leber congenital amaurosis
Adeno-associated virus vector	A002 (AAV2/8- hCARp.hCNGB3)	Achromatopsia
Adeno-associated virus vector	AAV2.REP1 (AAV-mediated REP1)	Choroideremia
Adeno-associated virus vector	NSR-REP1 (AAV2-REP1)	Choroideremia
Adeno-associated virus vector	rAAV2.REP1	Choroideremia
Adeno-associated virus vector	SPK-7001 (AAV2-hCHM)	Choroideremia
Adeno-associated virus vector	rAAV2tYF-PR1.7-hCNGB3	Achromatopsia
Adeno-associated virus vector	AAV-RPGR	X-linked retinitis pigmentosa
Adeno-associated virus vector	ABO-101 (rAAV9.CMV.hNAGLU)	Sanfilippo syndrome type B
Adeno-associated virus vector	ABO-102 (scAAV9.U1a.hSGSH)	Sanfilippo syndrome type A
Adeno-associated virus vector	BIIB087 (rAAV2tYF-CB-hRS1)	X-linked retinoschisis
Adeno-associated virus vector	BIIB088	X-linked retinitis pigmentosa
Adeno-associated virus vector	SB-525	Hemophilia A
Adeno-associated virus vector	SHP654/BAX 888	Hemophilia A
Adeno-associated virus vector	SPK-8011	Hemophilia A
Adeno-associated virus vector	Valoctocogene Roxaparvovec (BMN 270)	Hemophilia A
Adeno-associated virus vector	AMT-060	Hemophilia B
Adeno-associated virus vector	AMT-061 (AAV5-hFIXco-Padua)	Hemophilia B

Modality/Type of Intervention	Name (Brand Name if Applicable) of Intervention	Indication
Adeno-associated virus vector	Fidanacogene Elaparvovec (SPK-9001, PF-06838435)	Hemophilia B
Adeno-associated virus vector	PF-06939926 (BMB-D001)	Duchenne muscular dystrophy
Adeno-associated virus vector	SGT-001	Duchenne muscular dystrophy
Adeno-associated virus vector	AAVrh74.MHCK7.micro-Dystrophin	Duchenne muscular dystrophy
Adeno-associated virus vector	AVXS-101*	Spinal muscular atrophy
Adeno-associated virus vector	MYO-101 (scAAVrh74.MHCK7.hSGCB)	Limb-Girdle muscular dystrophy, type 2E
Adeno-associated virus vector	MYO-102 (scAAVrh74.tMCK.hSGCA)	Limb-Girdle muscular dystrophy, type 2D
Adeno-associated virus vector	MYO-201 (rAAVrh74.MHCK7.DYSF.DV)	Limb-Girdle muscular dystrophy, type 2B /Miyoshi Myopathy
Adeno-associated virus vector	rAAV1.tMCK.human-alpha-sarcoglycan	Limb-Girdle muscular dystrophy, type 2D
Adeno-associated virus vector	VY-AADC	Parkinson's disease
Adenovirus, oncolytic	Tasadenoturev (DNX-2401)	Brain cancer
Adenovirus, vaccine	Ad26.ZEBOV	Ebola
CRISPR/Cas9—CAR-T-cell therapy	Anti-mesothelin CAR-T Cells	Solid tumor cancers
CRISPR/Cas9—CAR-T-cell therapy	CD7.CAR/28zeta CAR-T Cells	T-cell acute lymphoblastic leukemia, T-cell non-Hodgkin lymphoma
CRISPR/Cas9—CAR-T-cell therapy	PD-1 Knockout EBV-CTL	Gastric carcinoma, nasopharyngeal carcinoma, T-cell lymphoma, adult Hodgkin lymphoma, diffuse large B-cell lymphoma
CRISPR/Cas9—CAR-T-cell therapy	PD-1 Knockout T Cells	Prostate cancer, bladder cancer, non–small cell lung cancer, renal cell carcinoma, esophageal cancer
CRISPR/Cas9—CAR-T-cell therapy	UCART019	B-cell leukemia or lymphoma
CRISPR/Cas9—CAR-T-cell therapy	Universal Dual Specificity CD19 and CD20 or CD22 CAR-T Cells	B-cell leukemia or lymphoma
CRISPR-Cas9—autologous CD34+ human Hematopoietic Stem and Progenitor Cells	CTX001	Beta-thalassemia
Antisense	IONIS-MAPTRx	Alzheimer's disease
Antisense	RG6042 (IONIS-HTTRx)	Huntington's disease
Antisense	Volanesorsen	Familial chylomicronemia syndrome, familial partial lipodystrophy
Autologous cell therapy	Strimvelis (GSK2696273)	Severe combined immunodeficiency
Autologous cell therapy	Lenti-D	Cerebral adrenoleukodystrophy (Lorenzo's oil disease)
Autologous cell therapy	LentiGlobin (BB305)	Beta-thalassemia and sickle cell disease
Autologous cell therapy	OTL-101	Adenosine deaminase severe combined immunodeficiency
Autologous cell therapy	OTL-200 (GSK2696274)	Metachromatic leukodystrophy
Autologous cell therapy	EB-101	Recessive dystrophic epidermolysis bullosa
Autologous cell therapy	FCX-007	Recessive dystrophic epidermolysis bullosa

Modality/Type of Intervention	Name (Brand Name if Applicable) of Intervention	Indication
Autologous cell therapy	FCX-013	Moderate to severe localized scleroderma
CAR-T-cell therapy	bb2121	B-cell maturation antigen-expressing multiple myeloma, multiple myeloma
CAR-T-cell therapy	BCMA (EGFRt/BCMA-41BBz CAR-T cell)	Multiple myeloma
CAR-T-cell therapy	JCAR014	Non-Hodgkin lymphoma
CAR-T-cell therapy	JCAR016	Acute myeloid leukemia, non–small cell lung cancer, mesothelioma
CAR-T-cell therapy	JCAR018	Non-Hodgkin lymphoma, pediatric acute lymphoblastic leukemia
CAR-T-cell therapy	JCAR020	Ovarian cancer
CAR-T-cell therapy	JCAR023	Pediatric neuroblastoma
CAR-T-cell therapy	JCAR024	ROR1+ cancers (solid tumors, blood cancers)
CAR-T-cell therapy	JCARH125	B-cell maturation antigen target in late-line myeloma
CAR-T-cell therapy	Lisocabtagene maraleucel (Liso-Cel, JCAR017)	Non-Hodgkin lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, mantle-cell lymphoma, primary mediastinal B-cell lymphoma
Injectable retroviral replicating vector that encodes a prodrug activator enzyme, cytosine deaminase (CD)	Vocimagene amiretrorepvec (Toca 511 & Toca FC)	Glioma
RNAi	ALN-TTRsc02	Acquired transthyretin amyloidosis
RNAi	AMG 890 (ARO-LPA)	Apolipoprotein A reduction
RNAi	ARO-AAT	Alpha-1 antitrypsin deficiency liver disease
RNAi	ARO-HBV	Chronic hepatitis B infection
RNAi	Cemdisiran (ALN-CC5)	Complement mediated disease
RNAi	Fitusiran (ALN-AT3sc)	Hemophilia A, B
RNAi	Givosiran (ALN-AS1)	Acute hepatic porphyrias
RNAi	Inclisiran (ALN-PCSsc)	Hypercholesterolemia
RNAi	Lumasiran (ALN-GO1)	Primary hyperoxaluria type 1
RNAi	Revusiran (ALN-TTRsc)	Transthyretin-Mediated Amyloidosis, familial amyloidotic polyneuropathy, ATTR amyloidosis, familial amyloid neuropathies, mediated familial amyloidotic cardiomyopathy
Wyeth strain vaccinia virus/ granulocyte-macrophage colony-stimulating factor expression	Pexastimogene Devacirepvec (Pexa-Vec, JX-594)	Cancer (various)
ZFN	SB-318	MPS I (Scheie, Hurler-Scheie, and Hurler syndromes)
ZFN	SB-913	MPS II (Hunter syndrome)
ZFN	SB-FIX	Hemophilia B
ZFN	ST-400	Beta-thalassemia
ZFN—CAR-T-cell therapy	SB-728-T	HIV
ZFN—Stem cells	SB-728-HSPC	HIV

Abbreviations: CAR-T, chimeric antigen receptor T cell; RNAi, RNA interference; CRISPR, clustered regularly interspaced short palindromic repeats; ZFN, zinc finger nuclease

Notes: Shading indicates antisense, genetically modified oncolytic viral therapy replication-competent, attenuated derivative of herpes simplex virus type 1; CAR-T; or RNAi gene therapy.
*AVXS-101 (Avexis/Novartis) to treat spinal muscular atrophy was approved on May 24, 2019 as Zolgensma

Our search identified 76 therapies that meet the FDA's definition of gene therapy and that have not yet been FDA approved ("pipeline" therapies). The most common type of therapy was AAV (37%). Other common types were CAR-T-cell therapy (13%), RNAi (13%), and autologous cell therapy (11%). The remaining interventions and frequencies were CRISPR/Cas9—CAR-T-cell therapy (8%), ZFN (5%), antisense (4%), adenovirus (3%), CRISPR-Cas9—autologous CD34+ human hematopoietic stem and progenitor cells (1%), and injectable retroviral replicating vector that encodes a prodrug activator enzyme, cytosine deaminase (1%), Wyeth strain vaccinia virus/granulocyte-macrophage colony-stimulating factor expression (1%), ZFN—CAR-T-cell therapy (1%), and ZFN-stem cell therapy (1%).

The identified therapies are being used to treat multiple disease types, including vision disorders (eg, choroidemia), muscular dystrophy (eg, Duchenne), blood disorders (eg, hemophilia), Sanfilippo syndrome, cancer, HIV, and Parkinson's disease.

We asked key informants to name any pipeline therapies that are likely to gain approval in the next 5 years. In total, our key informants identified 6 therapies, also included in Table 3:

- AVXS-101 (Avexis/Novartis) to treat spinal muscular atrophy (2 nominations) was approved on May 24, 2019 as Zolgensma
- Valoctocogene Roxaparvovec (Biomarin) to treat hemophilia A (1 nomination)
- SPK-9001 (Spark Therapeutics) to treat hemophilia A (2 nominations)
- SPK-8011 (Spark Therapeutics) to treat hemophilia B (1 nomination)
- AMT-061 (uniQure) to treat hemophilia B (1 nomination)
- LentiGlobin (Bluebird bio) to treat beta thalassemia (2 nominations)

The fact that key informants were aware of the above 6 therapies among the large number of potential pipeline therapies that we identified suggests that these 6 may be closer to approval than the other therapies. AVXS-101, Valoctocogene Roxaparvovec, SPK-9001, and SPK-8011 are AAV interventions, and we identified completed trials with promising evidence for AVXS-101[9] and for SPK-9001.[10] As noted above AVXS-101 was approved as Zolgensma on May 24, 2019. LentiGlobin is an autologous cell intervention and it, along with Valoctocogene Roxaparvovec, SPK-801, and AMT-061, are still being tested in ongoing trials that have yet to complete recruitment.

CAR-T, Autologous Cell, ZFN, Antisense, RNAi, Genetically Modified Oncolytic Herpes Virus Gene Therapy

Eligible interventions for this report included those that used either CAR-T; autologous cell, ZFN; antisense; RNAi; or oncolytic viral therapy replication-competent, attenuated derivative of herpes simplex virus type 1 therapies. Below we describe the indications and their US prevalence for the 8 approved therapies that are within the scope of this report and as yet unapproved technologies based on the potential pipeline therapies identified in Table 3.

CAR-T Therapy Indications

Approved

Our search identified 2 CAR-T therapies: Yescarta (Axicabtagene ciloleucel) and Kymriah (Tisagenlecleucel). Yescarta is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Kymriah is approved to treat (1) patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse; and (2) adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. DLBCL is an aggressive cancer and the most common type of non-Hodgkin lymphoma in the United States.[11] Based on 2011-2015 data, the estimated number of new cases per year was 5.5 per 100 000 adults.[12] The estimated new cases of leukemia in 2018 in which the bone marrow produces cancerous white blood cells was 60 300.

Unapproved

Ten new CAR-T therapies are in trials to treat multiple types of cancer.

- BCMA (EGFRt/BCMA-41BBz CAR-T cell) and bb2121 are being used to treat multiple myeloma, which affects plasma cells. The American Cancer Society estimates that the lifetime risk in the United States is 0.76% and that 32 110 new cases will be diagnosed in 2019.[13]
- JCAR014, JCAR018, and Lisocabtagene maraleucel (Liso-Cel, JCAR017) are being used to treat non-Hodgkin lymphoma, which includes mycosis fungoides, anaplastic large-cell lymphoma, and precursor T-lymphoblastic lymphoma and accounts for 4% of cancers in the United States.[14] An estimated that 74 680 adults and children will be diagnosed with non-Hodgkin lymphoma in 2019.[15]
- JCAR016 and JCAR018 are being used to treat leukemia, which is a cancer of the blood. An estimated 61 780 new cases will be diagnosed in 2019.[16]
- JCAR020 is being used to treat ovarian cancer. In 2015, an estimated 224 940 women in the United States were living with ovarian cancer.[17]
- JCAR023 is being used to treat pediatric neuroblastoma, which accounts for about 6% of all cancers in children; the average age of diagnosis is between 1 and 2 years.[18]
- JCAR024 is being used to treat solid tumor cancers (eg, sarcomas, carcinomas, lymphomas), which are defined as abnormal masses that do not contain cysts or liquid areas[19] so they can affect multiple organs (eg, colon). Across all types of cancer, an estimated 1 732 450 new cases will be diagnosed in 2019.[20]

- JCARH125 and Lisocabtagene maraleucel (Liso-Cel, JCAR017) are being used to treat B-cell lymphoma, which is as described above.

Autologous Cell Therapy Indications

Approved

No autologous cell therapies have been FDA approved.

Unapproved

Multiple autologous cell therapies are in trials to treat several types of conditions:

Skin disorders

- Genetically modified autologous fibroblasts (EB-101 and FCX-007) have been used to treat recessive dystrophic epidermolysis bullosa, which is an inherited skin disorder characterized by blistering of the skin and mucous membranes. The estimated prevalence in the United States is 1 per 2 040 816.[21]
- Genetically modified autologous fibroblasts (FCX-013) have been used to treat localized scleroderma, which is characterized by fibrosis of the skin that causes cutaneous plaques or strips. The estimated prevalence is about 1 to 9 per 100 000.[22]

Neurological disorders

- Autologous CD34+ cells transduced with lentiviral vector (OTL-200 [GSK2696274]) have been used to treat metachromatic leukodystrophy, which is a rare neurometabolic disorder that affects the white matter of the brain, characterized by the accumulation of a fatty substance (sulfatide) in the brain and other areas of the body. The prevalence of the late infantile form and the juvenile form is 1 in 40 000 and 1 in 150 000, respectively.[23]
- Autologous CD34+ cells transduced with lentiviral vector (Lenti-D) have been used to treat adrenoleukodystrophy, which is an X-linked recessive genetic disorder that affects the white matter of the nervous system and the adrenal cortex. Adrenoleukodystrophy can cause attention deficit disorder; progressive loss of intellectual function; and vision, hearing, and motor deterioration. The prevalence is about 1 per 20 000 to 1 per 50 000 births, and most of those affected are males.[24]

Immunodeficiency disorders

- Autologous CD34+ cells transduced with retroviral vector (Strimvelis [GSK2696273]) have been used to treat severe combined immunodeficiency (SCID), which is caused by an adenosine deaminase deficiency and is characterized by severe lymphopenia and very low immunoglobulin levels that result in immunodeficiency. The estimated annual incidence is between 1 in 200 000 and 1 in 1 000 000 live births.[25]

Blood disorders

- Autologous hematopoietic stem cells transduced with lentiviral vector (LentiGlobin [BB305]) have been used to treat beta-thalassemia, which is a rare inherited blood disorder. The severity of beta-thalassemia can range from mild to severe, for which patients require regular blood transfusions throughout their lives. The incidence of symptomatic cases is estimated to be approximately 1 in 100 000 people globally.[26] This approach has also been used to treat sickle cell anemia, a disorder in which hemoglobin cells are sickle-like in shape. In 2010, the total US incidence estimate for sickle cell trait was 15.5 cases per 1000 births.[27]

Antisense Therapy Indications

Approved

Four antisense therapies have been approved to treat several severe diseases:

- Kynamro (Mipomersen sodium) was approved to treat homozygous familial hypercholesterolemia, which is a rare inherited disorder of lipoprotein metabolism characterized by increased low-density lipoprotein cholesterol and premature cardiovascular disease. The global prevalence is estimated to be about 1 in 160 000 to 1 in 1 million.[28]
- Eteplirsen (Exondys 51) was approved to treat Duchenne muscular dystrophy, which is a genetic disorder that manifests most severely in males (1 in 3500 to 5000 males) and leads to progressive muscle degeneration.[29]
- Spinraza (Nusinersen) was approved to treat spinal muscular atrophy, which is a neuromuscular disease that results in muscle weakness and paralysis. The estimated incidence is 1 in 6000 to 1 in 10 000 live births.[30]
- Tegsedi (Inotersen) was approved to treat polyneuropathy of hereditary transthyretin amyloidosis, which results in amyloid deposits throughout the body and is characterized by sensory, motor, and autonomic neuropathy and/or cardiomyopathy. The estimated prevalence in the United States is 1 in 100 000 individuals.[31,32]

Unapproved

Our search identified 3 antisense therapies that are being tested in different patient populations.

Neurodegenerative disorders

- IONIS-MAPTRx is being used to treat Alzheimer's, which is a form of dementia and the sixth leading cause of death in the United States, with an estimated prevalence of 5.7 million in 2018.[33]
- RG6042 (IONIS-HTTRx) is being used to treat Huntington's disease, which is a rare, neurodegenerative disorder characterized by uncontrolled movements, emotional problems, and loss of cognition. The estimated prevalence is 3 to 7 per 100 000 people of European ancestry and may be less common in some other populations.[34]

Metabolic disorders

- Volanesorsen is being used to treat familial chylomicronemia syndrome, which is a rare genetic metabolic disorder caused by a deficiency of the enzyme lipoprotein lipase that limits the proper digestion of certain fats and results in massive accumulation of fatty droplets called chylomicrons and an increase of plasma triglycerides. It is estimated to occur in approximately 1 in 250 000 people.[35]
- Volanesorsen is also being used to treat familial partial lipodystrophy, which is caused by a mutation in one of several genes that play a role in fat storage and is characterized by an abnormal distribution of fat around the body. The estimated prevalence is 1 in 1 million people.[36]

RNAi Therapy Indications

Approved

One RNAi-based therapy has been FDA approved to treat hereditary transthyretin amyloidosis with polyneuropathy.

- Patisiran (Onpattro, ALN-TTR02) was approved to treat polyneuropathy of hereditary transthyretin amyloidosis, as described above.

Unapproved

Ten RNAi therapies are being tested in trials to treat a diverse set of conditions.

Amyloidosis

- ALN-TTRsc02 and Revusiran (ALN-TTRsc) are being used to treat acquired transthyretin amyloidosis, which causes amyloid deposits that affect the nerves and/or heart, and sometimes the kidneys, eyes, and synovial tissues. Its prevalence in the United States is estimated not to exceed 6400 patients.[37]

Cardiovascular disorders

- AMG 890 (ARO-LPA) and Inclisiran (ALN-PCSsc) are being used to treat hypercholesterolemia, which is characterized by high levels of low-density lipoprotein cholesterol that leaves people at risk of heart disease and stroke.[38] In 2011-2012, an estimated 78 million U.S. adults (nearly 37%) had high cholesterol.[39]

Liver disorders

- ARO-AAT is being used to treat alpha-1 antitrypsin deficiency (alpha-1), which is an inherited disorder that may lead to the development of lung and/or liver disease. The prevalence is estimated at about 1 per 1500 to 1 per 3500 people of European ancestry.[40]
- ABO-HBV is being used to treat chronic hepatitis B virus, which can cause liver disease. The 2004 incidence rate in the United States is estimated to be 2.1 per 100 000.[41]

Immune disorders

- Cemdisiran (ALN-CC5) is being used to treat complement mediated disease, which occurs when infection or injury produces chronic inflammation that results in inflammatory or autoimmune diseases, which is estimated to affect up to 23.5 million people in the United States of which complement-mediated disease account for 10%.[42]

Blood disorders

- Fitusiran (ALN-AT3sc) is being used to treat hemophilia A, which is a bleeding disorder that affects 1 in 5000 male births and is 4 times more common than hemophilia B. An estimated 20 000 people in the United States have hemophilia.[43,44]
- Givosiran (ALN-AS1) is being used to treat acute hepatic porphyria, which is caused by a deficiency of one of the enzymes in the heme biosynthesis pathway. It can be accompanied by neuro-visceral attacks that appear as intense abdominal pain, neurological symptoms, and psychological symptoms. The estimated prevalence is about 1 per 75 000.[45]

Kidney disorders

- Lumasiran (ALN-GO1) is being used to treat primary hyperoxaluria type 1, which is a rare condition characterized by recurrent kidney and bladder stones that can cause end stage renal disease. It is estimated to affect 1 in 58 000 individuals globally.[46]

ZFN Therapy Indications

No ZFN therapies have been FDA approved.

Unapproved

Six ZFN therapies are being tested in trials to treat a diverse set of conditions.

Metabolic disorders

- SB-318 is being used to treat Hurler-Scheie syndrome, which is the intermediate form of mucopolysaccharidosis type I (MPS I), a rare lysosomal storage disease characterized by skeletal deformities and a delay in development. The prevalence of MPS I has been estimated at 1 per 100 000, with Hurler-Scheie syndrome accounting for 23% of cases or a prevalence of approximately 1 per 435 000.[47]
- SB-913 is being used to treat mucopolysaccharidosis type II (MPS II), which is a rare inborn error of metabolism that affects every organ of the body. The disorder occurs in approximately 1 in 100 000 to 1 in 170 000 male births.[48]

Blood disorders

- SB-FIX is being used to treat hemophilia as described above.
- ST-400 is being used to treat beta-thalassemia as described above.

Immune disorders

- SB-728-T and SB-728-HSPC are being used to treat HIV, which is caused by a virus that attacks the immune system, specifically CD4 (T cells). At the end of 2016, an estimated 1.1 million people aged 13 and older had a diagnosed HIV infection in the United States.[49]

Genetically Modified Oncolytic Viral Replication-competent, Attenuated Derivative of Herpes Simplex Virus Type 1 Therapy Indications

Approved

One genetically modified oncolytic viral replication-competent, attenuated derivative of herpes simplex virus 1 intervention has been approved to treat cancer.

- Imlygic (Talimogene laherparepvec) was approved to treat melanoma, which is a cancer of melanocytes in the skin. An estimated 91 270 new cases were diagnosed in 2018.[50]

Key Question 1a. What are the different types or modalities of the intervention that have been used in clinical practices and clinical research studies?

Gene therapy interventions either modify or edit a patient's gene or introduce a protein-producing gene into the patient. Below we describe how antisense, RNAi, autologous cell, CAR-T, and genetically modified oncolytic viral interventions act by either modifying or delivering a gene and its expression to a patient.

Gene editing or replacement

Antisense and RNAi gene therapies both use complementary oligonucleotides that target sense messenger RNA (mRNA) to control gene expression of a diseased gene. They can also operate by manipulating pre-mRNA splicing to correct splice defects or induce exon skipping or exon inclusion.[51] Splicing in a single gene can create different combinations of coding RNA that result in multiple proteins. While antisense therapy acts by binding to the DNA, RNAi acts by degrading RNA. Antisense and RNAi can be delivered directly to the site of action (eg, nucleus) or with a delivery agent (eg, lipid particles).[52] However, nusinersen is an antisense intervention to treat spinal muscular atrophy, and because it does not cross the blood–brain barrier, it requires repeated delivery to the spinal space that holds cerebrospinal fluid to treat spinal muscular atrophy, which is a challenge for affected infants.

ZFNs were designed to recognize specific DNA sequences and then, when coupled with the sequence-independent nuclease domain of the restriction enzyme FokI, induce genomic changes.[53,54]

Gene delivery and expression

CAR-T therapy is an immunotherapy that acts by introducing a new gene by genetically engineering the patients' own T cells to produce receptors allowing them to attach to a specific antigen or protein on tumor cells. The process has been described in detail elsewhere.[55] It begins with leukapheresis to remove blood from the patient, separate the leukocytes, and then return the remaining blood to the patient.[55] The lymphocytes then must be shipped to a manufacturing facility where T cells are activated and modified with a viral vector that contains the CAR transgene. After growing and purifying the CAR-T cells for several days they can be infused back into the patient and the vector introduces the CAR into the patient's genome. After infusion into the patient, the engineered T cells recognize and kill cancer cells that express the antigen. Some disadvantages of using a patient's T cells are the difficulty to collect enough cells and the wait time prior to return of the engineered cells. Advances in using allogenic or "off-the-shelf" cells can overcome such difficulties.[56] Indeed, in August 2018, the FDA approved the first Investigational New Drug Application for allogenic CAR-T Cell therapy trial.[57]

Oncolytic viruses and herpes simplex virus (HSV) are vectors for transferring genes with the advantage that they have the capacity to transfer long sequences of DNA. Three types of vectors can be derived from HSV: replication-competent attenuated vectors, replication-incompetent attenuated vectors, and defective helper-dependent vectors. Oncologic viruses are able to infect and replicate within cancer cells without damaging surrounding cells that are normal. They lyse tumor cells and augment host antitumor immune response. Oncolytic viruses have been genetically engineered to preferentially target cancer cells.

Autologous cell gene therapy involves removing select cells from the patient (eg, resected tumor cells). Multiple types of cells may be used, including dendritic cells and hematopoietic stem cells. The cells must then be transported to a central processing center where they are genetically modified to express a healthy copy of a gene or to counteract disease-causing cells. The cells are then infused back into the patient depending on the indication. For example, modified autologous cells may be injected directly into a tumor.

Key Question 1b. What are potential/presumed advantages and disadvantages in contrast to current practices?

Advantages

Many of the potential and presumed advantages of gene therapies appear similar across all types of gene therapy. First and foremost, the advantages are cures for previously incurable and fatal diseases. Many diseases exist for which the only treatment is supportive care, or for which the treatment has dire side effects or is very costly. In cases in which the disease has a spectrum of severity, in our review of the literature we found that gene therapy typically targets the most refractory types. Based on our review and interviews with key informants, the greatest advantage of gene therapy is reducing suffering by addressing unmet need. A gene therapy would have an advantage over current therapy if it could negate any further need for future treatment. Although not all gene therapies can, theoretically some may cure the targeted condition with only one administration. Some clinical conditions may be currently manageable with current practices and repeated treatments.

CAR-T is one type of gene therapy that is expected to need only one administration with a few weeks of inpatient care, which would be a significant advantage over current treatments that require repeated procedures. For example, approved CAR-T therapies can treat B-cell lymphomas and leukemia without the need for repeated chemotherapy. Because CAR-T persists in the patient, the effect is long-lasting. However, in the trials that supported the approval of Kymriah and Yescarta, while positive response was significant and impressive, durability among all patients who had a complete remission was not observed after 1 year or more. Among the 61 pediatric B-cell precursor

acute lymphoblastic leukemia patients who had complete remission after Kymriah treatment, 20 had a relapse by 12 months.[8] In the adult relapsed or refractory large B-cell lymphoma patients, 57% (16 of 28) had a complete response after 6 months of treatment. However, among those in complete remission at 6 months, all remained in remission after a period of 7.7 to 37.9 months (median = 29.3 months).[58] Yescarta treatment was not completely durable after long-term follow-up. Initially, 54% of patients had a complete response after a minimum of 6 months, yet after a median follow-up of 15 months the complete response rate dropped to 40%.[7]

Although autologous cell gene therapy requires multiple doses, it is being tested to treat diseases that have few treatment options (eg, Huntington's). In addition, because the cells are derived from the patient, it does not require human leukocyte antigen (HLA)-matched donors.[i] For example, current treatment of severe combined immunodeficiency is bone marrow transplant to provide a new immune system using healthy hematopoietic stem cells from an HLA-matched donor. Bone marrow transplant is a painful procedure with mild to severe complication risk (eg, graft-versus-host disease) and a matched donor may not be available for all patients.

Antisense and RNAi can specifically target and efficiently modify gene expressions of interest. However, these approaches do require multiple treatments. Among the antisense interventions, Spinraza (Nusinersen) is injected into the cerebrospinal fluid 4 times within the first 2 months of treatment and then repeated once every 4 months during the maintenance period. Weekly treatments, on the other hand, are recommended for Kynamro (Mipomersen sodium) intrathecally, Eteplirsen (Exondys 51) intravenously, and Tegsedi (Inotersen) intravenously. The RNAi intervention Patisiran (Onpattro, ALN-TTR02) is also injected intravenously and the recommended dosing schedule is every 3 weeks.

Disadvantages

All types of gene therapies share many unknowns and uncertainty that relate to (1) how clinically effective treatments are versus the risk for adverse outcomes, (2) how gene therapies will be implemented in health care systems where providers may be unfamiliar with requisite procedures and patients are not well informed about what gene therapies are, (3) the ethical implications of altering the genome, and (4) how patients and payers will pay for potentially expensive gene therapy. However, more evidence is needed to know if these unknowns will become disadvantages.

Several cases of gene-related deaths slowed the progress gene therapy was making in early years of this research. Jesse Gelsinger was the first patient to die after receiving gene therapy, which resulted in the suspension of adenoviral trials.[59] Later, a French child developed a leukemia-like illness that was thought to have been caused by gene therapy.[60] Other tragic cases include a death due to fatal infection after a patient received immunosuppressive therapy for a gene therapy trial.[61] Longer-term disadvantages are related to risks that are still not understood, including future malignancy.

Other disadvantages may be related to the time patients must wait for treatment due to production requirements. The process of CAR-T treatment involves many steps with collaboration between doctors, health centers, and manufacturers. After a patient's T cells are extracted at a treatment center, they are sent to a manufacturing facility where they are engineered to recognize a specific protein or antigen and attack disease-causing cells. Then they are reinfused into the patient. The process requires an unprecedented level of collaboration between doctors, health centers, and manufacturers and would ideally last 10 days. However, for patients with aggressive cancers, any delay in treatment can have dire consequences for their survival. Treatment center location could be a factor in the length of time patients wait for treatment. There are currently more than 50 specialized treatment centers for Yescarta and more than 80 locations for treatment with Kymriah.

[i] When people have the same HLA markers (ie, HLA-matched), their tissues are immunologically similar.

During our interviews, one key informant expressed concern about the viability of small insurers, small self-insured employers, and even large self-insured employers with limited reinsurance, in the face of very high treatment prices. Because these therapies may provide large health gains and reduce future treatment prices, manufacturers may charge high up-front payment to reflect the value of the therapy. Such high short-term fees may limit access if the treatment is unaffordable, even if still considered to be good value. While price may be based on value, uncertainties in the clinical evidence base make it difficult to establish whether a treatment represents good value for the money. Recent experience suggests that the price may be a disadvantage of these therapies relative to others. New gene therapies are expensive to patients and payers. For example, the price for Eteplirsen (ExonDys 51), an antisense therapy for Duchenne muscular dystrophy, is reported to cost $300 000 to $400 000/year per patient for life,[62] which is more expensive than exercise and diet to minimize muscle contractures but may be more effective. The Institute for Clinical and Economic Review's (ICER's) white paper "GENE THERAPY: Understanding the Science, Assessing the Evidence, and Paying for Value" discusses in more detail the challenges gene therapy presents in the United States and potential solutions (eg, annualized payments or risk sharing).[63]

Other disadvantages discussed by key informants related to manufacturing and a need for greater understanding of the science and mechanisms of action to regulate and ensure quality in manufacturing. Gene therapies are regulated as products, but one key informant asked if they should be regulated as procedures. This raises the question of who should be able to administer gene therapy. Gene therapies could become like stem cell therapies, and might be administered with little regulation about who provides the therapy. For example, in Australia, autologous cell treatments were once exempt from the regulatory framework that applies to cell and gene treatments. Thus, the growth and use of unproven autologous cell interventions grew markedly in Australia.[64]

Key informants also noted that the current health care system is not yet structured to deliver gene therapy, in part because providers are not fully aware of new nonstandard gene therapies. For example, Imlygic requires intratumoral administration, which may be unfamiliar to medical oncologists.[65] Similarly, Imlygic is an oncolytic virus and the use of live, replicating viruses may not be familiar to many oncologists.[65] Moreover, patients seeking care may have to travel far to the few existing treatment centers that currently provide care with gene therapy, which may be costly and pose heavy burdens for families.

Key informants expressed concern about several other potential disadvantages. Many key informants were concerned with delivering interventions to target cells more effectively and balancing minimally effective dosages with adverse reactions. Finally, another key informant noted that much of the evidence for gene therapies includes small study samples while the indication is prevalent in larger populations (eg, patients older than 65). For example, we found in this report that many of the gene therapy trials treating cardiovascular disease are relatively small considering the numbers of patients in the studies compared with the burden of disease in the population. Thus, lack of generalizability of findings is a concern. Most key informants expressed concern about the state of science education, the average person's understanding of gene therapy, and how a patient weighs the risks and effectiveness information.

Key Question 1c. What are the safety issues or expected adverse events?

Some therapies produce physiologic responses that can be dangerous if not managed clinically. Cytokine release syndrome (CRS) occurs after CAR-T infusion when the patient's immune response is activated. CRS can be mild to life threatening, including high fever, fatigue, myalgia, nausea, anorexia, tachycardia/hypotension, cardiac dysfunction, and hepatic failure.[66,67] While corticosteroids can reverse CRS, they can also attenuate the long-term CAR-T effectiveness.[67,68] In the Kymriah study that

prompted FDA approval, cytokine release syndrome occurred in 77% of patients. However, these adverse events were managed with supportive care, and no cerebral edema was reported.[8]

In the above study, 40% of patients also experienced neurotoxicity, which is another adverse event associated with CAR-T in which patients can experience confusion, delirium, and seizure.[66,68] Neurotoxicity after CAR-T treatment has been reversible in some instances. However, because the causative pathophysiology is unknown, whether the neurotoxicity is related only to CD19-specific CAR-T cells or if it may also be a concern for other tumor-associated antigens is not clear.[66,68,69] Serious adverse events are associated with Yescarta (Axicabtagene ciloleucel). In the study that provided evidence for approval, both grade 3[ii] or higher cytokine release syndrome and neurologic events occurred in 13% and 28% of the patients, respectively. Three of the patients died during treatment.[7]

While autologous cell therapies use patients' own cells, they can produce a local inflammatory response when used as a vaccine. When autologous cells are used in combination with retroviral or lentiviral vectors, integration of the genetic material into the patients' DNA may occur and may induce tumor growth.

Antisense and RNAi and off-target effects have been observed when they bind to unintended sites, and efficiency can vary. In addition, Kynamro (Mipomersen sodium), which is an antisense therapy, can cause liver toxicity due to liver enzyme abnormalities and accumulation of fat in the liver, which could lead to progressive liver disease with chronic use.[70] The antisense intervention Tegsedi has been associated with risk of thrombocytopenia and glomerulonephritis.[71]

The most common adverse reactions reported by patients treated with Patisiran (Onpattro, ALN-TTR02; RNAi) are infusion-related reactions, including flushing, back pain, nausea, abdominal pain, dyspnea (difficulty breathing), and headache. Myocardial infarction, cardiac amyloidosis, osteomyelitis, cardiac failure, and renal failure have also been reported.[72,73]

Adverse events for Imlygic (Talimogene laherparepvec; genetically modified oncolytic viral therapy) are relatively mild to moderate (eg, flu-like symptoms), and serious grade 3 events (eg, cellulitis) are rare.[65]

[ii] Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

Context in Which Gene Therapy Is Used

Key Question 2a. What is the approval process and current approval/certification status for gene therapies?

In the United States, the FDA's Center for Biologics Evaluation and Research reviews and regulates the use of human gene therapies, cellular therapy products, and devices related to gene and cell therapy. Within the National Institutes of Health, the Office of Biotechnology Activities and the Recombinant DNA Advisory Committee (RAC) review gene therapy protocols. While both the FDA and RAC consider clinical and preclinical issues, the RAC also serves as an open forum for considering the ethical, legal, and societal issues.[74]

Gene therapy sponsors submit an Investigational New Drug application, the Biologics License Application, and the Investigational Device Exemption to the FDA. The Investigational New Drug application is a special permission exemption from the FDA. In the Investigational New Drug application, manufacturers must describe how they will conduct the study, possible risks that may be involved and what steps they will take to protect patients, and the evidence that supports the study. The FDA has published guidance documents[75] to facilitate the approval process. Manufacturers of gene therapy products must comply with FDA requirements for safety, purity, and potency before their therapies can be approved and sold. In August 2018, the NIH reported that the RAC will no longer review all gene therapy applications and will instead provide guidance in an advisory role.[76,77] The FDA will now review and approve gene therapies and biologic products as it does with other treatments and drugs.

The FDA has approved gene therapies after phase 3 randomized control trials. In cases in which the disease is severe and no alternative treatments exist, the FDA has based approval on single-arm phase 2 trials.

- Kynamro (Mipomersen sodium) is approved to treat homozygous familial hypercholesterolemia. It was first tested in healthy volunteers, then was approved after 4 phase 3 trials.[78-81] While results varied slightly, significant reduction in triglycerides and low-density lipoprotein were observed in all trials.
- Imlygic (Talimogene laherparepvec) is approved to treat melanoma. It was first tested in a phase 1 trial and later in phase 2 trials. After a randomized phase 3 trial[82] reported a durable response rate that was significantly higher in the treatment arm, the FDA granted approval.
- Eteplirsen (Exondys 51) is approved to treat Duchenne muscular dystrophy. It was first tested in a small phase 3 controlled trial of 12 patients that failed to provide the FDA enough clinical effective evidence for approval.[83] The clinical endpoint was the number of counted dystrophin-positive fibers. The FDA requested that the researchers quantify dystrophin amounts by a well-controlled western blot assay, and this was performed on additional biopsies taken after 188 weeks of treatment.
- Spinraza (Nusinersen) gained approval to treat spinal muscular atrophy after a randomized phase 3 sham-controlled trial[84] and an open-label dose-escalation study reported significant motor function improvement in the treated groups.[85]
- Tegsedi (Inotersen) gained approval for treatment of polyneuropathy of hereditary transthyretin amyloidosis after a phase 3 NEUR-TTR study reported that treated patients gained significant clinical disease progression improvement for adults with polyneuropathy due to hereditary transthyretin-mediated amyloidosis.[71]

- Yescarta (Axicabtagene ciloleucel) was approved to treat relapsed or refractory large B-cell lymphoma after significant health benefits were reported in a phase 2 multicenter trial.[7] Despite adverse events, the objective response rate was 82%, and the complete response rate was 54% after a median of 7.9 months of follow-up and attenuated after a median follow-up of 15 months to 40%.
- Kymriah (Tisagenlecleucel) also gained approval after just one study. It was first approved to treat children and young adult patients up to 25 years of age with refractory B-cell precursor acute lymphoblastic leukemia after a phase 2 multicenter trial reported that one infusion resulted in an overall remission rate of 81% and high survival rates.[8] The overall remission rate (as the rate of a best overall response of either complete remission or complete remission with incomplete hematologic recovery within 3 months) was 50% and the complete response rate was 32% after a median of 9.4 months of follow-up. Among the 61 patients with complete remission, 20 had a relapse by 12 months. Kymriah later gained approval to treat adult patients with relapsed or refractory large B-cell lymphoma multicenter, after a phase 2 trial enrolled 111 adult patients with diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma.[58] Complete remission occurred in 6 of 14 patients with diffuse large B-cell lymphoma (43%) at 6 months. At a median follow-up of 28 months, 86% of the diffuse large B-cell lymphoma patients and 89% of the lymphoma patients who had a response maintained it.
- Patisiran (Onpattro, ALN-TTR02) was approved to treat polyneuropathy in people with hereditary transthyretin-mediated amyloidosis after a phase 3 randomized trial reported significant treatment-related benefits, including muscle strength, sensation (pain, temperature, numbness), reflexes, and autonomic symptoms (blood pressure, heart rate, digestion).[73]

The FDA's Regenerative Medicine Advanced Therapy program provides support and assistance for the production of gene therapies that treat serious or life-threatening conditions and address unmet medical needs.[86] In June 2018, the Center for Biologics Evaluation and Research granted the Regenerative Medicine Advanced Therapy designation to 24 products.[86] Notably, as of January 2019, the FDA has more than 700 active gene therapy investigational new drug applications.[87] The FDA recently announced that it plans to provide policy guidance to accelerate approval to accommodate the rapidly expanding field of new gene therapy development.[88]

Key Question 2b. Are any additional accompanying resources or technologies required?

Prior to any gene therapy that requires injection delivery, patients may be given prophylactic antibiotics. CAR-T interventions require leukapheresis, which is a procedure to separate white blood cells from blood. Leukapheresis is needed to remove and separate patients' T cells so they can be modified. Some autologous cell interventions also require leukapheresis depending on which type of cell is removed from the patient. For example, in some cancer studies tumor biopsy or resection is required. Genetically modified oncolytic viral therapy can require craniotomy to remove tumor cells. Antisense therapies can require lumbar puncture, lipoprotein apheresis, or bone marrow transplant. An antisense oligodeoxynucleotide has been used to inhibit *c-myb* gene expression in autografted bone marrow for allograft-ineligible chronic myelogenous leukemia patients.[89]

Key Question 2c. What is the current state of adoption in practice and settings?

Gene therapy is available through standard care when the intervention is approved. For example, Yescarta is available to patients at authorized treatment centers. Gene therapy is also available by participation in a clinical trial. However, as the field is rapidly advancing, more treatments will likely be approved for use beyond trials.

Key informants noted several challenges facing adoption of gene therapies and the current gaps in our understanding of this question. For example, current approaches to payer approvals are based on population estimates for risk management and not on personalized medicine. Risks can be spread across populations but less so when patients' specific disease traits (eg, genetics) are used to develop and deliver tailored treatment.

Further, even though high upfront prices may be offset by downstream health benefits, covering the expensive gene therapies may not be sustainable with current insurance structures. The Centers for Medicare and Medicaid Services (CMS) will reimburse hospitals $400 000 for Yescarta and $500 000 for Kymriah for inpatient treatment. The patient is responsible for a $1340 deductible for inpatient treatment per benefit period.[90] However, when patients are treated in outpatient settings, they could be responsible for 20% ($79 000-$100 000). How other payers will handle payment is less clear. Payers and manufacturers are considering alternative payment scenarios that include staggered or long-term payment agreements and/or linking payment to patient outcomes.[91] As part of CMS's national coverage determination analysis of CAR-T, the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) met (in August 2018) to discuss whether and how existing patient-reported outcome (PRO) assessment tools should be incorporated into future clinical studies. While there was confidence in specific tools to measure PROs, some MEDCAC members voiced concern about the difficulty of collecting and interpreting such data.[92] **In February 2019, the** CMS proposed to cover FDA-approved CAR-T-cell therapy when the treatment is in a CMS-approved registry or clinical study, and patients are monitored for at least 2 years posttreatment.[93] CMS has not announced a decision, as of the writing of this report.

Key Question 2d. What are the operator factors, such as training and staffing?

Operator factors relate to the people and the processes by which they deliver gene therapy to patients. The manufacturing process is a major operator factor in the success of gene therapy. The clinical production process is challenged by consistent process control and the scale that is needed for commercial use. For example, limited cell line availability and lack of manufacturing capacity hinder the consistent production and characterization of cellular products. In July 2018, the FDA published guidance on what manufacturing information is needed to support the clinical development of investigational human gene therapies.[94] The need for rigorous and high-quality biomanufacturing processes increases the demands on staff training and hiring. Staffing challenges may limit commercial-scale production of gene therapies more so than facility availability.[95]

Other factors related to delivery include the need for additional infrastructure and treatment centers designed to deliver specific gene therapies. As described above, key informants also noted that the current health care system is not yet structured to deliver gene therapy, in part because providers are not fully aware of new nonstandard gene therapies.

Ongoing Premarket and Postmarket Gene Therapy Studies

Ongoing Trial Characteristics

Ongoing trials are those that have completed recruitment but have not yet published results. We identified 46 ongoing studies that are evaluating ongoing CAR-T, autologous cell, ZFN, antisense, RNAi, or oncolytic viral therapy/herpes simplex virus type 1 gene therapy interventions. The evidence tables provide details of all identified trials.

Table 4 provides an overview of the 6 currently ongoing trials evaluating antisense interventions. The antisense approaches are being evaluated for cardiovascular and muscular conditions.

Table 4. Ongoing Antisense Trials

Indication Author Trial Number Study Design Estimated Completion	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured
Cardiovascular disease Ionis Pharmaceuticals, 2014[96] Single-arm trial, N: 135 Completion date: 09/2022	Age group: Adults Familial amyloid polyneuropathy Treatment enrollment: None Treatment requisite: None	IONIS-TTR prescription No comparison group Follow-up: 60	Visual acuity; light detection; neuropathy impairment score; Norfolk Quality of Life Diabetic Neuropathy Questionnaire; polyneuropathy disability score; safety
Cardiovascular disease Akcea Therapeutics[97] NCT03544060 Single-arm trial, N: 100 Completion date: expanded access	Age group: Adults Familial chylomicronemia syndrome Treatment enrollment: If patients participated in the APPROACH trial, they must have completed the open-label extension trial for 1 year or longer; all other patients must be approved by Akcea on an individual basis. Treatment requisite: Patients of child-bearing potential use contraception or abstain from sexual activity during the study.	Volanesorsen (Waylivra, ISIS 304801) No comparison group Follow-up: 0	None

Indication Author Trial Number Study Design Estimated Completion	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured
Muscular conditions Sarepta Therapeutics[98] NCT02420379 Controlled trial, N: 40 Completion date: 01/2019	Age group: Children Duchenne muscular dystrophy Treatment enrollment: None Treatment requisite: None	Eteplirsen No treatment Follow-up: 24	Number of patients with treatment-emergent adverse events; change from baseline in percentage of dystrophin-positive skeletal muscle fibers
Muscular conditions Sarepta Therapeutics[99] NCT02255552 Controlled trial, N: 110 Completion date: 05/2019	Age group: Children Duchenne muscular dystrophy Treatment enrollment: None Treatment requisite: None	Eteplirsen No treatment Follow-up: 24	Change in 6-minute walk test distance from baseline; percentage of dystrophin-positive fibers; maximum inspiratory/expiratory pressure percentage predicted (Maximal Inspiratory Pressure/Maximal Expiratory Pressure % predicted)
Muscular conditions Biogen[100] NCT02865109 Trial (multiple groups), N: NR Completion date: NR (expanded access)	Age group: Children and adults Spinal muscular atrophy Treatment enrollment: NR Treatment requisite: NR	Nusinersen No comparison group Follow-up: NR	Safety

Indication Author Trial Number Study Design Estimated Completion	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured
Muscular conditions Biogen[101] NCT02462759 RCT, N: 21 Completion date: 04/2019	Age group: Children and adults Spinal muscular atrophy Treatment enrollment: None Treatment requisite: None	Nusinersen No treatment Follow-up: 30	Number of participants with adverse events and serious adverse events; change from baseline in clinical laboratory parameters; change from baseline in electrocardiograms; change from baseline in vital signs; change from baseline in neurological examination outcomes; activated partial thromboplastin time; partial thromboplastin time; international normalized ratio; urine total protein; change from baseline in head circumference; change from baseline in chest circumference; change from baseline in arm circumference; change from baseline in weight for age; change from baseline in weight for length; change from baseline in head to chest circumference ratio; change from baseline in body length; Nusinersen plasma concentration; Nusinersen cerebrospinal fluid concentration; Nusinersen plasma antibodies

Abbreviation: RCT, randomized controlled trial; NR, not reported

Table 5 documents 10 ongoing autologous cell trials. The autologous approaches are primarily being tested for cancer indications.

Table 5. Ongoing Autologous Cell Trials

Indication Author Trial Number Study Design Estimated Completion	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured
Blood disorders Irccs San Raffaele[102]; Aiuti, 2009[103]; Aiuti, 2007[104] NCT02453477 Trial (multiple groups), N: 10 Completion date: 08/2019	Age group: Children and adults Beta-thalassemia Treatment enrollment: None Treatment requisite: None	Autologous hematopoietic stem cells genetically modified with GLOBE lentiviral vector encoding for the human beta-globin gene Other: Group divided by ages Follow-up: 24	Overall survival; achievement of hematological engraftment; safety of the administration of autologous hematopoietic stem cells transduced with lentiviral vector-GLOBE; short-term safety and tolerability of the different conditioning regimens; overall safety and tolerability measured by AE recording; polyclonal engraftment; reduction in transfusion frequency up to transfusion independence; transfusion independence; adequate hemoglobin level; adequate engraftment of genetically corrected cells; transgene expression; improvement of health-related quality of life
Cancer The Netherlands Cancer Institute, 2019[105] NCT02654821 Single-arm trial, N: 12 Completion date: NR	Age group: Adults Progressive, inoperable stage IIIc or stage IV melanoma (including ocular or mucosal melanoma) Treatment enrollment: None Treatment requisite: Leukapheresis, nonmyeloablative chemotherapy with cyclophosphamide and fludarabine prior to infusion with transduced T cells	1D3 HM CysTCR retrovirally transduced T cells No comparison group Follow-up: 12	Objective response rate (RECIST 1.1); progression-free survival; induction efficacy of tumor-specific T-cell responses; overall survival; systemic inflammatory cytokine release after treatment

Indication Author Trial Number Study Design Estimated Completion	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured
Cancer Dana-Farber Cancer Institute, 2008[106] NCT00317603 Single-arm trial, N: 20 Completion date: 06/2019	Age group: Adults Metastatic breast cancer Treatment enrollment: All patients must have received at least one regimen of chemotherapy for metastatic disease. Patients with Human Epidermal Growth Factir Receptor 2-positive tumors must have received at least one trastuzumab-based therapy since tumor metastasis. Treatment requisite: After consent, patients must undergo a series of tests to confirm their eligibility. After confirmation, surgery is performed to collect a tumor sample or cancer-containing fluid (material used to generate the vaccine). Once cells are prepared, patients will receive delivery of the vaccination subdermally on day 1, 8, 15, and 29, and then every 2 weeks until the supply of vaccine is exhausted. At week 10, a chest, abdomen, and pelvic CT scan will be performed to measure disease progression. A small subset of patients will undergo Delayed-Type Hypersensitivity assessment, including a skin biopsy.	Autologous breast cancer cells engineered to secrete granulocyte-macrophage colony-stimulating factor No comparison group Follow-up: 36	Time to progression; overall survival

Indication Author Trial Number Study Design Estimated Completion	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured
Cancer Baylor College of Medicine[107] NCT00368082 Single-arm trial, N: 8 Completion date: 07/2031	Age group: Children and adults Lymphoma Treatment enrollment: None Treatment requisite: Tumor biopsy	TGFbeta-resistant LMP-specific CTLs No comparison group Follow-up: 180	Safety and maximum tolerated dose of 2 IV injections of autologous/syngeneic or allogeneic TGFb-resistant LMP-specific cytotoxic T-lymphocytes (CTLs); survival and immune function of TGFbeta-resistant LMP-specific CTLs; determine antiviral and antitumor effects of TGFbeta-resistant LMP-specific CTL
Immune deficiency NHS Foundation Trust Great Ormond Street Hospital for Children, 2018[108] NCT01380990 Single-arm trial, N: 10 Completion date: 12/2018	Age group: Children Adenosine Deaminase (ADA)-deficient severe combined immunodeficiency (SCID) Treatment enrollment: None Treatment requisite: Not reported	EF1alphaS-ADA lentiviral vector was transduced patient CD34+ cells No comparison group Follow-up: 36	Overall survival; reduction in frequency of infections; long-term immune reconstitution
Immune deficiency Orchard Therapeutics[109] NCT02999984 Single-arm trial, N: 10 Completion date: 06/2020	Age group: Children ADA-severe combined immunodeficiency disease Treatment enrollment: None Treatment requisite: None	Infusion of autologous cryopreserved EFS-ADA LV CD34+ cells No comparison group Follow-up: 24	Overall survival; event-free survival
Immune deficiency University of Pennsylvania[110] NCT01787994 Trial (multiple groups), N: 10 Completion date: 12/2017	Age group: Adults HIV Treatment enrollment: None Treatment requisite: None	MazF-T Other: Same treatment Follow-up: 36	Number of participants with adverse events following a single dose of MazF transduced cells; feasibility; antiviral effect of infusion

Indication Author Trial Number Study Design Estimated Completion	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured
Immune deficiency David Williams, 2018[111]; Hacein-Bey-Abina, 2014[112]; Clarke, 2018[113] NCT01129544 Single-arm trial, N: 8 Completion date: 03/2033	Age group: Children and adults Severe combined immunodeficiency, X-linked (SCID-X1) Treatment enrollment: None Treatment requisite: Each patient undergoes a bone marrow harvest, busulfan conditioning, and one-time infusion of his or her transduced bone marrow cells.	pSRS11.EFS.IL2RG.pre No comparison group Follow-up: 180	Posttransfusion CD3+ T-cell count; molecular characterization of gene transfer; ability to have an antibody response to vaccination; normalized nutritional status, growth, and development
Immune deficiency City of Hope Medical Center[114] NCT01961063 Single-arm trial, N: 3 Completion date: 06/2031	Age group: Adults Non-Hodgkin lymphoma in HIV-positive patients Treatment enrollment: None Treatment requisite: Collection of peripheral blood progenitor cells by filgrastim/plerixafor mobilization; patients received intravenous busulfan 2 days prior to infusion of transduced hematopoietic progenitor cells; patients of child-bearing potential must have used contraception prior to entering the study through 6 months after the study was completed; if needed, patients were on a prophylactic regimen for Pneumocystis carinii pneumonia	rHIV7-shI-TAR-CCR5RZ-transduced hematopoietic progenitor cells No comparison group Follow-up: 60	Time to absolute neutrophil count ≥ 500/uL; time to platelet recovery to ≥ 50 000/uL; PCR detection of vector-marked PBMC/marrow cells; PCR detection of RNA transgenes in lineage-specific progeny of transduced cells; ATI effect on HIV markers and CD4 count; number of transduced HSPC for engraftment
Immune deficiency University of Pennsylvania[115] NCT02388594 Trial (multiple groups), N: 15 Completion date: 02/2019	Age group: Adults HIV Treatment enrollment: None Treatment requisite: Cyclophosphamide	ZFN Modified CD4+ T Cells Other: ZFN-modified CD4+ T Cells and Cyclophosphamide Follow-up: 6	Number of participants with adverse events

Abbreviation: AE, adverse event; HIV, human immunodeficiency virus; ZFN, zinc finger nuclease

We also identified 17 ongoing CAR-T trials targeting a variety of cancer indications, as shown in Table 6.

Table 6. Ongoing CAR-T Trials

Indication Author Trial Number Study Design Estimated Completion	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured
Cancer National Cancer Institute[116] NCT02659943 Single-arm trial, N: 27 Completion date: 12/2021	Age group: Adults Lymphoma, B cell and lymphoma, non-Hodgkin Treatment enrollment: B-cell cancer not controlled by other therapies Treatment requisite: Apheresis, cyclophosphamide, and fludarabine	Anti-CD19-CAR-T cells No comparison group Follow-up: 12	Determine the safety and feasibility of administering T cells expressing a novel fully human anti-CD19 chimeric antigen receptor (CAR).
Cancer Roger Williams Medical Center[117] NCT02850536 Single-arm trial, N: 5 Completion date: 08/2018	Age group: Adults Adenocarcinoma and liver metastases Treatment enrollment: None Treatment requisite: Diagnostic angiography	Anti-CEA CAR-T cells No comparison group Follow-up: 3	Safety of CAR-T cell hepatic artery infusions delivered using the Surefire Infusion System (SIS) as measured by the number of participants with adverse events; radiographic treatment response by MRI; radiographic treatment response by PET; CAR-T detection in liver tumors; CAR-T detection in normal liver tissue; CAR-T detection in extrahepatic sites; serum cytokine levels; CEA level; tumor biopsy; safety of Direct Intrapancreatic CAR-T Retrograde Venous Infusions delivered using the SIS
Cancer Roger Williams Medical Center[118] NCT02416466 Single-arm trial, N: 8 Completion date: 11/2016	Age group: Adults Liver metastases Treatment enrollment: None Treatment requisite: None	Anti-CEA CAR-T cells No comparison group Follow-up: 4	Treatment response; serum cytokine levels; CAR-T detection in liver tumors, normal liver, and extrahepatic sites

Indication Author Trial Number Study Design Estimated Completion	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured
Cancer Seattle Children's Hospital[119] NCT01683279 Single-arm trial, N: 18 Completion date: 01/2031	Age group: Children and adults Relapsed leukemia Treatment enrollment: None Treatment requisite: None	Autologous CD19 CAR+ EGFTt + T cells No comparison group Follow-up: 2	Number of participants with adverse events; persistence of the CD19 CAR+ T cells; anti-leukemic activity of the CD19 CAR+ T cells
Cancer Fred Hutchinson Cancer Research Center[120] NCT02408016 Trial (multiple groups), N: 20 Completion date: NR	Age group: Adults Stage III to IV non–small cell lung cancer or mesothelioma Treatment enrollment: None Treatment requisite: Aldesleukin, cyclophosphamide, and therapeutic conventional surgery	Autologous WT1-TCRc4 gene-transduced CD8-positive TCM/TN lymphocytes No comparison group Follow-up: 180	Evidence and nature of toxicity; feasibility of naive T-cell (TN) and central memory T-cell (TCM) subsets; persistence of transduced T cells; frequency of transferred T cells at biopsied tumor sites between the T-cell (TN) and memory T-cell (TCM) groups; functional capacity of transferred cells, measured by production of intracellular cytokines; time to progression based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria and RECIST 1.1 mesothelioma modified
Cancer University of Pennsylvania[121] NCT02640209 Single-arm trial, N: 20 Completion date: 10/2019	Age group: Adults Relapsed or refractory chronic lymphocytic leukemia Treatment enrollment: None Treatment requisite: Confirmed diagnosis of CEA+ adenocarcinoma and liver metastases	CART 19 No comparison group Follow-up: 26	Number of adverse events
Cancer University of Pennsylvania[122] NCT02794246 Single-arm trial, N: 25 Completion date: 12/2020	Age group: Adults Multiple myeloma Treatment enrollment: "RVD" therapy (combination therapy with lenalidomide, bortezomib, and dexamethasone) Treatment requisite: None	CART19 cells No comparison group Follow-up: 36	Progression-free survival

Indication Author Trial Number Study Design Estimated Completion	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured
Cancer First Affiliated Hospital of Wenzhou Medical University[123] NCT03497819 Single-arm trial, N: 10 Completion date: 10/2020	Age group: Adults Pancreatic cancer Treatment enrollment: None Treatment requisite: None	CARTmeso CART19 No comparison group Follow-up: 3	Percentage of adverse events; overall response rate
Cancer China Southwest Hospital[124] NCT02846584 Single-arm trial, N: 100 Completion date: 12/2019	Age group: Children and adults Leukemia Treatment enrollment: Exhausted all prior treatment options Treatment requisite: Chemotherapy	CD19 or CD20 CAR-T cells bridging HSCT No comparison group Follow-up: 6	Overall survival rate of patients treated with anti-CD19 or anti-CD20 CAR-T cells; treatment response rate of anti-CD19 CAR-T-cell infusion; number of patients with adverse events
Cancer Memorial Sloan Kettering Cancer Center[125] NCT01840566 Single-arm trial, N: 17 Completion date: 04/2019	Age group: Adults Non-Hodgkin lymphoma Treatment enrollment: None Treatment requisite: High-dose chemotherapy and autologous stem cell transplantation	Chimeric antigen receptor modified T cells No comparison group Follow-up: 24	Maximum tolerated dose; safety; 2-year progression-free survival; overall survival

Indication Author Trial Number Study Design Estimated Completion	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured
Cancer Novartis Pharmaceuticals[126] NCT02228096 Single-arm trial, N: 64 Completion date: 12/2022	Age group: Adults Leukemia Treatment enrollment: None Treatment requisite: None	CTL019 No comparison group Follow-up: 6	Overall remission rate; percentage of patients who achieve remission without stem cell transplantation; relapse-free survival; event-free survival; overall survival; response as a function of baseline tumor burden (tumor load); CTL019 transgene levels by qPCR CTL019 cells by in qPCR blood and bone marrow; prevalence and incidence of immunogenicity to CTL019; frequent monitoring of concentrations of soluble immune factors in blood; lymphocyte subsets of B and T cells and description of associated safety events; persistence of CTL019 in blood, bone marrow, and CSF; maximum extent of expansion of CTL019 in blood
Cancer Novartis Pharmaceuticals[127] NCT02445248 Single-arm trial, N: 116 Completion date: NR	Age group: Adults Relapsed or refractory diffuse large B-cell lymphoma Treatment enrollment: None Treatment requisite: Apheresis and contraception (women of child bearing potential and all male patients)	CTL109; tisagenlecleucel; Kymriah No comparison group Follow-up: 60	Overall response rate; time to response; duration of overall response; event-free survival; progression-free survival; overall survival; in vivo cellular pharmacokinetic profile of CTL019 transduced cells into target tissues; incidence of immunogenicity to CTL019

Indication Author Trial Number Study Design Estimated Completion	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured
Cancer Southwest Hospital China[128] NCT02737085 Single-arm trial, N: 40 Completion date: 12/2019	Age group: Children and adults Diffuse large B-cell lymphoma Treatment enrollment: None Treatment requisite: None	D19-targeted and CD20-targeted CAR-T cell therapy No comparison group Follow-up: 24	Adverse events that are related to treatment
Cancer Gary Archer[129] NCT02664363 Trial (multiple groups), N: 3 Completion date: 09/25/19	Age group: Adults Glioblastoma and gliosarcoma Treatment enrollment: None Treatment requisite: None	EGFRvIII CAR-T cells No comparison group Follow-up: 18	Maximally tolerated dose; dose-limiting toxicity
Cancer University of Pennsylvania, 2021[130] NCT03054298 Trial (multiple groups), N: 30 Completion date: 03/2021	Age group: Adults Lung adenocarcinoma, ovarian cancer, peritoneal carcinoma, fallopian tube cancer, mesotheliomas pleural, and mesothelioma peritoneum Treatment enrollment: Chemotherapy Treatment requisite: None	Hu-CART meso cells No comparison group, Other: CAR-T + cyclophosphamide or chemotherapy Follow-up: 24	Clinical antitumor effect by standard criteria (RECIST); clinical antitumor effect by standard criteria (modified RECIST for mesothelioma); progression-free survival; progression overall survival
Cancer Baylor College of Medicine, 2015[131] NCT01822652 Trial (multiple groups), N: 11 Completion date: 10/2030	Age group: Children and adults Neuroblastoma Treatment enrollment: Pembrolizumab Treatment requisite: None	iC9-GD2 T cells No comparison group, Other: iC9-GD2 T cells + Cytoxan + Fludara + Keytruda Follow-up: 180	Expansion and functional persistence of iC9-GD2 T cells; time to progression of disease; change in serum cytokine and chemokine levels
Cancer University of Pennsylvania[132] NCT02388828 Single-arm trial, N: 10 Completion date: 03/2030	Age group: Adults Cancer Treatment enrollment: Received lentiviral modified T cells engineered to express an anti-mesothelin scFv chimeric antigen receptor Treatment requisite: None	Lentiviral-based CART meso therapy No comparison group Follow-up: 180	Number of adverse events

Abbreviation: CAR-T, chimeric antigen receptor T cell

Ten ongoing RNAi trials are described in Table 7; the trials target a variety of clinical indications.

Table 7. Ongoing RNAi Trials

Indication Author Trial Number Study Design Estimated Completion	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured
Cancer Amgen, 2019133 NCT02211131 RCT, N:150 Completion date: 04/2022	Age group: Adults Completely resectable stage IIIB, IIIC, or IVM1a melanoma Treatment enrollment: None Treatment requisite: None	Talimogene Other: Surgery + adjuvant/radiotherapy Follow-up: 24	Recurrence-free survival; histopathological tumor-free margin (R0) surgical resection; pathological complete response; local recurrence-free survival and distant metastases-free survival; overall survival; overall response
Cancer M.D. Anderson Cancer Center134 NCT02658812 Single-arm trial, N: 35 Completion date: 08/2021	Age group: Adults Breast cancer Treatment enrollment: None Treatment requisite: None	Talimogene laherparepvec No comparison group Follow-up: 5	Overall response rate defined as the percentage of complete response, partial response in overall patients; overall disease control rate; local overall response rate; local disease control rate; progression-free survival; overall survival; incidence of adverse events

Abbreviations: AEs, adverse events; mL, milliliter; RCT, randomized controlled trial

Table 8 documents 1 ZFN trial and 2 trials currently testing Talimogene laherparepvec in cancer patients.

Table 8. Ongoing ZFN and Genetically Modified Oncolytic Viral Therapy/Herpes Simplex Virus Type 1 Trials

Indication Author Trial Number Study Design Estimated Completion	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured
ZFN			

Indication Author Trial Number Study Design Estimated Completion	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured
Immune deficiency Sangamo Therapeutics, 2018[135] NCT02225665 Trial (multiple groups), N: 12 Completion date: NR	Age group: Adults HIV Treatment enrollment: None Treatment requisite: Cyclophosphamide is administered 2 days prior to the first infusion	SB-728mR-T No comparison group, Other: In combination with cyclophosphamide conditioning Follow-up: 12	Measurement of pentamer PCR for engraftment efficiency following cyclophosphamide conditioning; plasma HIV-1 RNA levels following HAART interruption; change in CD4+ T-cell counts in peripheral blood
Oncolytic Viral			
Cancer Amgen, 2019[133] NCT02211131 RCT, N: 150 Completion date: 04/2022	Age group: Adults Completely resectable stage IIIB, IIIC, or IVM1a melanoma Treatment enrollment: None Treatment requisite: None	Talimogene Other: Surgery + adjuvant/radiotherapy Follow-up: 24	Recurrence-free survival; histopathological tumor-free margin (R0) surgical resection; pathological complete response; local recurrence-free survival and distant metastases-free survival; overall survival; overall response
Cancer M.D. Anderson Cancer Center[134] NCT02658812 Single-arm trial, N: 35 Completion date: 08/2021	Age group: Adults Breast cancer Treatment enrollment: None Treatment requisite: None	Talimogene laherparepvec No comparison group Follow-up: 5	Overall response rate defined as the percentage of complete response, partial response in overall patients; overall disease control rate; local overall response rate; local disease control rate; progression-free survival; overall survival; incidence of adverse events

Abbreviations: HIV, human immunodeficiency virus; RCT, randomized controlled trial; ZFN, Zinc finger nuclease

Key Question 3a. What are indication/patient inclusion criteria in ongoing trials?

Across the identified ongoing trials, cancer conditions are the most common indication (48%).[105-107,116-134] The other indications are immune deficiency (15%),[108-111,114,115,135] cardiovascular disease (15%),[96,97,142-146] muscular conditions (9%),[102,147-149] and 2 other indications (4%; alpha 1-antitrypsin deficiency[150] and healthy adults or primary hyperoxaluria type 1[151]).

Patient inclusion criteria differ by indication and therapy. For example, some of the cancer studies require patients to have failed prior surgery or chemotherapy.[106] One trial in patients with

cardiovascular disease selected patients who were on the maximum tolerable statin dose.[143] The remaining ongoing trials largely did not describe eligibility criteria.

Patient populations are mostly adult patients (67%)[96,97,105,106,110,114-118,120-123,125-127,129,130,132-135,142-146,148-150]; however, 9% of the studies are testing interventions specifically for children[98,99,108,109] and 24% of the studies are testing interventions in both children and adults.[100-102,107,111,119,124,128,131,147,151]

Key Question 3b. What are the types of interventions in ongoing trials?

The 46 ongoing trials are testing predominantly CAR-T (37%),[116-132] autologous cell (22%),[102,105-111,114,115] RNAi (22%),[142-151] and antisense (13%)[96-101] gene therapy approaches. We also identified a small number of trials testing oncolytic viral therapy/herpes simplex virus type 1 (4%)[133,134] and a ZFN (2%)[135] approach.

Key Question 3c. What are the study designs/size in ongoing trials?

The most common study design in currently ongoing studies is a single-arm trial (57%),[96,97,105-109,111,114,116-119,121-128,132,134,144,148,149] followed by clinical trials with multiple study arms in which patients are treated with different doses of the same intervention (22%),[100,102,110,115,120,129-131,135,146] randomized controlled trials (RCTs) (17%),[101,133,142,143,145,147,150,151] and controlled trials with an untreated control group (4%).[98,99]

On average, the sample size in ongoing trials is 126 (standard deviation = 335). The sample sizes vary widely across trials and conditions and range from only 3 to 1617 enrolled participants. The 2 trials with only 3 patients were treating very rare conditions: glioblastoma/gliosarcoma[129] and non-Hodgkin lymphoma in HIV-positive patients.[114] The studies with the largest sample sizes are treating cardiovascular disease.[142,143]

Key Question 3d. What are the comparators in ongoing trials?

Most ongoing trials have no comparator. All of the clinical trials with multiple study arms compare groups of patients receiving different doses of the tested intervention. The RCTs compare gene therapy to either placebo,[142,143,145,147,150,151] no treatment,[101] or surgery with adjuvant radiotherapy.[133] We identified 2 ongoing nonrandomized trials that included an untreated control group.[98,99]

Key Question 3e. What are the prior/concurrent treatments in ongoing trials?

More than half of the ongoing trials did not describe concurrent or prior treatment (54%).[96,98-102,107-110,117-119,121-124,126,128-134,142-144,146] In several trials, women of child-bearing age must take contraception[97,127,147,149-151] and male patients must use a condom with spermicide.[145] Other concurrent treatments in ongoing trials include cell collection,[114] apheresis,[127] antibiotics,[115,116,135] and leukapheresis.[105]

Key Question 3f. What is the length of follow-up in ongoing trials?

Length of follow-up planned for currently ongoing trials is an average of 38.5 months (median = 24 months and standard deviation = 53 months) and ranges from less than 2 to 180 months with large variation by indication and trial. Ongoing immune deficiency trials have the longest follow-up, with a mean of 51 months, whereas the trials treating cancer and muscular conditions describe about 48 and 26 months of follow-up across studies, respectively. Cardiovascular and blood disorder trials are planning to follow patients for about 20 months on average.

Key Question 3g. What are the outcomes measured in ongoing trials?

The evidence tables above show the large variety of planned outcomes. Health-related outcomes vary by the type of indication and many are study specific. For example, rate of hemin administration is being measured for a gene therapy intervention in acute hepatic porphyria patients.[147] In trials testing interventions to treat cancer, tumor progression and remission is a common monitored outcome.[105,124,126,127] Across all studies, safety, toxicity, overall survival, improved health status, and disease progression are examples of other commonly measured outcomes.

Current Evidence Supporting Gene Therapy

Tables A1 to A6 in Appendix F document in detail each of the 256 completed studies that have published results and that tested CAR-T, autologous cell, ZFN, antisense, RNAi, or oncolytic viral therapy/herpes simplex virus type 1 gene therapy interventions.

Published Trials Characteristics

Table 9 summarizes the evidence according to indication and study design for the gene therapies. All trials in the table have reported at least partial results. The most common types of therapy were antisense (32%), autologous cell (31%), and CAR-T (21%). The other less common interventions were studies that tested oncolytic viral therapy/herpes simplex virus type 1 (9%), RNAi (6%), and ZFN (0.4%).

Table 9. Summary of Published Antisense, Autologous Cell, CAR-T, Genetically Modified Oncolytic Viral Therapy/Herpes Simplex Virus Type 1, RNAi, and ZFN

Indication	Study Design by Indication
Blood disorders (eg, hemophilia) (0.8%, n = 2)[152,153]	Controlled trial (50%, n = 1)[153] Trial (multiple groups) (50%, n = 1)[152]
Cancer (62%, n = 159)[7,8,58,66,82,89,154-306]	Single-arm trial (53%, n = 83)[7,8,58,66,89,156,158,159,161,167-169,173,175-179,181-187,191,194-196,198-201,205,207-210,213,215-217,219,220,222-224,226-229,233,234,236,237,239,240,242,244,245,247,249,255,259,261-272,275,282,283,285,291,303,304] Trial (multiple groups) (38%, n = 61)[154,155,157,160,162-166,170-172,174,180,188-190,192,193,197,202-204,206,211,212,214,218,221,225,231,232,235,238,246,248,253,254,256-258,260,278,279,281,284,288-290,292-295,297-302,305,306] Trial with untreated control group (3%, n = 5)[230,280,286,287,296] RCT (6%, n = 10)[82,241,243,250-252,273,274,276,277]
Cardiovascular disease (10%, n = 26)[72,78-81,307-330]	Single-arm trial (12%, n = 3)[72,308,320] Trial (multiple groups) (12%, n = 3)[307,314,323] Trial with untreated control group (4%, n = 1)[325] RCT (73%, n = 19)[78-81,309-313,315-319,321,322,324,326-330]
Immune deficiency (11%, n = 27)[331-357]	Single-arm trial (63%, n = 17)[331-334,338,339,341,346-355] Trial (multiple groups) (19%, n = 5)[335,342,344,356,357] Trial with untreated control group (4%, n = 1)[337] RCT (15%, n = 4)[336,340,343,345]
Inflammatory disorders (2%, n = 5)[358-362]	Single-arm trial (20%, n = 1)[358] Trial (multiple groups) (20%, n = 1)[362] RCT (60%, n = 3)[359-361]
Muscular conditions (5%, n = 14)[83-85,363-373]	Single-arm trial (14%, n = 2)[367,373] Trial (multiple groups) (50%, n = 7)[85,363,364,368-370,372] Trial with untreated control group (7%, n = 1)[83] RCT (29%, n = 4)[84,365,366,371]
Neurodegenerative disorders (2%, n = 4)[374-377]	Single-arm trial (50%, n = 2)[374,377] Trial (multiple groups) (25%, n = 1)[375] RCT (25%, n = 1)[376]

Indication	Study Design by Indication
Ocular disorders (0.8%, n = 2)[379,380]	Trial with untreated control group (50%, n = 1)[380] RCT (50%, n = 1)[379]
Respiratory conditions (0.4%, n = 1)[381]	RCT (100%, n = 1)[381]
Other (6%, n = 16)[71,73,382-395]	Single-arm trial (19%, n = 3)[384,385,391] Trial (multiple groups) (12%, n = 2)[386,389] Trial with untreated control group (6%, n = 1)[382] RCT (63%, n = 10)[71,73,383,387,388,390,392-395]

Abbreviations: RCT, randomized controlled trial

Key Question 4a. What are the indication/patient inclusion criteria in published studies?

Across all therapies, the most common indication was cancer (62%), followed by cardiovascular disorders (10%), immune deficiency (11%), muscular conditions (5%), inflammatory disorders (eg, arthritis) (2%), neurodegenerative disease (2%), ocular disorders (0.8%), blood disorders (eg, hemophilia) (0.8%), and respiratory conditions (eg, cystic fibrosis) (0.4%). Sixteen studies (6%) tested interventions across indications that were categorized as "Other," and these included transthyretin-mediated familial amyloid polyneuropathy, diabetes, overweight/obesity, asthma, and vaccination studies against Ebola.

More than half of the studies had no specific inclusion criteria regarding prior treatment (59%). However, among the studies that did, eligibility criteria required that patients had to have severe disease. For example, in multiple studies patients had to be refractory to standard treatment.[7,256,283] Of the studies, 76% were conducted in adult patient populations. The remaining studies tested interventions in children alone (12%) or in children and adults (9%), or the patient population was unclear (3%).

Key Question 4b. What are the types of interventions in published studies?

The 256 completed trials have tested predominantly antisense (32%), autologous cell (31%), CAR-T (21%), genetically modified oncolytic viral therapy/herpes simplex virus type 1 (9%), and RNAi (6%) interventions. We identified one study that tested a ZFN (0.4%) approach. The evidence tables in Appendix F provide more details for all included studies.

Key Question 4c. What are the study designs/size in published studies?

The 2 most common study designs in ongoing studies were single-arm trials (43%) and trials with multiple groups that were treated with different levels of the same therapy (32%). RCTs composed 21% of the completed or published studies, and only 4% were controlled trials. On average, the sample size was 42 (standard deviation = 92) and ranged from 1 to 1022. The 8 trials with only 1 patient were treating cancers,[176,229,247,291,396] such as multiple myeloma,[176] SCID,[347] or skin disorders,[384,393] whereas the studies with the largest sample sizes were treating prostate cancer.[251,252]

Key Question 4d. What are the comparators in published studies?

Studies with no comparator were the most common in our sample (74%). Other studies compared the gene therapy with placebo (17%), usual care (4%), healthy volunteers (0.4%), no treatment (0.4%), or another type of comparator, such as unmodified T cells.[343]

Key Question 4e. What are the prior/concurrent treatments in published studies?

Most studies reported no other treatment that was concurrent with the gene therapy (58%). However, when concurrent treatments were needed, they differed by indication. For example, concurrent chemotherapy[168,225] and interleukin 2[279,286,295] were required for some cancer gene therapies.[397-408] Leukapheresis was required for cancer treatments with CAR-T and autologous cell therapy.[7,8,58,154,159,162,166,175,194,281,283,285,287,289-292,302,306] Other examples of concurrent therapies included mobilization of peripheral blood progenitor cells with the cytokine granulocyte colony-stimulating factor in autologous cell therapies.[183,342]

Key Question 4f. What is the length of follow-up in published studies?

Length of follow-up was, on average, 23 months (median = 12 months and standard deviation = 35 months) and ranged from 1 to 180 months with variation by indication. Immune deficiency trials had the longest follow-up, of a mean of 38 months. Cancer trials followed patients for about 26 months whereas blood disorder, muscular condition, and ocular trials had about 15 months of follow-up. The trials treating cardiovascular disease, inflammatory disorders, and neurodegenerative disorders had relatively shorter follow-up, with averages of 6, 3, and 6 months, respectively. The group of trials that were categorized as "Other" indication had about 19 months of follow-up.

Key Question 4g. What are the outcomes measured in published studies?

The evidence tables in Appendix F document all outcomes measured and the authors' conclusion for the included trials. All identified trials measured safety and toxicity aspects. Health-related outcomes depended on the trial (some studies concentrated on safety alone) as well as the type of indication. While a quantitative summary of results in the form of a meta-analysis was beyond the scope of this report, below we describe reported positive clinical benefit versus suggestive, or no evidence of benefit, based on authors' summary of the findings.

Studies testing gene therapy in blood disorders (n = 2) measured hemoglobin and transfusions. Both studies (100%) concluded that the intervention had positive clinical health benefits (eg, eliminated the need for transfusion).

Studies assessing treatment of cancer (n = 159) measured tumor response, overall survival, progression-free survival, immune response, death, and quality of life. A minority of studies (20%) reported positive clinical benefit (eg, increased survival). For example, some studies reported complete remission,[58,154,219,225] complete tumor response,[190] and longer survival.[284] Most study authors (66%) indicated only suggestive evidence that warranted future research and 9% reported no clinical or suggestive evidence that the therapy is effective against cancer. Nine studies (6%) did not summarize effectiveness results.

Cardiovascular targeted gene therapy studies (n = 26) measured vital signs, death, amputation, exercise capacity, lipid profiles, 6-minute walk test, and quality of life. Authors in almost half of the studies (48%) indicated positive clinical benefit (eg, increased survival). Suggestive evidence that warranted future research was reported in 38% of studies, and 3% reported no clinical or suggestive evidence that the therapy is effective at reducing cardiovascular disease. Three studies (10%) did not address effectiveness outcomes in their conclusion.

Studies testing gene therapy in immune deficiency (n = 27) collected clinical indicators of immune response. For example, CD4+ and CD8+ T-cell responses were collected in HIV studies.[355,356] Only 23% of studies indicated positive clinical benefit (eg, antibody response). Results were largely described as suggestive where most studies (65%) indicated results that supported future work and 8% reported no clinical or suggestive evidence that the therapy is effective at treating immune deficiency. One study (4%) did not address clinical effectiveness.

Inflammatory disease studies (n = 5) reported outcomes related to inflammation markers, Crohn's disease activity index, and remission. No studies reported positive clinical benefit. Most studies (80%) indicated suggestive effects that support future research, and one study (20%) reported no clinical or suggestive evidence that the therapy is effective at treating inflammatory disease.

Studies of gene therapy in patients with muscular disorders (n = 14) measured muscle transduction and muscle response, 6-minute walk test, motor milestones, and survival. Less than half (40%) of the studies indicated positive clinical benefit (eg, slight improvement in walk test). For example, some studies testing the efficacy of Nusinersen reported better survival and improved motor function.[84,371] More than half (53%) of the studies reported only suggestive effects that support future studies. One study (7%) did not address effectiveness.

Among the studies in patients with neurodegenerative disorders (n = 4), the measured outcomes included lesion progression, neurological deficit, quality of life, motor ratings, timed walking tests, lesions, dystrophin, and survival. Authors in less than half of the studies (40%) reported positive clinical benefit (eg, improved motor skills), while 40% of the studies indicated only suggestive evidence that warranted future research in treating neurological disease. One study (20%) did not address clinical effectiveness.

Studies testing gene therapies for ocular disorders (n = 2) reported visual acuity and function outcomes. Among the 2 studies, 1 (50%) reported a positive clinical benefit (improved visual acuity). The other study (50%) reported only suggestive evidence that warranted future research in treating ocular disorders.

The respiratory disease targeted gene therapy study (n = 1) reported on sputum eosinophil influx asthmatic response. The study (100%) indicated only suggestive evidence that warranted future research.

The studies with otherwise categorized indications (n = 16) measured cardiometabolic markers (eg, hemoglobin A1C (HbA_{1c})), neuropathy impairment, hospitalization, mortality, and pulmonary function. Less than half (38%) of the study authors reported positive clinical benefits (eg, reduced HbA_{1c}). Almost half (44%) reported only suggestive evidence that warranted future research and 2 (13%) reported no clinical or suggestive evidence that the therapy is effective at treating the condition.

Key Question 4h. What are the adverse events in published studies?

Adverse events varied by indication. Below, we report the percentage of studies that reported treatment-related severe (grade 3 or higher) adverse events by indication. Because many studies have no untreated comparator, adverse event rates cannot be computed and the findings have to be interpreted with caution. Moreover, the studies that did not report treatment-related severe adverse events include those that either reported no events or did not address safety in the publication.

- Blood disorders: Serious adverse events (eg, venoocclusive liver disease[152]) were reported in 50% of the studies.
- Cancer: Serious adverse events were reported in 46% of the studies. For example, some patients experienced coma and death,[189] cytokine release syndrome,[171] and raised liver enzymes.[162] Liver enzyme disturbances required treatment termination in one study.[188] In 1% of the studies, adverse events were not discussed.
- Cardiovascular disease: Serious adverse events were reported in 48% of the studies. For example, adverse events included elevated liver enzymes[327] and flu-like symptoms.[313] In 7% of the studies, adverse events were not discussed.
- Immune deficiency: Serious adverse events were reported in 27% of the studies. For example, one death occurred because an opportunistic herpes viral infection became resistant after gene therapy. In 15% of the studies, adverse events were not discussed.

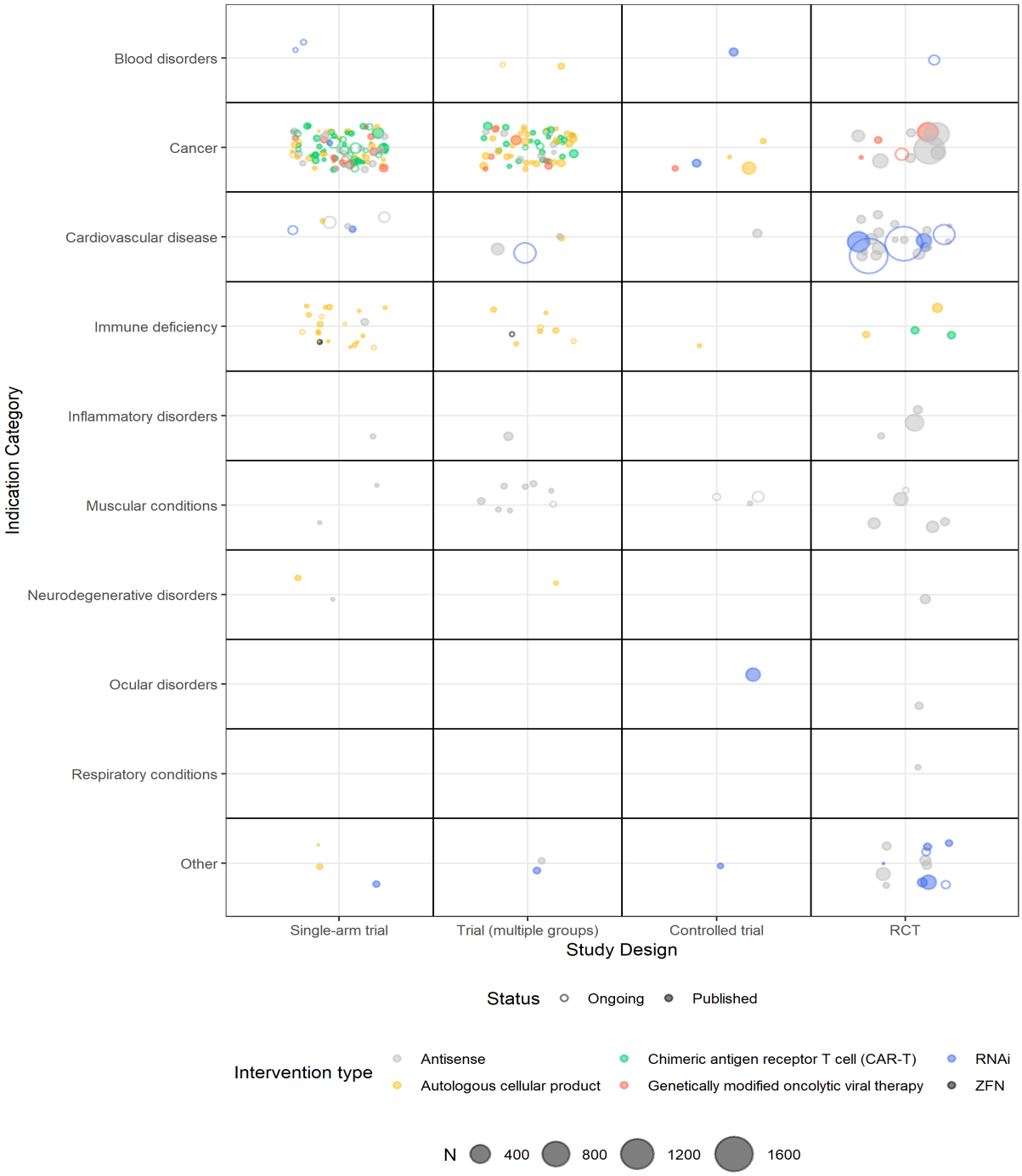
- Inflammatory disease: Serious adverse events were reported in 20% of the studies. For example, one patient died from pulmonary edema.[361] All studies discussed adverse events.
- Muscular conditions: Serious adverse events were reported in 20% of the studies. For example, some patients experienced myocarditis[365] and lumbar puncture syndrome.[370] In 7% of the studies, adverse events were not discussed.
- Neurodegenerative disease: Serious adverse events were reported in 20% of the studies. For example, some patients experienced neutropenia.[374] All studies discussed adverse events.
- Ocular disorders: No serious adverse events were reported across all studies.
- Respiratory conditions: No serious adverse events were reported across all studies.
- Other: Serious adverse events were reported in 31% of the studies. For example, some patients experienced cardiac failure,[73,385] death,[71] neutropenia,[409] and urinary renal damage[390] in the identified trials.

Evidence Map of Ongoing and Completed Trials

The visual evidence map summarizes the evidence supporting CAR-T, autologous cell, ZFN, antisense, RNAi, and oncolytic viral therapy/herpes simplex virus type 1 gene therapy interventions. In Figure 2, we present the 302 trials (reported in 445 publications) as bubbles, where bubble size indicates the number of patients in the study. Evidence maps for each intervention separately are shown in Appendix E. The studies are plotted according to indication category and study design.

The evidence is largest for treating cancer and all types of interventions we reviewed here are well represented in the cancer trials. The study designs for the cancer trials are based largely on single-arm trials or those with multiple groups, and they vary in sample size. Some larger RCT trials test antisense and oncolytic viral therapy/herpes simplex virus type 1 gene therapy interventions in cancer but few controlled trials do. Relatively fewer studies have occurred in patients with blood disorders; muscular conditions; or inflammatory, neurodegenerative, ocular, or respiratory disorders. Many of these studies are based on small sample sizes, likely because the diseases are rare. However, mounting evidence from RCTs evaluates the use of antisense and RNAi interventions in cardiovascular disease, including some large ongoing trials of RNAi interventions. For example, 2 large studies with more than 1500 patients are testing RNAi treatment in patients with atherosclerosis, which is a common condition and the leading cause of vascular disease globally.[142,143,410] The trials treating immune deficiency appear to be largely based on autologous cell interventions in single-arm or multiple group trials, although there are a few RCT trials in immune deficiency patients, including one CAR-T trial. A few antisense trials with small patient sample sizes have tested treatment of muscular conditions and neurodegenerative disorders. While these trials are mostly based on single-arm and multiple groups, a few RCTs have been completed. We identified very few trials in blood disorders and they tested or are testing autologous cell and RNAi interventions. Among the few trials in patients with ocular disorders or respiratory conditions, the interventions are RNAi and antisense and they include RCTs and a controlled trial. The trials in otherwise specified conditions are largely based on RCTs that tested RNAi and antisense interventions.

Figure 2. Gene Therapy Evidence Map—Antisense, Autologous Cell, CAR-T, Genetically Modified Oncolytic Viral Therapy/Herpes Simplex Virus Type 1, RNAi, and ZFN



Abbreviation: RCT, randomized controlled trial, CAR-T, chimeric antigen receptor t cell; CAR-T, chimeric antigen receptor T cell, RNAi, RNA interference, CRISPR, clustered regularly interspaced short palindromic repeats; ZFN, zinc finger nuclease
Notes: Trial (trial with multiple arms receiving different doses but no untreated control group); Controlled trial (intervention and untreated control group); Single-arm (prospective case series). Evidence map based on searches to November 2018. The bubbles are staggered in their vertical and horizontal placement for greater visibility.

Important Issues Raised by Gene Therapy

Key Question 5a. What are the implications of the current level of adoption and future diffusion, given current level of evidence—efficacy/safety, ethical, disparity, resource allocation, and decision making?

In this review, we identified 306 complete studies and ongoing trials that evaluated or are evaluating gene therapy treatment using antisense, autologous cell product, CAR-T, genetically modified oncolytic viral therapy/herpes simplex virus type 1, RNAi, and ZFN technologies. Among the ongoing trials, CAR-T are the most common (n = 17, 37%), followed by autologous cell (n = 10, 22%), RNAi (n = 10, 22%), antisense (n = 6, 13%), oncolytic viral therapy/herpes simplex virus type 1 (n = 2, 4%), and ZFN (n = 1, 2%) interventions. Among the 256 complete studies, the evidence base differs according to intervention and indication. The most common intervention that has been tested is antisense-based therapy (n = 81, 32%). Trials that tested autologous cell (n = 80, 31%) and CAR-T (n = 55, 21%) also compose substantial proportions of the evidence base. While we identified quite a few ongoing trials testing RNAi interventions, we found relatively few studies that have been completed (n = 16, 6%). Conversely, we found more complete trials that have tested genetically modified oncolytic viral therapy/herpes simplex virus type 1 (n = 23, 9%) than those that are still ongoing. Trials testing ZFN were the rarest; we found only one trial in each of the ongoing and completed trial groups.

Most studies are based on either trials with multiple groups that were treated with different levels of the same therapy or single-arm trials. However, RCTs are increasingly being implemented in cancer, cardiovascular disease, immune deficiency, and otherwise categorized indication trials. Sample sizes are relatively small across the studies, likely due to the rarity of the indications. Yet, it appears that gene therapy is increasingly being applied to more common diseases in research studies. For example, we identified studies in which gene therapy was used to treat melanoma,[156,173,214,234,288,292] which is the second most common cancer in adolescent and young adult populations.[411] Other examples of common diseases being treated with gene therapy intervention include HIV,[333,335,336,339,340,343,345,353-356] hepatitis B,[391,395] and diabetes.[387,390] We observed larger sample sizes in the RCTs for the more common diseases, such as cardiovascular conditions, or for vaccine trials. Most studies evaluated safety and indicators of biodistribution. Thus, results largely suggested positive health benefits. However, among the large group of studies for cardiovascular disease, almost half reported clinical benefit, such as increased survival. On the other hand, cancer appears to be more recalcitrant to the tested gene therapies than cardiovascular disease because only 20% reported positive clinical benefit. Yet, like the cardiovascular trials, most of the remaining studies reported promising results that supported future research. Gene therapy trials to treat immune disorders appear to have the same clinical results profile as the cancer trials. About 40% of the studies that tested treatments in muscular disorders and neurodegenerative disorders reported positive clinical benefit, with few studies reporting null or negative effects. Among the smaller groups of studies that evaluated treatment in blood disorders, inflammatory disorders, ocular disorders, and respiratory conditions, the results are generally split between positive and suggestive findings, except for blood disorders, where both studies reported positive clinical benefit.

The large number of promising findings in contrast to clinical benefit suggests that, given how early in development many of these interventions are, the maximal tolerable dose and toxicity are still the primary outcomes. Such safety studies are still needed given the number of severe adverse events reported. Except for the group of studies in patients with ocular disorder and respiratory conditions, all studies reported some level of serious adverse events. About half of the cardiovascular disease and cancer studies reported serious harms, including death. In the groups of studies that tested gene

therapies for inflammatory disease and otherwise categorized indications, treatment-related deaths were also reported.

All key informants discussed issues they thought were important to patients. These experts stated that patients were mostly concerned with the basic components of obtaining and receiving gene therapy, including treatment availability, effectiveness, safety, price, and risks. However, the key informants were concerned about the lack of scientific education and understanding in the public about how gene therapies work. Thus, patients may be left to make decisions about care without a thorough understanding of the risks and benefits.

A few key informants suggested that because the true (eg, curative) value of gene therapies is still unknown, other factors should also be considered in pricing. For example, added transparency regarding the resources invested into research and development may need to be considered in addition to the social or individual benefit of patients living longer and healthier lives. Finally, one key informant expressed concern about providing insurance for gene therapies in an actuarily sound manner if rare diseases are individually rare but collectively affect about 25 million people in the United States. The key informant suggested that no insurance-based solution may exist, and that patients may need to bear the fee for the treatment themselves (eg, through a lifelong loan), even though this option may be politically unfavorable and regressive. ICER's report provides a more through discussion of payment options and their implications.[63]

Ethical Challenges

Key informants raised several ethical challenges regarding gene therapy. Gene therapy does have the potential to alter the germline, which could impact the genome of subsequent generations without their consent. Given that many unknowns still exist about unanticipated harmful effects of gene therapy and policy implications, the American College of Medical Genetics and Genomics holds the position that genome editing within embryos raises many technical and ethical concerns, including off-target effects, unknown epigenetic effects impacts on normal gene expression, and the ethics surrounding which genetic variants should be considered candidates.[412] The American Society of Human Genetics holds the position that it is inappropriate to perform germline gene editing that culminates in human pregnancy.[413] Even with somatic cell gene therapy, ethical issues arise when patients are children and consent is given by parents. For example, parents could seek out gene therapy for nondisease enhancement of their children.

While drug pricing presents ethical issues that are not unique to gene therapy, significant ethical concerns may exist for expensive gene therapies. Few groups of patients may be able to afford expensive lifesaving gene therapies, and the impact of expensive gene therapies on payers and insurance premiums could also disproportionately burden subpopulations. In addition, some key informants voiced the need for more transparency regarding the balance between pricing, private pharmaceutical company profit, and the public funding of gene therapy research.

Key informants were also concerned about the general population's lack of scientific understanding. Without improving science education, patients may not have a strong enough understanding of the potential risks of undertaking certain therapies to provide fully informed consent.

Key Question 5b. What are the key issues pertaining to decisional uncertainty?

Key informants noted concerns about the unknown benefits and risks that are involved in the gene therapies. For example, patients may underestimate the risk of taking a novel gene therapy versus a less efficacious standard therapy because the alternatives are limited. Moreover, patients must consider the unknown long-term effects of altered genes, and the insurance-related and indirect (eg, leave from work, traveling) price of receiving new and expensive therapies. For example, Yescarta and Kymriah require treatment at one of their treatment centers. These are not geographically allocated equally

across the United States, so traveling long distances for treatment may pose significant burden on patients and their families. Another important issue is that safety trials treated with the minimum dose may have no clinical benefit. So, patients who participate in a safety trial viral-based vector therapy (eg, autologous CD34+ cells transduced with lentiviral vector) may then no longer be able to participate in a future effectiveness trial because they are then immune to the virus. In addition, gene therapies that use viral or bacterial vectors could result in shedding where viral or bacterial particles could spread to other people.

Payers also face uncertainty regarding reimbursement for gene therapy because of the unknowns for up-front payment, durability, and impact on later fees. As new therapies are approved, payers need to decide whether to include the therapy in their plan. This issue is further complicated by the fact that gene therapies were initially used to treat rare conditions but are increasingly being used to treat more common diseases, such as cardiovascular disease and Alzheimer's. Thus, payers' decisions may impact large proportions of their covered population.

Key Question 5c. What are potential areas of research focus for PCORI and others?

To address the gaps in knowledge that might support the use and approval of gene therapies, several areas of research may warrant future work. To better understand how clinically effective treatments are versus the risk for adverse outcomes, future research could examine in more detail how effective each intervention type is at treating disease by indication and patient population. Moreover, several key informants noted a need for patient registries with long-term follow-up to increase the clinical effectiveness evidence base. Long-term follow-up will be especially important for the CAR-T therapies for which one treatment is expected to cure. Other research could examine disparities in gene therapy access and treatment, and the implications for treatment success or for adverse events. For example, is there gender bias in concurrent pregnancy prophylaxis treatment? Several key informants suggested developing Centers of Excellence for gene therapies where training, manufacturing, and intervention delivery are closely monitored to provide high standards of care. Suggested future research includes examining how different models for organizing and monitoring delivery can ensure that high-quality manufacturing processes and health care delivery standards are followed.

Other research could examine how training and education programs for providers and patients might improve provider familiarity with procedures and patient understanding of risks of unintended effects and how the therapy works. Understanding how people feel about the risks and potential promise of gene therapies and how providers communicate the issues to their patients could help shed light on the ethical implications of altering the genome. Qualitative (eg, focus groups) and quantitative (eg, surveys) research could lay the groundwork for describing current ethical issues.

Key informants across clinician and patient advocate groups suggested that relaxing some of the regulatory processes that determine FDA approval could also streamline drug development. For example, research could optimize vector delivery and gene transfer without having to return to the very beginning of the regulatory process. Thus, an intervention backbone could be approved so that, when specific gene target applications are proposed, only the modification to the intervention would need review for approval. Key informants also suggested relaxing some of the preclinical requirements as a means to improve the approval process. For example, in September 2018, the NIH and FDA removed the need for Recombinant DNA Advisory Committee review as well as NIH reporting for gene therapy protocols.[414] However, future research may be needed to identify where and how to address regulatory bottlenecks to facilitate drug development and approval while accelerating delivery of high-quality treatments to patients. In addition, future work could assess how gene therapy trials change over time, and whether methodological concerns arise or may be resolved as ongoing studies are completed.

Given the tremendous uncertainty about how to pay for gene therapies, we suggest future work exploring microsimulation modeling of different payer policy scenarios. Microsimulations would allow researchers to examine impacts of health care system changes on access to different gene therapies across different interventions and patient populations. Moreover, given the rapid pace at which research is advancing and results are being published, an automated system to curate and track the mounting evidence may be needed to inform key informants and potentially update model parameters.

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Please note that, where possible, we have included the links that go directly to the full text articles or have included the PubMed ID (PMID) for further information. The PMID is the record number in the free search engine PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) that contains more information on the publication.

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Appendix

Appendix A: Report Methodology

The project aimed to produce a landscape review of multiple data sources. Our landscape review includes an evidence map based on the published studies and ongoing trials that evaluate the application of gene therapy approaches.

Literature Searches

We searched multiple data sources to cover critical aspects of current and future gene therapy interventions. Specifically, our goal was to describe the evidence base for FDA-approved gene therapies that are currently used to treat or cure conditions. In addition, we describe the evidence for pending or ongoing clinical trials testing applications that may be poised to gain FDA approval as well as the conditions that are relevant for future applications. The FDA has approved gene therapies based on the results of single-arm trials when a life-threatening condition has no alternative treatment and its severity[6] justifies not performing controlled trials. Thus, we included controlled and uncontrolled trials. Finally, we describe the important issues for stakeholders (eg, patients) that the genetic technologies/interventions raise.

To identify currently FDA-approved gene therapies and applications, we referred to the FDA website that lists approved products (https://www.fda.gov/NewsEvents/ProductsApprovals/default.htm). We first reviewed the list of "Approved Cellular and Gene Therapy" products available on the FDA website (July 2018). We continued to monitor the FDA site for 2018 novel therapeutic approvals not otherwise captured on the aforementioned page, searching each drug name. For each therapy, we used the FDA approval letters and accompanying documentation to determine indication, orphan designation status, approval date for each approved indication, whether additional resources are required to utilize the therapy, whether repeat procedures are expected, summary information on adverse events, and anything else that might impact uptake of the therapeutic. If the FDA approval letter did not specify which clinical trials resulted in the approval, we searched the therapy name (generic and branded) on ClinicalTrials.gov and abstracted all associated registered clinical trials.

To collect evidence about the current use of approved gene therapies in patients, we searched for empirical published literature across clinical trials in the databases PubMed and EMBASE. We limited our searches to English-language studies of human subjects and focused on trials of at least 3 months' duration. The search strategy included a combination of indexing terms (MeSH terms in MEDLINE/PubMed and EMTREE terms in EMBASE) and free-text terms. A further key source of literature was the Web of Science. The Web of Science systematically catalogs conference abstracts, a source of the latest research information that is often not yet captured in the traditional scientific output (ie, journal manuscripts indexed in research databases). An Evidence-based Practice Center librarian experienced in transparent and comprehensive literature searches conducted the literature searchers. Effective search strategies often require thorough knowledge of indexing terms and scientific database functionality. Searches explicitly addressed the available evidence on the applications in treating human disease and the current and anticipated applications. The review identified remaining evidence gaps that future research studies should address.

To capture new advances that are near approval, we searched the gray literature online with a selection of the search terms above and subscribed to the newsletter of Gene Therapy.net. We identified trials that are currently ongoing in ClinicalTrials.gov (US research). In addition, we checked a database maintained by the *Journal of Gene Medicine* (http://www.abedia.com/wiley/search.php) and reviewed information on Gene Therapy Net (http://www.genetherapynet.com/united-states-of-

america.html). We limited our searches to US news releases within the past 12 months from November 2018 to identify therapies that may be approved in the near future. Gene Therapy Net also provides information on legislative issues. Many nonacademic government and trade publications discuss promising pipeline technologies and products. For example, Pink Sheet of Pharma Intelligence (https://pink.pharmaintelligence.informa.com) publishes news on gene therapy for pharmaceutical professionals on a wide array of topics, including topics of regulation and research/development/strategies. We also searched Lexis-Nexis Academic (https://advance.lexis.com/) for information on developing technologies. We conferred with content experts and screened pertinent online resources, such as Massachusetts Institute of Technology's (MIT's) NEW Drug Development ParadIGmS (NEWDIGS) site. New Drug Applications (NDAs) represent therapies that are closer to approval than the hundreds of Investigational New Drugs (INDs), so while we explored NDAs we did not include INDs in our search for near approval therapies. The newly released FDA suite of 6 draft guidance documents for industry (https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances) also provided information for disease-specific clinical and preclinical considerations for gene therapy development. We imported all relevant literature into an EndNote library. In both reports 1 and 2, we describe the evidence for types of research pipeline interventions that we found more than once in our literature search, independent of whether the studies are completed or still in progress. For example, we found only one pipeline gene therapy using Wyeth strain vaccinia virus/granulocyte-macrophage colony-stimulating factor expression, so we did not include this modality in our trial search. As we reviewed the evidence of current and impending gene therapies, we described the prevalence of the indications. We used statistics from published literature and national estimates drawn from the National Cancer Institute Surveillance, Epidemiology, and End-Results (SEER, https://seer.cancer.gov/data/) registry data.

Literature Review Procedure

Two independent reviewers screened search outputs to ensure we did not miss relevant citations. All citations deemed potentially relevant by at least one reviewer were obtained as full text. Full-text publications were screened against the eligibility criteria. We documented the reasons for exclusion in a citation management database. One reviewer abstracted and appraised publications, while content and methodological experts checked summaries.

Inclusion Criteria

We applied explicit inclusion and exclusion criteria designated a priori following a *PICOTSS* framework, as follows:

- Participants: Participants receiving any gene therapy were eligible for inclusion. Studies may include men and women of all ages but need to include human participants.
- Interventions: Eligible interventions included those that either replaced a disease-causing gene with a healthy copy of the gene, inactivated a disease-causing gene that is not functioning properly, or introduced a new or modified gene into the body to help treat a disease.
- Comparator: Any comparator or no comparator studies were eligible.
- Outcomes: Outcomes of interest included disease-related effectiveness/benefit indicators such as complete response (eg, remission); partial response; disease recurrence; mortality; patient-centered outcomes, including psychosocial outcomes such as anxiety and worry; and treatment-associated adverse events/harms (eg, cytokine release syndrome).
- Timing: Any treatment duration and follow-up of included studies were eligible.
- Setting: Any setting was eligible.

- Study design: Primary clinical research studies were eligible. Eligible publications either self-identified as experimental or described a planned scientific evaluation of gene therapy. Eligible study designs included randomized controlled trials, clinical trials with experimental assignment without randomization, and single-arm trials (eg, experimental case series). Observational studies were excluded. Conference abstracts were excluded.
- Studies published in English since 1989 were eligible.

CAR-T, autologous cell, antisense, RNAi, ZFN, genetically modified oncolytic herpes virus report

- Interventions: Eligible interventions included all trials that used CAR-T, autologous cell, antisense, RNAi, ZFN, or genetically modified oncolytic herpes virus as part of the evaluated gene therapy approach.

The literature flow diagram is shown in Appendix C.

Data Extraction

We used a standardized form with explicit and pilot-tested categorization rules to extract the data. For each study, we extracted the author and publication year (if applicable), indication/inclusion criteria, type of intervention, study design and study size, comparator, concurrent and prior treatments, length of follow-up, outcomes measures, authors' conclusions of the effect, and reported adverse events.

We used the following categories for indication:

- Immune deficiency
- Blood disorders (eg, hemophilia)
- Ocular disorder
- Neurodegenerative disorders
- Cancer
- Cardiovascular disease
- Respiratory conditions (including cystic fibrosis)
- Inflammatory disease (including arthritis)
- Muscular conditions
- Other

We consolidated all reports of the same participants into one study entry. This often included trial registry records, progress reports, subgroup analyses, and the main trial publication.

Evidence Map

The evidence map is based on a bubble plot. Each "bubble" represents an identified study. The evidence map documents ongoing (open bubbles) and published (filled bubbles) gene therapy trials. The evidence map shows the presence and absence of evidence.

Evidence Tables

We also provide the reader with evidence tables to provide a concise overview. We differentiated ongoing and partially (eg, preliminary results have been published) or fully published studies. We limited our search to ongoing studies that have completed recruiting and are more likely near the FDA approval stage than non-RCTs that are still recruiting patients.

Other Gene Therapy Examples

Both reports in this series on gene therapies selected interventions based on their frequency in research and practice and likelihood of receiving FDA approval status in the near future. Our literature review searches identified a number of gene intervention approaches that were not selected for the reports but that may also represent promising approaches. The list below provides the references of identified studies for the interested reader.

The gene therapy approaches included many novel or unique interventions, such as selective hydrodynamic gene therapy.[415] These approaches targeted primarily cancer indications.[403,407,416-438] Other indications were blood disorders,[439-442] cardiovascular disease,[443-446] immune deficiency,[447-454] inflammatory disorders,[455-459] muscular conditions,[460,461] respiratory conditions,[462-464] neurogenerative disorders,[465] ocular disorders,[466] or other.[467,468]

A considerable evidence base also exists for plasmid-based interventions.[469-507] However, none of the currently FDA-approved gene therapy approaches are plasmid based and the approach has not received substantial attention in the gray literature as a potential pipeline therapy. In addition, we identified some recombinant protein and gene transfer therapy approaches,[508-513] but the same caveats apply.

Appendix B: Search Strategies

Published Literature

PubMed

Run November 2, 2018

Filters activated: Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Controlled Clinical Trial, Randomized Controlled Trial, Publication date from 1989/01/01, Humans, English.

(((gene-editing[title/abstract] OR "gene editing"[title/abstract]) AND (therap*[title/abstract] OR treatment*[title/abstract]))
OR
("gene therapy"[title/abstract] OR "gene therapies"[title/abstract] OR "gene engineering"[title/abstract] OR "gene transfer"[title/abstract]) OR "RNA targeted therapeutic"[tiab] OR "RNA-targeted therapeutics"[tiab]
OR
("Gene Editing/ethics"[Mesh] OR "Gene Editing/instrumentation"[Mesh] OR "Gene Editing/legislation and jurisprudence"[Mesh] OR "Gene Editing/standards"[Mesh] OR "Gene Editing/statistics and numerical data"[Mesh] OR "Gene Editing/trends"[Mesh] OR "Gene Editing/utilization"[Mesh] OR "Genetic Therapy/adverse effects"[Mesh] OR "Genetic Therapy/classification"[Mesh] OR "Genetic Therapy/epidemiology"[Mesh] OR "Genetic Therapy/ethics"[Mesh] OR "Genetic Therapy/instrumentation"[Mesh] OR "Genetic Therapy/legislation and jurisprudence"[Mesh] OR "Genetic Therapy/methods"[Mesh] OR "Genetic Therapy/mortality"[Mesh] OR "Genetic Therapy/nursing"[Mesh] OR "Genetic Therapy/psychology"[Mesh] OR "Genetic Therapy/standards"[Mesh] OR "Genetic Therapy/statistics and numerical data"[Mesh] OR "Genetic Therapy/therapeutic use"[Mesh] OR "Genetic Therapy/therapy"[Mesh] OR "Genetic Therapy/trends"[Mesh] OR "Genetic Therapy/utilization"[Mesh] OR "Gene Transfer Techniques/adverse effects"[Mesh] OR "Gene Transfer Techniques/drug effects"[Mesh] OR "Gene Transfer Techniques/immunology"[Mesh] OR "Gene Transfer Techniques/therapy"[Mesh] OR "Gene Transfer, Horizontal/adverse effects"[Mesh] OR "Gene Transfer, Horizontal/drug effects"[Mesh] OR "Gene Transfer,

Horizontal/immunology"[Mesh] OR "Gene Transfer, Horizontal/therapeutic use"[Mesh]))
OR
CAR-T[title/abstract] OR "CAR-T" [title/abstract] OR ("CAR Modified"[title/abstract] AND T[title/abstract]) OR ("chimeric antigen receptor" [title/abstract] AND "T" [title/abstract]) OR CART-19[title/abstract] OR CRISPR/Cas[title/abstract] OR "clustered regularly interspaced short palindromic repeats"[tiab] OR "zinc-finger nucleases" [title/abstract] OR "zinc finger nucleases" [title/abstract] OR "zinc finger nuclease" [title/abstract] OR "zinc finger nuclease" [title/abstract] OR ZFN[title/abstract] OR TALEN[title/abstract] OR "TAL effector nucleases"[title/abstract] OR "TAL effector nuclease"[title/abstract] OR "Transcription activator-like effector nucleases"[title/abstract] OR "Transcription activator-like effector nuclease"[title/abstract] OR "Transcription activator like effector nucleases"[title/abstract] OR "Transcription activator like effector nuclease"[title/abstract]
OR
"voretigene neparvovec-rzyl" OR luxturna[title/abstract] OR "axicabtagene ciloleucel" OR "Axi-Cel"[title/abstract] OR "KTE-C19"[title/abstract] OR KTEC19[title/abstract] OR yescarta[title/abstract] OR tisagenlecleucel[title/abstract] OR CTL019[title/abstract] OR CTL-019[title/abstract] OR kymriah[title/abstract] OR "talimogene laherparepvec"[title/abstract] OR imlygic[title/abstract] OR Provenge[title/abstract] OR "sipuleucel-T" [title/abstract] OR "adeno associated virus"[title/abstract] OR "adenoassociated virus"[title/abstract] OR ("adeno-associated virus"[tiab] AND gene*[tiab]) OR ("herpes simplex virus"[tiab] AND gene*[tiab]) OR (HSV[tiab] AND gene*[tiab]) OR tegsedi[tiab] OR inotersen[tiab] OR (("oncolytic virus"[tiab] OR "oncolytic viral"[tiab]) AND (gene*[tiab] OR engineered[tiab] OR modified[tiab]))
NOT
("trial protocol"[ti] OR "study protocol"[ti])
Results: 940

(Autologous[tiab] AND cell*[tiab] AND (gene[tiab]OR genes[tiab] OR genetic*[tiab] OR RNA[tiab] OR DNA[tiab])) OR lentiglobin OR bb305 OR 'otl 101' OR 'otl 200' OR gsk269274 OR 'eb 101' OR 'fcx 007' OR 'fcx 013'
Results: 315

(RNAi[tiab] OR "RNA interference"[tiab]) OR ("ribonucleic acid"[tiab] AND interfer*[tiab]) OR "interfering ribonucleic acid"[tiab] OR siRNA[tiab] OR miRNA[tiab] OR patisran OR onpattro OR ALN-TTr02 OR ALN-TTRsc02 OR "AMG 890" OR ARO-LPA OR ARO-AAT OR ARO-HBV OR Cemdisiran OR ALN-CC5 OR Fitusiran OR ALN-AT3sc OR ALN-AS1 OR Inclisiran OR ALN-PCSsc OR Lumasiran OR ALN-GO1 OR Revusiran OR ALN-TTRsc)
AND
(gene*[tiab] AND therap*)
NOT
(marker* OR biomarker*)
Results: 24

(antisense[tiab] AND gene*[tiab]) OR mipomersen OR Kynamro OR eteplirsen OR "exondys 51" OR nusinersen OR spinraza OR tegsedi OR inotersen OR ionis-maptrx OR rg6042 OR ionis-httrx OR volanesorsen
Results: 89

Embase
Run November 2, 2018

Limits: ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [english]/lim AND [humans]/lim AND [embase]/lim AND [1989-2018]/py
(gene-editing):ab,ti OR (“gene editing”):ab,ti AND ((therap*):ab,ti OR (treatment*):ab,ti)
OR
(“gene therapy”):ab,ti OR (“gene therapies”):ab,ti OR (“gene engineering”):ab,ti OR (“gene transfer”):ab,ti OR (“RNA targeted therapeutic”):ab,ti OR (“RNA-targeted therapeutics”):ab,ti
OR
(CAR-T):ab,ti OR (“CAR T”):ab,ti OR ((“CAR Modified”):ab,ti AND (T):ab,ti) OR ((“chimeric antigen receptor”):ab,ti AND (T):ab,ti) OR (CART-19):ab,ti OR (CRISPR):ab,ti OR (“clustered regularly interspaced short palindromic repeats”):ab,ti OR (“zinc-finger nucleases”):ab,ti OR (“zinc-finger nuclease”):ab,ti OR (“zinc finger nucleases”):ab,ti OR (“zinc finger nuclease”):ab,ti OR (ZFN):ab,ti OR (TALEN):ab,ti OR (“TAL effector nucleases”):ab,ti OR (“TAL effector nuclease”):ab,ti OR (“transcription activator-like effector nucleases”):ab,ti OR (“transcription activator-like effector nuclease”):ab,ti OR (“transcription activator like effector nucleases”):ab,ti OR (“transcription activator like effector nuclease”):ab,ti
OR
(“voretigene neparvovec-rzyl”):ab,ti OR (luxturna):ab,ti OR (“axicabtagene ciloleucel”):ab,ti OR (“Axi-Cel”):ab,ti OR (“KTE-C19”):ab,ti OR (KTEC19):ab,ti OR (yescarta):ab,ti OR (tisagenlecleucel):ab,ti OR (CTL019):ab,ti OR (CTL-019):ab,ti OR (kymriah):ab,ti OR (“talimogene laherparepvec”):ab,ti OR (imlygic):ab,ti OR (Provenge):ab,ti OR (“sipuleucel-T”):ab,ti OR (“adeno associated virus”):ab,ti OR (“adenoassociated virus”):ab,ti OR ((“adeno-associated virus”):ab,ti AND (gene*):ab,ti) OR ((“herpes simplex virus”):ab,ti AND (gene*):ab,ti) OR ((HSV):ab,ti AND (gene*):ab,ti) OR (tegsedi):ab,ti OR (inotersen):ab,ti OR (("oncolytic virus”):ab,ti OR (“oncolytic viral”):ab,ti AND ((gene*):ab,ti OR (engineered):ab,ti OR (modified):ab,ti))
NOT
(“trial protocol”):ti OR (“Study protocol”):ti
EXCLUDE: CONFERENCE ABSTRACT; CONFERENCE REVIEW; EDITORIAL; NOTE; REVIEW; SHORT SURVEY; LETTER; CONFERENCE PAPER
Results: 515 – duplicates = 251

(autologous:ab,ti AND cell*:ab,ti AND (gene:ab,ti OR genes:ab,ti OR genetic*:ab,ti OR rna:ab,ti OR dna:ab,ti) OR lentiglobin OR bb305 OR 'otl 101' OR 'otl 200' OR gsk269274 OR 'eb 101' OR 'fcx 007' OR 'fcx 013')
Results: 177 – duplicates with PubMed above = 87

((RNAi):ab,ti OR (“RNA interference”):ab,ti OR (“ribonucleic acid” AND interfer*):ab,ti OR (“interfering ribonucleic acid” OR siRNA OR miRNA):ab,ti OR patisran OR onpattro OR ALN-TTr02 OR ALN-TTRsc02 OR “AMG 890” OR ARO-LPA OR ARO-AAT OR ARO-HBV OR Cemdisiran OR ALN-CC5 OR Fitusiran OR ALN-AT3sc OR ALN-AS1 OR Inclisiran OR ALN-PCSsc OR Lumasiran OR ALN-GO1 OR Revusiran OR ALN-TTRsc
AND
(gene*):ab,ti AND (therap*):ab,ti
NOT
(marker* OR biomarker*)
Results: 35 – duplicates with PubMed above = 29

((antisense):ab,ti AND (gene*):ab,ti) OR mipomersen OR Kynamro OR eteplirsen OR “exondys 51” OR nusinersen OR spinraza OR tegsedi OR inotersen OR ionis-maptrx OR rg6042 OR ionis-httrx OR volanesorsen)

Results: 266 – duplicates with PubMed above = 223

Web of Science

Run November 2, 2018
English: Article
Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=1989-2018
(TS=(gene-editing) OR TS=("gene editing")) AND (TS=(therap*) OR TS=(treatment*))
OR
TS=("gene therapy") OR TS=("gene therapies") OR TS=("gene engineering") OR TS=("gene transfer") OR TS=("RNA targeted therapeutic") OR TS=("RNA-targeted therapeutics")
OR
TS=(CAR-T) OR TS=("CAR T") OR (TS=("CAR Modified") AND TS=(T)) OR (TS=("chimeric antigen receptor") AND TS=(T)) OR TS=(CART-19) OR TS=(CRISPR/Cas) OR TS=("clustered regularly interspaced short palindromic repeats") OR TS=("zinc-finger nucleases") OR TS=("zinc-finger nuclease") OR TS=(ZFN) OR TS=(TALEN) OR TS=("zinc finger nuclease") OR TS=("zinc finger nucleases") OR TS=("TAL effector nucleases") OR TS=("TAL effector nuclease") OR TS=("transcription activator-like effector nucleases") OR TS=("transcription activator-like effector nuclease") OR TS=("transcription activator like nucleases") OR TS=("transcription activator like nuclease")
OR
(TS=("voretigene neparvovec-rzyl") OR TS=(luxturna) OR TS=("axicabtagene ciloleucel") OR TS=("Axi-Cel") OR TS=("KTE-C19") OR TS=(KTEC19) OR TS=(yescarta) OR TS=(tisagenlecleucel) OR TS=(CTL019) OR TS=(CTL-019) OR TS=(kymriah) OR TS=("talimogene laherparepvec") OR TS=(imlygic) OR TS=(Provenge) OR TS=("sipuleucel-T") OR TS=("adeno associated virus") OR TS=("adenoassociated virus") OR (TS=("adeno-associated virus") AND TS=(gene*)) OR (TS=("herpes simplex virus") AND TS=(gene*)) OR (TS=(HSV) AND TS=(gene*)) OR TS=(tegsedi) OR TS=(inotersen) OR (TS=("oncolytic virus" OR "oncolytic viral") AND TS=(gene* OR engineered OR modified)))
AND
TS=("randomized controlled trial") OR TS=(RCT) OR TS=("controlled clinical trial") OR TS=("clinical trial")
NOT
TS=(rat OR rats OR monkey OR monkeys OR primates OR primate OR macaque* OR mouse OR mice OR dog OR canine OR canines OR rabbit OR rabbits)
NOT
TI=("trial protocol") OR TI=("study protocol")
EXCLUDE: Proceedings Papers; Book Chapters also, in EndNote (all results), pulled out pig/horse articles and some additional "overviews" not called "Reviews"
Results:
TOTAL: 898 – duplicates = 672
TOTAL: 1863

(TS=(autologous) AND TS=(cell) AND (TS=(gene OR genes OR genetic* OR rna OR dna)) OR TS=(Strimvelis OR Lenti-D OR "elivaldogene tavalentivec" OR Lentiglobin OR BB305 OR OTL-101 OR OTL-200 OR GSK269274 OR EB-101 OR FCX-007 OR FCX-013)
AND
TS=("randomized controlled trial") OR TS=(RCT) OR TS=("controlled clinical trial") OR TS=("clinical trial")

NOT
TS=(rat OR rats OR monkey OR monkeys OR primates OR primate OR macaque* OR mouse OR mice OR dog OR canine OR canines OR rabbit OR rabbits)
NOT
TI=("trial protocol") OR TI=("study protocol")
EXCLUDE: Proceedings Papers;
Results: 199 – duplicates with above = 134

(TS=(RNAi) OR TS=("RNA interference") OR TS=("ribonucleic acid" AND interfer*) OR TS=("interfering ribonucleic acid") OR TS=(siRNA OR miRNA OR patisran OR onpattro OR ALN-TTr02 OR ALN-TTRsc02 OR "AMG 890" OR ARO-LPA OR ARO-AAT OR ARO-HBV OR Cemdisiran OR ALN-CC5 OR Fitusiran OR ALN-AT3sc OR ALN-AS1 OR Inclisiran OR ALN-PCSsc OR Lumasiran OR ALN-GO1 OR Revusiran OR ALN-TTRsc))
AND
(TS=(gene) AND TS=(therap*))
NOT
(TS=(marker* OR biomarker*)
AND
TS=("randomized controlled trial") OR TS=(RCT) OR TS=("controlled clinical trial") OR TS=("clinical trial")
NOT
TS=(rat OR rats OR monkey OR monkeys OR primates OR primate OR macaque* OR mouse OR mice OR dog OR canine OR canines OR rabbit OR rabbits)
NOT
TI=("trial protocol") OR TI=("study protocol")
EXCLUDE: Proceedings Papers;
Results: 38 – duplicates with above = 36

(TS=(antisense) AND TS=(gene*)) OR TS=(mipomersen OR Kynamro OR eteplirsen OR "exondys 51" OR nusinersen OR spinraza OR tegsedi OR inotersen OR ionis-maptrx OR rg6042 OR ionis-httrx OR volanesorsen)
AND
TS=("randomized controlled trial") OR TS=(RCT) OR TS=("controlled clinical trial") OR TS=("clinical trial")
NOT
TS=(rat OR rats OR monkey OR monkeys OR primates OR primate OR macaque* OR mouse OR mice OR dog OR canine OR canines OR rabbit OR rabbits)
NOT
TI=("trial protocol") OR TI=("study protocol")
EXCLUDE: Proceedings Papers;
in EndNote (all results), pulled out pig/horse articles and some additional "overviews" not called "Reviews"
Results: 79 – duplicates with above = 61

Gray Literature

ClinicalTrials.gov
November 2, 2018

Searching the "other" field – limiting to: Active, not recruiting, Completed, Suspended, Terminated, Withdrawn Studies
Modalities
"Zinc finger nuclease" OR "Zinc-finger nuclease" OR "Zinc-finger nucleases" OR "Zinc finger nucleases" OR ZFN OR "Transcription Activator-like Effector Nucleases" OR "Transcription Activator-like Effector Nuclease" OR "TAL effector nuclease" OR "TAL effector nucleases" OR TALEN OR CRISPR OR CRISPR/Cas9 OR "Clustered Regularly Interspaced Short Palindromic Repeats" OR CAR-T OR "chimeric antigen receptor" OR (Adenovirus AND "gene therapy") OR (Adenovirus AND "gene transfer") OR Oncolytic Virus OR Luxturna OR "Voretigene neparvovec" OR "Axicabtagene ciloleucel" OR KTE-C19 OR Yescarta OR Tisagenlecleuce OR Kymriah OR "talimogene laherparepvec" OR Imlygic OR Tegsedi OR Inotersen
Results: 360
Other Biological Approved Products
("Recombinant protein" AND "gene therapy") OR ("Recombinant protein" AND "gene transfer") OR "Allogenic cord blood hematopoietic progenitor cell therapy" OR "Allogenic umbilical cord blood" OR "autologous cell product" OR "autologous cellized scaffold product" OR "autologous cellised scaffold product" OR Allocord OR Azficel OR laviv OR Andexxa OR Clevecord OR Gintuit OR Hemacord OR Ducord OR ("gene therapy" AND RNA) OR ("gene transfer" AND RNA) OR patisiran OR (lentivirus AND "gene therapy") OR (Lentivirus AND "gene transfer") OR (vector AND "gene therapy") OR (vector and "gene transfer") OR "adeno associated virus" OR "adenoassociated virus" OR ("adeno-associated virus" AND gene*) OR ("herpes simplex virus" AND gene*) OR (HSV AND gene*) OR ("oncolytic viral")
Results: 251 – duplicates with modalities = 177
TOTAL: 537

((autologous AND cell*) AND (gene OR genes OR genetic* OR rna OR dna)) OR Strimvelis OR Lenti-D OR "elivaldogene tavalentivec" OR Lentiglobin OR BB305 OR OTL-101 OR OTL-200 OR GSK269274 OR EB-101 OR FCX-007 OR FCX-013
Results: 4

RNAi OR "RNA interference" OR ("riboneucleic acid" AND interfer*) OR "interfering ribonucleic acid" OR siRNA OR miRNA OR patisran OR onpattro OR ALN-TTr02 OR ALN-TTRsc02 OR "AMG 890" OR ARO-LPA OR ARO-AAT OR ARO-HBV OR Cemdisiran OR ALN-CC5 OR Fitusiran OR ALN-AT3sc OR ALN-AS1 OR Inclisiran OR ALN-PCSsc OR Lumasiran OR ALN-GO1 OR Revusiran OR ALN-TTRsc
AND
gene AND therap*
NOT
marker* OR biomarker*
Results: 0

(antisense AND gene*) = 0
(mipomersen OR Kynamro OR eteplirsen OR "exondys 51" OR nusinersen OR spinraza OR tegsedi OR inotersen OR ionis-maptrx OR rg6042 OR ionis-httrx OR volanesorsen) = 45
Results: 45

FDA Records

We used the list of "Approved Cellular and Gene Therapy" products available on the FDA website (accessed July 2018) and monitored the FDA site for 2018 novel therapeutic approvals.

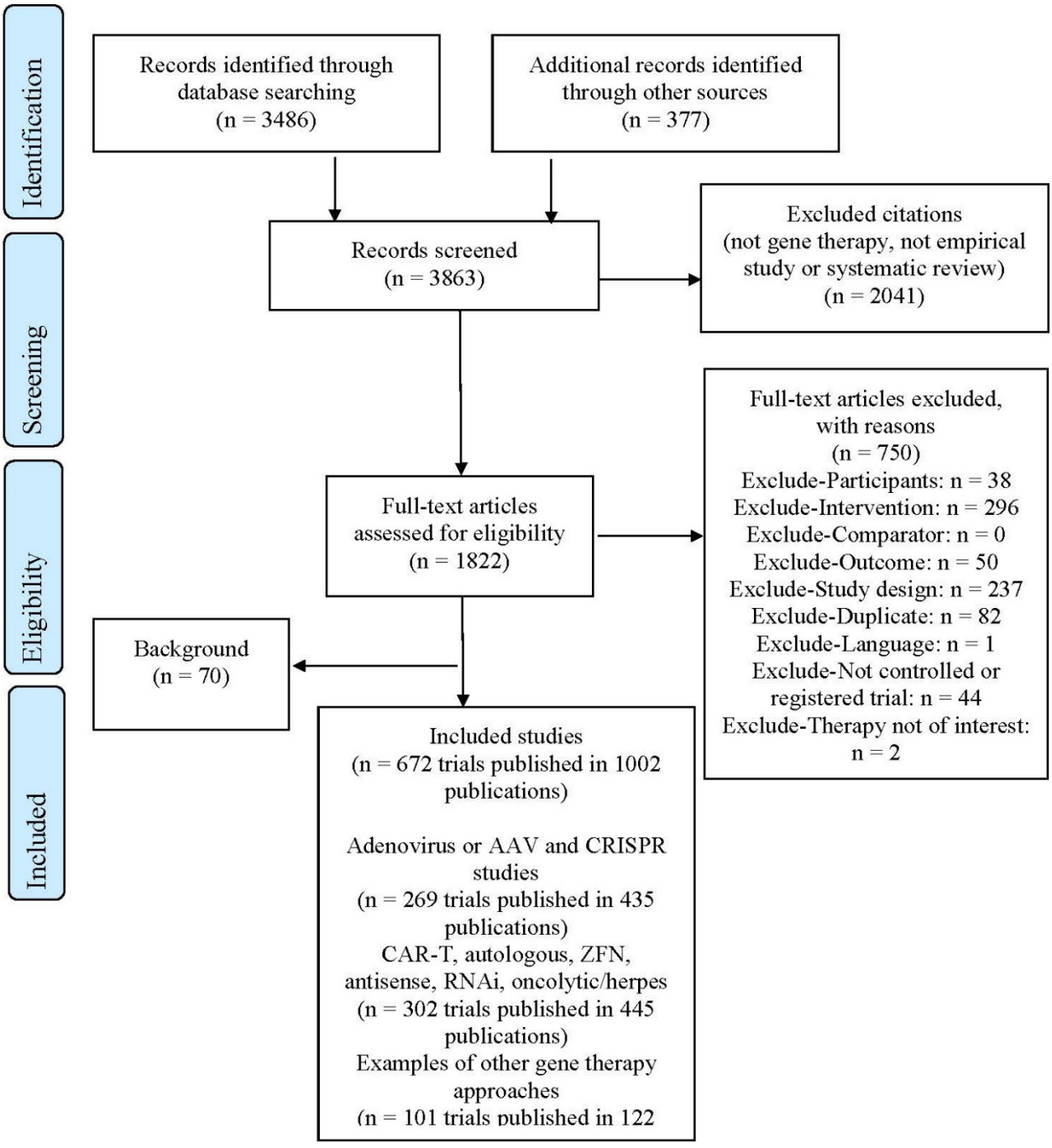
LexisNexis and Web Searches

We used the search terms “gene therapy” and “nda” in combination with a source restriction to “Pink Sheet: Pharma Intelligence” and date restrictions of (January 1, 2017 and August 30, 2018) or (January 1, 2017 and September 15, 2018). We abstracted names of any gene therapies that were mentioned. Next, we searched the name of each of the gene therapies for specific information in ClinicalTrials.gov as well as in the Google search engine. In the Google search engine, we used the name of each gene therapy alone and in conjunction with “fda designation” to determine the modality and indication, determine/confirm the current phase of the therapy, and determine if it had received any specific FDA designation (Fast Track, Breakthrough, Orphan Drug, Rare Pediatric Disease, or Regenerative Medicine Advanced Therapy).

Gene Therapy Clinical Trials Worldwide

We used the database maintained by the *Journal of Gene Medicine* (http://www.abedia.com/wiley/search.php) to check for less frequent therapies, to ensure that all relevant trials had been identified

Appendix C: Literature Flow Diagram



Appendix D: Stakeholder and Key Informant Interview Information

Interviews

We conducted key informant interviews to gather detailed information about gene therapy from a variety of perspectives. The purpose of the interviews was to collect perspectives from patients or patient advocates, clinicians, payers/insurers, public policymaker representatives, and industry. The goal was to ensure that perspectives of different stakeholders have been considered and are reflected in the research approach. Our application to RAND's Human Subjects Protection Committee (HSPC: 2018-0560) was approved for exempt status on August 24, 2018.

Recruitment

We developed the key informant list by first selecting relevant stakeholder groups. Next, the team searched the internet to identify possible representatives of the stakeholder groups. If we could not reach the key informant or they declined, we referred to our list to identify an alternate key informant. We also asked anyone who declined if they could recommend someone else. We emailed individuals and organizations requesting their participation in phone interviews. These emails included a 1-page brief description of the assessment written in plain English. We informed the individual that we contacted him or her because of his or her experience (as either a patient/advocacy group member, clinician, payer/insurer, public policy representative, industry member, or industry analyst—*depending on the interviewee*). At this time, we asked the individual if he or she would agree to participate in our assessment and if there were any other individuals he or she suggested we contact for their relevant experience.

We contacted 45 individuals: 15 clinicians, 7 patients and patient advocates, 8 payers/insurers, 5 public policymaker representatives, and 10 industry representatives/industry analysts. Among those we contacted, 2 clinicians, 2 patient advocates, 2 payers/insurers, 2 public policymaker representatives, and 2 industry analysts participated. We invited industry professionals, although none agreed to participate.

Procedure

We conducted semistructured telephone interviews with each key informant that lasted approximately 1 hour. The interviews were guided by a list of set questions, but we gave the interviewees the latitude to expand or move to other topics that they thought were important to discuss. We aimed to understand the process by which potential gene therapies progress from the laboratory bench to patient treatment options, and to identify positive and negative impacts of the therapies for a variety of stakeholders, including patients/consumers, payers/insurers, purchasers/employers, and public policymakers. The interviewer asked about barriers and facilitators to gene therapy implementation, adjustments to policies and procedures, safety, efficacy, and cost. The interview questions were designed for a wide set of stakeholder perspectives and not all questions were relevant to each interviewee. Thus, interviewees were free to skip questions that they felt they could not answer.

Informed consent protocol

Interviewers read the information below before proceeding with the interview.

Research Description
The goal of this study is to use an evidence map format and landscape review to describe the current evidence base available for gene therapy applications. The evidence map will include a central figure that visualizes the state of the research. The evidence maps provide a visual overview, communicating the results of multiple dimensions to best document a research area. As part of this work, we will conduct key stakeholder interviews to gather detailed information about gene therapy from a variety of perspectives. Informative research questions need to consider a range of stakeholders. In particular, patient-centered outcomes should not be selected by clinicians and policy makers but require engaging patients in the research process. The key informant interviews will include a range of respondents from patients or patient advocates, clinicians, payers/insurers, public policy maker representatives, industry, and industry analysts. The goal is to ensure that perspectives of different stakeholders have been considered and are reflected in the research approach. This project is supported by the Patient-Centered Outcomes Research Institute (PCORI) and facilitated by the RAND Corporation.

Risks and Benefits
There will be no risks related to participation in this study. During the completion of the interview, if a question is not applicable to you or you feel uncomfortable answering, please complete it to the best of your ability. The project aims to improve our understanding of approved gene therapies as well as those that may become available for use in the next five years, as a critical means to spread knowledge that will benefit patients, researchers, and practitioners.

Duration
Your participation will last about an hour.

Participation and Withdrawal
Participation in this study is entirely voluntary. You have the right not to participate at all, to leave the project at any time, and can decline to be acknowledged as a panelist. Deciding not to participate or choosing to leave the study will not result in any negative consequences. If you decide that you cannot participate, we will ask that you nominate someone to join the panel in your place (if possible).

Confidentiality
Your name will not be linked to your interview responses in any feedback of results to the group and your name and your responses will not be stored together. Your interview responses will be kept confidential. Study results will be accessible only to the study team. Interview responses and discussion points will be documented in aggregate form across participants. You will be asked for consent to be acknowledged as a key stakeholder in future publications describing the results of the project.

Contact Information
If you have questions about this research, please email Dr. Andrea Richardson (arichard@rand.org) or Dr. Susanne Hempel (susanne_hempel@rand.org). If you have questions about your rights as a research participant or need to report a research-related injury or concern, you can contact RAND's Human Subjects Protection Committee toll-free at 866 697 5620 or by emailing hspcinfo@reand.org. If possible, when you contact the Committee, please reference Study # 2017-0640.

Consent
Your consent to participate in this project will be implied by selecting the option, "Yes, I consent to participate in this study (continue to survey)," and by submitting your responses after completion.

Interview guide

Introduction
Brief Project Background
Reason for Reaching Out/Expertise of Stakeholder Representative
Questions to Discuss During Phone Conversations:

- Are any interventions missing from our preliminary search strategy?
- Which clinical effectiveness outcomes should be assessed when evaluating the effects of gene therapy?
- Which adverse events should be assessed when evaluating the effects of gene therapy?
- Which other outcomes should be assessed?
- What is an appropriate timeframe for the assessment?
- What information is important to patients that has not been the focus of expert discussions or has been neglected in existing research?
- What are the decisional dilemmas for patients?
- What considerations will help key stakeholders [will be specified] to decide the value of the intervention?

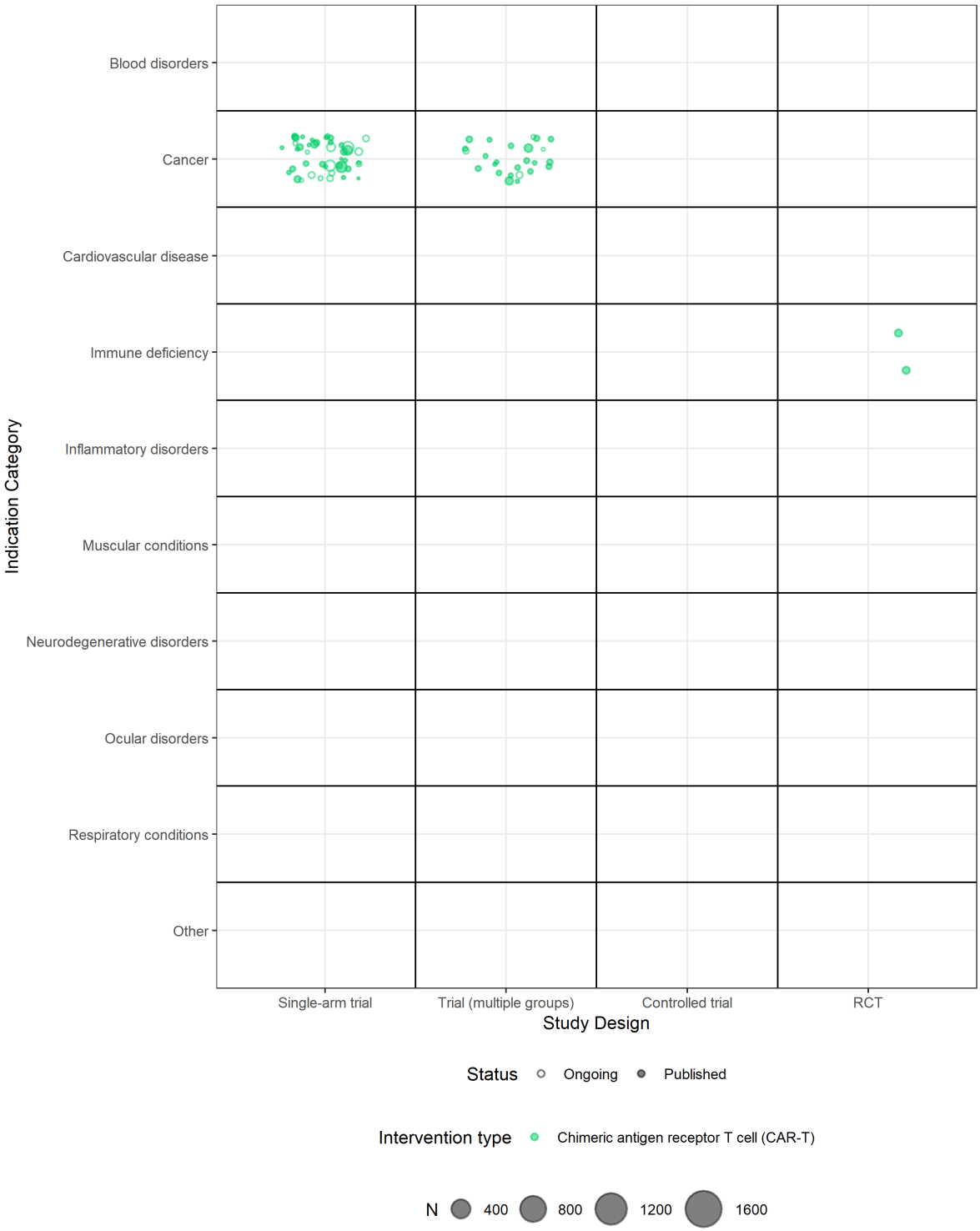
- Our evidence map can display only a limited number of dimensions to establish a picture of the existing evidence base. Using the draft example, which dimensions do you think are critical to display (eg, number of patients, number of successful interventions, study design distribution, replication by independent researchers, clinical effectiveness, severity of adverse events, costs, quality of evidence across studies)?
- Which new developments are close to approval? Please do not share any proprietary information that you may know.
- What are the major challenges you see facing gene therapy advances?
- Are there ethical considerations that should be discussed?
- What are your major hopes you see facing gene therapy treatments?
- What are the major gaps in our understanding that need to be addressed to improve the development and FDA-approved gene therapies?
- Is public policy lacking with respect to gene therapy approval and use?
- What suggestions do you have to bring more approved gene therapies from bench to bedside?

Interview Data Collection and Analysis Strategy

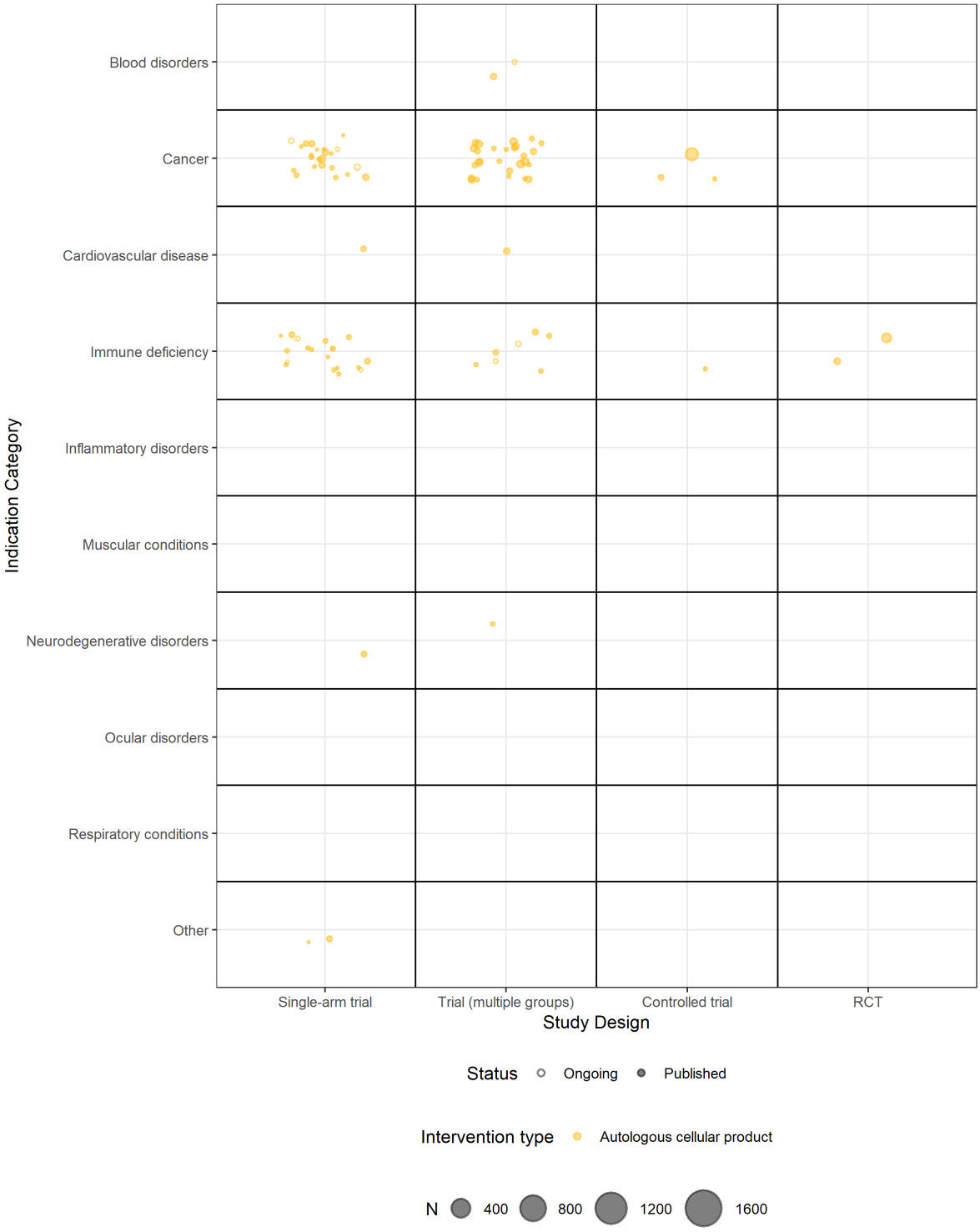
Interviews were conducted by phone with one researcher and one note taker, and, if the interview participant agreed, recorded to ensure information was accurately captured. Interview results were documented in aggregated and deidentified format. We analyzed the content of the interviews by sorting and drawing themes from responses according to the topic that was addressed.

Appendix E: Evidence Maps Stratified by Intervention

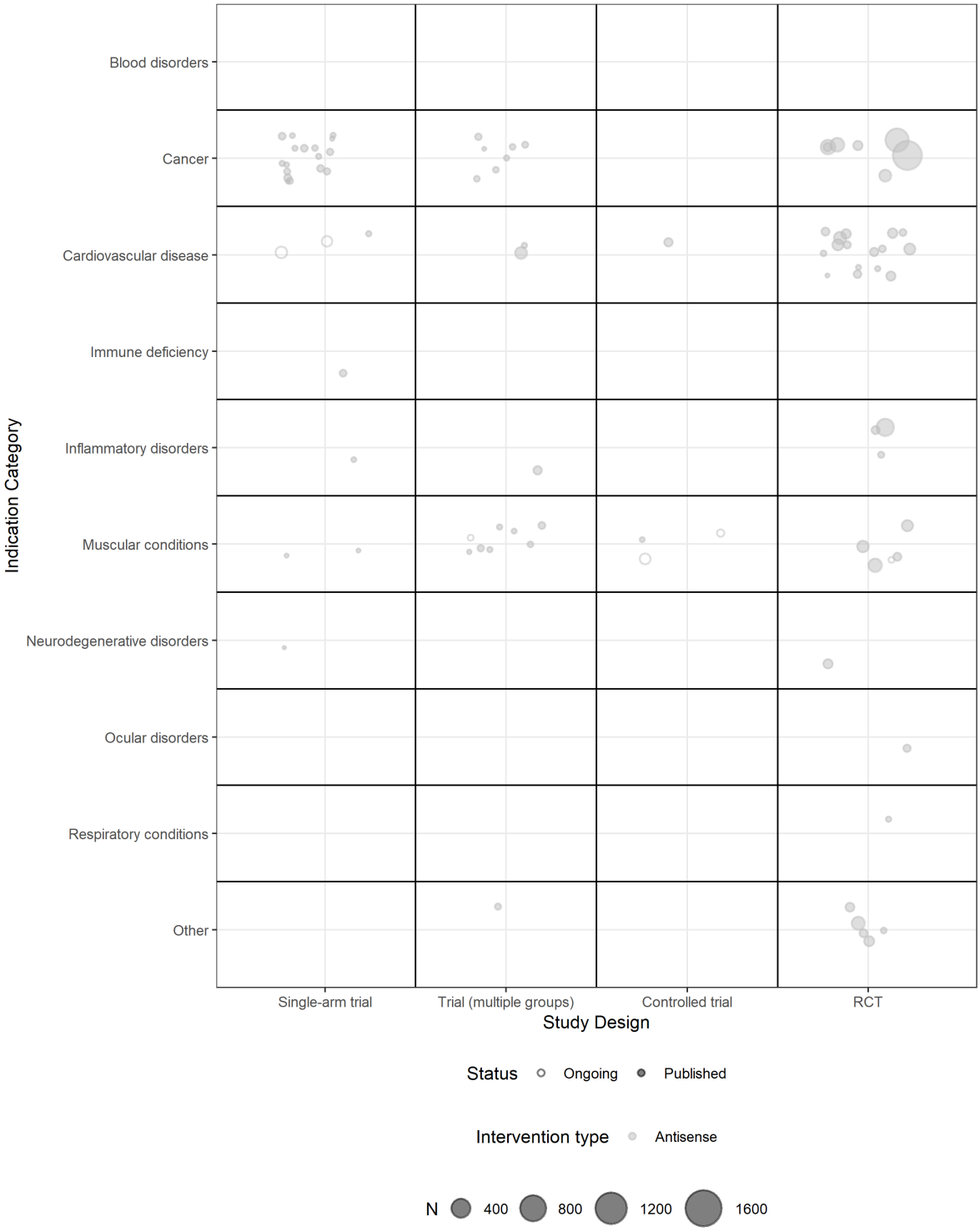
Appendix Evidence Map 1. CAR-T Trials



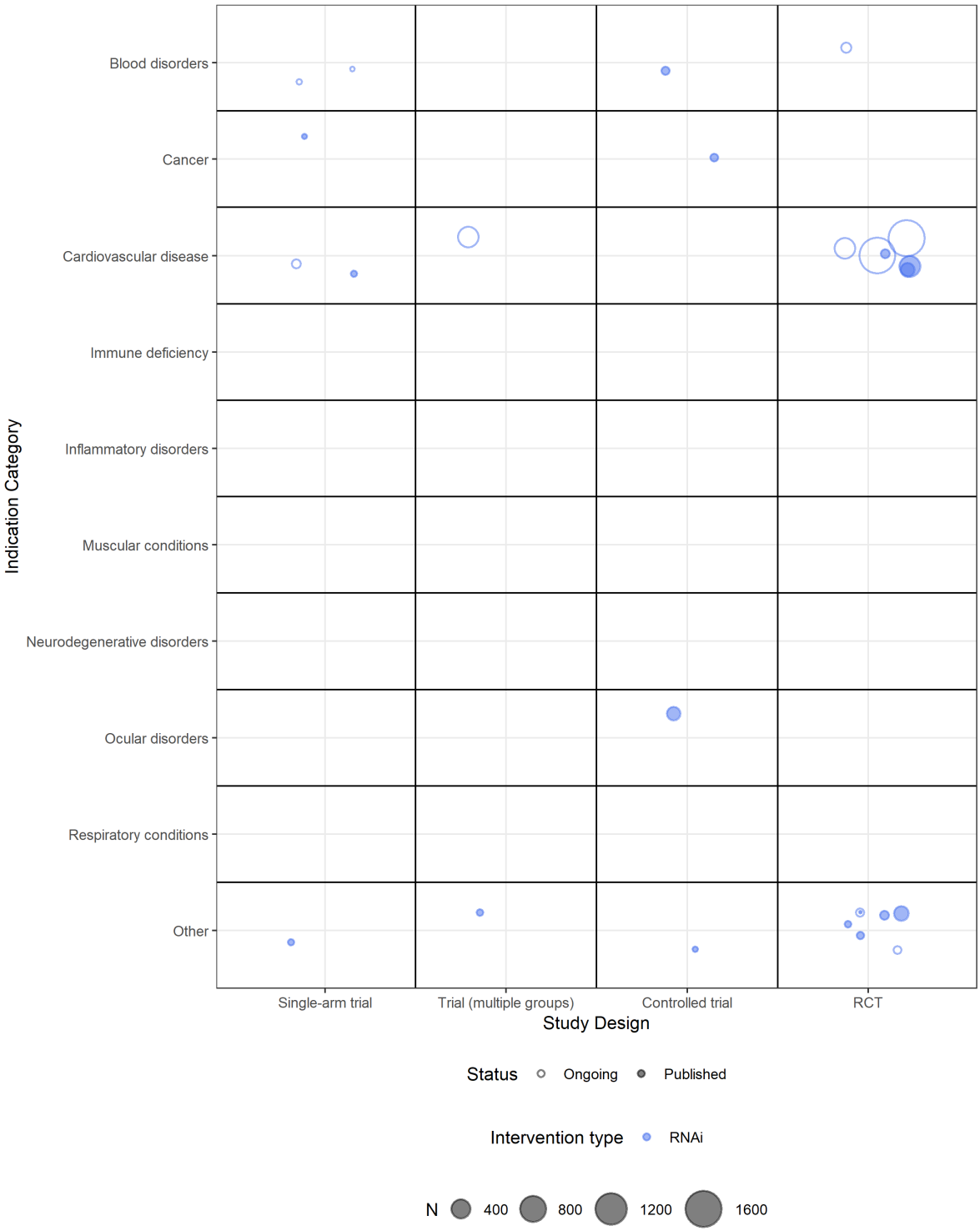
Appendix Evidence Map 2. Autologous Cell Trials



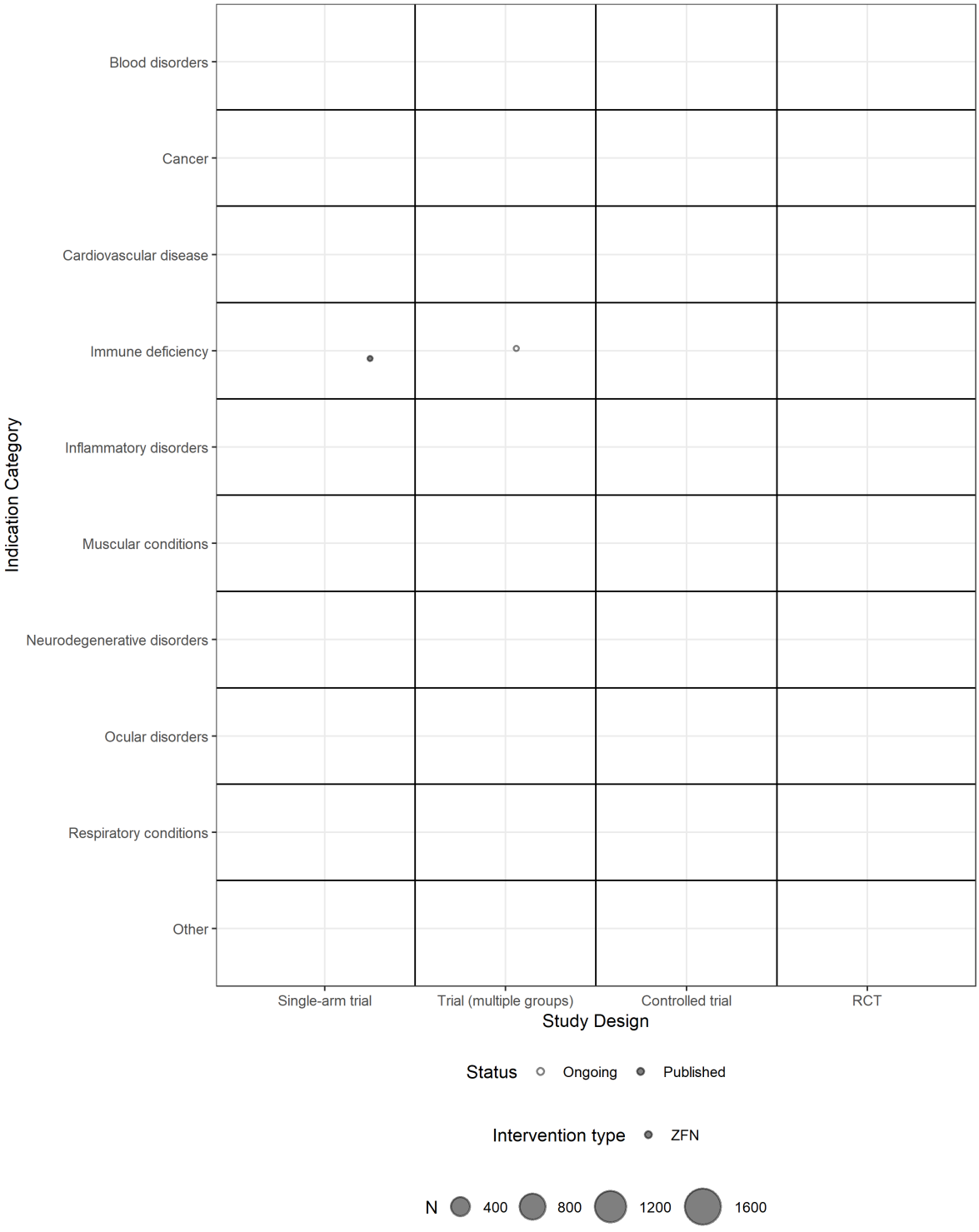
Appendix Evidence Map 3. Antisense Trials



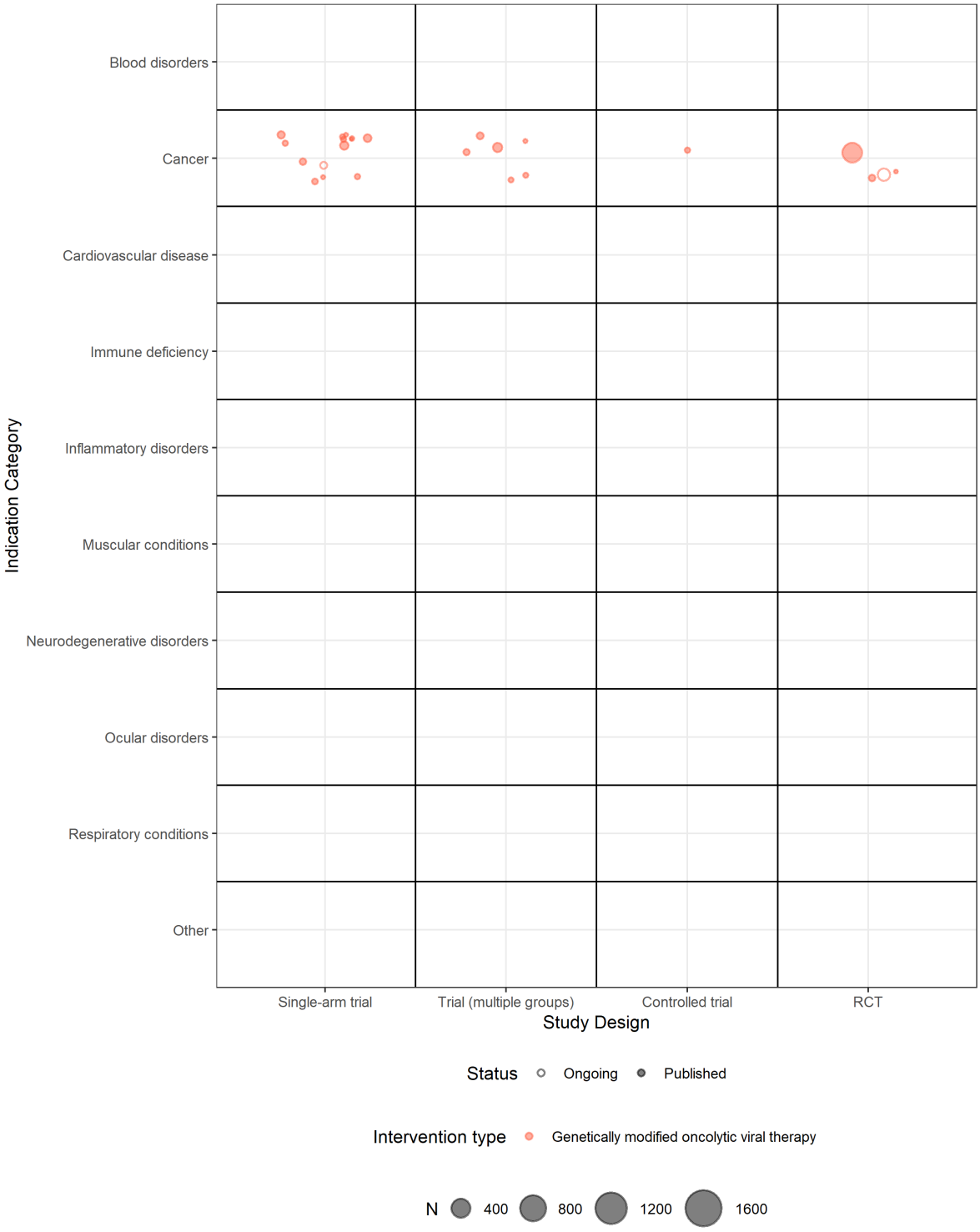
Appendix Evidence Map 4. RNAi Trials



Appendix Evidence Map 5. ZFN Trials



Appendix Evidence Map 6. Genetically Modified Oncolytic Viral Therapy Trials



Appendix F: Evidence Tables Published Trials

Appendix Table A1. Evidence Table Published Antisense Trials

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Liu, 2008[263] ID NR Single-arm trial N: 42	Age group: Age group unclear Advanced solid malignancies Treatment enrollment: None Treatment requisite: Standard chemotherapy premedications	Antisense Bcl-2 oligonucleotide G3139 No comparison group Follow-up: 1	Dose escalation and toxicity; objective response; G3139 plasma and tumor concentrations; carboplatin and paclitaxel pharmacokinetics; Bcl-2/Bax transcription in PBMCs and tumors; Bcl-2/Bax protein expression in peripheral blood lymphocytes and tumors	None	Although the maximal tolerated dose was not reached, the observed toxicities were consistent with what one would expect from carboplatin and paclitaxel alone. In addition, achievable intratumoral G3139 concentrations can result in Bcl-2 down-regulation in solid tumors and PBMCs.
Cancer Tolcher, 2001[275] ID NR Single-arm trial N: 12	Age group: Adults Hormone-refractory prostate cancer Treatment enrollment: None Treatment requisite: None	Antisense oligodeoxynucleotide (G3139) No comparison group Follow-up: 3	Prostate-specific antigen	Neutropenia	This represents an important experimental strategy to address Bcl-2-mediated chemotherapy resistance and will provide additional insights into the emerging role of docetaxel in the treatment of advanced prostate cancer.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Schmid, 2017[273] NCT02423590 RCT N: 140	Age group: Adults Squamous cell lung cancers Treatment enrollment: Stage IIIB disease that is unsuitable to radio-chemotherapy or stage IV disease or recurrent non-small-cell lung carcinoma (NSCLC); recurrent disease must not be amenable to resection or radical radiotherapy with curative intent. Treatment requisite: None	Antisense oligonucleotide apatorsen (OGX-427) Usual care: Active comparator: Gemcitabine/Carboplatin Follow-up: 7.5	Progression-free survival as measured by investigator-assessed (using RECIST 1.1) progression-free survival	GC+A was associated with increased toxicity compared with GC alone, with myelosuppression and infection being the most common adverse events.	This trial failed to demonstrate a benefit for adding apatorsen to standard chemotherapy in newly diagnosed squamous cell carcinoma.
Cancer Desai, 2005[265] ID NR Single-arm trial N: 36	Age group: Adults Advanced solid tumors Treatment enrollment: Surgery, immunotherapy, chemotherapy, and radiation Treatment requisite: None	Antisense oligonucleotide GTI-2040 No comparison group Follow-up: 6	Toxicity; tumor response; pharmacokinetics; pharmacodynamics	Fatigue (n = 1), infection (n = 1), bowel obstruction (1), AST (n = 2), ALT (n = 2), and bilirubin (n = 1)	The recommended dose of GTI-2040 given on this infusion schedule is 185 mg/m2/day. GTI-2040 appears to have a manageable toxicity profile and is generally well tolerated as a single agent.
Cancer Rosenberg, 2018[250] ID NR RCT N: 200	Age group: Children Metastatic urothelial carcinoma Treatment enrollment: Relapse after chemotherapy Treatment requisite: Antihistamine or an H2 antagonist prior to each of the 3 loading doses, and docetaxel	Apatorsen Usual care Follow-up: 35	Overall survival	Grade 3 to 5 adverse events (n = 77) in treated group	Combined therapy with apatorsen and docetaxel treatment met its predefined overall survival endpoint in patients with platinum-refractory metastatic urothelial carcinoma in this phase 2 trial. This trial is hypothesis generating, requiring further study before informing practice.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Yu, 2018[276] ID NR RCT N: 74	Age group: Adults Metastatic castration-resistant prostate cancer Treatment enrollment: None Treatment requisite: None	Apatorsen Usual care: Standard of care only Follow-up: 3	Disease progression	Dizziness, pulmonary embolism, hemolytic uremic syndrome, and chronic inflammatory demyelinating polyradiculoneuropathy	Apatorsen + prednisone did not change the proportion of CRPC patients without disease progression at 12 weeks compared with prednisone but was associated with significant PSA declines.
Cancer Reilley, 2018[278] ID NR Trial (multiple groups) N: 30	Age group: Adults Lymphoma Treatment enrollment: None Treatment requisite: Biopsy and peripheral blood mononuclear cell collection	AZD9150 No comparison group Follow-up: 11	Tumor size; toxicity	No serious treatment-related adverse events were reported.	AZD9150 was well tolerated and demonstrated efficacy in a subset of patients with diffuse large B-cell lymphoma.
Cancer Rom, 2009[266] ID NR Single-arm trial N: 28	Age group: Adults Primary breast cancer Treatment enrollment: None Treatment requisite: Standard-dose docetaxel (Taxotere), adriamycin, and cyclophosphamide (TAC)	Bcl-2 antisense oligodeoxynucleotide oblimersen No comparison group Follow-up: 1	Bioanalysis and selection of reagents; collection of samples; RNA isolation; reverse transcription; QCs	None	We demonstrated feasibility to process clinical samples and to obtain good-quality RNA from tumor biopsies and indicated the potential of oblimersen to lower Bcl-2 mRNA in breast cancer.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Morris, 2002[269] ID NR Single-arm trial N: 35	Age group: Adults Advanced cancer Treatment enrollment: None Treatment requisite: Paclitaxel	BCL-2 antisense oligonucleotide (G3139) No comparison group Follow-up: 1	Safety; pharmacokinetics; effects on Bcl-2 protein expression; clinical effects	Fatigue (n = 1), transaminitis (n = 1), abdominal pain (n = 1), hepatic enlargement (n = 1), urinary retention (n = 1), leukopenia (n = 1), thrombosis (n = 2), infection (n = 1), hyperglycemia (n = 1), dyspnea (n = 1), skin rash (n = 1), and palpitations (n = 1)	BCL-2 antisense therapy is well tolerated. Relative to other dose-finding studies of G3139, fatigue was somewhat more prominent in this study, possibly because of the protracted IV infusion schedule of the antisense oligonucleotide. Current randomized trials are using the highest daily dose established in this study given by shorter infusion periods (ie, 7 mg/kg/day for 5-7 days) to enhance the antitumor activity of standard cytotoxic drugs.
Cancer Chi, 2017[252] NCT01188187 RCT N: 1022	Age group: Adults Metastatic castration-resistant prostate cancer Treatment enrollment: None Treatment requisite: Docetaxel and prednisone	Clusterin Other Follow-up: 24	Overall survival	Neutropenia (n = 98) and sepsis (n = 77)	Addition of custirsen to first-line docetaxel and prednisone was reasonably well tolerated, but overall survival was not significantly longer for patients with metastatic castration-resistant prostate cancer treated with this combination, compared with patients treated with docetaxel and prednisone alone.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Dritschilo, 2006[267] ID NR Single-arm trial N: 17	Age group: Adults Advanced solid tumors Treatment enrollment: Chemotherapy Treatment requisite: Radiation therapy	Combined liposomal formulation of raf antisense oligonucleotide (LErafAON) No comparison group Follow-up: 2	Dose escalation; extent of exposure; dose modification	Dyspnea (n = 1), hypoxia (n = 1), tachypnea (n = 1), and wheezing (n = 1)	This is the first report of the combined modality treatment using antisense oligonucleotides with radiation therapy in patients with advanced cancer. A dose of 2.0 mg/kg of LErafAON administered twice weekly is tolerated with premedication and does not enhance radiation toxicity in patients. The observation of dose-dependent, infusion-related reactions has led to further modification of the liposomal composition for use in future clinical trials.
Cancer Stevenson, 1999[261] ID NR Single-arm trial N: 31	Age group: Adults Refractory malignancies Treatment enrollment: Chemotherapy/radiotherapy Treatment requisite: None	C-raf-1 antisense oligonucleotide ISIS 5132 (CGP 69846A) No comparison group Follow-up: 7	Toxicity; responses; ISIS 5132 pharmacokinetics; effect of ISIS 5132 on c-raf-1 mRNA expression	Anemia (n = 5) and fatigue (n = 2)	ISIS 5132 is well tolerated at doses up to 6.0 mg/kg when administered as a thrice weekly 2-hour infusion for 3 consecutive weeks. The pharmacokinetic behavior of the drug is reproducible, and suppression of target gene expression is observed in circulating PBMCs.
Cancer Blumenstein, 2013[277] ID NR RCT N: 63	Age group: Adults Metastatic castration-resistant prostate cancer Treatment enrollment: None Treatment requisite: None	Custirsen Placebo Follow-up: 36	Clusterin; prostate-specific antigen; overall survival	None	Lowered serum clusterin levels during custirsen treatment when in combination with either chemotherapy regimen were predictive of longer survival in mCRPC. These results support further evaluation of serum CLU as a therapeutic biomarker.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Beer, 2017[251] ID NR RCT N: 635	Age group: Adults Prostate cancer Treatment enrollment: Metastatic castration-resistant prostate cancer Treatment requisite: None	Custirsen (OGX011) Usual care Follow-up: 5	Overall survival; disease progression	Serious adverse events were reported in 155 (49%) of the treatment group versus 132 (42%) in the untreated group.	We noted no survival benefit in men with metastatic castration-resistant prostate cancer with additional treatment of custirsen to cabazitaxel and prednisone treatment. Cabazitaxel and prednisone remains the standard of care for patients with metastatic castration-resistant prostate cancer progressing after docetaxel chemotherapy.
Cancer Lai, 2009[256] ID NR Trial (multiple groups) N: 17	Age group: Adults Squamous cell carcinoma of the head and neck Treatment enrollment: Refractory to standard therapy Treatment requisite: None	EGFR AS No comparison group Follow-up: 30	Tumor volume	No grade 3 or 4 or dose-limiting toxicities were reported.	Intratumoral EGFR AS was safe and resulted in antitumor activity in patients with advanced squamous cell carcinoma of the head and neck. Baseline levels of high EGFR and low STAT3 may be associated with antitumor effects.
Cancer Bianchini, 2013[254] ID NR Trial (multiple groups) N: 22	Age group: Adults Prostate cancer Treatment enrollment: Castration-resistant Treatment requisite: None	EZN-4176 No comparison group Follow-up: 3	Toxicity; prostate-specific antigen	Adverse events (n = 3) and elevated liver enzymes (n = 1)	EZN-4176 activity at the doses and schedules explored was minimal. The highest dose was associated with significant but reversible transaminase elevation.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Shah, 2009[255] ID NR Single-arm trial N: 12	Age group: Adults Merkel cell carcinoma Treatment enrollment: Metastatic or regionally recurrent disease, and at least 3 weeks since last chemotherapy Treatment requisite: None	G3139 (Genasense) No comparison group Follow-up: 2	Toxicity; tumor indicator lesion(s)	Grade 4 lymphopenia (n = 1), grade 3 renal failure (n = 1), grade 3 cytopenia (n = 5), aspartate aminotransferase/ alanine aminotranferease elevation (n = 3), hypophosphatemia (n = 2), and pain (n = 1)	Bcl-2 antisense therapy (G3139) was well tolerated among patients with advanced Merkel cell carcinoma. While probable antitumor activity was documented in 1 patient, no objective responses per Response Evaluation Criteria in Solid Tumors criteria were observed.
Cancer van de Donk, 2004[199] ID NR, abstract describes "trial" Single-arm trial N: 10	Age group: Adults Refractory or relapsing multiple myeloma Treatment enrollment: Patients must have completed at least 2 lines of chemotherapy that included vincristine, adriamycin, and dexamethasone (VAD) chemotherapy. Treatment requisite: 7-day infusion with G3139 with vincristine, adriamycin, and dexamethasone (VAD) regimen included on days 4 to 7; treatment was repeated in 4-week cycles for 3 or more cycles and antibacterial and antifungal prophylaxis were administered as per location protocol.	G3139; Genasenset; oblimersen sodium No comparison group; Other: In combination with vincristine, adriamycin, and dexamethasone (VAD) chemotherapy Follow-up: Until death	Tumor response evaluation according to the Blade criteria (partial response, minor response, complete response, relapse, progression); Bcl-2 and lymphocyte subsets quantification	Grade 3 events: leucopenia (n = 2), neutropenia (n = 3), lymphopenia (n = 8), thrombocytopenia (n = 4), anemia (n = 1), thrombosis (n = 1), catheter-related infection (n = 1), infection (n = 2), and injection site reaction (n = 1) Grade 4 events: leucopenia (n = 3) and neutropenia (n = 3)	The results indicate that G3139 may overcome classical resistance and restore sensitivity of multiple myeloma cancer cells to vincristine, adriamycin, and dexamethasone (VAD) chemotherapy.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Kirschbaum, 2016[262] ID NR Single-arm trial N: 24	Age group: Adults Leukemia Treatment enrollment: Radiation, allogeneic transplant, prior drug therapy, prior anthracycline, prior hypomethylation agents, and prior mylotarg Treatment requisite: None	GTI-2040, an antisense oligonucleotide No comparison group Follow-up: 1	Toxicity; clinical activity; pharmacokinetic studies; molecular correlative studies	Nausea (n = 2), somnolence/depressed level of consciousness (n = 1), fatigue (n = 1), cardiac ischemia/infarction/troponin (n = 1), hemoglobin (n = 4), transaminases (2), platelets (n = 5), hypotension (n = 1), infection (pneumonia) (n = 1), and leukocytes (n = 1)	There were no objective responses to GTI-2040 in this study; 7 of 24 patients were able to complete the predetermined 3 infusion cycles. Pharmacokinetic and pharmacodynamic studies were performed, indicating a trend toward increasing intracellular drug levels and decreasing *RRM2* gene expression with increasing doses. This dose schedule may be considered if appropriate combinations are identified in preclinical studies.
Cancer Duffy, 2016[257] ID NR Trial (multiple groups) N: 24	Age group: Adults Carcinoma or colorectal cancer Treatment enrollment: Irinotecan-refractory colorectal cancer Treatment requisite: Irinotecan	ISIS 183750 No comparison group Follow-up: 12	Safety; maximally tolerated dose	Grade 3 or 4 neutropenia (n = 8), hypoalbuminemia (n = 6), diarrhea and/or dehydration (n = 7), and electrolyte abnormalities (n = 6)	Although no objective responses were observed, stable disease was seen in 7 of 15 (47%) patients who were progressing before study entry, 6 of whom were stable at the time of the week 16 CT scan. We also confirmed through mandatory pretherapy and posttherapy tumor biopsies penetration of the ASO into the site of metastasis.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Davis, 2003[259] ID NR Single-arm trial N: 7	Age group: Children Solid cancers Treatment enrollment: None Treatment requisite: None	MG98 No comparison group Follow-up: 1	Pharmacokinetic analysis; pharmacodynamic analysis; toxicity; pharmacodynamic analysis; hemoglobin F levels in peripheral blood; DNA MeTase; vimentin and Gadd45 mRNA levels in PBMC; antitumor activity	None	This schedule of MG98 given as a 21-day continuous intravenous infusion every 4 weeks was poorly tolerated in the highest doses; therefore, further disease site–specific evaluation of the efficacy of this agent will utilize a more favorable, intermittent dosing schedule. Pharmacodynamic evaluations undertaken in an attempt to explore and validate the biological mechanisms of MG98 did not show dose-related effects.
Cancer Klisovic, 2008[260] ID NR Trial (multiple groups) N: 23	Age group: Adults High-risk myelodysplasia and acute myeloid leukemia Treatment enrollment: Hydroxyurea, ESA, and combination chemotherapy Treatment requisite: None	MG98 No comparison group Follow-up: 2	Pharmacodynamic studies; toxicities; pharmacokinetics; clinical response	Neutropenia (n = 3), anemia (n = 8), leukopenia (n = 3), lymphopenia (n = 2), thrombocytopenia (n = 3), fatigue (n = 2), fever (n = 1), infection (n = 6), hemorrhage (n = 1), hypertension (n = 1), hypotension (n = 1), syncope (n = 1), diarrhea (n = 1), gingivitis (n = 1), ileus (n = 1), nausea (n = 2), and vomiting (n = 2)	No pharmacodynamic or clinical activity was observed at MG98 doses and schedules administered. Despite this, pursuing *DNMT1* down-regulation remains a sound approach for targeting aberrant epigenetics in AML/MDS.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Plummer, 2009[268] ID NR Single-arm trial N: 33	Age group: Adults Advanced solid tumors Treatment enrollment: Chemotherapy, radiotherapy, and primary surgery Treatment requisite: None	MG98 No comparison group Follow-up: 2	Toxicity; pharmacokinetics; pharmacodynamics; antitumor activity	Fatigue (n = 1), headache (n = 1), myalgia (1), neutropenia (n = 1), transaminitis (n = 8), elevated alkaline phosphatase (n = 4), nausea (n = 1), and thrombocytopenia (n = 1)	MG98 was well tolerated with early evidence of clinical activity. Proof of mechanism was observed and measurement of DNMT1 expression in peripheral blood mononuclear cells may be useful in future phase 2 development.
Cancer Stewart, 2003[264] ID NR Single-arm trial N: 19	Age group: Adults Solid tumors Treatment enrollment: Chemotherapy, radiotherapy, and immunotherapy Treatment requisite: None	MG98 No comparison group Follow-up: 9	DLT and dose recommended for phase 2 studies; other toxic effects; complement activation; response; pharmacokinetics; DNMT1 mRNA expression	None	The recommended dose of MG98 was 360 mg/m2 given by 2-hour infusion twice a week for 3 out of every 4 weeks. Phase 2 trials using this dose and schedule are underway.
Cancer Winquist, 2006[271] ID NR Single-arm trial N: 17	Age group: Adults Metastatic renal carcinoma Treatment enrollment: None Treatment requisite: None	MG98 No comparison group Follow-up: 2	Objective response or absence of progression for at least 8 weeks	Transaminitis was observed in patients with prior nephrectomy and appeared to be associated with altered drug exposure in these patients.	The lack of objective responses observed may be explained by a lack of target effect or the choice of tumor type.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Margolin, 2007[258] ID NR Trial (multiple groups) N: 23	Age group: Adults Metastatic renal cancer Treatment enrollment: At most one prior systemic therapy Treatment requisite: alpha-IFN	Oblimersen No comparison group Follow-up: 3	Tumor response	Fatigue (n = 5), hypophosphatemia (n = 5), hyperglycemia (n = 3), lymphopenia (n = 3), hyponatremia (n = 2), and transaminase elevation (n = 2)	Oblimersen as given in this study with alpha-IFN does not appear to warrant further study in advanced renal cancer. Combinations with newer agents may show greater promise.
Cancer Chanan-Khan, 2009[274] ID NR RCT N: 224	Age group: Adults Advanced multiple myeloma Treatment enrollment: None Treatment requisite: None	Oblimersen sodium Usual care Follow-up: 24	Time to tumor progression	The oblimersen/dexamethasone regimen was generally well tolerated, with fatigue, fever, and nausea, the most common adverse events reported.	Final results of this study demonstrated no significant differences between the 2 groups in TTP or objective response rate.
Cancer Gertz, 2005[253] ID NR Trial (multiple groups) N: 9	Age group: Adults Waldenström's macroglobulinemia Treatment enrollment: None Treatment requisite: Acetaminophen, allopurinol, and prehydration	Oblimersen sodium No comparison group Follow-up: 1	Maximum tolerable dose; IgM	Grade 3 fatigue and anorexia (n = 1), nonhematologic grade 3 toxicity (n = 2), grade ≥ 3 hematologic toxicity (n = 5), and severe neutropenia (n = 3)	Presented herein are early data on the phase 1 portion of a phase 1/2 study of oblimersen in Waldenström's macroglobulinemia to identify the maximum tolerated dose and to evaluate response in patients with symptomatic Waldenström's macroglobulinemia.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Luger, 2002[89] ID NR Single-arm trial N: 25	Age group: Adults Chronic myelogenous leukemia Treatment enrollment: Sequence-specific sensitivity to the c-myb–targeted oligodeoxynucleotide Treatment requisite: Bone marrow transplant and prophylactic phenytoin	ODN No comparison group Follow-up: 4	Toxicity; cytogenic response	Bacteremia (n = 3), gastrointestinal bleeding (n = 2), hyperbilirubinemia (n = 3), fungemia (n = 1), hypocalcemia (n = 3), deep venous thrombosis (n = 1), and death (n = 7)	Conclusions regarding clinical efficacy of ODN marrow purging should not be drawn from this small pilot study. However, the results lead to the speculation that enhanced delivery of ODN, targeted to critical proteins of short half-life, might lead to the development of more effective nucleic acid drugs and the enhanced clinical utility of these compounds in the future.
Cancer Chia, 2009[272] ID NR Single-arm trial N: 15	Age group: Adults Metastatic breast cancer Treatment enrollment: None Treatment requisite: None	OGX-011 No comparison group Follow-up: 1	Objective response	There were no grade 4 nonhematologic toxicities or treatment-related deaths.	The combination of OGX-011 and docetaxel at 75 mg/m2 is well tolerated and clinical activity was seen in these patients with metastatic breast cancer, but the number of responses was insufficient to meet the criteria for proceeding to the second stage of accrual.
Cancer Olivares, 2011[270] ID NR Single-arm trial N: 23	Age group: Adults Advanced or metastatic noncurable solid tumor Treatment enrollment: X-ray therapy and surgery Treatment requisite: None	TGF-b2 antisense GM-CSF gene-modified autologous tumor cell (TAG) vaccine No comparison group Follow-up: 24	Tumor response; safety; immune response	None	Bifunctional vaccines should be further evaluated.
Cardiovascular disease Graham, 2013[309]; National Institute of Diabetes[514] NCT02639286 RCT N: 7	Age group: Adults Healthy participants Treatment enrollment: None Treatment requisite: None	Antisense inhibition of human apoC-III Placebo Follow-up: None	Plasma apoC-III and triglyceride levels	No	Antisense inhibition of apoC-III in preclinical models and in a phase 1 clinical trial with healthy participants produced potent, selective reductions in plasma apoC-III and triglyceride, 2 known risk factors for cardiovascular disease.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cardiovascular disease Kastelein, 2006[327] ID NR RCT N: 36	Age group: Adults Dyslipidemia Treatment enrollment: None Treatment requisite: None	Antisense oligonucleotide inhibitor of apoB Placebo Follow-up: 3	ApoB; total cholesterol; VLDL; LDL-C; high-density lipoprotein (HDL); triglyceride	Elevated alanine aminotransferase (ALT) levels	Administration of an antisense oligonucleotide to human apoB resulted in a significant, prolonged, and dose-dependent reduction in apoB and LDL-C. Although injection site reactions were common, adherence to protocol was unaffected.
Cardiovascular disease Viney, 2016[318] ID NR RCT N: 122	Age group: Adults Elevated lipoprotein(a) Treatment enrollment: None Treatment requisite: None	IONIS-APO(a) Placebo Follow-up: 8	Lipoprotein(a); safety	No treatment-related serious adverse events were reported.	IONIS-APO(a)-LRx is a novel, tolerable therapy to reduce Lp(a). IONIS-APO(a)-LRx might mitigate Lp(a)-mediated cardiovascular risk and is being developed for patients with elevated Lp(a) concentrations.
Cardiovascular disease Akdim, 2011[317]; Furtado, 2012[515]; Kastle Therapeutics, 2007[516] NCT00216463 RCT N: 50	Age group: Adults Hyperlipidemia Treatment enrollment: Fasting stable LDL-cholesterol ≥ 130 mg/dL (3.36 mmol/L) and triglycerides < 400 mg/dL (4.55 mmol/L) Treatment requisite: None	ISIS 301012 Placebo Follow-up: 3	LDL cholesterol; apoB containing lipoproteins	Injection site reaction and hepatic enzyme increase	Mipomersen administered as monotherapy in subjects with mild-to-moderate hyperlipidaemia produced potent reductions in all apoB-containing lipoproteins. Higher doses were associated with hepatic transaminase increases.
Cardiovascular disease Tsimikas, 2015[319] ID NR RCT N: 16	Age group: Adults Healthy volunteers Treatment enrollment: None Treatment requisite: None	ISIS-APO(a)Rx Placebo Follow-up: 1	Total cholesterol; apoB; LDL-C; HDL-C; VLDL-C; triglyceride	No serious adverse events were reported.	ISIS-APO(a)Rx results in dose-dependent reductions of plasma Lp(a). The safety and tolerability support additional clinical development of ISIS-APO(a)Rx as a potential therapeutic drug to reduce the risk of cardiovascular disease and calcific aortic valve stenosis in patients with elevated Lp(a) concentration.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cardiovascular disease Akdim, 2010[316]; Kastle Therapeutics[517] NCT00231569 RCT N: 74	Age group: Adults Hypercholesterolemia Treatment enrollment: None Treatment requisite: None	Mipomersen Placebo Follow-up: 3	LDL cholesterol	Injection site reactions (mild-to-moderate erythema and hepatic transaminase increases)	Mipomersen might hold promise for treatment of patients who do not reach target LDL cholesterol levels on stable statin therapy. Further studies are needed to address the mechanisms and clinical relevance of transaminase changes after mipomersen administration.
Cardiovascular disease Akdim, 2010[322]; Kastle Therapeutics[518] NCT00281008 RCT N: 44	Age group: Adults Heterozygous familial hypercholesterolemia Treatment enrollment: Stable conventional lipid- lowering therapy and low-fat diet Treatment requisite: None	Mipomersen Placebo Follow-up: 2	LDL	Injection site reactions and influenza-like symptoms (n = 3)	Mipomersen had an incremental LDL cholesterol–lowering effect when added to conventional lipid-lowering therapy.
Cardiovascular disease Flaim, 2014[312]; Kastle Therapeutics[519] NCT01061814 RCT N: 84	Age group: Adults Homozygous familial hypercholesterolemia Treatment enrollment: None. Healthy volunteers were used in this study. Treatment requisite: None. Healthy volunteers were used in this study.	Mipomersen Placebo Follow-up: 3	Total cholesterol; LDL cholesterol; HDL cholesterol; triglycerides; apolipoprotein B (apoB)	No serious adverse events were reported.	Taken together, results from this short-term phase 1 study and the phase 3 studies in patients indicate a lack of systemic inflammation associated with mipomersen. These findings collectively support further evaluation of alternative dosing regimens for mipomersen in longer-term studies involving patients at high risk for coronary heart disease.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cardiovascular disease Li, 2014[323] ID NR Trial (multiple groups) N: 18	Age group: Adults Homozygous familial hypercholesterolemia Treatment enrollment: None Treatment requisite: None	Mipomersen No comparison group Follow-up: 1	Safety	No adverse events were reported.	The combination of warfarin and mipomersen appeared to be safe and well tolerated. The dosage adjustment of warfarin or mipomersen may not be necessary with coadministration.
Cardiovascular disease McGowan, 2012[80]; Kastle Therapeutics[520]; Duell, 2016[521] NCT00794664 RCT N: 58	Age group: Adults Severe hypercholesterolemia Treatment enrollment: Maximally tolerated lipid-lowering therapy Treatment requisite: Maximally tolerated lipid-lowering therapy and stable low-fat diet	Mipomersen Placebo, Other: Maximally tolerated lipid-lowering therapy plus either placebo or mipomersen Follow-up: 1	Total cholesterol (TC); high-density lipoprotein cholesterol (HDL-C); low-density lipoprotein cholesterol (LDL-C); triglycerides (TG); lipoprotein(a) [Lp(a)]; apolipoprotein B–100; apolipoprotein A1	Two patients reported drug-related serious adverse events: One patient experienced increased ALT and AST increased with hepatic steatosis and the other patient experienced a cerebrovascular accident, angina pectoris with Prinzmetal angina.	Mipomersen significantly reduced LDL-C, apolipoprotein B, total cholesterol and non-HDL cholesterol, and lipoprotein(a). Mounting evidence suggests it may be a potential pharmacologic option for lowering LDL-C in patients with severe hypercholesterolemia not adequately controlled using existing therapies.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cardiovascular disease Raal, 2010[78]; Patel, 2010[324]; Raal, 2016[326]; Duell, 2016[521] Kastle Therapeutics[522]; Kastle Therapeutics LLC[523] NCT00607373 RCT N: 51	Age group: Children and adults Homozygous familial hypercholesterolemia Treatment enrollment: None Treatment requisite: None	Mipomersen Placebo Follow-up: 12	Percentage change in LDL cholesterol concentration from baseline; percentage change from baseline in apolipoprotein B, total cholesterol, and non-HDL cholesterol concentrations; changes in concentrations of lipoprotein(a), triglycerides, VLDL cholesterol, HDL cholesterol, apolipoprotein A1, and ratio of LDL cholesterol to HDL cholesterol	None	Mean concentrations of LDL cholesterol at baseline were 11·4 mmol/L (SD 3·6) in the mipomersen group and 10·4 mmol/L (3·7) in the placebo group. The mean percentage change in LDL cholesterol concentration was significantly greater with mipomersen.
Cardiovascular disease Reyes-Soffer, 2016[320] ID NR Single-arm trial N: 17	Age group: Adults Dyslipidemia Treatment enrollment: None Treatment requisite: None	Mipomersen Placebo Follow-up: 2	apoB in VLDL, IDL, LDL, and triglyceride	None	Our human data are consistent with long-standing models of posttranscriptional and posttranslational regulation of apoB secretion and are supported by in vitro and in vivo experiments. Targeting apoB synthesis may lower levels of apoB lipoproteins without necessarily reducing VLDL secretion, thereby lowering the risk of steatosis associated with this therapeutic strategy.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cardiovascular disease Santos, 2015[314]; Duell, 2016[521]; Kastle Therapeutics, 2014[524] NCT00694109 Trial (multiple groups) N: 141	Age group: Children and adults Familial hypercholesterolemia Treatment enrollment: None Treatment requisite: None	Mipomersen No comparison group Follow-up: 6	LDL-C; apoB; total cholesterol density lipoprotein cholesterol; LDL/HDL ratio; triglycerides(TG); VLDL cholesterol; high-density lipoprotein cholesterol (HDL-C); apolipoprotein A-I (apo A-I); lipoprotein(a) (Lp[a])	Injection site reactions and flu-like symptoms	Long-term treatment with mipomersen for up to 104 weeks provided sustained reductions in all atherosclerotic lipoproteins measured and a safety profile consistent with prior controlled trials in these high-risk patient populations.
Cardiovascular disease Stein, 2012[79]; Vogt, 2013[328]; Kastle Therapeutics[525]; Duell, 2016[521] NCT00706849 RCT N: 124	Age group: Adults Familial hypercholesterolemia with coronary artery disease Treatment enrollment: None Treatment requisite: None	Mipomersen Placebo Follow-up: 7	LDL-C	Injection site reactions and influenza-like symptoms	Mipomersen is an effective therapy to further reduce apolipoprotein B-containing lipoproteins, including LDL and lipoprotein(a), in HeFH patients with coronary artery disease on statins and other lipid-lowering therapy. The significance of hepatic fat and transaminase increases remains uncertain at this time.
Cardiovascular disease Thomas, 2013[81]; Kastle Therapeutics[526] NCT00770146 RCT N: 158	Age group: Adults Hypercholesterolemia Treatment enrollment: On stable, maximally tolerated statin therapy for 8 weeks; on stable, low-fat diet for 12 weeks; and at stable weight for 6 weeks Treatment requisite: None	Mipomersen Placebo Follow-up: 7	LDL cholesterol levels	Injection site reactions and flu-like symptoms	Mipomersen significantly reduced LDL cholesterol, apolipoprotein B, and lipoprotein(a) in patients with hypercholesterolemia with, or at risk for, coronary heart disease not controlled by existing therapies.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cardiovascular disease Visser, 2010[315]; Kastle Therapeutics[527] NCT00362180 RCT N: 21	Age group: Adults Familial hypercholesterolemia Treatment enrollment: Lipid-lowering therapy Treatment requisite: None	Mipomersen Placebo Follow-up: 5	Efficacy; H-MRS; safety	None	Mipomersen administration for 13 weeks to subjects with FH is associated with a trend toward an increase in IHTG content.
Cardiovascular disease Visser, 2012[313]; Kastle Therapeutics[528] NCT00707746 RCT N: 34	Age group: Adults Hypercholesterolemia Treatment enrollment: None Treatment requisite: None	Mipomersen Placebo Follow-up: 7	LDL cholesterol (LDL-c); apoB; lipoprotein a [Lp(a)]	Injection site reactions and flu-like symptoms	The present data suggest that mipomersen is a potential therapeutic option in statin-intolerant patients at high risk for CVD. The long-term follow-up of liver safety is required.
Cardiovascular disease Waldmann, 2017[321] ID NR RCT N: 15	Age group: Adults Severe LDL-hypercholesterolemia and atherosclerosis Treatment enrollment: Despite maximal possible lipid-lowering therapy, patients fulfilled German criteria for lipoprotein apheresis Treatment requisite: Lipoprotein apheresis	Mipomersen Usual care Follow-up: 7	Lipid parameters	Elevated liver enzymes (n = 1) and moderate-to-severe injection site reactions or flu-like symptoms (n = 6)	Mipomersen reduced LDL cholesterol (significantly) and Lp(a) (nonsignificantly) in patients on maximal lipid-lowering drug therapy and regular apheresis, but is often associated with side effects.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cardiovascular disease Yu, 2016[325] ID NR Controlled trial N: 58	Age group: Adults Hypercholesterolemia Treatment enrollment: None Treatment requisite: None	Mipomersen Moxifloxacin IV Follow-up: 2	HR, RR, PR, QRS, and QT intervals	None	Mipomersen showed no effect on QT intervals in both phase 1 dose escalation and tQT studies. These results support the proposal that QT assessment can be made in a phase 1 dose escalation study, and no tQT study may be necessary if the phase 1 dose escalation study showed a negative QT effect.
Cardiovascular disease Yang, 2016[329] ID NR RCT N: 80	Age group: Adults Hypertriglyceridemia Treatment enrollment: None Treatment requisite: None	Volanesorsen Placebo Follow-up: 6	ApoB; lipoprotein (a) [Lp(a)]; apoA-I	None	Volanesorsen uniformly lowers apoC-III on apoB-100, Lp(a), and apoA-I lipoproteins, and may be a potent agent to reduce triglycerides and cardiovascular risk mediated by apoC-III.
Immune deficiency Sereni, 1999[353] ID NR Single-arm trial N: 36	Age group: Adults HIV Treatment enrollment: Monotherapy with zidovudine or didanosine Treatment requisite: None	Trecovirsen No comparison group Follow-up: 1	Pharmacokinetics; tolerability	Isolated, transitory increase in activated partial thromboplastin time	In summary, trecovirsen, an antisense phosphorothioate oligonucleotide, was well tolerated when administered to HIV-positive volunteers at single intravenous dose up to 2.5mg/kg when administered as a 2-hour intravenous infusion.
Inflammatory disorders Yacyshyn, 2007[360] ID NR RCT N: 331	Age group: Children and adults Crohn's disease Treatment enrollment: None Treatment requisite: Stable Crohn's medications and prednisone	Alicaforsen Placebo Follow-up: 3	Clinical remission rate	No treatment-related adverse events were reported.	Alicaforsen failed to demonstrate efficacy in its primary outcome measures. Alicaforsen was well tolerated.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Inflammatory disorders Feagan, 2018[362]; Feagan, 2017[529]; Feagan, 2015[530] ID NR Trial (multiple groups) N: 63	Age group: Adults Active Crohn's disease Treatment enrollment: None Treatment requisite: None	GED-0301 No comparison group Follow-up: 4	Crohn's disease activity index; safety	No treatment-related adverse events were reported.	These findings suggest that GED-0301 is a benefit in active Crohn's disease.
Inflammatory disorders Sewell, 2002[359] ID NR RCT N: 26	Age group: Adults Elevated tumor necrosis factor-alpha Treatment enrollment: None Treatment requisite: None	ISIS 104838 Placebo Follow-up: 1	Safety; tumor necrosis factor-alpha	No serious adverse events were reported.	Inhibition of tumor necrosis factor-alpha production ex vivo was reported.
Inflammatory disorders Warren, 2015[361] ID NR RCT N: 51	Age group: Adults Rheumatoid arthritis Treatment enrollment: None Treatment requisite: Methotrexate and other disease-modifying antirheumatic drug	ISIS-CRPRx Placebo Follow-up: 4	Inflammation markers; high-sensitivity C-reactive protein; safety	Fatal pulmonary edema (n = 1)	ISIS-CRPRx selectively reduced high-sensitivity C-reactive protein in a dose-dependent manner and was well tolerated in patients with rheumatoid arthritis. Its utility as a therapy in rheumatoid arthritis remains unclear.
Inflammatory disorders Monteleone, 2012[358] ID NR Single-arm trial N: 15	Age group: Adults Active Crohn's disease Treatment enrollment: Systemic corticosteroid, budesonide, and mesalamine Treatment requisite: None	Smad7 antisense oligonucleotide (GED0301) No comparison group Follow-up: 3	Safety and pharmacokinetics; changes in circulating cytokine-secreting T cells following GED0301 treatment; clinical response	None	GED0301 treatment reduced the percentage of inflammatory cytokine-expressing CCR9-positive T cells in the blood. The study shows for the first time that GED0301 is safe and well tolerated in patients with active CD.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Muscular conditions Kinali, 2009[373]; Imperial College London, 2009[531] NCT00159250 Single-arm trial N: 7	Age group: Adults Duchenne muscular dystrophy Treatment enrollment: None Treatment requisite: None	AVI-4658 No comparison group Follow-up: None	Mean intensity of dystrophin	None	Intramuscular AVI-4658 was safe and induced the expression of dystrophin locally within treated muscles.
Muscular conditions Goemans, 2018[366] ID NR RCT N: 186	Age group: Children Duchenne muscular dystrophy Treatment enrollment: None Treatment requisite: None	Drisapersen Placebo Follow-up: 12	6-minute walk distance	Most participants reported at least one AE, most of which were mild to moderate (7% in drisapersen, 3% in placebo).	Results suggest that drisapersen could have benefit in a less impaired population of DMD.
Muscular conditions Voit, 2014[365] ID NR RCT N: 53	Age group: Children Duchenne muscular dystrophy Treatment enrollment: None Treatment requisite: None	Drisapersen Placebo Follow-up: 7	6-minute walk distance	Vomiting (n = 1), myocarditis (n = 1), peripheral edema (n = 1), pain (n = 1), and hematuria (n = 1)	Continuous drisapersen provided some benefit in 6-minute walk distance versus placebo at week 25. The safety findings are similar to those from earlier studies.
Muscular conditions Matsuo, 2018[367] NCT02667483 Single-arm trial N: 7	Age group: Children Duchenne muscular dystrophy Treatment enrollment: None Treatment requisite: None	DS-5141B No comparison group Follow-up:	Dystrophin expression	None	None

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Muscular conditions Cirak, 2011[369]; Sarepta Therapeutics[532] EudraCT number 2007-004695-39, NCT00844597 Trial (multiple groups) N: 19	Age group: Children Genetically confirmed Duchenne muscular dystrophy with an out-of-frame deletion eligible for correction by skipping exon 51 Treatment enrollment: The patient must be receiving standard of care for Duchenne muscular dystrophy (DMD) as recommended by the North Star UK and TREAT-NMD1. Parent(s) or legal guardian and subject underwent a screening child psychiatric interview to evaluate trial/protocol expectations and family and child psychosocial and psychiatric adjustment. Treatment requisite: Pretreatment muscle biopsy to confirm that there were less than 5% dystrophin-positive revertant fibers; if not available, biceps brachii muscle biopsy taken pretreatment + posttreatment sample was taken from the contralateral biceps 2 weeks after the last dose.	Eteplirsen No comparison group Follow-up: 4	Step activity monitoring	2 SAE but unrelated to the study drug; 1 SAE (cardiomyopathy), possibly related to the study drug	The safety and biochemical efficacy that we present show the potential of AVI-4658 to become a disease-modifying drug for Duchenne muscular dystrophy.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Muscular conditions Mendell, 2016[83]; Mendell, 2013[533]; Mendell, 2016[534]; Mendell, 2014[535]; Dworzak, 2017[536]; Kinane, 2018[537]; Mendell, 2016[538]; Charleston, 2018[539]; Lowes, 2017[540]; Sarepta Therapeutics[541]; Sarepta Therapeutics[542] NCT01396239, NCT01540409 (follow-up) Controlled trial N: 12	Age group: Children Duchenne muscular dystrophy Treatment enrollment: None Treatment requisite: None	Eteplirsen Placebo Follow-up: 60	Loss of ambulation; pulmonary function	Eteplirsen was well tolerated.	Eteplirsen-treated patients showed a slower rate of decline in ambulation compared with untreated matched controls.
Muscular conditions Komaki, 2018[363] ID NR Trial (multiple groups) N: 10	Age group: Children Duchenne muscular dystrophy Treatment enrollment: Mutation confirmation Treatment requisite: None	NS-065/NCNP-01 No comparison group Follow-up: 4	Safety; dystrophin expression	No serious adverse events were reported.	These results suggest that NS-065/NCNP-01 has a favorable safety profile and promising pharmacokinetics, warranting further study in a phase 2 clinical trial.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Muscular conditions Biogen[372]; Biogen[543] NCT01703988 Trial (multiple groups) N: 34	Age group: Children Spinal muscular atrophy Treatment enrollment: None Treatment requisite: None	Nusinersen No comparison group Follow-up: 3	Adverse events (AEs), serious AEs (SAEs), discontinuations due to AEs, and highest severity of AEs; plasma pharmacokinetics: maximal observed plasma drug concentration (Cmax); plasma pharmacokinetics: time to reach Cmax in plasma, cerebrospinal fluid (CSF) Pharmacokinetics: Predose CSF Drug Concentrations, Urine Pharmacokinetics: Renal Clearance	0% to 25% of patients with SAEs	None
Muscular conditions Farrar, 2018[368] ID NR Trial (multiple groups) N: 16	Age group: Children and adults Spinal muscular atrophy Treatment enrollment: Homozygous *SMN1* deletions or heterozygous *SMN1* mutations, onset of symptoms before 6 months of age, and inability to sit independently Treatment requisite: Discussion of clinical efficacy, safety, and side effects of nusinersen, and the uncertainties regarding the short-term and long-term impact of this therapy on disease progression in SMA	Nusinersen Usual care Follow-up: 11	Motor milestone response	None reported	The nusinersen expanded access program highlights difficulties in achieving early diagnosis and/or prevention, evolution of optimal clinical care in a time of uncertain prognostication, resource implications, and ethical issues in clinical practice for SMA type 1.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Muscular conditions Finkel, 2016[85]; Biogen[544]; Biogen[543] NCT01839656 Trial (multiple groups) N: 20	Age group: Children Spinal muscular atrophy Treatment enrollment: None Treatment requisite: None	Nusinersen No comparison group Follow-up: 36	Improvement in motor milestones as assessed by Section 2 of the HINE; event-free survival; CHOP-INTEND motor function scale; neuromuscular electrophysiology; adverse events (AEs) and/or serious adverse events (SAEs); concentration of nusinersen in cerebro	No safety concerns. All participants experienced adverse events (570 events in total), with most being mild (359 events [63%]) or moderate (153 events [27%]) in severity. 77 serious adverse events were reported in 16 participants, all not related or unlikely related to the study drug	Administration of multiple intrathecal doses of nusinersen showed acceptable safety and tolerability, pharmacology consistent with its intended mechanism of action, and encouraging clinical efficacy. Results informed the design of an ongoing, sham-controlled, phase 3 clinical study of nusinersen in infantile-onset spinal muscular atrophy.
Muscular conditions Finkel, 2017[84]; Biogen[545]; Finkel, 2017[546]; Kuntz, 2018[547]; Finkel, 2016[548]; Servais, 2017[549] NCT02193074 RCT N: 122	Age group: Children Spinal muscular atrophy Treatment enrollment: None Treatment requisite: None	Nusinersen Sham procedure Follow-up: 13	Motor-milestone response; event-free survival	The incidence and severity of adverse events were similar in the 2 groups.	Among infants with spinal muscular atrophy, those who received nusinersen were more likely to be alive and have improvements in motor function than those in the control group. Early treatment may be necessary to maximize the drug's benefit.
Muscular conditions Hache, 2016[370]; Chiriboga, 2016[378];	Age group: Children Spinal muscular atrophy Treatment enrollment: None Treatment requisite: None	Nusinersen No comparison group Follow-up: 6	Number of participants who experience AEs and SAEs (time frame: up to 88 days); number of participants with clinically significant	No complications occurred in 50 (68%) lumbar punctures; in 23 (32%) procedures,	Lumbar punctures were successfully performed in children with spinal muscular atrophy; lumbar puncture–related adverse event frequency

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Biogen[543]; Biogen[550]; Biogen[551] NCT01494701 and NCT01780246 (follow-up) Trial (multiple groups) N: 28			neurological examination abnormalities (time frame: up to 88 days); number of participants with clinically significant vital sign abnormalities [time frame: up to 88 days] number of participants with clinically significant physical examination abnormalities [time frame: up to 88 days] number of participants with clinically significant weight abnormalities [time frame: up to 88 days] number of participants with clinically significant laboratory parameters [time frame: up to 88 days] number or participants with clinically significant cerbrospinal fluid (CSF) laboratory parameters [time frame: up to 88 days] Number of participants with clinically significant electrocardiograms (ECGs) abnormalities [time frame: up to 88 days]	adverse events were attributed to lumbar puncture. The most common adverse events were headache (n = 9), back pain (n = 9), and post–lumbar puncture syndrome (n = 8).	was similar to that previously reported in children.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
			number of participants who use concomitant medications [time frame: up to 88 days] PK parameters of nusinersen (ISIS 396443): Maximum observed plasma drug concentration (Cmax) [time frame: plasma at 1, 2, 4 and 20 hours after dosing] PK parameters of nusinersen: Time to reach maximum observed concentration (Tmax) [time frame: Plasma at 1, 2, 4 and 20 hours after dosing] PK parameters of nusinersen: Area under the plasma concentrations time curve from the time of the intrathecal (IT) dose to the last collected sample (AUCinf) [time frame: Plasma at 1, 2, 4 and 20 hours after dosing] PK parameters of nusinersen (ISIS 396443): Apparent terminal elimination half-life (t1/2), if possible [time frame: Plasma at 1, 2, 4 and 20 hours after dosing]		

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Muscular conditions Mercuri, 2018[371]; Mercuri, 2017[552]; Biogen[553] NCT02292537 RCT N: 126	Age group: Children Spinal muscular atrophy Treatment enrollment: None Treatment requisite: None	Nusinersen Sham procedure Follow-up: 15	Hammersmith Functional Motor Scale–Expanded (HFMSE) score	The overall incidence of AEs was similar between the groups.	Among children with later-onset SMA, those who received nusinersen had significant and clinically meaningful improvement in motor function as compared with those in the control group.
Muscular conditions Goemans, 2011[364] ID NR Trial (multiple groups) N: 12	Age group: Children Duchenne muscular dystrophy Treatment enrollment: Mutation confirmation Treatment requisite: None	PRO051 No comparison group Follow-up: 15	6-minute walking distance; dystrophin; safety	No serious adverse events were reported.	PRO051 showed dose-dependent molecular efficacy in patients with Duchenne muscular dystrophy, with a slight improvement in the 6-minute walk test after 12 weeks of extended treatment.
Neurodegenerative disorders Limmroth, 2014[376] ID NR RCT N: 77	Age group: Adults Relapsing-remitting multiple sclerosis Treatment enrollment: At least 9 T2 lesions or at least 4 T2 lesions if one was gadolinium (Gd)-enhancing; at least 1 relapse in the previous 12 months, but no relapses in the previous 4 weeks; and Expanded Disability Status Scale (EDSS) score 0 to 6.0 Treatment requisite: None	ATL1102 Placebo Follow-up: 4	Number of new active lesions	No serious adverse events were reported.	ATL1102 significantly reduced disease activity after 8 weeks of treatment and was well tolerated. This trial provides evidence for the first time that antisense oligonucleotides may be used as a therapeutic approach in treating neuroimmunologic disorders.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Neurodegenerative disorders van Deutekom, 2007[377] ID NR Single-arm trial N: 4	Age group: Children Duchenne muscular dystrophy Treatment enrollment: Correctable deletions by exon-51 skipping and no evidence of dystrophin on previous diagnostic muscle biopsy Treatment requisite: None	PRO051 No comparison group Follow-up: 1	Dystrophin-positive fibers	No adverse events were reported.	Intramuscular injection of PRO051 induced dystrophin synthesis in 4 patients with Duchenne muscular dystrophy, suggesting that further studies might be feasible.
Ocular disorders Cursiefen, 2009[379] ID NR RCT N: 40	Age group: Adults Corneal neovascularization Treatment enrollment: None Treatment requisite: None	GS-101 Placebo Follow-up: 18	Area covered by pathologic corneal blood Vessels	No adverse events were reported.	Interim results suggest that GS-101 eye drops at an optimal dose of 86 g/day are an effective and noninvasive approach specifically to inhibit and regress active corneal angiogenesis, a major risk factor for corneal graft transplantation and graft rejection. Safety concerns were not detected.
Acromegaly Trainer, 2018[389] ID NR Trial (multiple groups) N: 26	Age group: Adults Acromegaly Treatment enrollment: Acromegaly treatment naïve or who had not taken other acromegaly medications for at least the following periods of time prior to IGF-I and GH screening tests: bromocriptine: 6 weeks; carbergoline: 8 weeks; quinagolide: 8 weeks; octreotide (subcutaneous): 4 weeks; pegvisomant: 8 weeks; octreotide LAR: 4 months; lanreotide (all presentations): 4 months, Treatment requisite: None	ATL1103 No comparison group Follow-up: 2	Change in IGF-I at week 14	ATL1103 was well tolerated, although 84.6% of patients experienced mild-to-moderate injection site reactions.	This study provides proof of concept that ATL1103 is able to significantly lower IGF-I in patients with acromegaly.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Other: Liver infection GlaxoSmithKline[395]; Han, 2017[554] ID NR RCT N: 56	Age group: Adults Chronic hepatitis B Treatment enrollment: None Treatment requisite: None	GSK3389404 Placebo Follow-up: 4	Complement split factors; safety	No serious adverse events were reported.	GSK404 demonstrated a favorable safety profile, dose proportional pharmacokinetics, short plasma half-life, and no plasma accumulation after weekly doses across a dose range of 10 mg to 120 mg. GSK404 is currently being evaluated in chronic hepatitis B patients in a phase 2a study.
Hereditary transthyretin amyloidosis Benson, 2018[71]; Maurer, 2018[555]; Pinto, 2018[556]; Waddington-Cruz, 2018[557]; Benson, 2017[558]; Wang, 2017[559]; Wilton, 2015[560]; Ionis Pharmaceuticals, 2017[561]; Benson, 2015[562]; Heitner, 2016[563]; Conceicao, 2018[564]; Vita, 2018[565] NCT01737398 RCT N: 172	Age group: Adults Transthyretin-mediated familial amyloid polyneuropathy Treatment enrollment: None Treatment requisite: None	Inotersen Placebo Follow-up: 15	Neuropathy impairment; quality of life	Thrombocytopenia and glomerulonephritis were managed with enhanced monitoring; 5 deaths occurred in the inotersen group, none in the placebo group, and glomerulonephritis and thrombocytopenia in 3 inotersen patients each.	Inotersen improved the course of neurologic disease and quality of life in patients with hereditary transthyretin amyloidosis.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Other: Overweight with type 2 diabetes Digenio, 2018[387] ID NR RCT N: 92	Age group: Adults Overweight with type 2 diabetes Treatment enrollment: Uncontrolled hyperglycemia (HbA_{1c} greater than or equal to 7.5%) Treatment requisite: Lifestyle counseling	IONIS-PTP-1BRx Placebo Follow-up: 9	HbA_{1c}; leptin; adiponectin; body weight	No serious adverse events were reported.	IONIS-PTP-1BRx treatment produced prolonged reductions in HbA_{1c}, improved medium-term glycemic parameters, reduced leptin and increased adiponectin levels, and reduced body weight.
Other: Diabetes mellitus Van Meer, 2016[390] ID NR RCT N: 69	Age group: Adults Diabetes Treatment enrollment: None Treatment requisite: None	ISIS 388626 Placebo Follow-up: 3	Safety; renal damage markers	Creatinine increase. The creatinine increases were accompanied by a rise in the levels of urinary renal damage markers [β-2-microglobulin (B2M), total protein, kidney injury molecule (KIM1), alpha-glutathione S-transferase (aGST), and N-acetyl-β-(D)-glucosaminid.	In conclusion, ISIS 388626 treatment induced glucosuria at a dose level of 200 mg/week. This intended pharmacological effect was small, amounting to approximately 1% of the total amount of filtered glucose. Changes in serum and urinary markers were indicative of transient renal dysfunction, most probably of tubular origin. Whether the glucosuria is caused by specific SGLT2 inhibition or general tubular dysfunction or a combination remains uncertain.
Other:Homozygous familial hypercholesterolemia Li, 2014[388]ID NR RCT N: 20	Age group: Adults Healthy volunteers Treatment enrollment: None Treatment requisite: None	Mipomersen Placebo Follow-up: 1	Pharmacokinetics; safety and tolerability	None	Single SC doses of 50 mg to 200 mg were safe and well tolerated when administered to Japanese subjects. Comparison of PK between Japanese and Western subjects does not support any need for dose adjustment in the Japanese population in future clinical development.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Respiratory conditions Gauvreau, 2008[381] ID NR RCT N: 17	Age group: Adults Mild atopic asthma Treatment enrollment: None Treatment requisite: None	TPI ASM8 Placebo Follow-up: 1	Sputum eosinophil influx; asthmatic response	None	TPI ASM8 reduces the allergen-induced increase in target gene mRNA and airway responses in individuals with mild asthma.

Abbreviations: AEs, adverse events; ID, identification number; N, number of participants; NR, not reported; PBMC, peripheral blood mononuclear cell; RCT, randomized controlled trial; RNA, ribonucleic acid

Appendix Table A2. Evidence Table Published Autologous Cell Trials

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Blood disorders Thompson, 2018[152]; Bluebird, 2018[566]; Bluebird, 2019[567]; Ribeil, 2017[568] NCT02633943 (combines NCT01745120 and NCT02151526) Trial (multiple groups) N: 22	Age group: Children and adults β-thalassemia, sickle cell Treatment enrollment: Transfusion dependent Treatment requisite: Enhanced red-cell transfusion for at least 3 months prior to mobilization (in phase 2 study only), mobilization and apheresis, myeloablative conditioning, and washout	LentiGlobin BB305 No comparison group Follow-up: 24	Total hemoglobin; total modified hemoglobin; decrease (or discontinuation) of red blood cell transfusions; vector copy number; iron metabolism (phase 2 only); hemolysis (phase 2 only); dyserythropoiesis (phase 2 only)	No serious adverse events attributed to the vector. All serious adverse events related to the phase 1 study: venoocclusive liver disease (grade 3, n = 2), klebsiella infection (grade 3, n = 1), cardiac ventricular thrombosis (grade 3, n = 1), cellulitis (grade 3, n = 1), device-related thrombosis (grade 2, n = 1), hyperglycaemia (grade 3, n = 1), gastroenteritis (grade 3, n = 1), and diarrhea infectious (grade 2, n = 1). All serious adverse events related to the phase 2 study: tooth infection (grade 3, n = 1), pneumonia (grade 2, n = 1), and major depression (grade 3, n = 1); adverse events in the first sickle cell disease patient were consistent with busulfan conditioning.	Gene therapy with autologous CD34+ cells transduced with the BB305 vector reduced or eliminated the need for long-term red-cell transfusions in 22 patients with severe β-thalassemia without serious adverse events related to the drug product. Results for 1 patient with sickle cell disease show that 15 months after treatment, the level of therapeutic antisickling beta-globin remained high without recurrence of sickle crises and with correction of the biologic hallmarks of the disease.
Cancer Trudel, 2001[249] ID NR, protocol approved by Health Protection Branch of Canada Single-arm trial N: 8	Age group: Adults Multiple myeloma Treatment enrollment: Chemotherapy Treatment requisite: None	Adenovirus engineered, autologous plasma cells No comparison group Follow-up: 15	Local immune response; systemic immune responses; clinical outcome	None	These results demonstrate that the generation of adenovector modified plasma cell vaccines is technically feasible and can be safely administered posttransplant.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Burch, 2004[198] ID NR, title uses "trial" Single-arm trial N: 21	Age group: Adults Androgen-independent prostate carcinoma Treatment enrollment: None Treatment requisite: None	APC8015 No comparison group Follow-up: 22	Response to treatment; treatment-related toxicity; immune response	None	This study demonstrates a definite clinical response of androgen-independent prostate cancer to APC immunotherapy.
Cancer Di Nicola, 2004[283]; Di Nicola, 2003[569] ID NR Single-arm trial N: 6	Age group: Adults Melanoma Treatment enrollment: Refractory to standard treatment Treatment requisite: Leukapheresis	Autologous dendritic cells transduced with a modified vaccinia Ankara virus encoding human tyrosinase gene No comparison group Follow-up: 40	Survival	No serious adverse events were reported.	These results suggest that vaccination with MVA-hTyr–transduced dendritic cells is well tolerated, can possibly produce clinical responses, and activates tyrosinase- and vaccinia virus–specific T cells in vivo.
Cancer Luiten, 2005[288] ID NR Trial (multiple groups) N: 28	Age group: Adults Melanoma Treatment enrollment: None Treatment requisite: None	Autologous GM-CSF–transduced tumor cells No comparison group Follow-up: 96	Overall survival; progression-free survival; toxicity	No serious adverse events were reported.	Whether the induction of autoimmune vitiligo may prolong disease-free survival of metastatic melanoma patients who are rendered as having no evidence of disease before vaccination is worthy of further investigation.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Adair, 2014[183] NCT00669669 Single-arm trial N: 7	Age group: Adults Glioblastoma Treatment enrollment: Newly diagnosed patients received surgical resection (>50%) of primary tumor and radiation therapy. Treatment requisite: Mobilization with granulocyte colony-stimulating factor (G-CSF) followed by leukapheresis; carmustine treatment prior to infusion of modified cells; up to 24 cycles of adjuvant chemotherapy (temozolomide or O6-benzylguanine/temozolomide)	Autologous hematopoietic stem cells No comparison group, Other: All patients treated with combination of chemotherapy after gene therapy Follow-up: 180	Best clinical response (partial response, complete response, progressive disease, stable disease); progression-free survival; overall survival	Stated that none observed, but not discussed in detail	Our results show that P140K modified HSCs and progenitor cells, in combination with dose-intense TMZ and O6BG, is a clinically feasible alternative to standard therapy for poor prognosis, MGMThi GBM patients.
Cancer Davis, 2010[192] ID NR, protocol reviewed by NCI Institutional Review Board, the NIH Office of Biotechnology Activities, and the Food and Drug Administration Trial (multiple groups) N: 26	Age group: Adults Metastatic cancer Treatment enrollment: None Treatment requisite: Nonmyeloablative, lymphodepleting chemotherapy	Autologous lymphocytes expressing mTCR No comparison group Follow-up: 6	Serum IgG binding to TCR-transduced lymphocytes; serum inhibition of TCR function in vitro; CR chain specificity of immune response	None	In summary, patients treated with mTCR can develop an immune response to gene-modified cells in a minority of cases, but this may not affect clinical outcome.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Soiffer, 2003[202] ID NR Trial (multiple groups) N: 35	Age group: Adults Metastatic melanoma Treatment enrollment: Surgery, interferon, chemotherapy, radiation therapy, interleukin-2, limb perfusion therapy, and other vaccines Treatment requisite: None	Autologous melanoma cells engineered to secrete granulocyte-macrophage colony-stimulating factor (GM-CSF) by retroviral-mediated gene transfer No comparison group Follow-up: 36	Toxicities; vaccination reactions; antiadenoviral humoral responses; delayed-type hypersensitivity reactions; immune responses in metastases; clinical outcomes	None	Vaccination with irradiated, autologous melanoma cells engineered to secrete GM-CSF by adenoviral-mediated gene transfer augments antitumor immunity in patients with metastatic melanoma.
Cancer Palmer, 1999[211] ID NR Trial (multiple groups) N: 12	Age group: Adults Malignant melanoma Treatment enrollment: Chemotherapy or radiotherapy Treatment requisite: None	Autologous melanoma cells genetically engineered to secrete interleukin 2 (IL-2) No comparison group Follow-up: 15	Immune response to vaccination; tumor response	None	Patient vaccination with autologous, genetically engineered tumor cells is feasible and safe.
Cancer Moore, 2018[224] NCT01586403 Single-arm trial Completed N: 3	Age group: Adults Melanoma Treatment enrollment: None Treatment requisite: None	Autologous T cells transduced with the tyrosinase-reactive TIL1383I TCR No comparison group Follow-up: 17	Clinical response	None	In 2 of these 3 patients, adoptive transfer of tyrosinase-reactive TCR-transduced T cells into metastatic melanoma patients had clinical and/or biological activity without serious adverse events.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Fakhrai, 2006[231] ID NR Trial (multiple groups) Completed N: 6	Age group: Adults Advanced glioma Treatment enrollment: Surgery and radiation therapy Treatment requisite: None	Autologous tumor cells genetically modified by a transforming growth factor-beta 2 antisense vector No comparison group Follow-up: 21	Survival; progressive disease; stable disease; partial remission; complete response	None	The overall median survival was 68 weeks. Median survival of the responding patients was 78 weeks, compared with a historic value of 47 weeks for glioma patients treated conventionally. There were indications of humoral and cellular immunity induced by the vaccine. These findings support further clinical evaluation of vaccines comprised of TGF-b antisense-modified tumor cells
Cancer Nemunaitis, 2004[284] ID NR Trial (multiple groups) N: 43	Age group: Adults Non–small cell lung cancer Treatment enrollment: None Treatment requisite: None	Autologous tumor cells genetically modified with an adenoviral vector to secrete human granulocyte-macrophage colony-stimulating factor No comparison group Follow-up: 28	Survival; tumor response; toxicity	No serious adverse events were reported.	Longer survival was observed in patients receiving vaccines secreting GM-CSF at more than 40 ng/24 h per 106 cells than in patients receiving vaccines secreting less GM-CSF, suggesting a vaccine dose–related survival advantage.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Chang, 2000[286] ID NR Controlled trial N: 5	Age group: Adults Melanoma Treatment enrollment: None Treatment requisite: Interleukin 2	Autologous tumor cells transduced to secrete granulocyte-macrophage colony-stimulating factor Other: Wild-type tumor vaccine Follow-up: 36	Tumor response	The adverse events were associated only with interleukin-2.	Complete tumor remission in 1 patient provides a rationale to pursue this approach further.
Cancer Schreiber, 1999[248] ID NR Trial (multiple groups) N: 41	Age group: Adults Metastatic malignant melanoma Treatment enrollment: None Treatment requisite: None	BIWB1 No comparison group Follow-up: 19	Continuously progressive disease; short-term stable disease; prolonged stable disease	SAEs (events): 21 including hematemesis, melena, anemia, paresis, pleural effusion, pneumonia, acute renal failure, and ascites (no specific counts)	These data indicate that IL-2-producing, autologous cancer cells can be safely administered to stage IV melanoma patients and could conceivably be of benefit to patients with less advanced disease.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Devereux, 1998[215] ID NR Single-arm trial N: 3	Age group: Children and adults Relapsed Hodgkin disease or high-grade non-Hodgkin lymphoma Treatment enrollment: None Treatment requisite: Patients received chemotherapy with cyclophosphamide or etoposide/methylprednisolone/cytarabine/cisplatin regimen followed by lenograstim 24 h later; peripheral blood stem cells were harvested usually at days 8 and 15 (dependent on white cell count) for 3 consecutive days; the collected cells were further purified for CD34+ cells and then retrovirally transduced to express MDR-1; patients received BCNU/etoposide/Ara-C/melphalan regimen conditioning chemotherapy followed by infusion of transduced cells 24h after the end of the regimen; filgrastim was administered starting at day 7 until neutrophil count recovery; a bone marrow aspirate was	CD34+ cells were transduced with MDR-1 and reinfused back into patients. No comparison group Follow-up: Until death	Polymerase chain reaction (PCR) for vector-derived product; clinical outcomes (complete remission, survival)	No adverse events were observed.	The effect of multidrug resistance (MDR-1) gene substrate drugs hasn't been tested yet as all patients remain in remission of their disease.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
	collected from patients at 3 months post-transplant				
Cancer Morse, 2003[290] ID NR Trial (multiple groups) N: 37	Age group: Adults Carcinoembryonic antigen-expressing malignancies Treatment enrollment: None Treatment requisite: Leukapheresis	CEA RNA-pulsed dendritic cells No comparison group Follow-up: 27	Tumor marker; survival	No serious adverse events were reported.	It is feasible and safe to administer mRNA-loaded dendritic cells to patients with advanced malignancies.
Cancer Schmidt-Wolf, 1999[294] ID NR Trial (multiple groups) N: 10	Age group: Adults Renal cancer, colon cancer, lymphoma Treatment enrollment: None Treatment requisite: None	Cytokine-induced killer cells transfected with IL-2 No comparison group Follow-up: 2	Tumor response	No serious adverse events were reported.	We demonstrate that cytokine-induced killer cells transfected with the IL-2 gene can be administered without major side effects and are promising for future therapeutic trials.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Steele, 2011[298] ID NR Trial (multiple groups) N: 27	Age group: Adults Melanoma Treatment enrollment: Exhausted all prior treatment options Treatment requisite: None	Dendritic cell vaccine transfected with DNA encoding melan A and gp100 No comparison group Follow-up: 4	Tumor response; toxicity	Severe arm pain (n = 1) and atrial fibrillation (n = 1)	Vaccination with mature dendritic cells transfected with DNA encoding antigen had biological effect causing tumor regression and inducing diverse T lymphocyte responses.
Cancer Kyte, 2016[285] ID NR Single-arm trial N: 31	Age group: Adults Melanoma Treatment enrollment: None Treatment requisite: Leukapheresis, one cohort received adjuvant interleukin 2	Dendritic cells loaded with autologous tumor-mRNA No comparison group Follow-up: 140	Overall survival; safety	No serious adverse events were reported.	A favorable safety profile and evidence of survival benefit warrant further studies of the RNA/DC vaccine. The vaccine appears insufficient as monotherapy, but there is a strong rationale for combination with checkpoint modulators.
Cancer Caruso, 2004[302] ID NR Trial (multiple groups) N: 9	Age group: Children and adults Brain cancer Treatment enrollment: None Treatment requisite: Leukapheresis	Dendritic cells pulsed with tumor RNA No comparison group Follow-up: 21	Tumor response; toxicity	No serious adverse events were reported.	This study reported that DCRNA vaccines are safe and feasible in children with tumors of the central nervous system with a single leukapheresis.
Cancer Lesterhuis, 2010[287] ID NR Controlled trial N: 16	Age group: Adults Liver or colorectal cancer Treatment enrollment: None Treatment requisite: Leukapheresis	Dendritic cells transfected with CEA mRNA Other: Peptide pulsed dendritic cells Follow-up: 77	Progression-free survival	None	Dendritic cell CEA mRNA transfection did not improve induction of tumor-specific immune response in colorectal cancer patients compared with DC CEA peptide pulsing.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Heiser, 2002[281] ID NR Trial (multiple groups) N: 13	Age group: Adults Prostate cancer Treatment enrollment: None Treatment requisite: Leukapheresis	Dendritic cells transfected with prostate-specific antigen RNA No comparison group Follow-up: 5	Safety; prostate-specific antigen	No adverse events were reported.	Vaccine safety, successful in vivo induction of PSA-specific immunity, and impact on surrogate clinical endpoints provide a scientific rationale for further clinical investigation of RNA-transfected DCs in the treatment of human cancer.
Cancer Su, 2003[289] ID NR Trial (multiple groups) N: 10	Age group: Adults Renal cell carcinoma Treatment enrollment: Nephrectomy Treatment requisite: Leukapheresis	Dendritic cells transfected with total renal tumor RNA No comparison group Follow-up: 29	Disease-specific death	No serious treatment-related adverse events were reported.	The results provide scientific rationale for continued clinical investigation of this polyvalent vaccine strategy in the treatment of metastatic renal cell carcinoma and, potentially, other cancers.
Cancer Mahvi, 2002[204] ID NR ID NR Trial (multiple groups) N: 16	Age group: Adults Metastatic melanoma or soft tissue sarcoma Treatment enrollment: None Treatment requisite: Surgical excision of 1-cm tumor nodule for vaccine preparation	Freshly resected tumor specimens were processed into a cell suspension, irradiated, and then exposed to particle-mediated gene transfer. No comparison group Follow-up: Death (more than 72 months as of the publication)	Time to disease progression; survival	No vaccine-related toxicity was observed in groups 1 and 2 during the 14 days after the vaccination. For group 3, no vaccine-related toxicity with a minimum of 3 months of follow-up.	This technique of gene transfer was safe and feasible, but resulted in clinically relevant levels of gene expression in a small set of patients.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Moiseyenko, 2005[197] ID NR Trial (multiple groups) N: 21	Age group: Adults Disseminated malignant melanoma and metastatic renal cell carcinoma Treatment enrollment: Cytoreductive operations, chemotherapy with dacarbazine, interferon-a before the vaccine therapy, and immunotherapy Treatment requisite: None	Gene therapy with autologous tumor cells modified with tag7/PGRP-S gene No comparison group Follow-up: 3	Toxicity; DTH skin testing; clinical responses; immunological responses	None	The approach suggested here appears to be well tolerated and produces several durable clinical effects. Further studies are required to determine whether promising effects on immune activation will result in an actual clinical benefit for patients with malignant melanoma and renal cell carcinoma.
Cancer Simons, 1997[218] ID NR Trial (multiple groups) N: 18	Age group: Adults Metastatic renal cell carcinoma Treatment enrollment: None Treatment requisite: None	Granulocyte-macrophage colony-stimulating factor gene-transduced vaccines Other: Dose-escalation study with equivalent doses of autologous, irradiated RCC vaccine cells with or without ex vivo human GM-CSF gene transfer Follow-up: 1	Safety; immune response	None	This phase 1 study demonstrated the feasibility, safety, and bioactivity of an autologous GM-CSF gene-transduced tumor vaccine for RCC patients.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Tani, 2004[222] ID NR Single-arm trial N: 4	Age group: Adults Renal cell cancer Treatment enrollment: None Treatment requisite: None	Granulocyte-macrophage colony-stimulating factor gene-transduced vaccines No comparison group Follow-up: 62+	Progressive disease; stable disease; mixed response; survival	None	Our results suggest that GVAX substantially enhanced the antitumor cellular and humoral immune responses, which might have contributed to the relatively long survival times of our patients in the present study.
Cancer Meijer, 2002[205] ID NR Single-arm trial N: 20	Age group: Adults Metastatic melanoma and renal cell cancer Treatment enrollment: Surgery, chemotherapy, interferon alpha, radiotherapy, and interleukin-2 Treatment requisite: Tumor harvesting	HLA-B7/beta2-microglobulin gene-modified autologous tumor cells No comparison group Follow-up: 1	Expansion of tumor vaccine draining lymph node (TVDLN); clinical results; immunologic results; systemic immunity	None	Successful expansion of adequate TVDLN was accomplished in 19 of 20 harvests of unmodified vaccines and in 18 of 20 gene-modified vaccines. No major toxicities were noted after vaccination with autologous tumor cells or adoptive transfer of ex vivo activated TVDLN lymphocytes. Typical IL-2-related toxicities were observed in all patients. No objective tumor regressions were observed.
Cancer Nemunaitis, 1998[213] ID NR Single-arm trial N: 5	Age group: Children and adults Metastatic melanoma Treatment enrollment: None Treatment requisite: None	IFN-g No comparison group Follow-up: 35+	Stable disease; progressive disease	SAEs: 9 events in 5 patients	We found that injections of autologous tumor cells transduced by IFN-gamma gene were well tolerated. However, the ability to develop primary autologous melanoma cell lines were limited, and only a minority of patients were injected.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Sun, 1998[214]; Moller, 1998[570]; Schadendorf, 1995[571]; Moller, 2000[572] ID NR Trial (multiple groups) N: 6	Age group: Adults Melanoma Treatment enrollment: Exhausted all prior treatment options Treatment requisite: None	IL-12 gene modified No comparison group Follow-up: 12	Toxicity	No serious adverse events were reported.	Vaccination induced immunological changes in a group of advanced, terminally ill patients. These changes suggest an increased antitumor immune response.
Cancer Pizza, 2004[280] ID NR Controlled trial N: 161	Age group: Adults Metastatic renal cell cancer Treatment enrollment: None Treatment requisite: None	IL-2 (ACHN-IL-2) Usual care Follow-up: 172	Overall survival rate; measurable metastases; new bone lesions; serum and urine biochemical parameters; electrocardiogram measures	No serious treatment-related adverse events were reported.	Our vaccination protocol is safe, devoid of adverse events, and promising.
Cancer Kyte, 2006[196] ID NR Single-arm trial N: 22	Age group: Adults Advanced malignant melanoma Treatment enrollment: None Treatment requisite: None	Individualized melanoma vaccine based on transfection of autologous dendritic cells (DCs) with autologous tumor-mRNA No comparison group Follow-up: 3	Safety; immune response; clinical response	None	We conclude that immuno-gene-therapy with the described DC-vaccine is feasible and safe, and that the vaccine can elicit in vivo T-cell responses against antigens encoded by the transfected tumor-mRNA. The response rates do not suggest an advantage in applying in. vaccination.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Abdel-Wahab, 1997[217] ID NR Single-arm trial N: 20	Age group: Adults Melanoma Treatment enrollment: None Treatment requisite: None	Interferon-g (IFN-g) gene–modified autologous 1 Carol Vervaert, M.T.1 melanoma tumor cells No comparison group Follow-up: 16	Generation of IFN-g–modified melanoma tumor cells; identification of the serum antigen by immunoprecipitation with postimmune sera	None	These data suggest that gene therapy with IFN-g–transduced melanoma cells is safe and worthy of further investigation in patients with less advanced stage malignant melanoma.
Cancer Kang, 2001[207] ID NR, protocol reviewed by NIH and Korean Ministry Single-arm trial N: 9	Age group: Adults Disseminated cancer Treatment enrollment: None Treatment requisite: None	Interleukin 12 No comparison group Follow-up: None	Tumor response; toxicity (assessed by complete blood count with differential and platelet counts, blood chemistries, coagulation profile)	No significant adverse events related to study treatment occurred.	These data indicate that gene therapy by peritumoral injection of IL-12-producing autologous fibroblasts is feasible and promising in patients with advanced cancer.
Cancer Sobol, 1999[209] ID NR, protocol reviewed by NIH-RAC and FDA Single-arm trial N: 10	Age group: Adults Colorectal carcinoma Treatment enrollment: None Treatment requisite: None	Interleukin 2 No comparison group Follow-up: 3	Complete blood count with differential; platelet count	Fatigue and/or flu-like symptoms (n = 7), and delayed-type hypersensitivity-like skin reactions at sites of the second or subsequent vaccinations (n = 7)	Some patients with colorectal cancer have low frequencies of tumor cytotoxic T-cell precursors that may be increased by this well-tolerated form of IL-2 gene therapy, which warrants further clinical evaluation.
Cancer Okada, 2007[282] ID NR Single-arm trial N: 12	Age group: Adults Glioma Treatment enrollment: None Treatment requisite: Gancyclovir	Interleukin-4 gene transfected fibroblasts No comparison group Follow-up: 10	Tumor volume; toxicity	No serious adverse events were reported.	Despite feasibility challenges, successful generation of type-1 dendritic cells and preliminary safety in the current study provide a strong rationale for further efforts to develop novel glioma vaccines.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Parney, 2006[195] IND No. 056621 Single-arm trial N: 6	Age group: Adults Recurrent glioblastomas and melanomas Treatment enrollment: None Treatment requisite: None	Irradiated autologous tumor cells transduced with B7-2 and GM-CSF genes using a retroviral vector No comparison group Follow-up: 37	Toxicity; inflammatory/immune reactions; clinical status	None	Combined B7-2 and GM-CSF immunogene therapy for glioblastomas and melanomas using autologous tumor cells has many technical pitfalls hindering large-scale application and evaluation. As a result, this pilot study was too limited to draw meaningful conclusions regarding safety or anti-tumor immunity. While immunotherapy has been promising in pre-clinical studies, alternate strategies will be required to bring these benefits to patients.
Cancer Wilgenhof, 2015[292] ID NR Trial (multiple groups) N: 30	Age group: Adults Melanoma Treatment enrollment: None Treatment requisite: Leukapheresis and interferon alfa-2b	Messenger RNA-electroporated dendritic cell No comparison group Follow-up: 96	Overall survival	No treatment-related serious adverse events were reported.	Adjuvant therapy following the resection of melanoma metastases with autologous mRNA-electroporated dendritic cells, combined with interferon alfa-2b, is tolerable and results in long-term overall survival rates justifying further evaluation in a randomized clinical trial.
Cancer Vik-Mo, 2013[304] ID NR Single-arm trial N: 7	Age group: Adults Glioblastoma Treatment enrollment: Postoperative chemo-radiotherapy Treatment requisite: Temozolomide and leukapheresis	mRNA-transfected dendritic cells No comparison group Follow-up: 35	Progression-free survival	Grade 3 fatigue (n = 1)	These results suggest that vaccination against glioblastoma stem cells is safe, well tolerated, and may prolong progression-free survival.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Kubuschok, 2012[293] ID NR Trial (multiple groups) N: 7	Age group: Adults Pancreatic cancer Treatment enrollment: Ki-Ras codon 12 mutation Treatment requisite: None	Mutated ras-transfected, EBV-transformed lymphoblastoid cell lines No comparison group Follow-up: 26	Overall survival; toxicity	No treatment-related serious adverse events were reported.	Our results suggest that lymphoblastoid cell lines genetically modified with antigen represent a valuable and easily available tool for in vivo autologous tumor vaccination.
Cancer Russell, 2007[297] ID NR Trial (multiple groups) N: 7	Age group: Children Neuroblastoma Treatment enrollment: None Treatment requisite: None	Neuroblastoma tumor cells genetically modified to secrete IL-2 and lymphotactin No comparison group Follow-up: 6	Tumor response; toxicity	Grade 3 fever (n = 1), anemia (n = 1), and thrombocytopenia (n = 1)	Autologous tumor cell vaccines combining transgenic lymphotactin with IL-2 seem to have little toxicity in humans and can induce an antitumor immune response and may overcome active recurrent neuroblastoma.
Cancer Morgan, 2013[189] NCT01273181 Trial (multiple groups) N: 9	Age group: Adults Metastatic melanoma, synovial sarcoma, and esophageal cancer Treatment enrollment: Nonmyeloablative lymphodepleting regimen Treatment requisite: None	nti-MAGE-A3 TCR gene therapy No comparison group Follow-up: 15	In vivo properties of MAGE-A3 TCR engineered T cells and clinical response; neurologic toxicity following the infusion of MAGE-A3 TCR engineered T cells; IFN-γ serum levels; detection of MAGE-A gene expression	None	Five patients experienced clinical regression of their cancers, including 2 ongoing responders. Beginning 1 to 2 days postinfusion, 3 patients (no. 5, 7, and 8) experienced mental status changes and 2 patients (no. 5 and 8) lapsed into comas and subsequently died.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Robbins, 2015[301] Robbins, 2011[573]; Johnson, 2009[574] ID NR Trial (multiple groups) N: 38	Age group: Adults Melanoma Treatment enrollment: None Treatment requisite: Lymphodepleting chemotherapy consisting of cyclophosphamide and fludarabine	NY-ESO-1 TCR-transduced T cells No comparison group Follow-up: 72	Survival; tumor response	No serious adverse events were reported.	The adoptive transfer of autologous T cells transduced with a retrovirus encoding a TCR against an HLA-A00201 restricted NY-ESO-1 epitope can be an effective therapy for some patients bearing refractory synovial cell sarcomas and melanomas.
Cancer Parkhurst, 2011[303] ID NR Single-arm trial N: 3	Age group: Adults Colorectal cancer Treatment enrollment: Exhausted all prior treatment options Treatment requisite: Lymphodepleting chemotherapy and interleukin 1	Retrovirally transduced to express this T-cell receptor No comparison group Follow-up: 6	Tumor response; toxicity	None	This is the first report of objective regression of metastatic colorectal cancer mediated by adoptive T-cell transfer and illustrates the successful use of a T-cell receptor. It also emphasizes the destructive power of small numbers of highly avid T cells.
Cancer Van Nuffel, 2012[291] ID NR Single-arm trial N: 1	Age group: Adults Melanoma Treatment enrollment: Exhausted all prior treatment options Treatment requisite: Leukapheresis	TriMix-DC No comparison group Follow-up: 12	Tumor response; toxicity	No serious adverse events were reported.	This case report suggests that administration of autologous TriMix-DC by the intradermal and intravenous route can mediate a durable tumor response accompanied by a broad T-cell response in a chemorefractory stage IV-M1c melanoma patient.
Cancer Wilgenhof, 2013[299] ID NR Trial (multiple groups) N: 15	Age group: Adults Melanoma Treatment enrollment: Unresectable Treatment requisite: None	TriMixDC-MEL No comparison group Follow-up: 35	Overall survival; progression-free survival; toxicity	No serious adverse events were reported.	Immunotherapy with TriMixDC-MEL is safe and immunogenic. Antitumor activity with durable disease control was observed across the investigated intravenous-dose levels.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Mackiewicz, 1998[212] ID NR Trial (multiple groups) N: 22	Age group: Children and adults Melanoma Treatment enrollment: None Treatment requisite: None	Tumor cells and an HLA-Al/A2-positive allogeneic melanoma cell line genetically engineered to secrete IL-6 and sIL-6R No comparison group Follow-up: 12	Tumor response; safety	None	The vaccine treatment is safe and induced cellular (antitumor) immune responses, and although clinical efficacy requires further testing, the feasibility of this approach as potential treatment of metastatic melanoma was demonstrated.
Cancer Veelken, 1997[300] ID NR Trial (multiple groups) N: 15	Age group: Adults Malignant tumors Treatment enrollment: None Treatment requisite: None	Tumor cells and IL-2-secreting allogeneic fibroblasts No comparison group Follow-up: 14	Tumor progression	No serious adverse events were reported.	Malignant melanoma and renal-cell carcinoma appear to be promising for testing similar approaches in future therapeutic trials.
Cancer Zhang, 2015[305] ID NR Trial (multiple groups) N: 33	Age group: Adults Melanoma Treatment enrollment: None Treatment requisite: Tumor resection	Tumor-infiltrating lymphocytes genetically engineered to secrete single-chain interleukin 12 No comparison group Follow-up: 21	Tumor response; toxicity	Grade 3 liver function toxicity (n = 5), grade 3 fever (n = 5), grade 3 idiopathic thrombocytopenia Purpura (n = 1), grade 3 hypoxia (n = 1), grade 3 thrombotic microangiopathy (n = 1), grade 3 interstitial pneumonitis (n=1), grade 4 liver toxicity (n = 3), and grade 4 prolonged myelosuppression (n = 1)	In this first-in-man trial, tumor-infiltrating lymphocytes transduced with interleukin 12 mediated tumor responses in the absence of interleukin 2 administration using cell doses 10- to 100-fold lower than conventional tumor-infiltrating lymphocytes. However, due to toxicities, likely attributable to the secreted nterleukin 12, further refinement will be necessary before this approach can be safely used in the treatment of cancer patients.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer van den Berg, 2015[229] NL.37327.000.11 Single-arm trial N: 1	Age group: Adults Melanoma Treatment enrollment: None Treatment requisite: None	Utologous T-cell receptor transduced T cells No comparison group Follow-up: Cyclophosphamide, fludarabine, and interleukin-2	Toxicity	1 patient experienced cerebral hemorrhage, epileptic seizures, cardiac arrest, and then death due to multiple organ failure.	High levels of inflammatory cytokines alone or in combination with semi-acute heart failure and epileptic seizure may have contributed to the occurrence of the acute and lethal event. Protocol modifications to limit T-cell activation-induced toxicity are discussed.
Cancer Coosemans, 2013[306] ID NR Trial (multiple groups) N: 6	Age group: Adults Uterine cancer Treatment enrollment: Exhausted all prior treatment options Treatment requisite: Leukapheresis and chemotherapy	Wilms' Tumor Gene 1–loaded dendritic cells No comparison group Follow-up: 43	Progression-free survival; overall survival; toxicity	No serious adverse events were reported.	Oncological and immunological responses were observed and findings support further research.
Cardiovascular disease Flugelman, 2017[307] NCT00956332 Trial (multiple groups) N: 23	Age group: Adults Chronic critical limb ischemia Treatment enrollment: No standard therapy options and/or failed other therapies Treatment requisite: None	Modified to express angiopoietin 1, combined with autologous venous smooth muscle cells modified to express vascular endothelial growth factor No comparison group Follow-up: 12	Amputation-free survival; rest pain; quality of life; 6-minute walk test; ratio of the highest systolic blood pressure of either the dorsalis pedis or the posterior tibial arteries at the ankle, divided by the highest systolic blood pressure in the arm.	None	Outcomes did not differ between the dose groups. No severe adverse events were observed related to the therapy.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cardiovascular disease Grossman, 2016[308] NCT00390767 Single-arm trial N: 12	Age group: Adults Peripheral artery disease Treatment enrollment: None Treatment requisite: None	MultiGeneAngio (MGA) No comparison group Follow-up: 12	Clinical safety and tolerability	Recurrent transient ischemic attack, nonindex external iliac artery occlusion, acute index leg ischemia, and myocardial infarction	MGA, an autologous, transduced, dual cell-based therapy, was well tolerated and safe in this phase 1 study. The therapy was not associated with any worsening of vascular function and safety measures.
Immune deficiency Routy, 2010[354] ID NR Single-arm trial N: 10	Age group: Adults Human immunodeficiency virus (HIV) Treatment enrollment: None Treatment requisite: Antiretroviral therapy and leukapheresis	AGS-004 No comparison group Follow-up: 5	CD8+ T-cell counts	No serious treatment-related adverse events were reported.	No evidence of autoimmunity, changes in viral load, or changes in absolute CD4+ and CD8+ T-cell counts were observed.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Immune deficiency Aiuti, 2013[334]; GlaxoSmithKline, 2018[575] NCT01515462 Single-arm trial N: 3	Age group: Children Wiskott-Aldrich syndrome (WAS) Treatment enrollment: Ineligible for hematopoietic stem cell transplant or no donor available Treatment requisite: G-CSF mobilized peripheral blood collection (backup or for reinfusion) for one patient, bone marrow collection to isolate CD34+ cells for viral transduction, conditioning regimen for myeloablation with busulfan + fludarabine + CD20 antibody prior to infusion	Autologous CD34+ No comparison group Follow-up: 32	Symptom improvement; improvement in infection frequency and severity; improvement in platelet counts and T-cell proliferative responses	Autoimmune thrombocytopenia (n = 1), sepsis (n = 1), disseminated intravascular coagulation (n = 1), acute respiratory distress syndrome (n = 2), multiple respiratory aspiration-related infections (n = 1), and interstitial aspiration pneumonia (n = 1)	Although extended clinical observation is required to establish long-term safety, lentiviral gene therapy represents a promising treatment of WAS.
Immune deficiency Assistance Publique-Hôpitaux de Paris, 2011[352]; Clarke, 2018[113]; Hacein-Bey-Abina, 2014[112] NCT01410019 Single-arm trial N: 5	Age group: Children X-linked severe combined immunodeficiency (SCID-X1) Treatment enrollment: None Treatment requisite: Collection of CD34+ cells from each patient (method not described)	Autologous CD34+ cells transduced with pSRS11.EFS.IL2RG.pre, a self-inactivating gammaretroviral vector No comparison group Follow-up: Indefinite	Transduction efficacy; immune reconstitution (phenotype, number, and function of different cell subpopulations); improvement or complete restoration of immunity	Not yet reported	None

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Immune deficiency Bordignon, 1995[350]; Bordignon, 1993[576] ID NR Single-arm trial N: 2	Age group: Children ADA-severe combined immunodeficiency disease (SCID) Treatment enrollment: Pegademase bovine (PEG-ADA) treatment failure independent of any acute illness or open infection and distinctly confirmed thrice Treatment requisite: Patients continued to receive PEG-ADA throughout the study period in decreasing amounts; bone marrow cells and peripheral blood lymphocytes were collected and transduced with 1 of 2 retroviral vectors; cells were infused back into patients (5 to 9 injections over 10-24 months)	Bone marrow or peripheral blood lymphocytes were retrovirally transduced to produce ADA No comparison group Follow-up: Until death	Immune reconstitution assays; expression of the ADA gene	Adverse events were not discussed.	These results demonstrate successful gene transfer into long-lasting progenitor cells, normalization of the immune repertoire, and restoration of immunity.
Immune deficiency Gaspar, 2011[338]; Howe, 2008[577]; Schwarzwaelder, 2007[578] ID NR Single-arm trial N: 10	Age group: Children X-linked severe combined immunodeficiency Treatment enrollment: None Treatment requisite: None	CD34(+) No comparison group Follow-up: 107	Clinical status	None	Gene therapy for SCID-X1 without myelosuppressive conditioning effectively restored T-cell immunity and was associated with high survival rates for up to 9 years.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Immune deficiency Malech, 1997[348] ID NR Single-arm trial N: 5	Age group: Adults Chronic granulomatous disease Treatment enrollment: None Treatment requisite: None	CD34(+) No comparison group Follow-up: 6	Ex vivo culture and transduction of CD34 PBSCs in serum-free medium and gas-permeable container; presence of NADPH oxidase-positive neutrophils in the peripheral blood after intravenous administration of ex vivo transduced autologous CD34 PBSCs. Results of Safety Studies and Long-Term Clinical Follow Up	None	Peak correction occurred 3 to 6 weeks after infusion and ranged from 0.004% to 0.05% of total peripheral blood granulo-cytes. Corrected cells were detectable for as long as 6 months after infusion in some individuals.
Immune deficiency Cavazzana-Calvo, 2000[346]; National Institute of Allergy, 2011[579] ID NR Single-arm trial N: 2	Age group: Children Severe combined immunodeficiency Treatment enrollment: Confirmed gene mutations Treatment requisite: None	CD34+ No comparison group Follow-up: 10	Growth; psychomotor development	No serious adverse events were reported.	Gene therapy was able to provide full correction of disease phenotype and clinical benefit.
Immune deficiency Mitsuyasu, 2000[345] ID NR RCT N: 24	Age group: Adults HIV Treatment enrollment: Antiretroviral medications, protease inhibitors, non-nucleoside reverse transcriptase inhibitors, and hydroxyurea Treatment requisite: Interleukin-2	CD4 gene-modified autologous CD4 and CD8 T cells Other: CD8 T cells administered with interleukin-2 Follow-up: 2	Toxicity; rectal biopsy	Toxicity, CD4-modified T-cell survival in peripheral blood, antiviral activity of CD4 T cells, and CD4 T-cell trafficking and activity against gut-associated HIV reservoirs	There was no significant mean change in plasma HIV RNA or blood proviral DNA in either treatment arm. This sustained, high-level persistence of gene-modified T cells demonstrates the feasibility of ex vivo T-cell gene therapy in HIV-infected adults and suggests the importance of providing HIV-specific T-helper function.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Immune deficiency Riddell, 1996[349] ID NR; protocol approved by the Recombinant DNA Advisory Committee, and the Food and Drug Administration Single-arm trial N: 6	Age group: Age group unclear Human immunodeficiency virus-1 (HIV) Treatment enrollment: None Treatment requisite: Peripheral blood mononuclear cells (PBMCs) were obtained from each patient to prepare HyTK-transduced CD8+ HIV gag-specific cytotoxic T-lymphocytes (CTLs) and subsequent clones; cells were transferred back to each patient by intravenous infusion over 30 minutes (4 escalating doses at 2 week intervals)	CD8+ HIV-specific cytotoxic T cells No comparison group Follow-up: 1	HyTK-specific cytotoxic response; gag-specific cytotoxicity; detection of HyTK-positive T cells after adoptive transfer	Not discussed	Five of 6 patients developed cytotoxic T-lymphocyte (CTL) responses specific for the novel protein and eliminated the transduced CTLs; this rejection suggests that strategies to make gene-modified cells less susceptible to host immune surveillance and response will be necessary for clinical application.
Immune deficiency Allard, 2012[355] ID NR Single-arm trial N: 17	Age group: Adults HIV Treatment enrollment: None Treatment requisite: Leukapheresis	Dendritic cells electroporated with mRNA encoding Tat, Rev, and Nef No comparison group Follow-up: 24	CD4+ and CD8+ T-cell counts	No serious adverse events were reported.	The vaccine was safe and well tolerated, and produced vaccine-specific immune responses. No correlation with clinical parameters could be found.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Immune deficiency Hacein-Bey-Abina, 2002[344]; Hacein-Bey-Abina, 2008[580] ID NR, protocol reviewed by the French Drug Agency Trial (multiple groups) N: 5	Age group: Children X-linked severe combined immunodeficiency Treatment enrollment: None Treatment requisite: None	Ex vivo gene therapy No comparison group Follow-up: 30	Safety; immune function	No adverse effects resulted from the procedure.	Ex vivo gene therapy with GC can safely correct the immune deficiency of patients with X-linked severe combined immunodeficiency.
Immune deficiency Levine, 2006[351] ID NR Single-arm trial N: 5	Age group: Adults HIV Treatment enrollment: Drug-resistant HIV infection Treatment requisite: Apheresis	Gene-modified autologous CD4 T No comparison group Follow-up: 36	Viral load; CD4 count; immune function	None	There is no evidence for insertional mutagenesis after 21 to 36 months of observation. Immune function improved in 4 subjects. Lentiviral vectors appear promising for gene transfer to humans.
Immune deficiency Hacein-Bey Abina, 2015[332] ID NR Single-arm trial N: 7	Age group: Children Wiskott-Aldrich syndrome Treatment enrollment: None Treatment requisite: Collection of hematopoietic stem cells from bone marrow or peripheral blood for transduction, myeloablative conditioning (busulfan, fludarabine) prior to infusion	Gene-modified CD34+ cells No comparison group Follow-up: 42	Improvement in frequency and severity of infections, bleeding episodes, autoimmune episodes, eczema, platelet count, and lymphocyte analysis and function	Death (n = 1) due to opportunistic herpes viral infections that became drug resistant after gene therapy (died 7 months after gene therapy).	This study demonstrated the feasibility of the use of gene therapy in patients with Wiskott-Aldrich syndrome. Controlled trials with larger numbers of patients are necessary to assess long-term outcomes and safety.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Immune deficiency Onodera, 1998[347] ID NR Single-arm trial N: 1	Age group: Children ADA-severe combined immunodeficiency disease Treatment enrollment: None Treatment requisite: None	Genetically modified autologous T lymphocytes transduced with the human ADA cDNA containing retroviral vector LASN No comparison group Follow-up: 18	Clinical course; identification of mutations responsible for ADA deficiency; retroviral mediated gene transfer into peripheral T cells	None	The results obtained in this trial agree with previously published observations and support the usefulness of T lymphocyte-directed gene transfer in the treatment of ADA SCID.
Immune deficiency Gaspar, 2011[337] ID NR Controlled trial N: 6	Age group: Children Adenosine deaminase-deficient severe combined immunodeficiency Treatment enrollment: ERT and chemotherapy Treatment requisite: None	Hematopoietic stem cell gene therapy Healthy volunteers Follow-up: 43	Cellular immune recovery; humoral immune recovery; metabolic correction	None	All patients survived, with a median follow-up of 43 months (range = 24 to 84 months). Four of the 6 patients recovered immune function because of engraftment of gene-corrected cells. In 2 patients, treatment failed because of disease-specific and technical reasons: Both restarted ERT and remain well.
Immune deficiency DiGiusto, 2010[339] ID NR Single-arm trial N: 7	Age group: Adults HIV Treatment enrollment: None Treatment requisite: None	Lentiviral vector-modified CD34(+) cells No comparison group Follow-up: 18	Safety	None	We have developed methods for the isolation, genetic modification, and infusion of CD34+ cells that support clinical investigation of stem cell gene therapy strategies for HIV.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Immune deficiency Tebas, 2013[335] NCT00295477 Trial (multiple groups) N: 17	Age group: Adults HIV Treatment enrollment: None Treatment requisite: None	Lexgenleucel-T No comparison group Follow-up: 180	Safety; effects of infusion on viral load before ATI; effects on the timing of viral recrudescence and set point during ATI; the change in CD4 T-cell counts from baseline to ATI	None	We conclude that gene-modified T cells have the potential to decrease the fitness of HIV-1 and conditionally replicative lentiviral vectors have a promising safety profile in T cells.
Immune deficiency Great Ormond Street Hospital for Children[357]; Hacein-Bey-Abina, 2014[112] NCT01175239 Trial (multiple groups) N: 9	Age group: Children Severe combined immunodeficiency Treatment enrollment: Confirmed IL2RG mutations Treatment requisite: None	Moloney murine leukemia virus–based γ-retrovirus vector ex- pressing interleukin-2 receptor γ-chain (γc) complementary DNA No comparison group Follow-up: 39	Severe adverse events	No treatment-related severe adverse events were reported.	This therapy was found to retain efficacy in the treatment of SCID-X1. The long-term effect on leukemogenesis remains unknown.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Immune deficiency Amado, 2004[342] ID NR Trial (multiple groups) N: 10	Age group: Adults Human Immunodeficiency Virus Type-1 (HIV-1) Treatment enrollment: None Treatment requisite: Mobilization of peripheral blood progenitor cells (PBPC) with the cytokine granulocyte colony-stimulating factor for 6 days, including PBPC procurement by apheresis on days 5 and 6; CD34+ cells were selected, cultured, and transduced; transduced cells were were pooled and then infused into autologous recipient patients without myelosuppression.	Retroviral transduction with Rz2 into CD34+ hematopoietic stem cells No comparison group Follow-up: Until death	Adverse events and feasibility	Severe adverse events: Musculoskeletal connective tissue and bone pain (n = 1), severe anxiety (n = 1), and nonspecific gastroenteritis post–cell infusion (n = 1, not considered to be caused by the study drug or study procedure)	These findings support the idea of gene therapy as a modality to effect immune reconstitution with cells engineered to inhibit HIV replication; further, this report represents the first demonstration of long-term maintenance of a potential therapeutic transgene in HIV disease.
Immune deficiency Chinen, 2007[341] ID NR, protocol reviewed by NIH-RAC and FDA Single-arm trial N: 3	Age group: Children X-linked severe combined immunodeficiency (XSCID) Treatment enrollment: 4 T cell–depleted, haploidentical parent–derived BMTs, intravenous immune gamma globulin (IVIG) and antibiotic, antiviral, and antifungal prophylaxis, maternal T cell–depleted haploidentical BMT without bone marrow conditioning Treatment requisite: None	Retrovirus-transduced autologous peripherally mobilized CD34 hematopoietic cells No comparison group Follow-up: 7	Ex vivo transduction of patient CD34 PBSCs and infusion of transduced cells; gene marking and changes in the number and function of immune cell lineages; general clinical status after gene therapy; safety monitoring	None	T-cell function significantly improved in the youngest subject (aged 10 years), and multilineage retroviral marking occurred in all 3 children.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Immune deficiency van Lunzen, 2007[356] ID NR Trial (multiple groups) N: 13	Age group: Children and adults HIV Treatment enrollment: Highly active antiretroviral therapy Treatment requisite: Highly active antiretroviral therapy	T lymphocytes transduced with a retroviral vector that expresses an HIV entry–inhibitory peptide No comparison group Follow-up: 12	CD4 and CD8 responses; toxicity	No serious adverse events were reported.	Gene-modified and transferred cells were safe, led to sustained levels of gene marking, and may improve immune competence in HIV-infected patients with advanced disease and multidrug-resistant virus.
Immune deficiency Cicalese, 2016[331] NCT00598481 Single-arm trial N: 18	Age group: Adults Adenosine deaminase (ADA) deficiency Treatment enrollment: Haplo-SCT and PEG-ADA Treatment requisite: None	Transduced autologous CD341-enriched cell fraction No comparison group Follow-up: 84	Survival; engraftment and purine metabolism; immune reconstitution; severe infections; growth and activity; baseline predictors of efficacy; unsuccessful responses to therapy; adverse effects	None	Overall survival was 100% over 2.3 to 13.4 years (median = 6.9 years). Gene-modified cells were stably present in multiple lineages throughout follow-up. GT resulted in a sustained reduction in the severe infection rate from 1.17 events per person-year to 0.17 events per person-year

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Immune deficiency TreatmentUpdate, 2009[340]; Mitsuyasu, 2009[581] ID NR RCT N: 74	Age group: Adults HIV Treatment enrollment: All participants were on highly active antiretroviral therapy (HAART). Treatment requisite: Patients had their blood drawn; bone marrow stem cells (CD34+ cells) were isolated from each sample and the remaining blood was infused back into participants. The stem cells were infected with an altered weakened mouse leukemia virus that carried OZ1. The infected stem cells were then expanded in vitro and then infused back into patients.	Transduced CD34+ cells with mouse virus containing OZ1 Placebo Follow-up: 24	Detection of HIV-resistant cells from blood cells; CD4+ and CD8+ T-cell counts; HIV viral load	Three serious complications occurred in the placebo group.	Improvements in CD4+ T-cell counts and viral load were modest, but these results represent a promising trend in those measures.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Neurodegenerative disorders Eichler, 2017[374]; Bluebird, 2020[582] NCT01896102 Single-arm trial N: 17	Age group: Children Cerebral adrenoleukodystrophy Treatment enrollment: None Treatment requisite: Apheresis, conditioning chemotherapy, and granulocyte colony-stimulating factor (G-CSF) treatment postinfusion for expedited engraftment	CD34+ hematopoietic stem cells transduced with lentiviral vector No comparison group Follow-up: 24	Gadolinium enhancement; lesion progression; gross neurologic dysfunction by assessing 15 different disabilities (those that hamper the patient from functioning independently); survival; no major functional disabilities	Grade 3 and above adverse events: Central line infection (n = 1), febrile neutropenia (n = 1), cystitis (BK virus, possibly related, n = 1), fever (n = 1), spinal fracture (n = 1), neutropenic fever (n = 2), oral mucositis (n = 1), total incontinence (MFD, n = 1), cortical blindness (MFD, n = 1), loss of communication (MFD, n = 1), wheelchair dependence (n = 1), respiratory distress (n = 1), and adenoviral infection with rhabdomyolysis and hepatic failure (n = 1)	Lenti-D gene therapy may be a safe and effective alternative to allogeneic stem cell transplantation in boys with early-stage cerebral adrenoleukodystrophy. Additional follow-up is needed to fully assess the duration of response and long-term safety.
Neurodegenerative disorders Tuszynski, 2002[375]; Tuszynski, 2015[583] ID NR Trial (multiple groups) N: 8	Age group: Adults Alzheimer's disease Treatment enrollment: Not discussed Treatment requisite: Skin biopsy to collect fibroblasts and stereotaxic neurosurgery	Transduced with retroviral vector to secrete human nerve growth factor (NGF) No comparison group Follow-up: Until death	Cognitive function	No serious adverse events in the 2 patients treated so far	None

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Other: Skin disease De Rosa, 2014[384]; Mavilio, 2006[584] ID NR, authorized by the Italian Ministry of Health Single-arm trial Completed N: 1	Age group: Age group unclear Junctional epidermolysis bullosa Treatment enrollment: None Treatment requisite: None	Genetically modified holoclones No comparison group Follow-up: 78	Clinical examination (appearance, tactile sensitivity, pain sensitivity)	Safe	The epidermis was sustained by a discrete number of long-lasting, self-renewing transgenic epidermal stem cells that maintained the memory of the donor site, whereas the vast majority of transduced transit amplifying progenitors were lost within the first few months after grafting
Other: Infection Chen, 2005[391] ID NR Single-arm trial N: 19	Age group: Adults Chronic hepatitis B Treatment enrollment: None Treatment requisite: Lamivudine	HBsAg-loaded dendritic cells No comparison group Follow-up: 12	Hepatitis B viral DNA	None	Regardless of serum alanine transaminase levels but also those with normal ALT levels can respond to dendritic cell vaccine treatment, and the treatment combining dendritic cells with lamivudine can eliminate viruses more effectively.

Abbreviation: ADA, adenosine deaminase; AEs, adverse events; DNA, deoxyribonucleic acid; FDA, U.S. Food and Drug Administration; ID, identification number; N, number of participants; NIH, National Institutes of Health; NA, not available; NR, not reported; RAC, NIH Recombinant DNA Advisory Committee; RCT, randomized controlled trial; RNA, ribonucleic acid

Appendix Table A3. Evidence Table Published CAR-T Trials

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Brown, 2015[177]; Brown, 2016[585] NCT00730613 Single-arm trial N: 3	Age group: Adults Recurrent glioblastoma Treatment enrollment: None Treatment requisite: None	(CAR)-engineered, autologous primary human CD8þ cytotoxic T-lymphocytes (CTL) targeting IL13Ra2 for the treatment of recurrent glioblastoma (GBM) No comparison group Follow-up: None	Characterization of autologous IL13-zetakineþ CTL clones; safety of IL13-zetakineþ CAR-T-cell administration; decreased tumor IL13Ra2 expression following therapy; evidence of tumor responses by MRI	None	These findings provide promising first-in-human clinical experience for intracranial administration of IL13Ra2-specific CAR-T cells for the treatment of GBM, establishing a foundation on which future refinements of adoptive CAR-T-cell therapies can be applied.
Cancer O'Rourke, 2017[158]; University of Pennsylvania[586]; Johnson, 2015[587] ID NR Single-arm trial N: 10	Age group: Adults Recurrent glioblastoma Treatment enrollment: Surgery, bevacizumab, and chemotherapy Treatment requisite: Leukapheresis	(CART)–EGFRvIII No comparison group Follow-up: 18	Safety; tumor progression; overall survival	Neurologic events (n = 3), seizure (n = 1), and neurologic decline (n = 1)	Although intravenous infusion results in on-target activity in the brain, overcoming the adaptive changes in the local tumor microenvironment and addressing the antigen heterogeneity may improve the efficacy of EGFRvIII-directed strategies in glioblastoma multiforme.
Cancer Brudno, 2016[227] ID NR Single-arm trial N: 20	Age group: Adults B-cell malignancies Treatment enrollment: None Treatment requisite: None	Allogeneic anti-CD19 CAR-T No comparison group Follow-up: 30	Stable disease; progressive disease; partial response; complete remission; minimal residual disease	SAEs: 84 events in 12 patients	Allogeneic anti-CD19 CAR-T cells can effectively treat B-cell malignancies that progress after alloHSCT. The findings point toward a future when antigen-specific T-cell therapies will play a central role in alloHSCT.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Kochenderfer, 2015[182]; Kochenderfer, 2012[588]; National Institutes of Health, 2015[589,590]; Morgan, 2006[591]; Rossi, 2018[592] NCT00924326 Single-arm trial N: 15	Age group: Adults Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies Treatment enrollment: None Treatment requisite: Apheresis to generate CAR-T cells, cyclophosphamide and fludarabine conditioning (leukocyte depletion) prior to infusion	Anti-CD19 CAR-T No comparison group Follow-up: 23	Clinical response (complete response, partial response, stable disease, not evaluable); time to relapse; overall survival; progression-free survival	Grade 3 or higher: hypotension (n = 4), confusion (n = 3), acute renal failure (n = 1), fever (n = 12), aphasia (n = 1), facial nerve palsy (n = 1), headache (n = 3), urinary tract infection (n = 4), nausea (n = 1), hypoxia (n = 2), dyspnea (n = 2), tachycardia (n = 1), bacteremia (n = 6), malaise (n = 1), vascular leak syndrome (n = 1), death (n = 1), influenza (n = 1), pneumonitis (n = 1), obtundation (n = 1), elevated creatinine (n = 1), myoclonus (n = 1), fatigue (n = 1), upper extremity thrombosis (n = 2), creatinine increase (n = 1), encephalopathy (n = 1), neuropathy (n = 1), and gait disturbance (n = 1)	These results demonstrate the feasibility and effectiveness of treating chemotherapy-refractory B-cell malignancies with anti-CD19 CAR-T cells.
Cancer Kochenderfer, 2013[186] NCT01087294 Single-arm trial N: 10	Age group: Age group unclear B-cell malignancy Treatment enrollment: Stem cell transplant Treatment requisite: None	Anti-CD19-CAR-T No comparison group Follow-up: 18	Complete response; partial response; stable disease; progressive disease	SAEs: 16 events in 4 patients	These results show for the first time that donor-derived allogeneic anti-CD19-CAR-T cells can cause regression of B-cell malignancies resistant to standard DLIs without causing graft-versus-host disease (GVHD).

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Katz, 2015[179]; Saied, 2014[593] NCT01373047 Single-arm trial N: 8	Age group: Adults Liver metastases Treatment enrollment: None Treatment requisite: None	Anti-CEA CAR-T No comparison group Follow-up: None	Serum IFNg concentrations	None	We have demonstrated the safety of anti-CEA CAR-T HAIs with encouraging signals of clinical activity in a heavily pretreated population with large tumor burdens.
Cancer Maus, 2013[184]; University of Pennsylvania, 2015[594] ID NR Single-arm trial N: 4	Age group: Adults Mesothelioma and pancreatic adenocarcinoma Treatment enrollment: None Treatment requisite: Serum collection for cytokine monitoring	Antimesothelin CAR mRNA No comparison group Follow-up: 7	Safety	Anaphylaxis and cardiac arrest (n = 1)	This is the first description of clinical anaphylaxis resulting from CAR-modified T cells, most likely due to IgE antibodies specific to the CAR. These results suggest that the potential immunogenicity of CARs derived from murine antibodies may be a safety issue for mRNA CARs, especially when administered using an intermittent dosing schedule.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Junghans, 2016[172] BB-IND 12084 Trial (multiple groups) N: 6	Age group: Adults Metastatic or recurrent and hormone refractory (castrate-resistant) prostate cancer Treatment enrollment: Received pelvic radiation and failed androgen (5 of 6 patients) deprivation Treatment requisite: T-cell collection, filgrastim (granulocyte colony-stimulating factor, G-CSF) mobilization and leukapheresis, nonmyeloablative chemotherapy 8 days prior, and interleukin-2 (IL2) infusion for 28 days posttherapy	Anti-PSMA Designer CAR-T No comparison group Follow-up: 1	Clinical response; prostate-specific antigen (PSA) reduction; prostate-specific antigen (PSA) delay	Neutropenia (n = 5), neutropenic fever (n = 5), thrombocytopenia (n = 3), anemia (n = 1), hypocalcemia (n = 1), hypophosphatemia (n = 1), and appendicitis (n = 1)	Clinical responses were obtained but were suggested to be restrained by low plasma IL2 when depleted by high levels of engrafted activated T cells.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer National Cancer Institute, 2016[238] NCT01218867 Trial (multiple groups) N: 24	Age group: Adults Metastatic cancer, metastatic melanoma, and renal cancer Treatment enrollment: Received at least one systemic standard care (or effective salvage chemotherapy regimens) for metastatic disease, if known to be effective for that disease, and have been either nonresponders (progressive disease) or cancer recurred Treatment requisite: Cyclophosphamide, aldesleukin, and fludarabine	Anti-VEGFR2 CAR CD8 No comparison group Follow-up: 72	Response to therapy; in vivo survival of chimeric T-cell receptor (CAR) gene-engineered cells	SAEs: 5 Int (patients)	None (table results only)
Cancer Till, 2008[279] ID NR Trial (multiple groups) N: 7	Age group: Adults Lymphoma Treatment enrollment: Leukapheresis Treatment requisite: Interleukin 2	Autologous CD20-specific T cells No comparison group Follow-up: 12	Clinical responses by International Working Group criteria; humoral immune response	No serious adverse events were reported.	These results report the safety, feasibility, and potential antitumor activity of adoptive T-cell therapy using this approach.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Park, 2007[194] ID NR Single-arm trial N: 6	Age group: Adults Primary refractory or relapsed metastatic neuroblastoma Treatment enrollment: Alkylator-based induction chemotherapy, radiation therapy, surgery, myeloablative autologous, stem cell transplantation, and salvage therapies Treatment requisite: Leukapheresis	Autologous CE7R/HyTK+ CD8+ cytolytic T-lymphocyte (CTL) clones No comparison group Follow-up: 12	Successful generation of genetically modified T cells; phenotype and function of autologous CE7R+/HYTK+CD8+ cytolytic T lymphocyte clones; retention of chimeric antigen receptor expression and chimeric antigen receptor redirected effector function following ex vivo expansion to clinical cell doses, In vivo persistence of transferred T cells, Safety of escalating cell doses, responses to therapy	None	This feasibility/safety trial, which is the first to use the adoptive transfer of L1-CAM redirected CAR-expressing CTLs in humans, demonstrated that, despite intensive prior therapy, cell products could be manufactured and released for most of enrolled patients and that the transfer of cells did not result in the overt targeting of L1-CAM-expressing neural tissues.
Cancer Ritchie, 2013[187] ID NR Single-arm trial N: 5	Age group: Adults Acute myeloid leukemia Treatment enrollment: Excluded if had immunotherapy, chemotherapy, or granulocyte colony-stimulating factor (G-CSF) within 4 weeks Treatment requisite: Apheresis and fludarabine + cytarabine conditioning chemotherapy prior to infusion	Autologous chimeric antigen receptor (CAR) anti-LeY T-cell therapy No comparison group Follow-up: 84	Best response; disease progression	No grade 3 or 4 toxicity was observed.	Our study supports the feasibility and safety of CAR-T-cell therapy in high-risk AML, and demonstrates durable in vivo persistence.
Cancer Neelapu, 2017[7]; Locke, 2017[595]; Kite[596]	Age group: Adults Refractory large B-cell lymphoma	Axicabtagene ciloleucel No comparison group	Objective response rate (complete response, partial response, stable disease, not evaluated);	Death (n = 3) Adverse events (in at least 30% of patients, grade 3 or higher):	Patients with refractory large B-cell lymphoma who received CAR-T-cell therapy with axi-cel had high levels of durable

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
NCT02348216 Single-arm trial N: 111	Treatment enrollment: Refractory disease (stable disease or progression on last therapy regimen) Treatment requisite: Leukapheresis and conditioning chemotherapy	Follow-up: 15	time to response; duration of response; disease progression; best response; progression-free survival; overall survival	pyrexia (n = 14), neutropenia (n = 79), anemia (n = 43), hypotension (n = 14), thrombocytopenia (n = 38), fatigue (n = 2), decreased appetite (n = 2), headache (n = 1), diarrhea (n = 4), hypoalbuminemia (n = 1), hypocalcemia (n = 6), tachycardia (n = 2), febrile neutropenia (n = 31), encephalopathy (n = 21), thrombocytopenia (n = 38), vomiting (n = 1), hypokalemia (n = 3), hyponatremia (n = 10), decrease in white cell count (n = 29), cytokine release syndrome related symptoms (pyrexia, n = 11; hypotension, n = 9; hypoxia, n = 9; tachycardia, n = 1), and neurologic events symptoms (encephalopathy, n = 21; confused state, n = 9; tremor, n = 1; aphasia, n = 7; somnolence, n = 7; agitation, n = 4; memory impairment, n = 1; mental-status change, n = 2)	response, with a safety profile that included myelosuppression, the cytokine release syndrome, and neurologic events.
Cancer Lamers, 2013[188]; Lamers, 2016[597] ID NR Trial (multiple groups) N: 12	Age group: Adults CAIX-expressing metastatic renal cell carcinoma Treatment enrollment: None Treatment requisite: None	CAIX CAR-engineered T cells No comparison group Follow-up: 33	Evaluation of on-target toxicity; CAIX mAb blood levels; CAR-T cell blood levels; posttreatment peripheral blood mononuclear cell show CAIX-specific T-cell functions	CAR-T-cell infusions induced liver enzyme disturbances reaching CTC grades 2 to 4, which necessitated cessation of treatment in 4 of 8 patients.	This report shows that CAIX-targeting CAR-T cells exerted antigen-specific effects in vivo and induced liver toxicity at the lowest dose of 0.2 × 109 T cells applied, illustrating the potency of receptor-modified T cells.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Ali, 2016[171] NCT02215967 Trial (multiple groups) N: 13	Age group: Age group unclear Multiple myeloma with uniform B-cell maturation antigen (BCMA) expression Treatment enrollment: None Treatment requisite: Apheresis (to collect peripheral blood mononuclear cells [PBMCs]) and leukocyte depletion	CAR-BCMA T No comparison group Follow-up: 6	Clinical response; response duration; time to progression; overall survival	Toxicities attributable to CAR-BCMA T cells: cytokine release syndrome at 1x106CAR1 T cells/kg dose (n = 2), at 3x106CAR1 T cells/kg dose (n = 1), and at 9x06 CAR1 T cells/kg dose (n = 2, patients also had prolonged cytopenias)	Importantly, we have shown that CAR-BCMA T cells have powerful activity against MM that was resistant to standard therapies. These results should encourage further efforts to enhance anti-BCMA CAR-T cell therapies. The striking activity of anti-BCMA CAR-T cells against MM indicates that CAR-T cells targeting BCMA have great potential to be an effective new treatment of MM.
Cancer Thistlethwaite, 2017[160] NCT01212887 Trial (multiple groups) N: 14	Age group: Adults Carcinoembryonic antigen cancer (CEA) Treatment enrollment: All patients had metastatic gastrointestinal malignancies. Treatment requisite: Preconditioning chemotherapy, MFEζ T cells and systemic IL2	Carcinoembryonic antigen (CEACAM5)-specific CAR-T No comparison group Follow-up: 12	MFEζ T-cell engraftment; serum carcinoembryonic antigen	Grade 3 tachypnea and pulmonary infiltrates (n = 1 cohort 4), respiratory distress 5 days following T-cell infusion and admitted to the critical care unit (n = 1 cohort 4), grade 3 neutropenicsepsis (n = 1 cohort 4), grade 3 decreased appetite (n = 2 cohort 2), and grade 4 neutropenic sepsis and grade 2 intracranial hemorrhage (n = 1 cohort 2)	While improved CAR designs and T-cell production methods could improve the systemic persistence and activity, methods to control CAR-T "on-target, off-tissue" toxicity are required to enable a clinical impact of this approach in solid malignancies.
Cancer Hu, 2017[166]; Hu, 2016[598] ChiCTR-OCC-15007008 Trial (multiple groups) N: 15	Age group: Children and adults Relapsed/refractory acute lymphocytic leukemia (R/R ALL) Treatment enrollment: None Treatment requisite: Leukapheresis and lymphodepletion	CART19 No comparison group Follow-up: Unclear	Clinical response (clinical response, stable disease, progressive disease); overall survival; progression-free survival; time to relapse	Cytokine release syndrome (none, n = 5; grade 1, n = 3; grade 2, n = 1; grade 3, n = 6) and high fever (all patients with CRS developed fever, not separated by grade)	This trial demonstrated potent antileukemia activities of CART19s in Chinese patients with R/R ALL. Disease relapse remained the main obstacle. However, patients with a high risk of relapse after CART19s might benefit from subsequent haploidentical hematopoietic stem cell transplantation.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Kalos, 2011[191]; Maude, 2014[69]; Porter, 2011[599]; Fraietta, 2018[600]; Porter, 2015[601]; University of Pennsylvania, 2015[602]; Feng, 2017[603] NCT01029366 Single-arm trial N: 3	Age group: Adults Advanced, chemotherapy-resistant chronic lymphocytic leukemia (CLL) Treatment enrollment: None Treatment requisite: Apheresis and lymphodepletion	CART19 No comparison group Follow-up: 24, then roll over into long-term study (total 180)	Various lab-based measurements to track engraftment and function of cells; clinical response	Significant toxicities were observed in all patients (no grades given) and included high fevers, rigors, dyspnea, transient cardiac dysfunction, febrile syndrome, and hypotension.	Evidence for on-target toxicity included B-cell aplasia as well as fewer plasma cells and hypogammaglobulinemia. On average, each infused CAR-expressing T cell was calculated to eradicate at least 1000 CLL cells. Furthermore, a CD19-specific immune response was demonstrated in the blood and bone marrow, accompanied by complete remission, in 2 of 3 patients.
Cancer University of Pennsylvania[236] NCT02588456 Single-arm trial N: 5	Age group: Adults Relapsed or refractory B-cell acute lymphoblastic leukemia Treatment enrollment: Chemotherapy Treatment requisite: None	CART22 cells transduced with a lentiviral vector to express anti-CD22 scFv TCRz:41BB administered by IV infusion No comparison group Follow-up: 36	Number of adverse events	None	Terminated due to lack of efficiency

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Hege, 2017[164] ID NR Trial (multiple groups) N: 23	Age group: Adults Metastatic colorectal cancer with solid tumors Treatment enrollment: No prior treatment with immunotherapy, retroviral gene therapy, or the same treatment antibody Treatment requisite: Preexisting percutaneous catheters and infusion pumps in place from previous infusion chemotherapy protocols, and coadministration of IFN-alpha, lymphapheresis	CART72 No comparison group Follow-up: 3	Tumor biomarkers carcinoembryonic antigen; radiologic tumor response	Grade 3 adverse events possibly related to CART72 in trial C-9701 included retinal artery occlusion that developed 3 days following the second CART72 infusion (1 patient) and chills (1 patient). In trial C-9702, 1 patient (303D) developed fever, abnormal liver function tests, anemia, and leukocytosis 6 days following the second CART72 cell administration (first infusion of 1010 cells), prompting a 4-day hospitalization.	These findings demonstrate the relative safety of CART72 cells. The limited persistence supports the incorporation of costimulatory domains in the CAR design and the use of fully human CAR constructs to mitigate immunogenicity.
Cancer Feng, 2016[226]; Guo, 2018[604]; Feng, 2017[603] NCT01869166 Single-arm trial N: 11	Age group: Adults Non–small cell lung cancer Treatment enrollment: None Treatment requisite: Cyclophosphamide	CAR-T-EGFR No comparison group Follow-up: 15	Partial remission; stable disease; progressive disease	SAEs: 1 patient	Pathological eradication of EGFR-positive tumor cells after EGFR-targeted CAR-T cell treatment can be observed in tumor biopsies, along with the CAR-EGFR gene detected in tumor-infiltrating T cells in all 4 biopsied patients. The EGFR-targeted CAR-T cell therapy is safe and feasible for EGFR-positive advanced relapsed/refractory NSCLC.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Feng, 2017[221] NCT01935843 Trial (multiple groups) N: 11	Age group: Adults Advanced biliary tract cancers and pancreatic cancers Treatment enrollment: None Treatment requisite: None	CARTHER2 cell infusion No comparison group Follow-up: 9	Toxicities; clinical response; expansion and persistence of CART-HER2 cells in vivo	Lymphopenia (n = 6), gastrointestinal hemorrhage (n = 1), acute fever/ chill (n = 1), and transaminase elevation (n = 1)	Data from this study demonstrated the safety and feasibility of CART-HER2 immunotherapy, and showed encouraging signals of clinical activity.
Cancer Zhang, 2016[228]; Dai, 2015[605] NCT01864889 Single-arm trial N: 3	Age group: Adults B-cell lineage acute lymphoblastic leukemia Treatment enrollment: None Treatment requisite: None	CD19 No comparison group Follow-up: 13	Complete remission	SAEs: 7 events in 3 patients	Combined analyses of laboratory biomarkers with their clinical manifestations before and after salvage treatment showed that the persistent immunosurveillance mediated by CAR-T-19 cells would inevitably potentiate the leukemia-killing effectiveness of subsequent chemotherapy in patients who showed relapse after CAR-T-19-induced remission.
Cancer Wang, 2016[175] NCT01318317 Single-arm trial N: 16	Age group: Adults B-cell non-Hodgkin lymphoma Treatment enrollment: None Treatment requisite: Leukapheresis	CD19 CAR-T No comparison group Follow-up: 14	Days post T-cell infusion, CAR area under the curve, peak expansion, and maximum persistence	None	Data from these phase 1 clinical trials support the safety and feasibility of administering TCM-derived CD19 CAR-T cells for NHL patients following HSCT.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer The Affiliated Hospital of the Chinese Academy of Military Medical Sciences, 2016[247]; Cai, 2016[606] NCT02799550 Single-arm trial N: 1	Age group: Adults Lymphoblastic leukemia Treatment enrollment: Vindesine, mitoxantrone, cyclophosphamide, and dexamethasone Treatment requisite: None	CD19-chimeric antigen receptor T cells No comparison group Follow-up: 1	Toxicity; response to treatment; engraftment; expansion of donor-derived CAR-T cells in vivo; cytokine changes; survival	None	Our preliminary results suggest that coinfusion of haplo-identical, donor-derived CAR-T cells and mobilized PBSCs may induce full donor engraftment in relapsed and refractory ALL including elderly patients, but complications related to donor cell infusions should still be cautioned.
Cancer Turtle, 2017[159]; Turtle, 2016[607]; Turtle, 2016[608]; Hay, 2017[609]; Gust, 2017[610] NCT01865617 Single-arm trial N: 24	Age group: Adults Chronic lymphocytic leukemia (CLL) with relapsed or refractory CD19+ B-cell malignancies who experienced treatment failure after receiving the anti-CD20 antibody rituximab and fludarabine or bendamustine, and had also previously received ibrutinib Treatment enrollment: Relapsed or refractory CD19+ B-cell malignancies who experienced treatment failure after receiving the anti-CD20 antibody rituximab and fludarabine or bendamustine, and had previously received ibrutinib Treatment requisite: Leukapheresis (peripheral	CD19 chimeric antigen receptor-modified T cells No comparison group Follow-up: median 6.6	Complete remission; partial remission; detection of disease in marrow; progression-free survival; overall survival; lymph node response	Severe cytokine release syndrome and/or neurotoxicity (n=17)	CD19 CAR-T cells are highly effective in high-risk patients with CLL after they experience treatment failure with ibrutinib therapy.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
	blood mononuclear cells or PBMCs) for generating CAR-T cells, followed 3 weeks later by lymphodepletion chemotherapy by cyclophosphamide and/or fludarabine				
Cancer Rossig, 2017[165] ID NR Trial (multiple groups) N: 11	Age group: Children Acute lymphoblastic leukemia Treatment enrollment: Stem cell transplant Treatment requisite: EBV vaccination	CD19 chimeric antigen receptors (CAR) T cells No comparison group Follow-up: 7	Complete response; partial response; duration of response	SAEs: 6 patients/events	This study demonstrates the feasibility of multicenter studies of CAR-T cell therapy and the potential for enhancing persistence with vaccination.
Cancer Lee, 2015[66]; Stroncek, 2016[611] NCT01593696 Single-arm trial N: 21	Age group: Children and adults Acute lymphoblastic leukemia Treatment enrollment: None Treatment requisite: None	CD19-CAR-T No comparison group Follow-up: None	Overall survival	None	CD19-CAR-T cell therapy is feasible and safe, and mediates potent anti-leukemic activity in children and young adults with chemotherapy-resistant B-precursor acute lymphoblastic leukemia.
Cancer Baylor College of Medicine, 2014[239]; Xu, 2014[612] NCT00586391 Single-arm trial N: 14	Age group: Adults Lymphoid malignancies Treatment enrollment: None Treatment requisite: Ipilimumab	CD19CAR-28-zeta T cells No comparison group Follow-up: 180	Adverse event data per patient; survival and function of CD19CAR-T cells; number of patients with tumor response; correlation of additional doses and cumulative rise in the percentage of circulating gene-modified cells	None	Preclinical models showed that increasing the frequency of CD81 CD45RA1CCR71 CAR-T cells in the infused line by culturing the cells with IL-7 and IL-15 produced greater antitumor activity of CAR-T cells mediated by increased resistance to cell death, following repetitive encounters with the antigen, while preserving their migration to secondary lymphoid organs.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Gardner, 2017[162] NCT02028455 Trial (multiple groups) N: 45	Age group: Children and adults B-lineage acute lymphoblastic leukemia Treatment enrollment: None Treatment requisite: Leukapheresis to collect cells for generation of CAR-T cells, lymphodepletion with fludarabine and cyclophosphamide prior to infusion	CD19-directed chimeric antigen receptor (CAR) T cells No comparison group Follow-up: 10	Minimal residual disease–negative rate; persistence of transferred T cells; disease response; overall survival; relapse rate; progression-free survival	Grade 3 or higher adverse events: increased alanine aminotransferase (n = 3), increased aspartate aminotransferase (n = 1), chills (n = 1), cytokine release syndrome (n = 18), febrile neutropenia (n = 2), headache (n = 1), hypotension (n = 1), left ventricular dysfunction (n = 1), encephalopathy (n = 7), hydrocephalus (n = 1), seizure (n = 3), and tremor (n = 1)	These data demonstrate that manufacturing a defined-composition CD19 CAR-T cell identifies an optimal cell dose with highly potent antitumor activity and a tolerable adverse effect profile in a cohort of patients with an otherwise poor prognosis.
Cancer Kebriaei, 2016[169] NCT01492036 (patients from NCT00968760 and NCT01497184) Single-arm trial N: 26	Age group: Children and adults Advanced non-Hodgkin lymphoma Treatment enrollment: None Treatment requisite: None	CD19-specific CAR-T No comparison group Follow-up: 32	Complete remission	None	CD19-specific CAR-T cells generated with SB and AaPC platforms were safe, and may provide additional cancer control as planned infusions after HSCT. These results support further clinical development of this nonviral gene therapy approach.
Cancer Wang, 2017[168] NCT02259556 Single-arm trial N: 18	Age group: Children and adults Relapsed or refractory Hodgkin lymphoma Treatment enrollment: Chemotherapy Treatment requisite: Chemotherapy	CD30 chimeric antigen receptors No comparison group Follow-up: 14	Progression-free survival	SAEs: 2 patients	CART-30 cell therapy was safe, feasible, and efficient in relapsed or refractory lymphoma and guarantees a large-scale patient recruitment.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Ramos, 2017[157] NCT01316146 Trial (multiple groups) N: 9	Age group: Adults Relapsed or refractory Hodgkin lymphoma (HL) and anaplastic large cell lymphoma (ALCL) Treatment enrollment: No anti-30 antibody-based therapy (within past 4 weeks), no investigational agents or tumor vaccines (within past 6 weeks), and no current use of systemic steroids Treatment requisite: Blood collection	CD30.CAR-Ts No comparison group Follow-up: 12	Clinical/best response (complete response [CR], partial response, stable disease, or progressive disease); current outcome; survival	No adverse events observed were considered related to therapy.	CD30.CAR-Ts are safe and can lead to clinical responses in patients with HL and ALCL, indicating that further assessment of this therapy is warranted.
Cancer Tang, 2018[220] ID NR Single-arm trial N: 3	Age group: Children and adults Acute myeloid leukemia Treatment enrollment: Chemotherapy Treatment requisite: Bone marrow examination	CD33-CAR NK-92 No comparison group Follow-up: 6	Adverse events	None	At doses up to 5 × 109 (5 billion) cells per patient, no significant adverse effects were observed. CAR NK-92 cells can be produced at much lower cost compared with CAR-T cells, and we believe after being optimized they will be widely accessible for the treatment of cancer.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Wang, 2015[181] NCT01864902 Single-arm trial N: 1	Age group: Adults Refractory acute myeloid leukemia Treatment enrollment: CAG (aclacinomycin, cytarabine, and granulocyte colony-stimulating factor) regimen Treatment requisite: None	CD33-directed chimeric antigen receptor-modified T cells (CART-33) No comparison group Follow-up: 2	Phenotype, antitumor activities, and in vivo expansion of CART-33 cells; toxicities; clinical response	None	In this study, we demonstrated a comparable in vitro antileukemia activity of CART-33 cells with that found in previous reports and reported their first clinical use for the treatment of 1 chemotherapy refractory advanced AML patient. The infusion of CART-33 alone cells led to marked disease degradation in the early stage, indicating a potent in vivo cytotoxic effect of CART-33 on CD33+ blasts. However, CD33+ leukemic cells gradually augmented until a florid progression was observed in the later stage of cell therapy.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Zhang, 2017[163] NCT02349724 Trial (multiple groups) N: 10	Age group: Adults Carcino-embryonic antigen (CEA)–positive metastatic colorectal cancers Treatment enrollment: No antitumor therapy for at least 2 weeks before enrollment Treatment requisite: Peripheral blood collected from patients (to isolate peripheral blood mononuclear cells [PBMCs] to activate and culture T cells); lymphodepletion for 5 days (3 days of CAR-T cell therapy and fludarabine [FLU] 25 mg/kg/day for the last 2 days)	CEA CAR-T No comparison group Follow-up: Unclear	Reduction in tumor lesion size; clinical response (progressive disease, stable disease)	No severe adverse events related to CAR-T cell therapy were observed. Related to the lymphodepletion: reduced lymphocyte counts (grade 3, n = 3; grade 4, n = 9) and reduced neutrophil counts (grade 3, n = 4; grade 4, n = 2); other grade 3 events observed: increased gamma-glutamyl transferase (GGT, grade 3, n = 2), increased alkaline phosphatase (ALP, grade 3, n = 1), and duodenal perforation (n = 2)	We demonstrated that CEA CAR-T cell therapy was well tolerated in CEA+ CRC patients even in high doses, and some efficacy was observed in most of the treated patients.
Cancer Fitzgerald, 2017[167]; University of Pennsylvania, 2016[613]; Gofshteyn, 2018[614]; Ruella, 2018[615]; Maude, 2014[69] NCT01626495 Single-arm trial N: 39	Age group: Children and adults Relapsed/refractory acute lymphoblastic leukemia Treatment enrollment: None Treatment requisite: Tocilizumab, corticosteroids, hydrocortisone, and methylprednisolone	Chimeric antigen receptor-modified T-cell therapy No comparison group Follow-up: 1	Cytokine release syndrome	None	Grade 3 to 4 cytokine release syndrome occurred in 46% of patients following T-cell therapy for relapsed/refractory acute lymphoblastic leukemia. Clinicians should be aware of expanding use of this breakthrough therapy and implications for critical care units in cancer centers.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Cheng, 2018[219] NCT02685670 Single-arm trial N: 7	Age group: Children and adults B-cell leukemia Treatment enrollment: Hematopoietic stem cell transplant Treatment requisite: Leukapheresis	Coinfused C D28- and 4-1BB-engineered CAR-T No comparison group Follow-up: 15	Safety evaluation; efficacy assessment	None	We found that such a clinical procedure was feasible and safe. Complete remission (CR) was observed in 5 of 7 enrolled patients, with 2 patients exhibiting durable CR lasting more than 15 months.
Cancer Schuster, 2017[58]; University of Pennsylvania[616] NCT02030834 Single-arm trial N: 28	Age group: Adults Refractory B-cell lymphomas Treatment enrollment: No curative treatment options available Treatment requisite: Leukapheresis, bridging therapy (discretion of treating physician), and staging and lymphodepletion of T lymphocytes (regimen at discretion of treating physician)	CTL019 No comparison group Follow-up: 180	Overall response rate at 3 months (including complete response); progression-free survival; duration of response; overall survival; probability of survival	Grade 3 or higher: death (n = 1), anemia (n = 3), other blood and lymphatic system disorders (n = 1), febrile neutropenia (n = 3), leukocytosis (n = 1), atrial fibrillation (n = 1), cardiac arrest (n = 1), optic nerve disorder (n = 1), abdominal pain (n = 1), other gastrointestinal disorders (n = 1), intra-abdominal hemorrhage (n = 1), small intestinal obstruction (n = 1), fatigue (n = 1), fever (n = 1), noncardiac chest pain (n = 1), cytokine release syndrome (n = 5), other infections and infestations (n = 1), lung infection (n = 4), sepsis (n = 1), skin infection (n = 1), small intestine infection (n = 1), various irregular laboratory results (n = 30, aggregate of various tests—fewer actual patients as some had multiple irregular labs), weight loss (n = 1), acidosis (n = 3), anorexia (n = 1), hypercalcemia (n =	High rates of durable remission were observed, with recovery of B cells and immunoglobulins in some patients. Transient encephalopathy developed in approximately 1 in 3 patients and severe cytokine-release syndrome developed in 1 in 5 patients.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
				1), hypocalcemia (n = 1), hyponatremia (n = 2), hypophosphatemia (n = 5), decreased joint range of motion (n = 1), other musculoskeletal and connective tissue disorder (n = 1), encephalopathy (n = 3), hydrocephalus (n = 1), spasticity (n = 1), syncope (n = 1), insomnia (n = 2), acute kidney injury (n = 2), hematuria (n = 1), aspiration (n = 2), dyspnea (n = 1), hypoxia (n = 1), laryngeal edema (n = 1), pulmonary edema (n = 1), hypertension (n = 3), and hypotension (n = 3)	
Cancer Garfall, 2015[176] University of Pennsylvania, 2015[617]; Garfall, 2018[618] NCT02135406 Single-arm trial N: 1	Age group: Adults Multiple myeloma Treatment enrollment: Lenalidomide, bortezomib, carfilzomib, pomalidomide, vorinostat, clarithromycin, and elotuzumab Treatment requisite: Leukapheresis	CTL019 cells, a cellular therapy consisting of autologous T cells transduced with an anti-CD19 chimeric antigen receptor No comparison group Follow-up: 12	Feasibility and toxic effects; clinical response; CTL019 engraftment, systemic inflammatory markers, and B-cell aplasia; CD19 expression in multiple myeloma cells	None	Autologous transplantation followed by treatment with CTL019 cells led to a complete response with no evidence of progression and no measurable serum or urine monoclonal protein at the most recent evaluation, 12 months after treatment.
Cancer University College London[244] NCT01195480 Single-arm trial N: 29	Age group: Children Acute lymphoblastic leukemia Treatment enrollment: NR Treatment requisite: NR	Donor-derived EBV-specific cytotoxic T cells (EBV-CTL) transduced with the retroviral	Toxicity attributable to transfer of CD19-zeta transduced CTL; biological efficacy as assessed by effect of CD19-zeta transduced CTL on minimal residual disease	CD19 CAR CTL persistence	Terminated due to lack of biological efficacy and CD19 CAR CTL persistence.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
		vector SFGalpha-CD19-CD3zeta No comparison group Follow-up: 12	levels in the bone marrow in the first year posttransduced CTL infusion; persistence and frequency of circulating CD19-zeta transduced CTL in the peripheral blood of recipients after adoptive transfer as assessed by flow cytometry and quantitative real-time PCR, In vitro anti-leukaemic response of circulating PBMC post adoptive transfer of CD19-zeta transduced CTL using interferon-gamma ELISPOT assays after stimulation with CD19+ve targets, Relapse rate, disease-free survival and overall survival at 1 and 2 years after adoptive immunotherapy with CD19ζ-transduced EBV-CTL		
Cancer Park, 2018[154]; Brentjens, 2013[619]; Park, 2018[620] NCT01044069 Trial (multiple groups) N: 53	Age group: Adults Acute lymphoblastic leukemia Treatment enrollment: Relapsed or refractory disease Treatment requisite: Leukapheresis and conditioning therapy	f CD19 CAR-Therapy No comparison group Follow-up: 65	Clinical effect: Complete remission, minimal residual disease, relapsed disease, overall survival, event-free survival	Cytokine release syndrome (grade 3 or higher, n = 14), death (n = 1), and neurotoxic effects (grade 3 or higher, n = 22)	19-28z CAR-T-cell therapy had favorable long-term remission rates in a population of patients with a low disease burden, who had significantly longer event-free survival and overall survival with a markedly lower incidence of toxic effects than did those with a high disease burden.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Louis, 2011[190]; Pule, 2008[621] NCT00085930 Trial (multiple groups) N: 19	Age group: Children and adults Neuroblastoma Treatment enrollment: None Treatment requisite: Blood collection to generation CAR-T cells, and Benadryl and Tylenol treatment prior to infusion of cells	GD2-CAR-T No comparison group Follow-up: 180	Best response; clinical response; clinical outcome; overall survival	Grade 3 localized pain (n = 1)	GD2-CAR-T cells can induce complete tumor responses in patients with active neuroblastoma; these CAR-T cells may persist in patients, and such persistence was associated with longer survival.
Cancer Ahmed, 2015[180] NCT00902044 Trial (multiple groups) N: 19	Age group: Children and adults Metastatic or recurrent (HER2)-positive sarcoma Treatment enrollment: None Treatment requisite: Peripheral blood collection (for peripheral blood mononuclear cells to generate T cells)	HER2-CAR-T No comparison group Follow-up: 37 (max), 10 (median)	Clinical response (stable disease, progressive disease, partial response, complete response)	1 observed adverse event related to the therapy infusion: high fever (n = 1)	This first evaluation of the safety and efficacy of HER2-CAR-T cells in patients with cancer demonstrates that cells can persist for 6 weeks without evident toxicities, setting the stage for studies that combine HER2-CAR-T cells with other immunomodulatory approaches to enhance their expansion and persistence.
Cancer Ahmed, 2017[161]; Baylor College of Medicine, 2014[622] NCT01109095 Single-arm trial N: 17	Age group: Children and adults Progressive glioblastoma Treatment enrollment: None Treatment requisite: None	HER2-CAR VSTs No comparison group Follow-up: 29	T-cell persistence and their antiglioblastoma activity	No dose-limiting toxicity, and few patients had seizures and/or headaches	Infusion of autologous HER2-CAR VSTs is safe, with some indication of clinical benefit, and evaluation in a phase 2b study is warranted.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Tchou, 2017[155]; University of Pennsylvania, 2018[623] NCT01837602 Trial (multiple groups) N: 6	Age group: Adults Metastatic breast cancer Treatment enrollment: None Treatment requisite: Apheresis, intratumoral injection of therapy, surgical excision of the tumor, and complete blood counts/chemistry	mRNA c-Met-CAR-T No comparison group Follow-up: Until death	No measurable clinical responses were observed.	6 grade 3 adverse events: pain at skin graft donor site on right thigh (n = 1), nausea and vomiting (n = 4), and anemia (n = 1). All grade 3 serious adverse events were deemed unrelated to the study drug.	Intratumoral injections of mRNA c-Met-CAR-T cells are well tolerated and stimulate an inflammatory response within tumors.
Cancer Siefker-Radtke, 2016[170] NCT01517464 Trial (multiple groups) N: 13	Age group: Adults Genitourinary cancers Treatment enrollment: Dexamethasone, diphenhydramine, famotidine, and acetaminophen Treatment requisite: None	SGT-94 No comparison group Follow-up: None	Therapy-related toxicity	Anemia (n = 1) and platelet count decreased (n = 1)	In conclusion, systemically delivered SGT-94 showed evidence of selective tumor targeting and was well tolerated with evidence of clinical activity. Additional studies are warranted to explore the activity of this drug as a single agent and in combination therapy.
Cancer Kochenderfer, 2017[225] ID NR, protocol approved by NIH Trial (multiple groups) N: 22	Age group: Adults Advanced-stage lymphoma Treatment enrollment: None Treatment requisite: Chemotherapy	T cells genetically modified to express chimeric antigen receptors (CARs) targeting CD19 (CAR-19) No comparison group Follow-up: 24	Remissions of lymphoma; toxicities	Neutrophils decreased (n = 6), leukocytes decreased (n = 3), dysphasia (n = 5), hypotension (n = 3), cognitive disturbance (n = 1), supraventricular tachycardia (n = 1), platelets decreased (n = 2), confusion (n = 1), and hemoglobin decreased (n = 1)	CAR-19 T cells preceded by low-dose chemotherapy induced remission of advanced-stage lymphoma and high serum IL-15 levels were associated with the effectiveness of the treatment.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Beatty, 2018[233]; University of Pennsylvania, 2015[624] ID NR (but trial stated in title) Single-arm trial N: 6	Age group: Adults Pancreatic carcinoma metastases Treatment enrollment: None Treatment requisite: None	T cells to transiently express a messenger RNA encoding a chimeric antigen receptor (CAR) specific for mesothelin No comparison group Follow-up: 15	Reduction in FDG uptake, primary PDAC; transient CAR expression	None	Our results provide evidence for the potential antitumor activity of messenger RNA CARTmeso cells, as well as PDAC resistance to the immune response.
Cancer Maude, 2018[8]; Novartis Pharmaceuticals[625] NCT02435849 Single-arm trial N: 75	Age group: Children and adults CD19+ relapsed or refractory B-cell lymphoblastic leukemia Treatment enrollment: Excluded patients who had received other anti-CD19 therapy Treatment requisite: Leukapheresis and lymphodepleting chemotherapy	Tisagenlecleucel No comparison group Follow-up: median 13.1 (ongoing)	Remission rate > 20%; complete remission (with or without laboratory confirmation); rate of complete remission (with or without laboratory confirmation); duration of remission; event-free survival; disease relapse; overall survival; cellular kinetics	Grade 3 or 4 adverse events: Cytokine release syndrome (n = 35), pyrexia (n = 10), decreased appetite (n = 11), hypotension (n = 15), increase in aspartate aminotransferase (n = 11), hypokalemia (n = 11), hypoxia (n = 14), hypophosphatemia (n = 9), and increase in blood bilirubin (n = 9)	A single infusion of tisagenlecleucel provided durable remission with long-term persistence in pediatric and young adult patients with relapsed or refractory B-cell ALL, with transient high-grade toxic effects.
Cancer Kershaw, 2006[295] ID NR Trial (multiple groups) N: 14	Age group: Adults Ovarian cancer Treatment enrollment: None Treatment requisite: Interleukin 2 and allogenic immunization	Utologous T cells gene modified to express a chimeric receptor No comparison group Follow-up: 12	Toxicity	Leukopenia (n = 1), hypotension (n = 3), platelet count decreased (n = 1), rigors (n = 1), hemoglobin (n = 1), diarrhea (n = 1), fatigue (n = 1), sinus tachycardia (n = 1), and dyspnea (n = 2)	Large numbers of gene-modified tumor-reactive T cells can be safely given to patients, but these cells do not persist long term. This report is the first to report the use of genetically redirected T cells for the treatment of ovarian cancer.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Baylor College of Medicine[237]; Tanaka, 2017[626] NCT01953900 Single-arm trial N: 26	Age group: Adults Osteosarcoma Neuroblastoma Treatment enrollment: None Treatment requisite: Aricella zoster vaccine and lymphodepleting chemotherapy	ZV-specific T cells (VZVST) expressing a CAR for GD2 No comparison group Follow-up: 1	Number of patients with dose-limiting toxicity; amount of T cells in the blood after the infusions; number of patients with a response to the T cells	None	None
Cancer Ramos, 2016[174] NCT00881920 Trial (multiple groups) N: 16	Age group: Adults B cell–derived malignancies Treatment enrollment: R-CHOP, 2CDA, R-BEAM/ASCT, dexamethasone/bortezomib, R-CHOP/XRT, FCR, R-ICE, TTR, CD19.CART, R-bendamustine, rituximab, R-fludarabine, R-hCVAD, carfilzomib/lenalidomide, R-ibrutinib, and R-ESHAP Treatment requisite: None	Kappa..CAR-T No comparison group Follow-up: 24	Toxicity; complete/partial response; stable disease	None	Kappa.CAR-T infusion is feasible and safe and can lead to complete clinical responses

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Immune deficiency Deeks, 2002[343] ID NR RCT Completed N: 40	Age group: Adults HIV Treatment enrollment: ≥24 weeks of stable treatment with at least 3 antiretroviral drugs, including at least 1 protease or nonnucleoside reverse transcriptase inhibitor Treatment requisite: None	CD4 gene–modified versus unmodified T cells Other: Unmodified T cells Follow-up: 6	Plasma/blood/rectal HIV DNA; rectal HIV RNA; HIV coculture; CD4 count	None	No significant between-group differences were noted in viral reservoirs following therapy. However, infusion of gene-modified, but not unmodified, T cells was associated with a decrease from baseline in HIV burden in 2 of 4 reservoir assays and a trend toward fewer patients with recurrent viremia. Both groups experienced a treatment-related increase in CD4+ T-cell counts.
Immune deficiency Scholler, 2012[336] NCT01013415 RCT N: 43	Age group: Age group unclear Human immunodeficiency virus (HIV) Treatment enrollment: None Treatment requisite: None	Gammaretroviral vector engineered T cells Other: Unmodified T cells Follow-up: 124	Safety and durability of gene transfer with integrating vectors	None	There was no evidence of vector-induced immortalization of cells as integration site distributions showed no evidence of persistent clonal expansion or enrichment for integration sites near genes implicated in growth control or transformation.

Abbreviation: AEs, adverse events; BCMA, B cell maturation antigen; CAR, chimeric antigen receptors; FDA, U.S. Food and Drug Administration; ID, identification number; N, number of participants; NSCLC, non-small-cell lung carcinoma; NIH, National Institutes of Health; NR, not reported; RAC, NIH Recombinant DNA Advisory Committee; RCT, randomized controlled trial; RNA, ribonucleic acid

Appendix Table A4. Evidence Table Published Genetically Modified Oncolytic Viral Therapy/Herpes Simplex Virus Type 1 Trials

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Gofrit, 2014[185] ID NR Single-arm trial N: 47	Age group: Adults Nonmuscle invasive bladder cancer Treatment enrollment: Intravesical surgery Treatment requisite: None	BC-819 No comparison group Follow-up: 12	Treatment response	SAEs: 2 patients	BC-819 prevented new tumor growth in two-thirds of the patients and ablated a third of the marker lesions. Prolonged time to recurrence was observed in responding patients. These results along with the good safety profile make BC-819 a potential medication for bladder cancer.
Cancer Zeh, 2015[230] ID NR Controlled trial N: 17	Age group: Adults Advanced solid tumors Treatment enrollment: All patients had advanced bulky tumors that progressed through standard systemic chemotherapy with 100% having prior surgery and a median of 3 systemic chemotherapy regimens. Treatment Requisite: None	Double deleted (VGF/TK) mutant (vvDD) No comparison group Follow-up: 1	Safety; toxicity; systemic symptoms; antitumor activity	At doses of 3×10^8 pfu and higher, all patients except one experienced fever and/or chills within 24 hours of injection; no grade 3 or 4 toxicities related to treatment occurred; mild liver function test abnormalities were common.	Intratumoral injection of the oncolytic vaccinia vvDD was well tolerated in patients and resulted in selective infection of injected and noninjected tumors and antitumor activity.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Weber, 1999[208] ID NR Single-arm trial N: 10	Age group: Adults Recurrence of a previously resected glioblastoma Treatment enrollment: None Treatment requisite: Surgery on day 0 for maximal tumor resection followed by injection of GLI 328 into either the resection cavity walls or residual tumor; ganciclovir treatment started 14 days after surgery for 14 days	GLI 328 No comparison group, Other: In combination with ganciclovir Follow-up: Until death	Clinical outcome/antitumor efficacy (survival, time to progression, tumor response, functional status)	2 patients were treated with dexamethasone for transient perifocal brain edema.	From the phase 2 trial data, it can be stated that the intracerebral administration of vector producer cells (VPCs) is safe, but efficacy statements are preliminary and need to be validated by the ongoing phase 3 study.
Cancer Prados, 2003[200] ID NR (described as trial) Single-arm trial N: 30	Age group: Adults Progressive or recurrent glioblastoma multiforme Treatment enrollment: Patients had to currently be receiving a stable or increasing dose of steroids and required prior treatment included previous surgery and radiation therapy 12 weeks or longer prior to study entry. Treatment requisite: Patients initially underwent a craniotomy and tumor resection for documentation; the treatment was injected at multiple sites of the surgical margin; an Ommaya reservoir was	GLI 328 (G1TkSvNa.7 vector stably transduced into PA317 cells) No comparison group, Other: In combination with ganciclovir Follow-up: Until death	Survival time; time of high-quality survival; time to clinical deterioration	90% of patients experienced at least one severe adverse event: seizure (n = 3); acute meningeal ventricular reaction (n = 4); hemiplegia/hemiparesis (n = 1); speech problem, somnolence, loss of appetite (n = 1); subdural hematoma (n = 1); cerebral edema, intracranial hypertension (n = 6); symptoms of tumor progression (n = 5); intracerebral hemorrhage (n = 1); deep venous thrombosis (n = 1); deep venous thrombosis + pulmonary embolism (n = 3); lymphopenia (n = 1); pancytopenia (n = 1); hyponatremia (n = 1); fever (n = 2); rigors, fever, nausea, vomiting (n = 1); pneumonia (n = 1); septicemia (from	This treatment modality appears to have some evidence of efficacy; however, toxicity may be related in part to the method of gene delivery.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
	implanted; additional treatment was administered on day 7 through the reservoir; ganciclovir was administered intravenously for 14 days starting on day 21; images were taken at the start of the protocol and at the end of each treatment cycle (up to 5 cycles).			central venous catheter; n = 2); perforated ulcer (n = 1); ileus (n = 1); subgaleal fluid collection (n = 1); Ommaya reservoir blockage (n = 2); Ommaya reservoir infection (n = 3); and surgical flap infection near Ommaya reservoir (n = 1).	
Cancer Ren, 2017[246] ID NR Trial (multiple groups) N: 9	Age group: Adults Advanced malignancy Treatment enrollment: None Treatment requisite: None	HSV-GM-CSF No comparison group Follow-up: 40	Safety; clinical endpoints	There were no grade 3 or greater AEs. Common AEs (occurring ≥20%) included fever (grade 1-2), injection site pain (grade 1-2), and fatigue (grade 1-2). The remainder of the AEs were grade 1 or 2, and of these AEs, those felt related to the treatment were fever and pain at injection site (definite), and tachycardia, hematuria, AV block, GGT increase, insomnia, constipation, diabetes, ecchymosis, and leukopenia (possible).	Strategies inducing the local activation of tumor-specific immune responses can be combined with adoptive cellular therapies to expand the adaptive T-cell responses systemically, and further studies are warranted.
Cancer Nemunaitis, 1999[210] ID NR Single-arm trial N: 17	Age group: Adults Metastatic melanoma Treatment enrollment: None Treatment requisite: None	IFN-g No comparison group Follow-up: 4	Progressive disease; complete response; stable disease; partial response	None	In conclusion, intratumor injection of IFN-g is safe and well tolerated. Evidence of antitumor activity is suggested in patients who receive multiple injections.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Smitt, 2003[203] ID NR Trial (multiple groups) N: 14	Age group: Adults Relapsing histologically confirmed malignant gliomas (grade IV) Treatment enrollment: None Treatment requisite: Craniotomy was performed to take frozen sections and remove tumor and then treatment was administered as ~50 injections of 0.2 mL each at intervals of 0.5 to 1.0 cm; ganciclovir was administered 2 times daily for 14 days, starting on the second postoperative day.	IG.Ad.MLPI.TK No comparison group, Other: In combination with ganciclovir Follow-up: Until death	Tumor response; time to progression (by MRI); overall survival	5 serious adverse events (SAEs) were reported: postoperative aphasia and right hemiparesis, cerebrospinal fluid (CSF) leak (prolonged hospitalization), thrombocytopenia, sepsis caused by Staphylococcus aureus, and neurological deterioration due to fever with pneumonia (new hospitalization).	The administration of the highest dose of IG.Ad.MLPI.TK by 50 injections into the wound bed following resection of recurrent malignant glioma, followed by ganciclovir treatment, was well tolerated.
Cancer Amgen, 2016[240] NCT02014441 Single-arm trial N: 61	Age group: Adults Unresected stage IIIB, IIIC, IVM1a, IVM1b, or IVM1c melanoma Treatment enrollment: None Treatment requisite: None	IMLYGIC (talimogene laherparepvec) No comparison group Follow-up: Until death	Detectable talimogene laherparepvec DNA (various sites); clearance of talimogene laherparepvec DNA (blood, urine); best overall response (WHO criteria for complete response, partial response, stable disease, progressive disease); objective response rate; time to response; duration of response; durable response rate; overall survival	Reported serious adverse events include atrial fibrillation (n = 1), cardiac failure congestive (n = 1), abdominal pain upper (n = 1), influenza-like illness (n = 1), pyrexia (n = 2), cholelithiasis (n = 1), cellulitis (n = 1), pneumonia (n = 1), sepsis (n = 1), skin infection (n = 1), increased body temperature (n = 1), posterior reversible encephalopathy syndrome (n = 1), delirium (n = 2), dyspnea (n = 1), arteriosclerosis (n = 1), deep vein thrombosis (n = 1), and hypotension (n = 1).	None

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Voges, 2003[201]; Jacobs, 2001[627] ID NR, approved by the Commission for Sematic Gene Therapy, Germany Single-arm trial N: 8	Age group: Adults Unresectable progressive or recurrent glioblastoma multiform (GBM) Treatment enrollment: None Treatment requisite: Stereotactic biopsy and intracerebral implantation of 1 to 2 silicon catheters; convection-enhanced delivery (CED) of liposome treatment through catheters; 4 days after liposome infusion, ganciclovir was administered by a 1-hour daily infusion for 14 days; scans (MRI, PET) were taken at multiple time points	Liposome delivery (not viral particles) No comparison group, Other: Combination with ganciclovir Follow-up: 12	Tumor response (by scans); calculated survival time; time to progression	No severe adverse events were reported.	Treatment was well tolerated without major side effects, and in 2 of 8 patients there was a greater than 50% reduction of tumor volume.
Cancer Hu, 2006[232] ID NR Trial (multiple groups) N: 26	Age group: Adults Breast, head and neck, and gastrointestinal cancers, and malignant melanoma Treatment enrollment: Failed prior therapy Treatment requisite: None	OncoVEXGM-CSF No comparison group Follow-up: 1	Survival; complete response; partial response; progressive disease; stable disease	SAEs: 16 events	The therapy is well tolerated and can be safely administered using the multidosing protocol described. Evidence of an antitumor effect was seen.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Ram, 1997[216] ID NR Single-arm trial N: 15	Age group: Adults Malignant brain tumors Treatment enrollment: All patients had already failed standard therapy (surgery, radiation therapy, and chemotherapy where applicable). Treatment requisite: Biopsy-confirmed diagnosis for each patient; anticonvulsant medications and dexamethasone were administered before stereotaxic injections guided by computed tomography (CT); patients received a tapering dose of dexamethasone for 2 weeks and a full 14-day course of ganciclovir.	PA317/G1TkSvNa.53 No comparison group, Other: In combination with ganciclovir Follow-up: Until death	Tumor response by MRI (partial or complete response); survival	2 patients experienced intratumoral hemorrhage and neurological deficits from the biopsy and implantation procedures, and 3 patients experienced seizures or more frequent seizures requiring anticonvulsant medications.	In this study, only very small tumors with a high density of vector-producing cells had a response, suggesting that the techniques to improve delivery and distribution of the therapy will need to be further developed for clinical utility.
Cancer Pecora, 2002[206] ID NR Trial (multiple groups) N: 79	Age group: Adults Advanced solid cancers Treatment enrollment: Subjects had tumors unresponsive to approved therapies. Treatment requisite: None	PV701 No comparison group Follow-up: Death (at least 30)	Time to tumor progression; tumor size; survival	Dehydration (n = 7), sepsis (n = 3), and death (n = 5, 4 due to progression of disease)	PV701 warrants further study as a therapeutic agent for cancer patients.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer White, 2008[193] ID NR Trial (multiple groups) N: 33	Age group: Adults Treatment-refractory advanced-stage cancer Treatment enrollment: None Treatment requisite: None	Reovirus type 3 Dearing (RT3D) No comparison group Follow-up: 2	Blood samples were evaluated for neutralizing antiretroviral antibody (NARA), peripheral blood mononuclear cells (PBMC) total and subsets, and cytokine response; tumors were assessed for clinical response (objective partial or complete response).	Grade 3 lymphopenia (n = 5) and grade 3 neutropenia (n = 3)	The results confirm that even heavily pretreated patients can mount a dynamic immune responses during treatment with RT3D; however, the responses are not clearly related to the administered treatment and dose.
Cancer Ribas, 2017[156]; Amgen[628]; Dummer, 2017[629] NCT02263508 Single-arm trial N: 21	Age group: Adults Melanoma Treatment enrollment: Patients were not surgical candidates. Treatment requisite: Biweekly pembrolizumab treatment starting on week 6 of study	Talimogene laherparepvec No comparison group. Other: Gene therapy + pembrolizumab combination in all patients, unclear Follow-up: 24	Objective response rate; progression-free survival; overall survival; change in lesion size (injected or not); number of lesions (injected or not)	Grade 5 adverse event attributed to disease progression (n = 1); grade 3 or higher attributed to talimogene laherparepvec: headache (n = 1); grade 3 or higher attributed to pembrolizumab: rash (n = 2), increase in alanine aminotransferase (n = 1), increase in aspartate aminotransferase (n = 1), hyperglycemia (n = 2), and pneumonitis (n = 1); grade 3 or higher attributed to talimogene laherparepvec and/or pembrolizumab: rash (n = 2), headache (n = 1), increase in alanine aminotransferase (n = 1), increase in aspartate aminotransferase (n = 1), and hyperglycemia (n = 2)	Oncolytic virotherapy may improve the efficacy of anti-PD-1 therapy by changing the tumor microenvironment.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer BioVex Limited, 2011[243] NCT01161498 RCT N: 5	Age group: Adults Squamous cell carcinoma of the head and neck (SCCHN) Treatment enrollment: None Treatment requisite: Radiation/cisplatin	Talimogene laherparepvec No comparison group Follow-up: 27	2-year event-free survival; clinical objective response (cOR); metabolic complete response (mCR); pathologic complete response (mCR); time to locoregional failure; time to distant failure; time to any failure; overall survival; disease-specific survival; participants with N1-2 disease at baseline requiring neck dissection	SAEs: Intervention (n = 2) and Control (n = 2)	None (table results only)
Cancer Chesney, 2018[234] NCT02173171 Single-arm trial N: 41	Age group: Adults Melanoma Treatment enrollment: Of the total of 41 patients in the EAP study, 21 (51.2%) received talimogene laherparepvec as the first treatment of their recurrent melanoma and 20 (48.8%) received it as second-line or later treatment of their recurrence(s). Treatment requisite: None	Talimogene laherparepvec No comparison group Follow-up: 1	Safety; tumor response	None	In the clinical practice setting, talimogene laherparepvec has a safety profile comparable to that observed in previous clinical trials.
Cancer Chesney, 2018[223]; Amgen[630] NCT02147951 Single-arm trial N: 2	Age group: Adults Melanoma Treatment enrollment: None Treatment requisite: None	Talimogene laherparepvec No comparison group Follow-up: 5+	Complete response	No safety issues	Talimogene laherparepvec was active in patients with advanced melanoma with disease progression following multiple previous systemic therapies; no new safety signals were identified.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer BioVex Limited, 2014[241] NCT01368276 RCT N: 31	Age group: Adults Melanoma Treatment enrollment: Participation in prior trial Treatment requisite: None	Talimogene laherparepvec No comparison group Follow-up: 22	Objective response rate; durable response rate	SAEs: Intervention (n = 9) and Control (n = 0)	None
Cancer BioVex Limited[242] NCT00402025 Single-arm trial N: 17	Age group: Adults Unresectable pancreatic Cancer Treatment enrollment: Failure of either standard therapy OR any one of the following: no alternative therapeutic of higher curative potential is available; investigator determination that patient could not tolerate alternative therapeutic due to unacceptable toxicity; or patient refusal to be treated with available alternative therapeutic Treatment requisite: None	Talimogene laherparepvec No comparison group Follow-up: 11	Safety; blood in urine; Anti-herpes Simplex Virus-1 antibodies; tumor response	SAEs varied from 67% to 90% per group.	None
Cancer Andtbacka, 2015[82]; Kaufman, 2017[631]; BioVex, 2013[632]; Harrington, 2016[633]; Andtbacka, 2016[634]; Andtbacka, 2016[635] NCT00769704 RCT N: 436	Age group: Adults Unresected stage IIIB to IV head and neck melanoma Treatment enrollment: None Treatment requisite: None	Talimogene laherparepvec (T-VEC) Other: Subcutaneous GM-CSF Follow-up: 44	Durable response rate: Rate of complete response plus partial response lasting 6 months continuously; best overall response and tumor burden; onset and duration of response; time to treatment failure	Cellulitis	T-VEC is the first oncolytic immunotherapy to demonstrate therapeutic benefit against melanoma in a phase 3 clinical trial.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cancer Puzanov, 2016[173] ID NR (abstract refers to trial) Single-arm trial N: 19	Age group: Adults Melanoma Treatment enrollment: None Treatment requisite: Ipilimumab	Talimogene laherparepvec (T-VEC) No comparison group Follow-up: 25	Confirmed response; partial response	SAEs: 5	T-VEC with ipilimumab had a tolerable safety profile, and the combination appeared to have greater efficacy than either T-VEC or ipilimumab monotherapy.
Cancer Schwarzenberger, 2011[235] ID NR Trial (multiple groups) N: 15	Age group: Adults Mesothelioma Treatment enrollment: Patients were required to be treatment naïve. Treatment requisite: Computer tomography 2 weeks prior to study and every 3 months after study completion; placement of indwelling catheter into pleural effusion; infusion of PA1STK cells (1-3 infusions depending on treatment group) followed by 7 days of ganciclovir treatment	The HSVtk gene was stably transduced into the human ovarian carcinoma cell line PA1STK. No comparison group, Other: In combination with ganciclovir Follow-up: Until death	Survival; time to disease progression; clinical response and response rate (complete response, partial response, stable disease)	No grade 3 or 4 adverse events were recorded.	While no objective clinical responses were observed by imaging, the results indicate significant immunological responses and validate the principal antitumor mechanisms.
Cancer Eissenberg, 2015[245] NCT00871702 Single-arm trial N: 8	Age group: Adults Relapsed hematological disease (acute myeloid leukemia, myelodysplastic syndrome) Treatment enrollment: None Treatment requisite: Some patients received corticosteroids and/or ganciclovir during or post donor lymphocyte infusion.	ΔU3CD34-TK75 γ-retrovirus transduced donor T cells (allogeneic) No comparison group Follow-up: Until death	Clinical outcome (complete remission, progressive disease, death); overall survival; circulating transduced T cells (by polymerase chain reaction and [18F]FHBG PET/CT imaging); immunogenicity against transduced T cells	Graft-versus-host disease (grade 3, n = 1; grade 4, n = 1)	The results of this phase 1 trial suggest that genetically modified allogeneic T cells can be safely infused into patients with relapsed hematologic malignancies, including relapse after an allogeneic stem cell transplantation.

Abbreviations: AEs, adverse events; FDA, U.S. Food and Drug Administration; ID, identification number; mL, milliliter; N, number of participants; NIH, National Institutes of Health; NR, not reported; RAC, NIH Recombinant DNA Advisory Committee; RCT, randomized controlled trial; RNA, ribonucleic acid

Appendix Table A5. Evidence Table Published RNAi Trials

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Blood disorders Pasi, 2017[153]; Alnylam Pharmaceuticals[636] NCT02035605 Controlled trial N: 51	Age group: Adults Hemophilia A or B Treatment enrollment: None Treatment requisite: None	Fitusiran Placebo Follow-up: 4	Plasma antithrombin levels; safety	Reactivation of hepatitis C viral infection and viral pneumonia	Once-monthly subcutaneous administration of fitusiran resulted in dose-dependent lowering of the antithrombin level and increased thrombin generation in participants with hemophilia A or B who did not have inhibitory alloantibodies.
Cancer Senzer, 2012[296]; Nemunaitis, 2014[637] BB-IND 14205 Controlled trial N: 45	Age group: Adults Advanced cancer Treatment enrollment: Exhausted all prior treatment options, minimum of 5 vaccine doses Treatment requisite: None	FANG No treatment Follow-up: 27	Survival; tumor response; toxicity	No treatment-related serious adverse events were reported.	FANG vaccine was safe and elicited an immune response that correlated with prolonged survival. Phase 2 assessment is justified.
Cancer Golan, 2015[178] NCT01188785 Single-arm trial N: 15	Age group: Adults Locally advanced pancreatic cancer Treatment enrollment: Chemotherapy Treatment requisite: None	siG12D-LODER No comparison group Follow-up: 2	Overall survival; time to metastasis; change in longest diameter; change in tumor volume; change in CA19-9 value	Pancytopenia (n = 1), abdominal pain (n = 2), and colonic obstruction (n = 1)	The combination of siG12D-LODER and chemotherapy is well tolerated and safe, and demonstrated a potential efficacy in patients with LAPC.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cardiovascular disease Alnylam Pharmaceuticals[311] NCT02314442 RCT N: 70	Age group: Adults Hypercholesterolemia Treatment enrollment: None Treatment requisite: None	ALN-PCSSC Placebo Follow-up: 11	The safety of ALN-PCSSC evaluated by the proportion of subjects experiencing adverse events (AEs), serious adverse events (SAEs), and Aes leading to study drug discontinuation; the pharmacokinetics (PK) of ALN-PCSSC; the effect of ALN-PCSSC on serum levels of LDL-C; the effect of ALN-PCSSC on plasma levels of PCSK9	NR	None
Cardiovascular disease Ray, 2017[330]; Leiter, 2018[638]; Ray, 2018[639]; The Medicines Company[640] ID NR RCT N: 501	Age group: Adults Elevated LDL cholesterol Treatment enrollment: None Treatment requisite: None	Inclisiran Placebo Follow-up: 7	Safety; LDL cholesterol	Serious adverse events were reported in 11% of the patients who received inclisiran and in 8% of the patients who received placebo.	We found that inclisiran lowers LDL cholesterol levels among patients at high cardiovascular risk who had elevated LDL cholesterol levels.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Cardiovascular disease Alnylam Pharmaceuticals, 2016[72] NCT01961921 Single-arm trial N: 27	Age group: Adults Familial amyloidotic Polyneuropathy Treatment enrollment: Patients must have previously received and tolerated patisiran (Onpattro, ALN-TTR02). Treatment requisite: None	Patisiran (Onpattro, ALN-TTR02) No comparison group Follow-up: 24	Change in serum TTR levels; change in modified neuropathy impairment score +7 (mNIS+7): changes in quality of life and disability measures (EuroQoL [Quality of Life]-5 Dimensions [EQ-5D], EuroQoL Visual Analog Scale [EQ-VAS], Rasch-built Overall Disability Scale [R-ODS]); change in gait speed (10-meter walk test); change in hand grip strength; change in nutritional status	Reported serious adverse events (SAEs) include cardiac amyloidosis (n = 1), myocardial infarction (n = 1), abscess limb (n = 1), osteomyelitis (n = 1), urinary tract infection (n = 1), ankle fracture (n = 1), femur fracture (n = 1), foot fracture (n = 1), ligament rupture (n = 1), thermal burn (n = 1), tibia fracture (n = 1), dehydration (n = 1), osteonecrosis (n = 2), esophageal carcinoma (n = 1), acute prerenal failure (n = 1), arthrodesis (n = 1), and venous thrombosis limb (n = 1).	None (results in table)
Cardiovascular disease Alnlylam Pharmaceuticals[310] NCT02319005 RCT N: 206	Age group: Adults Transthyretin-mediated familial amyloidotic cardiomyopathy Treatment enrollment: None Treatment requisite: None	Revusiran (ALN-TTRSC) Placebo Follow-up: 18	6-minute walking distance (6-MWD); serum TTR levels; composite cardiovascular (CV) mortality and CV hospitalization; New York Heart Association (NYHA) Class; Kansas City Cardiomyopathy Questionnaire (KCCQ); CV mortality; CV hospitalization; all-cause mortality	NR	None

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Ocular disorders Nguyen, 2012[380] ID NR Controlled trial N: 184	Age group: Adults Diabetic macular edema Treatment enrollment: None Treatment requisite: None	PF-04523655 Usual care: Laser Follow-up: 12	Best corrected visual acuity; central subfield retinal thickness; area of fluorescein leakage; mean change in patient self-reported visual functioning; vision-related quality of life as measured by NEI-VFQ-25 composite	No treatment-related serious adverse events were reported.	PF-04523655 showed a dose-related tendency for improvement in best corrected visual acuity in diabetic macular edema patients. Studies of higher doses are planned to determine the optimal efficacious dose.
Other: None Fitzgerald, 2014[383]; Alnylam Pharmaceuticals[641] NCT01437059 RCT N: 32	Age group: Adults Healthy volunteers Treatment enrollment: None Treatment requisite: None	ALN-PCS Placebo Follow-up: 6	Safety; fasting plasma PCSK9; serum LDL cholesterol	None	Our results suggest that inhibition of PCSK9 synthesis by RNA interference (RNAi) provides a potentially safe mechanism to reduce LDL cholesterol concentration in healthy individuals with raised cholesterol. These results support the further assessment of ALN-PCS in patients with hypercholesterolaemia, including those being treated with statins. This study is the first to show an RNAi drug being used to affect a clinically validated endpoint (ie, LDL cholesterol) in human beings.
Other: Transthyretin-mediated amyloidosis Zimmermann, 2017[392] ID NR RCT N: 41	Age group: Adults Transthyretin-mediated amyloidosis Treatment enrollment: None Treatment requisite: None	Hepatocyte-targeting GalNAc-siRNA Placebo Follow-up: 3	Safety	No treatment-related serious adverse events were reported.	These results demonstrate translation of this novel delivery technology, enabling clinical development of subcutaneously administered GalNAc-siRNAs for liver-based disease.

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Other: Amyloidosis Adams, 2018[73]; Alnylam Pharmaceuticals, 2017[642] NCT01960348 RCT N: 225	Age group: Adults Transthyretin-mediated familial amyloid polyneuropathy Treatment enrollment: None Treatment requisite: None	Patisiran Placebo Follow-up: 18	Modified Neuropathy Impairment Score +7: Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) Questionnaire; Neurological Impairment Score-Weakness (NIS-W) Score; Rasch-built Overall Disability Scale (R-ODS) Score; Timed 10-meter walk test (10-MWT, Gait Speed); Modified Body Mass Index; Autonomic Symptoms Questionnaire	Cardiac failure and acute kidney injury	Patisiran improved multiple clinical manifestations of hereditary transthyretin amyloidosis.
Other: Amyloidosis Suhr, 2015[386]; Alnylam Pharmaceuticals, 2013[643] NCT01617967 Trial (multiple groups) N: 29	Age group: Adults Transthyretin-mediated familial amyloid polyneuropathy Treatment enrollment: None Treatment requisite: None	Patisiran No comparison group Follow-up: 120	Adverse events (Aes), serious adverse events (SAEs), and study drug discontinuation; serum transthyretin protein; pharmacokinetic parameters of patisiran; plasma concentration; beta elimination half-life; patisiran—systemic clearance; apparent volume of distribution at steady state; patisiran renal clearance	The most common TEAE related to the study drug was mild-to-moderate infusion-related reaction (IRR), which occurred in 3 of 29 patients overall (10.3 %), all in the 0.3 mg/kg Q4W group; none of these TEAEs led to discontinuation of treatment.	Patisiran was generally well tolerated and resulted in significant dose-dependent knockdown of transthyretin protein in patients with FAP. Patisiran 0.3 mg/kg Q3W is currently in phase 3 development.
Other: Amyloidosis Alnylam Pharmaceuticals[385] NCT02292186 Single-arm trial N: 25	Age group: Adults Transthyretin cardiac amyloidosi Treatment enrollment: None Treatment requisite: None	Revusiran No comparison group Follow-up: 16	Serum TTR levels; mortality; hospitalization; 6-minute walk test performance	Cardiac failure, peripheral neuropathy, and hypotension	None

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Other: Lung and/or liver disease Turner, 2018[394] ID NR RCT N: 65	Age group: Adults Alpha-1 antitrypsin deficiency Treatment enrollment: None Treatment requisite: None	Targeting alpha-1 antitrypsin Placebo Follow-up: 4	Alpha-1 antitrypsin; forced pulmonary expiratory volume; safety	No serious adverse events were reported.	Patients homozygous with Z-alpha-1 antitrypsin and healthy volunteers responded similarly to ARC-alpha-1 antitrypsin treatment. Deep and durable reduction in serum alpha-1 antitrypsin concentrations was demonstrated.
Other: Skin disorder Leachman, 2010[393] ID NR RCT N: 1	Age group: Adults Pachyonychia congenita Treatment enrollment: None Treatment requisite: Diazepam, hydrocodone/acetaminophen, and lidocaine	Targets keratin 6a N171K Placebo Follow-up: 7	Callus and nail plate length and width	No serious adverse events were reported.	The callus regression seen on the patient's siRNA-treated foot warrants additional studies of siRNA in this and other dominant-negative skin diseases.
Other: Viral disease Dunning, 2016[382] PACTR201501000997429 Controlled trial N: 17	Age group: Adults Ebola virus disease Treatment enrollment: None Treatment requisite: Standard supportive care for Ebola virus disease	TKM-130803 Usual care: Standard supportive care for Ebola virus disease Follow-up: 1	Survival	Reported as an SAE: worsening tachypnoea in the 2 days following the second TKM-130803 infusion (n = 1), but also consistent with worsening Ebola virus disease	Administration of TKM 130803 at a dose of 0.3 mg/kg/day by intravenous infusion to adult patients with severe EVD was not shown to improve survival when compared with historic controls.

Abbreviations: AEs, adverse events; FDA, U.S. Food and Drug Administration; ID, identification number; mL, milliliter; N, number of participants; NIH, National Institutes of Health; NR, not reported; RAC, NIH Recombinant DNA Advisory Committee; RCT, randomized controlled trial; RNA, ribonucleic acid

Appendix Table A6. Evidence Table Published ZFN Trial

Indication Citations Trial ID Design N	Indication Concurrent/Prior Treatments	Intervention Comparator Months of Follow-up	Health Outcomes Measured	Adverse Events	Authors' Conclusions
Immune deficiency Tebas, 2014[333]; University of Pennsylvania, 2013[644] NCT00842634 Single-arm trial N: 12	Age group: Adults Human immunodeficiency virus (HIV) Treatment enrollment: None Treatment requisite: None	ZFN-modified autologous CD4 T cells No comparison group Follow-up: 9	The primary outcome was safety as assessed by treatment-related adverse events. Secondary outcomes included measures of immune reconstitution and HIV resistance.	Fever, chills, joint pain, and back pain all occurred in a single patient	CCR5-modified autologous CD4 T-cell infusions are safe within the limits of this study.

Abbreviations: ID, identification number; N, number of participants; ZFN, Zinc finger nucleases