



Today, we are CarelonRx, but when we created this document, we were IngenioRx. Our name may be new, but our commitment to you remains the same.

A circular inset image showing a woman with blonde hair tied back, wearing a white lab coat, looking through a microscope. The background is a soft-focus laboratory setting.

Drug and Biologic Pipeline Update

Q3 2021

IngenioRx's quarterly *Drug and Biologic Pipeline Update*

Our Q3 2021 edition highlights emerging therapies in the pharmaceutical pipeline. This quarter also offers insight on high-cost drug and biologic approvals. In addition, we examine new treatments on the horizon for epidermolysis bullosa. Our market trends section provides the latest on messenger ribonucleic acid (mRNA) technology, Shingrix label expansions, and potential Food and Drug Administration-approved bevacizumab formulations for wet age-related macular degeneration.

We continue to closely monitor the drug and biologic pipeline and provide this publication as part of our goals to improve health, lower total cost of care for pharmacy and medical, and estimate future cost impact.

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Unless otherwise noted, the information contained in this document was obtained from the Centers for Disease Control and Prevention (cdc.gov), the Food and Drug Administration (fda.gov), clinicaltrials.gov, releases from pharmaceutical manufacturers, and UpToDate.com (registration required). Information in this document is accurate as of August 3, 2021.



Top emerging new therapies

We expect these products to have significant impact on health plans and members.

VARENICLINE

Product:

Varenicline

Indication:

Treatment of the signs and symptoms of dry eye disease (DED)

Estimated FDA approval:

October 2021

Therapeutic class:

Nicotinic acetylcholine receptor (nAChR) agonist

Route of administration:

Nasal spray

FDA designations:

None

Manufacturer:

Oyster Point Pharma

Condition:

Dry eye disease (DED), often a chronic condition, occurs when either a reduced quantity or lower quality of tears are produced. The majority of the estimated 16 million people in the U.S. with DED do not have sight-threatening disease but may experience bothersome symptoms such as dry, red, itchy, or irritated eyes.^{1,2}

Role in treatment:

Varenicline, a nasal reformulation of smoking-cessation product Chantix (varenicline oral; Pfizer), would be the first nicotinic acetylcholine receptor (nAChR) agonist, as well as the first nasal formulation, approved by the Food and Drug Administration (FDA) for DED. Current treatment options include over-the-counter artificial tears and prescription therapies such as Cequa (cyclosporine ophthalmic; Sun Pharma), Eysuvis (loteprednol ophthalmic; Kala), Lacrisert (hydroxypropyl cellulose ophthalmic; Aton Pharma), Restasis (cyclosporine ophthalmic; Allergan), and Xiidra (lifitegrast ophthalmic; Novartis).

Efficacy:

In three trials, varenicline resulted in a statistically significant improvement in the primary endpoint of Schirmer's score, a measurement of the quantity of tears produced, compared to placebo. Secondary endpoint results, assessing improvement in eye dryness, varied by dose and trial.

Safety:

The majority of side effects with varenicline were mild and included headache, blurred vision, and sneezing. Approximately 50% of participants reported transient sneezing after a dose of varenicline. There were no serious treatment-related adverse events, including psychiatric events previously seen with Chantix.

Financial impact:

Analysts predict varenicline sales could reach a peak of \$1.5B per year in the U.S.³ Its nasal route of administration and novel mechanism of action may offer an attractive alternative to the more-traditional ophthalmic therapies for DED.

IngenioRx view:

Varenicline would be the first nasal spray FDA approved for the treatment for DED. It may be an option for people who desire a nonocular route or who cannot tolerate currently available ocular therapies for DED.

1 National Eye Institute, National Institutes of Health (NEI/NIH). *Dry Eye* (Accessed February 2021); nei.nih.gov

2 American Academy of Ophthalmology Cornea/External Disease Committee. *Dry Eye Syndrome Preferred Practice Pattern Guidelines, 2018*. (Accessed February 2021); aao.org

3 Decision Resources Group (accessed February 2021; registration required); insights.decisionresourcesgroup.com

BARDOXOLONE

Product:

Bardoxolone

Indication:

Alport syndrome

Estimated FDA approval:

February 2022

Therapeutic class:

Antioxidant inflammation modulator (AIM)

Route of administration:

Oral

FDA designations:

Orphan

Manufacturer:

Reata Pharmaceuticals

Condition:

Alport syndrome is a rare genetic condition that causes a progressive loss in the kidneys' ability to filter waste products from the blood. This may eventually lead to end-stage kidney disease (ESKD) and the need for dialysis or a transplant. Hearing loss and eye abnormalities are also common. Alport syndrome affects approximately 30,000 to 60,000 people in the U.S.⁴

Role in treatment:

Bardoxolone would be the first FDA-approved therapy for this condition. Current treatment options include symptom control and attempting to slow the decline of kidney function.⁴

Efficacy:

In the CARDINAL clinical trial, participants treated with bardoxolone experienced a statistically significant improvement in kidney function as measured by estimated glomerular filtration rate (eGFR) at Week 100 and Week 104, compared to those treated with placebo. The eGFR is a measure of the ability of the kidney to filter waste products out of blood.⁵

Safety:

Bardoxolone was generally well tolerated in the clinical trial with adverse events being mild to moderate. The most common were muscle spasms and increases in liver enzymes.⁵

Financial impact:

Analysts predict bardoxolone global sales could reach \$798M by 2027 for Alport syndrome.⁶ It is also in late-stage development for other renal conditions.

IngenioRx view:

Bardoxolone would be the first FDA-approved treatment for Alport syndrome. The question remains whether the effects on eGFR will modify the long-term course of the disease.

⁴ National Organization for Rare Disorders. *Alport Syndrome* (Accessed May 9, 2021); [NORD.org](https://rarediseases.org/rare diseases/alport-syndrome/)

⁵ GlobalNewswire. *Reata Announces FDA Accepted for Filing the NDA for Bardoxolone for the Treatment of Patients With Chronic Kidney Disease Caused by Alport Syndrome* (Accessed May 9, 2021); [globenewswire.com](https://www.globenewswire.com/NewsRoom/Detail.aspx?id=1055555)

⁶ Decision Resources Group (accessed May 2021; registration required); [insightsdecisionresourcesgroup.com](https://www.insightsdecisionresourcesgroup.com/)

TAPINAROF

Product:

Tapinarof

Indication:

Treatment of plaque psoriasis

Estimated FDA approval:

May 2022

Therapeutic class:

Aryl hydrocarbon receptor modulating agent (TAMA)

Route of administration:

Topical

FDA designations:

None

Manufacturer:

Dermavant Sciences

Condition:

Plaque psoriasis affects approximately 80% to 90% of the more than 8 million people with psoriasis in the U.S.^{7,8} Symptoms may fluctuate over time, but plaque psoriasis is a chronic inflammatory-driven disease that most frequently results in red, itchy, painful patches of skin, or plaques, in one or more areas of the body.

Role in treatment:

With a unique mechanism of action, tapinarof would be the first FDA-approved aryl hydrocarbon receptor modulating agent (TAMA) for plaque psoriasis. Guidelines provide recommendations for the use of these topical FDA-approved categories: topical steroids, vitamin D analogs, combination steroid/vitamin D analogs, and combination steroid/tazarotene products. For people with moderate-to-severe disease, prescribers often use oral or injectable therapies.⁹

Efficacy:

In two phase 3 trials, approximately 1 in 3 to 4 adults with mild, moderate, or severe disease met the primary endpoint of achieving clear or almost-clear skin with tapinarof compared to placebo after 12 weeks.

Safety:

The majority of side effects with tapinarof were mild to moderate and localized to the application site.¹⁰ There were no serious treatment-related adverse events.

Financial impact:

Analysts predict tapinarof pricing at about \$19 per day, with projected peak U.S. sales of over \$100M.¹¹ For people looking for a nonsteroidal topical therapy, tapinarof may provide another option with good efficacy and a modest side effect profile.

IngenioRx view:

Tapinarof would be the first FDA-approved TAMA for plaque psoriasis. It would likely join the other topical agents, calcipotriene, calcitriol, and tazarotene, as an alternative to steroids for people using topical therapies to control their disease. It remains to be seen if tapinarof could compete with oral agents in more moderate-to-severe disease.

7 National Psoriasis Foundation. *About Psoriasis* (Accessed February 4, 2021); psoriasis.org

8 National Psoriasis Foundation. *Plaque Psoriasis* (Accessed February 4, 2021); psoriasis.org

9 MedlinePlus U.S. National Library of Medicine. *Psoriasis* (Accessed February 4, 2021); medlineplus.gov

10 Gold LS, Bhatia N, Tallman AM, et al.: *A phase 2b, randomized clinical trial of tapinarof cream for the treatment of plaque psoriasis: Secondary efficacy and patient-reported outcomes*. *Journal of the American Academy of Dermatology* (January 2021): [jaad.org/article/S0190-9622\(20\)30957-9/pdf](https://jaad.org/article/S0190-9622(20)30957-9/pdf)

11 Decision Resources Group (accessed February 2021; registration required): insights.decisionresourcesgroup.com

In addition to the treatments listed previously, there are important drugs and biologics scheduled to receive FDA approval within the next 18 months.

*** Key:**

CAR-T: chimeric antigen receptor t-cell therapy

CGRP: calcitonin gene-related peptide

ESA: erythropoietin-stimulating agent

GnRH: gonadotropin-releasing hormone

HCM: hypertrophic cardiomyopathy

IL-17: interleukin-17

IV: intravenous

SC: subcutaneous

Rolling submission: when a drug company submits completed sections of its application for review instead of waiting until every section of the application is completed; decision date is assigned when the application is complete



Orphan drug or rare disease; expected to be high-cost but with minimal impact to overall drug or medical spend due to low utilization



Potential to significantly increase overall drug or medical spend



New entrant into high spend or trending category



No significant impact to incremental spend based on initial analysis

Other significant product approvals

We expect these products to reach the market in 2021/2022.**

Drug or biologic manufacturer	Indication/ route*	Place in therapy*	Estimated approval date	Impact on overall drug or medical spend
Atogepant AbbVie	Migraine prevention/oral	Addition to class: CGRP inhibitor for the prevention of migraines	Third quarter 2021	
Maralixibat Mirum	Alagille syndrome/oral	First in class: would be first FDA-approved treatment for this indication	09/29/2021	
RVT-802 Enzyvant	DiGeorge syndrome/IV	First in class: would be first FDA-approved treatment for this indication	10/08/2021	
Bimekizumab UCB	Plaque psoriasis/SC	Addition to class: IL-17 inhibitor will compete with other biologics	10/15/2021	
Varenicline Oyster Point	Dry eyes/nasal	Addition to class: first intranasal product developed for dry eyes	10/17/2021	
Vosoritide BioMarin	Achondroplasia/SC	First in class: would be first FDA-approved treatment for this indication	11/20/2021	
Ciltacabtagene autoleucel Johnson & Johnson	Multiple myeloma/IV	Addition to class: will likely be second CAR-T therapy approved for multiple myeloma	11/29/2021	
Filsuvez® (episalvan) Amryt	Epidermolysis bullosa/topical	First in class: dry extract from birch bark; would be first FDA-approved treatment for this indication	11/30/2021	

** As of August 3, 2021



Other significant product approvals (continued)

Drug or biologic manufacturer	Indication/ route*	Place in therapy*	Estimated approval date	Impact on overall drug or medical spend
Efgartigimod Argenx	Myasthenia gravis/IV	First in class: would compete with Soliris®	12/17/2021	
Zynteglo® / LentiGlobin™ (betibeglogene autotemcel) bluebird bio	Beta thalassemia/IV	First in class: would be first gene therapy approved for treatment of beta thalassemia; potential safety issues seen in sickle cell disease studies	2022 (rolling submission)	
Tezepelumab Amgen	Asthma/SC	First in class: in clinical trial, reduced exacerbations, irrespective of baseline blood eosinophil count	01/10/2022	
Mavacamten Bristol Myers Squibb	Symptomatic obstructive hypertrophic cardiomyopathy/oral	First in class: would be first drug developed to target the specific molecular defect of HCM	01/28/2022	
Bardoxolone Reata	Alport syndrome/oral	Addition to class: would be first FDA-approved treatment for this indication	02/25/2022	
Vadadustat Akebia Therapeutics	Anemia in chronic renal disease; dialysis dependent and independent/oral	Addition to class: second oral dosing option to compete with ESAs	03/29/2022	
Vutrisiran Alnylam	Hereditary transthyretin amyloidosis with polyneuropathy/SC	Addition to class: would compete with Onpattro® and Tegsedi®	04/14/2022	

** As of August 3, 2021

*** Key:**

CAR-T = chimeric antigen receptor therapy

IM = intramuscular

IV = intravenous

SC = subcutaneous

****** We define high cost as having an annual cost of \$100,000 to \$350,000. Ultra-high cost drugs or biologics would be therapies with an annual cost of greater than \$350,000. For therapies not yet approved, we estimate the cost based on analyst reports, type of therapy, indication, and/or similar FDA approvals.



Analysis: high-cost drugs and biologics

There is tremendous interest in the increasing cost of drugs and biologics entering the market. IngenioRx is carefully monitoring FDA approvals and potential approvals.

In 2020, 36% of the 50 FDA approvals had an annual cost of \$100,000 to \$350,000, considered high cost,** and 20% were priced over \$350,000 or ultra-high cost.**^{13, 14} These approvals represent either oncology therapies or agents for rare, orphan diseases.

As of May 2021, 41% of FDA approvals are considered high-cost and 21% are ultra-high-cost.¹⁵ The table below provides a summary of drugs and biologics pending FDA approval in 2021 or 2022 that are expected to be high-cost or ultra-high-cost.^{16, 17} Although these drugs and biologics are of interest due to high-costs, they are often unlikely to have a significant impact on drug or medical spend due to the rarity of the conditions being treated.

Drug or biologic *	Indication	Route *	Oncology	Orphan disease	Estimated FDA approval	Estimated high-cost or ultra-high-cost **
Belzutifan	Von Hippel Lindau disease-associated renal cell carcinoma	Oral	Yes	Yes	09/15/2021	\$100,000-\$350,000
Maralixibat	Alagille syndrome	Oral	No	Yes	09/29/2021	>\$350,000
RVT-802	DiGeorge syndrome	IV	No	Yes	10/08/2021	>\$350,000
Tisotumab vedotin	Cervical cancer	IV	Yes	No	10/10/2021	\$100,000-\$350,000
Mobocertinib	Non-small cell lung cancer, exon 20 mutations	Oral	Yes	Yes	10/26/2021	\$100,000-\$350,000
Vosoritide	Achondroplasia	SC	No	Yes	11/20/2021	>\$350,000
Ublituximab	Chronic lymphocytic leukemia	IV	Yes	Yes	11/29/2021	\$100,000-\$350,000
Ciltacabtagene autoleucel (CAR-T)	Multiple myeloma	IV	Yes	Yes	11/29/2021	>\$350,000
Episalvan	Epidermolysis bullosa	Topical	No	Yes	11/30/2021	\$100,000-\$350,000
Pacritinib	Myelofibrosis	Oral	Yes	Yes	11/30/2021	\$100,000-\$350,000

¹³ IBM Micromedex. RED BOOK. (Accessed May 2021; registration required): micromedexsolutions.com.

¹⁴ Novel Drug Approvals for 2020. (Accessed May 2021): [fda.gov](https://www.fda.gov/drugs/nda/new-drug-approvals).

¹⁵ Novel Drug Approvals for 2021. (Accessed May 2021): [fda.gov](https://www.fda.gov/drugs/nda/new-drug-approvals).

¹⁶ FDA Calendar. (Accessed May 2021): [rtnews.com](https://www.fda.gov/oc/foia/fda-calendar).

¹⁷ Orphan Drug Designations and Approvals. (Accessed May 2021): accessdata.fda.gov.

Orphan drugs and biologics costs

In 2019, 39% of orphan drugs and biologics cost greater than \$100,000 per year, but they are used to treat only 23% of individuals who have rare diseases. Fewer than 1% of people with rare diseases received a drug or biologic that cost more than \$500,000 per year.¹⁸



The average annual orphan drugs and biologics cost increased from \$7,136 in 1997 to \$186,758 in 2017.¹⁹



Orphan drugs and biologics are 25 times more expensive than nonorphan drugs and biologics.¹⁹

Analysis: high-cost drugs and biologics (continued)

Drug or biologic *	Indication	Route *	Oncology	Orphan disease	Estimated FDA approval	Estimated high-cost or ultra-high-cost
Efgartigimod	Myasthenia gravis	IV	No	Yes	12/17/2021	>\$350,000
Vutrisiran	Hereditary transthyretin amyloidosis with polyneuropathy	SC	No	Yes	12/19/2021	>\$350,000
AT-GAA (acid alpha-glucosidase/cipagluco- sidadase)	Pompe disease	IV	No	Yes	2021	>\$350,000
Recorlev® (levoketoconazole)	Cushing syndrome	Oral	No	Yes	01/02/2022	\$100,000-\$350,000
Surufatinib	Neuroendocrine tumors	Oral	Yes	Yes	01/03/2022	\$100,000-\$350,000
Balstilimab	Cervical cancer	IV	Yes	No	02/19/2022	\$100,000-\$350,000
Bardoxolone	Alport syndrome	Oral	No	Yes	02/25/2022	\$100,000-\$350,000
Sintilimab	Non-small cell lung cancer, nonsquamous	IV	Yes	No	March 2022	\$100,000-\$350,000
Zynteglo® (LentiGlobin™) (gene therapy)	Beta-thalassemia	IV	No	Yes	2022	>\$350,000

* Key

CAR-T = chimeric antigen receptor therapy

IM = intramuscular

IV = intravenous

SC = subcutaneous

¹⁸ IQVIA. Orphan Drugs in the United States. (Accessed May 2021): iqvia.com.

¹⁹ AHIP. Drug Prices for Rare Diseases Skyrocket While Big Pharma Makes Record Profits. (Accessed May 2021): ahip.org.



Update on epidermolysis bullosa

What is epidermolysis bullosa (EB)?

Epidermolysis bullosa (EB) is a rare disease that causes fragile skin that blisters and tears during normal daily activities.²⁴ Genetic mutations are responsible for the four main types, EB simplex (EBS), dystrophic EB (DEB), junctional EB (JEB), Kindler syndrome, and several subtypes of EB. DEB is caused by mutations in the *COL7A1* gene and can be further classified into recessive (RDEB) and dominant (DDEB) forms, with RDEB being more severe. Disease severity for EB ranges from mild-to-severe widespread disease that can significantly affect a person's quality of life, causing severe disability and potentially death.

Prevalence of EB: Beginning as early as infancy for most, EB affects approximately 25,000 to 50,000 people in the U.S.²⁰ EBS is the most common type, accounting for approximately 75% to 85% of cases, while Kindler syndrome is very rare with only 100 cases reported over the past 70 years. Estimates for JEB and DEB types vary.

EB treatments: There are no FDA-approved treatments for people with EB. Current care focuses on wound management and other supportive measures.

EB pipeline: Summarized in the table below are three localized gene-based therapeutics and one topical herbal agent in phase 3 development or higher. These agents differ in several ways, including their route and frequency of administration, but are similar in how they act locally at the site of wounds.

Key:

EB: epidermolysis bullosa

RDEB: recessive dystrophic epidermolysis bullosa

DDEB: dominant dystrophic epidermolysis bullosa

JEB: junctional epidermolysis bullosa

EBS: epidermolysis bullosa simplex

HSV-1: herpes simplex virus type 1

Drug or biologic manufacturer	Route and frequency/target	Place in therapy	Estimated approval (phase of development)
Gene-based therapeutics designed to increase expression of the COL7 protein at treated wound sites — seeking FDA-approval for the treatment of DEB			
D-Fi (FCX-007; dabocemagene autotifel) Castle Creek Biosciences	Multiple intradermal injections of gene-modified cells taken from a person/ <i>COL7A1</i> gene	- Competing to be first localized gene-based wound therapeutic for people age 2 and older with DEB - Would compete with other gene-based therapeutics in development, likely administered in a physician's office	2022 (phase 3)

²⁰ American Academy of Dermatology Association *Epidermolysis Bullosa* (Accessed May 2021): aad.org.

Key:**EB:** epidermolysis bullosa**RDEB:** recessive dystrophic epidermolysis bullosa**DDEB:** dominant dystrophic epidermolysis bullosa**JEB:** junctional epidermolysis bullosa**EBS:** epidermolysis bullosa simplex**HSV-1:** herpes simplex virus type 1

Update on epidermolysis bullosa (continued)

Drug or biologic manufacturer	Route and frequency/target	Place in therapy	Estimated approval (phase of development)
B-VEC (beremagene geperpavec; KB103) Krystal Biotech	Once weekly topical gel of nonintegrating, nonreplicating HSV-1 expressing <i>COL7A1</i> gene/ <i>COL7A1</i> gene	- Competing to be first localized gene-based wound therapeutic for people age 1 and older with DEB - Would compete with other gene-based therapeutics in development that are derived from the patient's own cells, with the potential manufacturing advantage as a ready-to-use topical gel formulation, allowing for self-application	2022 (phase 3)
EB-101 Abeona Therapeutics	One-time, surgically placed, gene-modified skin graft taken from a person/ <i>COL7A1</i> gene	- Competing to be first localized gene-based wound therapeutic for people age 6 and older with DEB - Would compete with other gene-based therapeutics in development with potential disadvantage of surgical application and potential advantage of longer durability	2023 (phase 3)
Topical herbal agent — seeking FDA-approval for the treatment of DEB and JEB			
Filsuvez (episalvan) Amryt Pharma	Topical gel/herbal agent made from birch tree bark	- Would be the first FDA-approved treatment of cutaneous manifestations of JEB and DDEB for people 21 days of age and older - Has not been evaluated in EBS	11/30/2021 (submitted)

The future of EB treatments: The EB treatment landscape could expand from 0 to 4 FDA-approved therapies over the next two years. All four therapies in development act locally at the site of each wound to speed and improve healing. A topical herbal gel, Filsuvez, has been submitted to the FDA for the treatment of cutaneous manifestations of JEB and DEB with potential to be the first FDA-approved agent for EB in late 2021. Three gene-based therapeutics, D-Fi, EB-101, and B-VEC, will compete for approval in 2022 and 2023, specifically for the treatment of people with DEB.

Gene-based therapeutics differ in several ways, including their route and frequency of administration, their manufacturing process, and age ranges currently evaluated in trials. These therapies do not target adjustment of the underlying genetic mutation that causes DEB. New wounds will require additional treatments. Early clinical data are promising and indicate improved wound healing; however, the durability of effect per wound is unknown. Therefore, it is unclear if, or how often, retreatment would be required at the same wound site.

Costs are unknown but expected to be high for each of these agents. While combination therapy has not been evaluated, theoretically there is potential for someone to use multiple therapies at different wound sites. It remains unclear how these agents will be used in clinical practice.

Market trends

Shingrix

Shingrix was approved in 2017 for the prevention of herpes zoster, also known as shingles, in adults age 50 years and older. A label expansion was approved recently to include the prevention of herpes zoster in adults age 18 years and older at increased risk of herpes zoster. Routine vaccinations were affected by COVID-19 as people may have delayed wellness care, including vaccines such as Shingrix.²¹ The label expansion in younger high-risk adults may potentially increase utilization. According to a 2016 study, the incidence of shingles has increased greater than four-fold over the last six decades across all age groups.²² The label expansion, combined with increased overall demand for vaccination, will drive growth for the next several years.²³

Lytenava

FDA approval is anticipated in 2022 of an intravitreal formulation of bevacizumab, Lytenava™. Initially seeking approval for wet age-related macular degeneration (wet AMD), Lytenava could replace the use of off-label Avastin and compete directly with other FDA-approved vascular endothelial growth factor (VEGF) inhibitors, Eylea®, Lucentis®, Beovu®, and Macugen®. Lytenava pivotal trial data for wet AMD was recently released in August 2021. If approved, Lytenava will be the only bevacizumab product FDA approved for wet AMD, with intentions to seek expansions in the future for diabetic macular edema (DME) and branch retinal vein occlusion (BRVO). By some estimates, the use of compounded Avastin accounts for 50% of intravitreal anti-VEGF use. Lytenava peak sales in the U.S. is expected to be \$100 to \$250M.²⁴

²¹ FiercePharma. As GSK enters key transition year, COVID-19 immunization could hurt Shingrix uptake: exec (Accessed May 12, 2021); [fiercepharma.com](https://www.fiercepharma.com).

²² Kosuke Kawai, Barbara P. Yawn, Peter Wollan, et al. Increasing incidence of herpes zoster over a 60-year period from a population-based study. *Clinical Infectious Diseases*. (July 2016); academic.oup.com.

²³ Decision Resources Group (Accessed May 2021; registration required); [insightsdecisionresourcesgroup.com](https://www.insightsdecisionresourcesgroup.com).

²⁴ Decision Resources Group (Accessed May 2021; registration required); [insightsdecisionresourcesgroup.com](https://www.insightsdecisionresourcesgroup.com).



The potential for messenger ribonucleic acid technology

The early stages of messenger ribonucleic acid (mRNA) technology can be traced back to animal experiments in the 1990s, when researchers investigated this novel technology as another tool in the treatment armamentarium for cancer and influenza. Subsequent years saw a growing interest in the application of mRNA technology for use in other viral illnesses, including human immunodeficiency virus (HIV), Ebola, and severe acute respiratory syndrome (SARS).

The introduction to mRNA for the worldwide community occurred in late 2020 when the first two mRNA-based vaccines for the prevention of coronavirus disease 2019 (COVID-19) were approved in the U.S. by the FDA through emergency use authorization (EUA). These vaccines were developed by Pfizer/BioNTech and Moderna. Clinical trials reported high efficacy rates of 94% to 95% after two interval doses, combined with a low rate of adverse reactions.²⁵ In general, previous vaccine technologies introduced a weakened or inactivated pathogen to the body to stimulate an immune response. However, mRNA-based vaccines provide the cells with the genetic code of the antigen or the spike protein of COVID-19. This code serves as instructions to the cells on how to make the foreign protein in order to mount a directed immune response. Once the protein is made, the cells quickly destroy the mRNA within a few days.

An initial hurdle for mRNA technology was getting the mRNA into the cell without the body launching an immune response against it. Scientists found that encapsulating the mRNA with a lipid shell allowed for uptake of the mRNA into cells without being degraded by the body's immune response.²⁶ As scientists continue to expand their knowledge of this technology, one proposed benefit of mRNA technology that is emerging is its potential for wide applicability by altering the encoded protein. Altering just the mRNA molecule's genetic sequence, or the instructions, allows for production of products that could have diverse therapeutic uses, while maintaining a standardized production process. This could save time and reduce cost compared with traditional drug or biologic manufacturing processes.



²⁵ Anand P, Stahel VP. Review the safety of Covid-19 mRNA vaccines: a review. *Patient Safety in Surgery*. (May 2021); pssjournal.biomedcentral.com/track/pdf/10.1186/s13037-021-00291-9.pdf

²⁶ Schlake T, Thess A, Fotin-Mleczek M, Kallen KJ. Developing mRNA-vaccine technologies. *RNA Biology*. (November 2012); ncbi.nlm.nih.gov/pmc/articles/PMC3597572/pdf/rna-9-1319.pdf

The potential for messenger ribonucleic acid technology (continued)

The early phase I and II clinical trials using mRNA technology as a therapeutic option in people infected with HIV-1 demonstrated a lack of an efficient immunologic response against HIV, despite the vaccine's safety profile.^{27, 28} There are more than 100 ongoing clinical trials, primarily in early (Phase I/II) stage looking at mRNA-based dendritic cell-based therapeutic vaccines for cancer applications, including, but not limited to, melanoma, prostate, lung, and brain cancer. Cancer research is looking at mRNA-encoded antigens that are delivered to dendritic cells to trigger the immune system to launch an antitumor response.²⁹ Beyond cancer, mRNA is being studied as a potential therapeutic approach in the treatment of other diseases such as cardiovascular disease and type II diabetes by using mRNA to stimulate a response to promote vascular healing.³⁰ Researchers are working to overcome challenges associated with increasing the scope of mRNA vaccine therapy for chronic conditions, including mRNA delivery and maintaining mRNA stability or extending its half-life, while minimizing the adverse event risk profile to the individual.³¹

In conclusion, live-attenuated and viral-vector vaccines have been used for decades as preventive measures to combat infectious diseases. There is a growing interest in exploring mRNA-based vaccine therapy to treat a variety of disease states. While the safety and efficacy profiles of mRNA technology seen with the COVID-19 vaccines appear promising, it remains to be seen how mRNA-based therapies will overcome potential challenges associated with establishing a place in the treatment of chronic diseases.

27 Allard SD, De Keersmaecker B, de Goede AL, et al. A phase I/IIa immunotherapy trial of HIV-1-infected patients with Tat, Rev and Nef expressing dendritic cells followed by treatment interruption. *Clinical Immunology* (March 2012): [sciencedirect.com/science/article/abs/pii/S1521661611003342?via=ihub](https://www.sciencedirect.com/science/article/abs/pii/S1521661611003342?via=ihub).

28 Gandhi RT, Kwon DS, Macklin EA, et al. Immunization of HIV-1-Infected Persons With Autologous Dendritic Cells Transfected With mRNA Encoding HIV-1 Gag and Nef: Results of a Randomized, Placebo-Controlled Clinical Trial. *Journal of Acquired Immune Deficiency Syndromes* (March 2016): <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4752409/>.

29 Rosa SS, Prozeres DMF, Azevedo AM, et al. mRNA vaccines manufacturing: Challenges and bottlenecks. *Vaccine*. (April 2021): [ncbi.nlm.nih.gov/pmc/articles/PMC7987532/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7987532/).

30 Gan LM, Lagerström-Fermér M, Carlsson LG, et al. Intradermal delivery of modified mRNA encoding VEGF-A in patients with type 2 diabetes. *Nature Communications* (February 2021): https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6382754/pdf/41467_2019_Article_8852.pdf.

31 Wadhwa A, Aljabbari A, Lokras A, et al. Opportunities and Challenges in the Delivery of mRNA-based Vaccines. *Pharmaceutics*. (January 2020) [ncbi.nlm.nih.gov/pmc/articles/PMC7076378/pdf/pharmaceutics-12-00102.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7076378/pdf/pharmaceutics-12-00102.pdf).



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