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From submission to prescription – technology's impact on healthcare's future

2021

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Letter from the editors

Bruce Feinberg, DO
Editor-in-Chief

Eli Phillips, Jr., PharmD, JD
Editor-in-Chief

One of the most well-known pharmacists in all of history was a 16th century French apothecary who rose to fame during one of the greatest pandemics in human history, the bubonic plague. His homeopathic concoctions – consisting largely of sawdust and rose petals – are credited with saving thousands from contracting the plague, likely resulting from boosting vitamin C levels while generating a scent that may have repelled fleas, which served as a primary vector for transmitting said plague. While these accomplishments are indeed impressive, his notoriety stems less from his treatment successes and more from his vision for the future that some would refer to as prophetic. His name was Michel de Nostradame, though most simply refer to him as Nostradamus.

Since those times, the term "medicine" has come to mean something radically different while still maintaining striking parallels to the past. Today, "medicine" as a consumable product is frequently manufactured in bulk with purity and precision while complying with strict requirements to demonstrate both safety and efficacy for its intended use. Although it may seem like an eternity has passed since the days of a local apothecary manipulating individualized dosages for each unique patient, the practice of prescription compounding still occurs at a relatively high frequency even now at local community or specialized compounding pharmacies. Alternatively, consider even the most advanced therapies in the cell and gene space and you will find that personalized medicine reigns supreme with a patient's own biological components being incorporated as a raw component into the treatment or cure. As technology improves, the divergence in the path before us will be to either highly generalized treatments where every patient receives the same therapeutic or highly personalized treatments where every patient receives a unique therapeutic. Put simply, the treatment will consist of either a product or a process.

Considering the term "medicine" as a profession, or the practice thereof, perhaps the parallels to the past are greater than the differences. It is today, as it always was, that providers of medicine are called upon to play a variety of roles: while diagnostician and treater (read together as 'healer') receive the most attention, there are additional roles such as coach, confidant, truthteller, and even soothsayer. That is to say, one who prognosticates on the progression of a disease or the likelihood of success on the merits of every available treatment and alternative.

In this edition of FOCUS magazine, we embrace the future at a time when, much like Nostradamus, it can be difficult to see past the plight of the present. Yet the science has continued to evolve and must continue to do so for the sake of patients.

Author biographies

Bruce A. Feinberg, DO serves as Vice President of Clinical Affairs and Chief Medical Officer for Cardinal Health Specialty Solutions. He works across the specialty solutions businesses, consulting with payers, providers, pharma, patients, and policymakers. Since joining Cardinal Health, Dr. Feinberg has made more than 70 peer-reviewed contributions to value-based healthcare literature. In 2015, Dr. Feinberg was honored as a PharmaVoice 100 most inspirational life-science leader.

Dr. Feinberg is the author of bestselling books and has been consulted by prominent national media outlets, including *The New York Times*, *The Wall Street Journal*, *Forbes*, and CNN. As host of The Weekly Check-Up on WSB Radio in Atlanta, he provides the community the latest health information and an opportunity to express their views on health and medicine.

Prior to joining Cardinal Health, Dr. Feinberg was the founder and CEO of Georgia Cancer Specialists (GCS), one of the first and largest integrated oncology specialty practices in the United States. At GCS, he pioneered health information technology, the pathways movement, and the oncology medical home, publishing the first report of their impact on financial and clinical outcomes in 1998.

Eli Phillips, PharmD, JD is a licensed pharmacist and attorney who joined Cardinal Health in June 2014. He currently serves as Vice President for Insights & Engagement and Regulatory Sciences within Cardinal Health Specialty Solutions where he is responsible for the strategy, growth, and financial performance of the business units.

He has previously held a variety of leadership positions, including head of Quality and Regulatory Affairs for each of the enterprise's Specialty Businesses. Prior to joining Cardinal Health, Dr. Phillips served as a professor in both pharmacy and law school settings, and served as Managing Member of Healthcare Advising, LLC, a private regulatory consulting and data analytics firm.

Dr. Phillips completed his pharmacy studies at Wilkes University in Wilkes-Barre, Pennsylvania and legal studies at Drexel University in Philadelphia where he earned certificates in Health Law and Intellectual Property Law. He currently serves as a member of the board of directors for Adaptive Sports Connection, a nonprofit organization whose mission is to empower children, adults, and veterans with physical and cognitive challenges, through sports and therapeutic outdoor recreation.

Ajeet Gajra, MD, MBBS, FACP serves as Vice President and Chief Medical Officer for Cardinal Health Specialty Solutions. A nationally recognized expert in lung cancer and geriatric oncology, Dr. Gajra is an ABIM board-certified medical oncologist/hematologist, with more than 16 years of clinical experience managing all types of cancers and blood disorders. His clinical experience includes serving as Professor of Medicine at SUNY Upstate Medical University, and serving as Associate Director of the Upstate Cancer Center, where he provided leadership and oversight of clinical operations as well as quality programs. He also served as Medical Director for the center, managing a team of oncologists, APPs and navigators, as well as multiple practice sites with infusion centers, and leading several value-based care initiatives, including OCM and ASCO-QOPI programs.

His research experience includes serving as Medical Director for Medical Affairs Oncology at ICON research, a global full-service CRO, where he led design, oversight, clinical development and regulatory interactions for phase I-IV trials in oncology and hematology including immuno-oncology, adoptive cell therapy and CAR T-cell therapy. Prior to that he has served as the Principal Investigator for more than 40 clinical trials including pharmaceutical sponsored, U.S. cooperative group and investigator initiated studies. He has over 100 peer-reviewed publications.

He received his MBBS and MD (Internal Medicine) from Delhi University in New Delhi, India and completed his residency at SUNY Upstate Medical University, where he also completed his fellowship medical oncology and hematology.

Cherrishe Brown-Bickerstaff, PhD, MPH is a Scientist in the Real-World Evidence & Insights team at Cardinal Health Specialty Solutions. She is an epidemiologist and health services researcher with over 10 years of experience evaluating programmatic, economic, clinical, and patient-reported outcomes across various therapeutic areas such as oncology, hematology, neurology, ophthalmology, and infectious disease. Prior to joining CHSS, Dr. Brown-Bickerstaff conducted research studies and executed statistical analysis using data from administrative claims databases, electronic medical record databases, surveillance registries, patient surveys, systematic reviews, and other sources for government agencies, including the Center for Medicaid and Medicaid Services, the State of Florida, and the Department of Defense. Dr. Brown-Bickerstaff holds a Doctorate in Pharmaceutical Sciences with a concentration in Health Outcomes Research and Pharmacoeconomics from Florida A & M University and Master of Public Health from the University of Florida.

Harlen Hays, MPH serves as the Director of Research Analytics in the Real-World Evidence & Insights team at Cardinal Health. He directs a team of analysts in the conduct of statistical analysis (and database management) of real-world data from medical chart review, administrative claims databases, electronic medical record databases, and other sources for biopharmaceutical manufacturers seeking to generate real-world evidence for internal projects, payer projects, medical communications, and regulatory bodies. In addition to his work at Cardinal Health, Mr. Hays has experience as an adjunct professor in Data Science and Data Strategy with both Rockhurst University in the College of Business, Influence and Information Analysis and Kansas City University in the Bioinformatics program.

Prior to Cardinal Health, Mr. Hays spent over a decade with the Cerner Corporation leading research, analytics, and data science projects for multiple markets.

Andrew Klink, PhD, MPH is Director of Real-World Evidence & Insights at Cardinal Health and serves as Lead Scientist on RWE studies. He has over 10 years of clinical and observational research experience in both academia and industry. His research has focused on methods to address confounding by indication in pharmacoepidemiology and health outcomes research. He has experience with RWE for FDA submissions, multilevel mixed-effects analysis, longitudinal analysis, comparative effectiveness, healthcare utilization and cost analyses, and patient-oriented research. Recent work by Dr. Klink in the areas of oncology, rheumatology, and gastroenterology have resulted in numerous peer-reviewed publications and presentations. He also serves as a reviewer for the *American Journal of Epidemiology*, *Journal of Health Economics & Outcomes Research*, and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Dr. Klink holds a Doctorate in Epidemiology and a Master of Public Health in Epidemiology from Drexel University and completed his undergraduate work in Medical Microbiology & Immunology at the University of Wisconsin-Madison.

Yolaine Jeune-Smith, PhD is Director of Scientific Writing and Strategic Research for the Insights and Engagement business unit at Cardinal Health Specialty Solutions. Dr. Jeune-Smith develops cross-business unit strategies related to thought leadership initiatives. In addition, she oversees a team of scientific and medical communication writers and graphic designers. Dr. Jeune-Smith has a combined 10 years of experience in healthcare, spanning basic science to qualitative research. She holds a doctoral degree in Materials Science Engineering from the University of Florida and a master's degree in Secondary Science Education from the University of South Florida.

Scott Swain, PhD, MPH is Director of Real-World Evidence and Regulatory Science in Insights and Engagement. His primary duties include developing strategies to incorporate alternative study designs, such as real-world evidence, to increase efficiency of clients' medical product development from early clinical phases through regulatory submission and post-marketing. Previously, as Lead Epidemiologist in the FDA/CDER Division of Epidemiology, Dr. Swain led the epidemiology team overseeing real-world evidence safety and efficacy issues for oncology, hematology, and medical imaging products. He has over a decade of experience with epidemiological study design, protocol and statistical analysis plan development, performing systematic literature reviews, and conducting research using large multi-level electronic healthcare datasets in regulatory, consulting, and academic settings. Dr. Swain earned an MPH in Epidemiology with a concentration in Infectious Disease at the George Washington University, as well as a PhD in Epidemiology and a certificate in Pharmacoepidemiology from Johns Hopkins University.

Amy Valley, PharmD, BCOP is Vice President of Clinical Strategy and Technology Solutions at Cardinal Health Specialty Solutions. In her current role, Dr. Valley's responsibilities focus on the strategy and execution for Provider Solutions and Clinical Services provided to specialty physician office and infusion center customers. Dr. Valley, who is a Board Certified Oncology Pharmacist, is a published clinician, educator and researcher with a concentration on oncology pharmacy practice. Dr. Valley has been with Cardinal Health Specialty Solutions since 2010, and has played an integral role in setting the vision and executing the build of the Specialty Solutions solution portfolio for physician office practices. Prior to joining Cardinal Health, Dr. Valley's career included positions as Director of Clinical Services for Pharmacy Systems, Inc. (PSI) and Vice President of Clinical Solutions for Pharmacy Healthcare Solutions (PHS), an AmerisourceBergen business. She is a graduate of The Ohio State University College of Pharmacy where she completed her B.S. in pharmacy degree. She completed her PharmD and specialty residency in oncology pharmacy practice at the University of Texas Health Science Center at San Antonio and the University of Texas at Austin.

Kristin M. Zimmerman Savill, PhD is a Senior Scientist in the Real-World Evidence & Insights team at Cardinal Health Specialty Solutions and serves as Lead Scientist/Principal Investigator on oncology real-world evidence studies. Dr. Savill has over 17 years of experience in oncology research, including 11+ years in the pharmaceutical and biotech industry. Her research has focused on assessing treatment patterns and clinical outcomes in real-world settings, evaluating factors that mediate clinical outcome, characterizing rare genetic disorders associated with cancer formation, developing novel therapeutic strategies, and investigating biological pathways that play a key role in tumorigenesis and survival. Prior to joining CHSS, Dr. Savill served as a Scientific Manager in the Development Sciences division at Genentech where she played an integral role in biomarker strategy for oncology programs. She completed her postdoctoral training in the Translational Oncology department at Genentech and holds a PhD in Biochemistry from the University of Sussex in the UK as well as a BSc in Psychobiology from UCLA.

Virtual summit events

Virtual summit series

The summits organized by Cardinal Health Specialty Solutions consist of multiple programs that bring together a wide variety of healthcare stakeholders to discuss topics that are critical to the practice of healthcare. Participants are encouraged to provide real-world input and share their knowledge of clinical and business issues.

Summits also provide an opportunity to engage an influential audience of providers and healthcare professionals from leading community practices in order to allow pharmaceutical and biotech companies to overcome the challenges of reaching minimally accessible audiences.

Due to the pandemic and in an abundance of caution for the safety of staff and partners, our summits are being conducted virtually for the foreseeable future. We will return to live summits when it is safe to do so, based on guidance from national health officials.

Consultative services

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- **Exhibits** – Showcase your product's promotional, market access or medical affairs information to a focused audience throughout the summit.
- **Meal presentations** – Present a 45-minute promotional message during meal breaks and gather feedback to inform your marketing strategy.
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  - Welcome packet
  - Table drops
- **Executive sponsorship**
  - Recognition by the moderator during the summit
  - Access to the event attendee list
  - Additional signage
  - Post-meeting highlights newsletter
  - Special pricing on additional summit activities

Learn more about summit partnership opportunities:

Contact Anthony Luttenberger at anthony.luttenberger@cardinalhealth.com to learn more.

At **Cardinal Health Specialty Solutions**, we create opportunities that help breakthrough treatments get to those who need them most: providers and the patients they serve. Whether it's guiding biopharma and medical device companies through global product approval or delivering critical medications and advanced technologies that enable providers to care for patients, our expertise helps our customers to thrive in an evolving landscape.

Contact: specialtysolutions@cardinalhealth.com **Website:** cardinalhealth.com/specialty

Focus on **futurism**

Futurism in health care: how medical advances in the 2020s will lead to longer, healthier lives

Introduction

For most of human history, our average lifespan has been 20 to 40 years, with most individuals dying from infectious diseases or injury. Through advances in hygiene and medicine, primarily over the last two centuries, our expected lifespan (and healthspan) has increased by several decades. Today, most people die as a direct result of complications from the time-related deterioration of our physiological functions – aging. As we grow older, we accrue damage at the cellular level resulting in morbidity and eventually mortality. Advances in chronic disease management have helped the average person stay healthier and live longer. However, despite modern medical technology, a maximum human lifespan of about 120 years has remained virtually unchanged for thousands of years.

A few years ago, Dr. Aubrey de Grey made the controversial prediction that the first person to live to be 1,000 years old is already alive today. His reasoning is as follows: today, we manage the diseases of aging one at a time like never-ending whack-a-mole. Alternatively, we could directly address the cellular processes of aging to prevent those diseases upfront. This approach could ultimately lead to "longevity escape velocity" – a point at which medical technology advances to the extent that for each year you live, your life expectancy increases by at least one year. Say, for example, we are 100 years away from the medical technology that will prolong human life indefinitely. But what if we are only 20 years from a 10-year extension, 30 years from a 20-year extension, and 50 years from a 50-year extension? Using this example, a person alive 20 years from now would have reached longevity escape velocity and could, theoretically, live for 1,000 years or more. Though Dr. de Grey's optimism on immortality may not be mainstream, his beliefs that the processes of aging can be slowed, stopped, and eventually reversed are gaining traction. Ray Kurzweil (acclaimed inventor and futurist) and Dr. David Sinclair (Harvard Medical School Professor) are two other well-known personalities who have been vocal in predicting an end to aging.

A common prediction from each of these "futurists" is that the medical advances that lead to the end of aging will come during the 2020s and 2030s in parallel with the rise of 3D printing, genetic engineering, artificial intelligence (AI), and nanotechnology. Whether or not you believe we can live to be 1,000 years old, the following are a few examples of medical technologies and approaches that will become mainstream over the next decade and have the potential to substantially extend the maximum human healthspan and lifespan.

Focus on futurism - **3D printing in medicine**

Harlen Hays, MPH

From onsite creation of medical equipment to simulation training to creating tissues and organs from autologous stem cells, 3D printing is already revolutionizing modern medicine. During the 2020 COVID-19 pandemic, one of the earliest shortages in healthcare was the availability of ventilators and ventilator parts. Engineers and 3D printing hobbyists quickly stepped in and produced low-cost options for hospitals, marking the first examples of 3D printing at scale in the healthcare industry. The Food and Drug Administration (FDA) provided guidance for 3D printing in healthcare[1] relating to the 3 R's (Regulation, Research, and Resource) but has yet to give guidance on the ethics and intellectual property debates.

Researchers have explored the efficacy and safety of utilizing 3D printing for surgical purposes. The use of pre-operative surgical simulations has already been shown to reduce complications, lower risk, and decrease resource utilization.[2] Opportunities to combine these simulations with robotics to create AI-driven surgeries for routine procedures, such as appendectomy or tonsillectomy, promises to improve patient outcomes. In the near term, 3D bioprinting could reduce and eventually eliminate the need for animal tissues with the ability to print multiple cell lines and complex non-transplantable organs.[3]

Advances in biotechnology continue to push the boundaries of regenerative therapies and modifications. Combinations of synthetic and intrinsic cellular structures make it possible to reconstruct rigid tissues such as the trachea.[4] Innovations could solve the organ transplant shortage that longer lifespans may exacerbate. Combined with cyberware and nanotechnology, the future for 3D bioprinting is in vivo; for example, at a trauma wound location, 3D bioprinting could be used for both clotting and repairing any injury.

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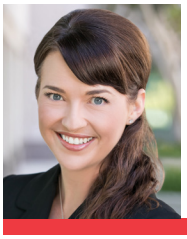
Focus on futurism - **Targeting the biology of aging to increase healthspan and lifespan: repurposing existing agents and developing new tools**



Kristin M. Zimmerman Savill, PhD

To date, the development and administration of therapeutic agents in the aging population has chiefly targeted disease-specific biology. While numerous therapeutics have helped prolong lifespan and successfully treat specific diseases, many individuals will experience multiple age-related diseases, each managed with distinct interventions that carry their own costs, logistical and personal considerations, and potential side effects. This disease-specific therapeutic approach is associated with economic and societal burdens and medical complications, and it does not directly address the underlying process of aging. However, with advances in geroscience, the study of aging, an increased understanding of the mechanisms of aging has opened the door to targeting aging itself, with an aim to increase healthspan and lifespan via methods such as "longevity pharmacology." This approach has the potential to be much more effective and efficient than strategies designed to treat individual diseases, and research in this area is being embraced by an increasing number of companies, investors, and clinical and academic research teams.

One of the most noteworthy examples of an existing agent currently undergoing evaluation for combating aging is the widely used antidiabetic agent, metformin. Findings from retrospective analyses demonstrated that type 2 diabetic patients who received metformin lived longer on average than matched healthy controls.[1] These findings have informed the design of the Targeting Aging with Metformin (TAME) trial, the first FDA-approved clinical trial directly targeting aging. Beyond metformin, excitement has continued to build around the possibility of targeting aging using novel or existing agents which block a biological signaling pathway mediated by the mTOR protein, following findings that mice fed with the frequently used mTOR-targeting agent rapamycin late in life lived longer[2] and that inhibition of a key component of this pathway, TORC1, in elderly patients was associated with a significant decrease in infection rate[3]. Precursors of nicotinamide adenine dinucleotide (NAD+) and sirtuin activators, which are critical for mitochondrial function, have also been implicated as extending lifespan

and/or healthspan, based on data from mouse models[4,5,6]. Therapeutics which target cellular senescence, a state in which cells can no longer divide and thought to play a significant role in aging, could represent useful tools in extending healthspan and lifespan. Some treatments, such as senolytic drugs, may target and clear senescent cells, while other therapies disrupt processes that may lead to senescence, such as telomere dysfunction.

These examples certainly do not represent an exhaustive list of agents and mechanisms being evaluated in anti-aging therapeutic strategies, and this field of research is rapidly expanding. In many ways, we are just at the cusp of learning how to translate our understanding of the biology of aging into effective anti aging therapeutic approaches which utilize longevity pharmacology. Findings from the TAME clinical trial and from evaluating other potential anti-aging therapeutics within the next 5-10 years will doubtlessly help us take steps toward a future in which humans regularly live longer and healthier lives than prior generations ever thought possible.

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Focus on futurism - **AI in medicine**

Harlen Hays, MPH

Healthcare and AI are not new collaborators. Recent advances and future impacts continue to fascinate both clinicians' and patients' imaginations, driven by various factors: increased processing power, cheap data storage, and the dissemination of broadband internet. Layer on the novelty of running machine learning algorithms from home (thank you Python & R), gamification, and it's the beginning of your favorite science fiction movie.

The rise of the machines, or more specifically machine learning (ML), likely came much earlier than most realize and are already significantly impacting healthcare. Kaggle (acquired by Google in 2017) provides a gamification experience to crowdsource the application of ML to multiple industries. In November 2018, Kaggle released a competition[1] named "Histopathologic Cancer Detection," which had over 1,000 teams attempt to utilize lymph node 32x32 pixel images to create an algorithm that could detect the presence of cancer. The top teams achieved an accuracy of ~98%, and the winner touted their ability to create artificial doctors. However, this raises ethical questions, including what would be considered an acceptable level of error and who is ultimately responsible for incorrect predictions (false positive and false negative results).

Applied to research, ML has produced new targeted therapies and de novo applications of existing therapies. Researchers in 2020 used deep learning techniques to identify potential compounds with active sites that are structurally distant from existing antibiotics, thus less likely to find resistant pathogens.[2] Phase I trials are starting with therapies designed by AI, reducing discovery time by nearly 80%, from 4.5 years to 1 year.[3]

Near-future potential exists for the application of AI in healthcare. Pure in silico clinical trials and drug development will spawn innovation and discovery. Rapid advancement for orphan diseases will occur due to the dramatic decrease in cost, time, and risk. Vaccines and genetic therapies will be discovered for diseases that do not yet exist, priming the body for potential attacks in an emergency preparedness mentality. Mitigation rather than reaction is the future, forcing research on the weak points of the human physical experience to anticipate failure points. In the coming decade, AI will be used to both develop and run medical devices such as pacemakers, artificial pancreas systems, brain-computer interfaces, and nanotechnology.

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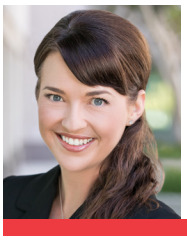
Focus on futurism - **Vaccines in the protection against life-altering and life-threatening disease**



Kristin M. Zimmerman Savill, PhD

The age-related decline of our immune system, or immunosenescence, plays a substantial role in the vulnerability of older adults to various types of illness and disease. Alterations in cellular immunity, antibody-mediated immunity, and lymph node architecture contribute to immunosenescence and lead to a higher incidence, severity, and mortality from infections and diseases such as cancer and diabetes. Various infections and diseases that have a significant negative impact on healthspan and lifespan may be prevented through existing or yet-to-be-developed vaccines, which work to stimulate an immune response to particular antigens or boost diminishing immunity. Throughout history, the development of vaccines has had a profound impact on the human population, and vaccines that protect against illnesses such as measles, smallpox, polio, and hepatitis, among others, have reduced mortality of the population in various age groups.

Vaccines that protect against influenza, pneumococcal disease, shingles, cancer (the human papillomavirus vaccine used to prevent cervical cancer, as an example), and, more recently, COVID-19, have become important tools in preventing certain threats to health in the aging population. Notably, certain vaccines may indirectly protect against health conditions beyond the illness that they were designed to prevent. Findings demonstrating this cross-disease protection include a report from a retrospective analysis of electronic health records that influenza vaccination is associated with a lower incidence of Alzheimer's disease (AD)[1], the observation that vaccination against pneumonia between ages 65 and 75 is associated with reduced risk of AD following vaccination[2], and findings that hepatitis B vaccination reduces the incidence of liver cancer[3,4]. Beyond just preventing certain diseases, vaccines are being developed to treat age-related conditions that have already developed, such as cancer, hypertension, dyslipidemia, type 2 diabetes, and AD. These interventional vaccines work to prime the body to defend itself against specific detrimental molecules within the body that help to drive these diseases and have the potential to become a key therapeutic option for treating chronic diseases in the coming years.

Overall, vaccines have become an incredibly critical part of our arsenal in the mission to extend human healthspan and lifespan. Advances in research and vaccine engineering that are currently unfolding will doubtlessly have a substantial impact on our ability to effectively prevent and manage age-related diseases in the next 5-10 years.

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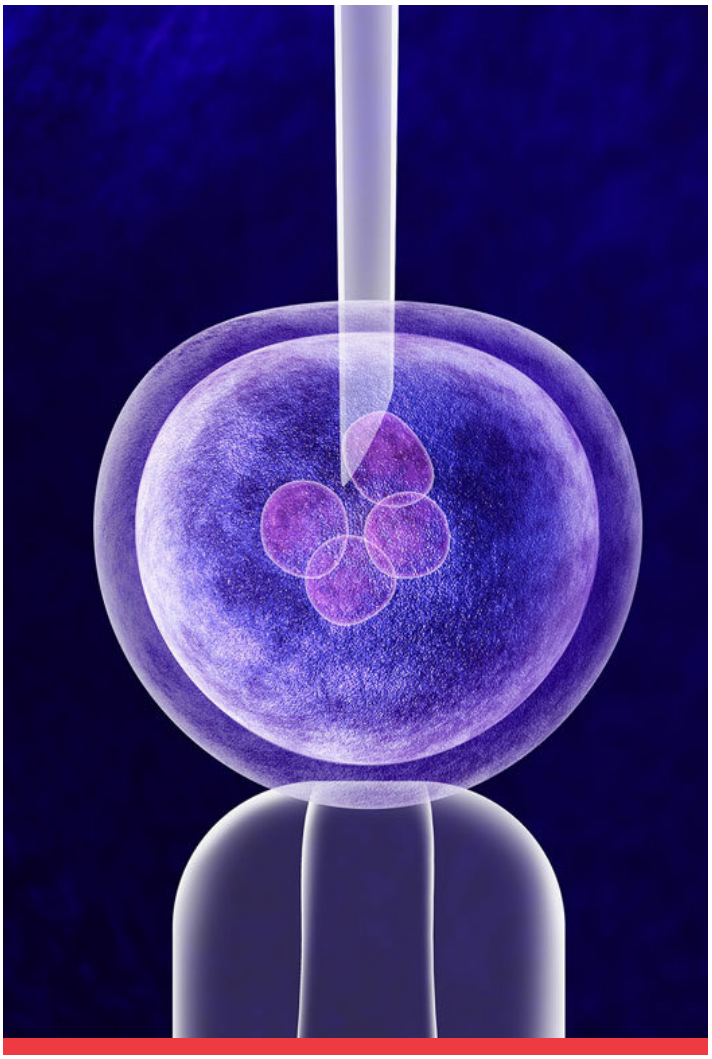
Focus on futurism - **Gene therapy**

Ajeet Gajra, MD, MBBS, FACP

Gene therapy refers to the strategy for curing or treating a disease by modifying, supplying, or blocking genes or gene products that cause a condition by their presence or absence. Gene therapy may seem an unlikely advance in a futurism-themed article for two reasons: first, gene therapy as a concept has been around since the late 1980s, and second, for many, the promise of gene therapy has already been delivered. Nearly 40 years ago, genetically engineered E. coli were producing human insulin for diabetes treatment. In recent years, two products that qualify as gene therapy have been approved by the FDA: Luxturna® (an adeno-associated virus vector-based gene therapy for the treatment of patients with confirmed biallelic retinal pigment epithelium-specific 65 [RPE65] mutation-associated retinal dystrophy) and Zolgensma® (for patients less than 2 years of age with spinal muscular atrophy [SMA] with biallelic mutations in the survival motor neuron 1 [SMN1] gene). In addition, genetic modification and re-infusion of autologous T-cells (e.g., via CAR-T therapy) are already in commercial use. However, the true potential of gene therapy is yet to be realized, especially with the advent of significantly improved gene-editing techniques.

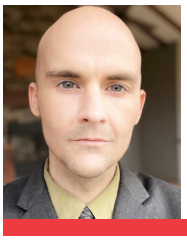


In its simplest definition, gene replacement therapy gives cells a new working copy of a missing or nonworking gene. This corrective gene, created in the laboratory as synthetic nucleic acid polymers, is packaged in a delivery vehicle (the vector) which carries the gene into the nucleus and allows for either integration of the synthetic material into the cell's native DNA or existence of the corrective gene independently from other cellular DNA. Ultimately, in both scenarios, when successful, the corrective gene will produce the missing, defective, or deficient protein, thereby restoring function. While gene replacement therapy may offset the impact of a mutation by inserting a functioning version of the gene, the defective genetic material typically remains in the genome. Alternatively, gene silencing refers to the reduction in expression of a disease-causing gene. A revolutionary advance has been the development of gene editing techniques in which a mutated gene is revised, removed, or replaced at the DNA level. Gene editing can be achieved via various techniques, but the frontrunner has been CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats-associated nuclease 9). The pace of output and applications of gene editing have accelerated remarkably due to its easy-to-use and multiplexing nature. Reflecting the importance of this innovation, researchers Emmanuelle Charpentier and Jennifer Doudna were awarded the Nobel Prize in Chemistry in 2020 for their groundbreaking work on CRISPR technology.

Barriers to progress in gene therapy have included the cost of manufacturing as well as early setbacks due to vector-associated adverse effects, immunogenicity, and the level and duration of expression. Additionally, various ethical concerns persist, which are being addressed globally.

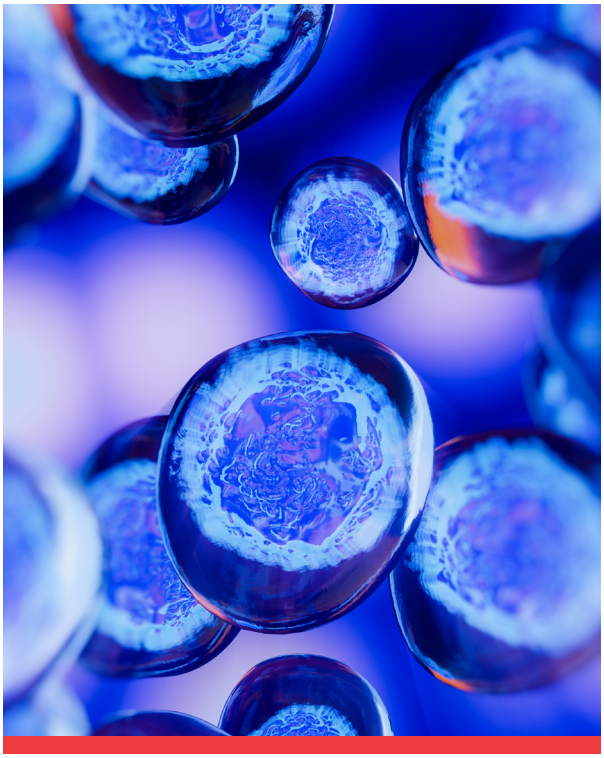
The number of commercially available gene therapy products will grow exponentially over the coming decade and likely beyond. Within two years, treatments for hemophilia, thalassemia, and other rare conditions defined by malfunction or absence of a single gene product (e.g., adenosine deaminase deficiency, Wiskott Aldrich syndrome, severe combined immunodeficiency, dyskeratosis congenita, Criggler-Najjar, etc.) will likely become available to patients. By the mid-2020s, therapies for cystic fibrosis, sickle cell disease, and various glycogen and lipid storage disorders could come to market. Within a decade, we may use gene therapy to reduce our susceptibility to chronic and infectious diseases and target specific acute and chronic disorders, addressing a wide range of indications spanning cardiomyopathy, stroke, HIV infection, malaria, and cancer. Aside from the above, gene therapy has broad applications, including the development of new foods with enhanced nutrition and taste (think spicy tomatoes), farm animal, and pet breeding, as well as the potential for "de-extinction" of species; though it may be a while before we can visit Jurassic Park zoo on the outskirts of town.

Focus on futurism - **Encapsulated cellular therapy: a functional cure for type 1 diabetes**



Scott Swain, PhD, MPH

Type 1 Diabetes Mellitus (T1DM) is a chronic disease caused by an autoimmune response whereby the insulin-producing cells in the pancreas are destroyed. Patients with T1DM must inject insulin and monitor blood glucose levels manually. Maintaining safe blood glucose levels requires a constant balancing act between blood glucose levels, insulin, caloric intake, exercise, sleep, stress, and many other factors. Even minor miscalculations in blood glucose management can be dangerous. Consequently, most T1DM patients struggle or fail to maintain glycemic control, even with recent advances in diabetes technology. Long-term complications of T1DM include neuropathy, retinopathy, blindness, heart disease, and kidney disease.



Today, the only "cure" for T1DM is an islet cell or pancreas transplant, which requires life-long immunosuppression medication, and even successful procedures may not result in insulin independence. The process is inefficient, often requiring multiple donors. Furthermore, the side effects and complications from immunosuppressive medication, the potential for rejection, and the high cost and difficulty of the procedure restrict transplantation to patients with frequent episodes of life threatening hypoglycemia or who are also receiving a kidney transplant.

T1DM is somewhat distinctive from most other diseases in that its underlying pathophysiology is a result of the loss of one cell type. Therefore, if those cells could be replaced with functioning versions, the disease would theoretically be cured. The idea behind encapsulated beta cell transplantation is that the insulin-producing cells are encased within a semi-permeable material that allows the cells to exchange nutrients and insulin with the patient's blood while also masking the cells from the patient's immune system, thus eliminating the need for immunosuppression. Rather than harvesting beta cells from organ donors, pancreatic islets can be cultured from stem cells, resulting in an endless supply. This technology has been demonstrated to be highly effective in animal models, and early human trials conducted by several pharmaceutical and academic institutions have demonstrated promising findings.[1]

Encapsulated cellular therapies have applications far beyond insulin replacement,[2] including enzyme or hormone replacement. These therapies may provide functional cures for a range of chronic diseases, including certain blood disorders, such as hemophilia,[3] lysosomal diseases, Parkinson's disease,[4] and other endocrine disorders.

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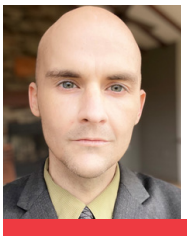
Focus on futurism - **Medical uses for brain-computer interface**



Scott Swain, PhD, MPH

Computers have access to nearly infinite data and mind-blowing processing power. However, our interactions with them are restricted by the speed with which we issue commands. Typing is slow. A brain-computer interface (BCI) comprises a sensor that reads neurological activity in the brain and software that interprets this data and relays commands used to operate hardware, thus bypassing our current communication bottleneck.

Want to feel inspired? Navigate to your favorite internet browser and search for videos of "bionic prosthetic arm." Today, there are multiple commercially available prosthetic arms comprised of built-in sensors that read muscle contractions and an on-board computer that translates this data to direct the movement in the robotic arm. Though these devices allow for fine motor movement, such as grasping, they are not technically BCI because they function based on peripheral nerve signals. Consequently, users' opinions of the usefulness of today's prosthetics remain mixed,[1] as they still lack the fine dexterity that would allow for writing, typing, or tying shoelaces. However, in the near future, prosthetic limbs will be controlled directly from signals generated within the brain. In doing so, these devices will gain, and likely surpass, the functionality of an unaltered limb.

BCI sensors can measure brain signals through the scalp via electroencephalogram or directly from within the cortex. But each of these methods has major drawbacks, such as data loss and extreme invasiveness, respectively. Therefore, researchers are increasingly focusing on developing BCI sensors implanted on the cortical surface via a minimally invasive procedure, which will likely be completely automated. Once implanted, AI software learns to read and interpret the user's neurological activity to distinguish between various intended actions while the user simultaneously learns how to best use the device. Some BCI devices also incorporate the sensation of touch, so the user can feel when they grasp an object in their prosthetic hand.

The potential for BCI goes well beyond prosthetic limbs. BCI devices could be used to power an exoskeleton, or as a neural shunt, to allow paraplegic patients to recover the use of their limbs. BCI will one day allow blind patients to see and deaf patients to hear.[2] BCI can be used to treat a wide range of neurological and cognitive diseases and could be used to improve diagnostics for brain disorders.[3] Integration of BCI with robotic-assisted surgery will allow surgeons to directly manipulate a scalpel with microscopic precision. Most of this technology exists today, though it needs to mature and become substantially less expensive before going mainstream. Furthermore, the ethical implications of having a data access point surgically implanted in our brains cannot be understated.

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Focus on futurism - **Nanotechnology**

Yolaine Jeune-Smith, PhD

Nanotechnology culminates everything together on a small scale, down to one-billionth, to be exact. Targeted drug delivery systems and methods to deliver genetic material to alter or repair our DNA and to stimulate the cell renewal process are already in existence. Nanotechnology improves upon existing processes to improve efficiency and effectiveness. Given rates of efficiency and sensitivity of standard targeted drug delivery, consider how much improvement we could expect by reducing the delivery vehicle by two or more orders of magnitude. The pharmacokinetic rate of uptake would increase. Faster delivery means improved pharmacodynamics and better outcomes because more of the drug gets to its target, especially for drugs with short half-lives. If more of the drug gets in, less needs to be given, potentially leading to fewer AEs and better quality of life. We want to extend life, but we want that life to be good, not arduous. Rather than utilizing resources to develop a newer, better drug, nanotechnology will allow us to improve existing products by enhancing the delivery system. This is where nanotechnology can shine.

Robotic-assisted surgery has dramatically improved surgical procedures and postsurgical recovery. Furthermore, endoscopic and laparoscopic surgery have significantly reduced the invasiveness of many surgeries. Now, imagine being able to do surgeries without having to anesthetize the patient or losing time from life due to extended recovery periods. Imagine performing surgery with no incision. Nanorobots could be deployed to sites of disease or trauma to begin repairing damage at the cellular level. Internal bleeding is a leading cause of death in light car crashes. If first responders could get accident or trauma victims a cocktail of such nanobots, many premature deaths could be prevented.

The anti-aging cosmetic market is expected to reach 60.3 billion U.S. dollars in the next five years. Yet, most of these effects are superficial, literally skin-deep, and only change the appearance of aging. That in itself could be improved with nanocarriers that could deliver antioxidants more precisely to the skin, hair, and nails. Many companies have taken advantage of that, but their products are still cosmetics as opposed to drugs. Nanotech is the anti-aging endgame that will ultimately allow us to detect, treat, and repair the earliest stages of damage at the cellular level. In due course, nanorobots delivering targeted anti-aging pharmaceuticals and gene therapies may directly reverse the aging process.

Conclusion

Cars have generally been designed to last for one or two decades. However, with proper care and maintenance, a car can function indefinitely. Similarly, with a proper diet, exercise, and a healthy lifestyle, humans can greatly increase their chances of a longer and healthier life. With advances in medical technology, we are gaining many powerful tools for extending the span of our health and longevity. Will human maintenance become more like that of a car? When a body part stops functioning properly, we'll soon have capabilities to fix or replace it that are far superior to those at hand today.

The many benefits of living longer may include increased time and capacity for experiencing time with loved ones, opportunity to enjoy longer or even different types of careers or educations, time to amend negative social and political situations, and the ability to watch future generations grow up. However, the potentially substantial extension of human lifespan resulting from medical technologies are accompanied by profound ethical, social, religious, economic, political, and personal implications. Unequal access to healthcare is already a serious issue, which could easily worsen as many of these medical breakthroughs will, at least initially, be very expensive. Even if we can ensure equal access, will we then create problems related to overpopulation or form an inverse pyramid population structure? Longer lives will affect our risk perception and mental health. Long-standing institutions such as friendship, marriage, becoming a parent, and retirement, will all have very different implications with a substantially prolonged expected lifespan.

The technologies described in this article have the capacity to improve and prolong uncountable lives. Humans tend to think linearly while nature, science, and technology move exponentially. Will we live to be 1,000? Maybe or maybe not. Whatever happens, in the coming decades, we will witness exponential technological advances that will fundamentally change what it means to be human.

Focus on **digital health**

Wielding digital health as a weapon to heal invisible wounds of war

Recently, Dr. Bruce Feinberg, Vice President of Clinical Affairs and Chief Medical Officer for Cardinal Health Specialty Solutions, interviewed two healthcare innovators who share a commitment to leveraging digital health technology to improve veteran access to effective mental health treatment for post-traumatic stress disorder (PTSD), depression, and other "invisible wounds of war and service." Here, we share edited excerpts of Dr. Feinberg's conversation with clinical psychologist Dr. Sheila Rauch, who serves as Deputy Director of the Emory Healthcare Veterans Program, and retired Army Lieutenant General Burke Garrett, who serves as Executive Advisor for the program.

Dr. Bruce Feinberg

Dr. Sheila Rauch

Lieutenant General Burke Garrett

Dr. Feinberg: When we think about the new world of artificial intelligence, telehealth, machine learning, wearables, and other digital health technologies, many of us don't typically associate those innovations with opportunities to improve care for patients living with mental illnesses like PTSD, depression, and anxiety. Yet, both of you are innovators in that space. To start, can you share a little about why this work is so important and your background in this area?

Dr. Rauch: I come from a family with many military service members, including my husband who was an Army Ranger. I was a psychologist specializing in PTSD before 9/11, and the day I saw those towers fall, I realized we'd be going to war to protect our country and that we would have a lot of people coming back from that experience in need of the experience that I had. The best thing I could do to serve my country at that point was to figure out how to expand mental health services for those veterans who returned home.

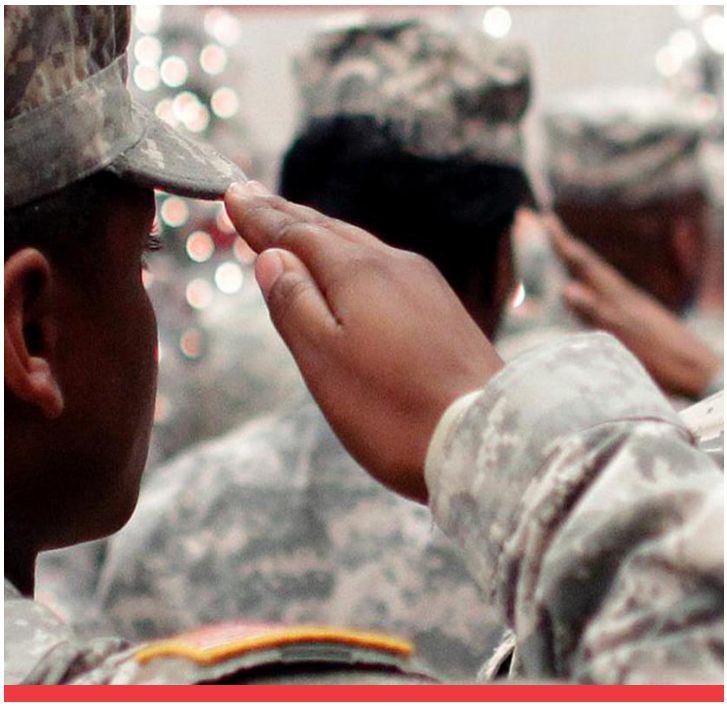
For the past five years, I've been leading with Dr. Barbara Rothbaum, the Emory Healthcare Veterans Program, which is one of four sites within the Wounded Warrior Project's Warrior Care Network. I've taken all of my experience working with veterans inside and outside of the Veterans Administration (VA) to create a two-week, intensive outpatient service program for service members who have served in post 9/11 wars. Since the onset of the COVID-19 pandemic, we've been increasingly leveraging telehealth services and exploring the use of other digital technologies to expand the scope of this program to reach more veterans.

Lt. Gen. Garrett: After 36 years of serving the nation on challenging missions around the world, you might think it'd be easy to just walk away. But, I've come to believe that service doesn't end when we take off our uniforms. I feel an obligation to take care of those who served our nation, many who served with me, and a responsibility to help them heal and live the lives they want to live. So, I'm blessed with the opportunity to work with the amazing team at the Emory Healthcare Veterans Program. It's just a new mission, closer to home.

As we approach the 20th anniversary of the 9/11 attacks, it's important to remember that American forces have been fighting somewhere in the world every day and night for the past two decades. Unfortunately, sufficient investments were not made in the VA to ensure we could provide appropriate care for service members who were wounded during these 20 years of war. We especially lagged in treating what we call the invisible wounds of war: PTSD, traumatic brain injury, depression, and anxiety.

Fortunately, the private sector and leading nonprofit innovators stepped up to help address this unmet need. America's 18 million veterans now have the option to receive mental health treatment at not just VA or private sector sites but at specialized treatment centers like the Wounded Warrior Project's Warrior Care Network, including the esteemed Emory Healthcare Veterans Program.

Dr. Feinberg: To help us understand the scope of this problem, can you tell us what percentage of U.S. veterans are impacted by mental health issues?



Lt. Gen. Garrett: Today in the U.S., 1 in 5 adults lives with a mental illness; and only half receive treatment. Veterans are a subset of that population and likely experience the same prevalence of mental illness. However, veterans are also disproportionately affected by mental health challenges like PTSD because of their increased exposure to traumatic events. The National Council for Behavioral Health reports that 30% of service members deployed to Iraq and Afghanistan have a mental health condition requiring treatment. It's estimated that as many as 400,000 service members live with invisible wounds of war, including PTSD and traumatic brain injury. However, PTSD doesn't have to be a life sentence with no hope of treatment. With proper treatment, vets can overcome PTSD and go on to live full and meaningful lives. That's where innovative programs, like the one we offer at Emory Healthcare, can make such an extraordinary impact.

Dr. Feinberg: What barriers prevent those impacted by the invisible wounds of service from seeking or getting the help they need? How realistic is the possibility of overcoming those barriers?

Dr. Rauch: We also need to remember that PTSD is an illness of avoidance. People suffering with PTSD often don't want to seek treatment. That's why it's so important that in the rare moment that a person suffering with PTSD does reach out to ask for help, we get the most effective treatment to that person at that moment. That's really tough to do because there aren't enough mental health providers, and there aren't enough providers who are trained in the most effective treatments for PTSD. The other consideration is that even when we get people into the treatments that work best, about 50% of veterans drop out of treatment – both in psychotherapy and medication. This is where the intensive outpatient models we use at Emory can really help. We have a 95% retention rate for people with PTSD completing our two-week, intensive outpatient program. Seventy-five percent of our patients report clinically significant reductions in PTSD after that two-week period. To begin to overcome the barriers of access, stigma, and cost, we make it easy for veterans to get care, give them a two-week intervention of life-changing treatment and get them back to their lives, hopefully without PTSD.

Lt. Gen. Garrett: From a veteran's perspective, there are three barriers to success in treating mental health: lack of access, significant stigma, and high financial costs. First, veterans face unique barriers to accessing adequate treatment. They must have an honorable or general discharge in order to access VA benefits. Then, they can face long waitlists to connect with care at our limited number of VA medical center locations, and many of our veterans are geographically isolated, living far distances from the nearest VA medical center. Second, the stigma around mental illness in the United States, and PTSD in particular, still runs strong and deep in our culture. Stereotypes that depict veterans with PTSD as dangerous or unpredictable can promote that stigma. Veterans with PTSD may fear embarrassment or shame just going to a facility for treatment, which can delay treatment. The third barrier is cost. Veterans who seek treatment may incur significant costs – including lost wages from taking time off work to get care; paying for childcare, travel, and lodging in cases when they need to travel to access care; and dealing with insurance copays in cases when they're accessing care outside of the VA, assuming they have insurance coverage at all. At Emory, to overcome these barriers, we cover the full costs of our outpatient treatment. I'm also hopeful that digital technologies and telehealth programs, like those deployed here at Emory, will help us to rapidly knock down the barriers to care for our service members and veterans.

Dr. Feinberg: How have you incorporated modern technology into 1:1 psychotherapy? How did it begin? How is it so transformative?

Dr. Rauch: Telehealth has been growing in use at the VA for years, but outside of the VA, it's been a challenge because of variances in state-to-state licensure laws. With the onset of COVID-19, many states relaxed those laws to allow mental health services to be provided across state lines. This advancement enabled us to build and extend a telehealth version of our two-week outpatient program to reach more patients suffering with PTSD. The expansion of the PsyPACT agreement between states now allows psychologists to practice in all states that have accepted the compact, 15 at present and growing every day. And the best news is that our telehealth program is proving to be just as effective as our face-to-face version. Patients participating in our telehealth program are experiencing reductions in PTSD and depression symptoms at the same rates as those who see us face-to-face. We are also able to reach more people this way, including people who didn't want to or didn't feel they could leave home to attend our in-person program. They can do this program during the day, from home, and then at night, they can take care of childcare and other responsibilities.

Dr. Feinberg: What role do wearables and other digital devices play in serving this population?

Lt. Gen. Garrett: I believe digital technology has enormous potential to help diagnose and treat PTSD, especially as wearable devices become ubiquitous. For example, imagine Private Garrett fighting in Afghanistan. He has a tough day, experiencing brutal trauma in a fire fight. His wearable device alerts him and his chain of command that his physiological and psychological indicators are all showing high levels of post-traumatic stress. Private Garrett texts Dr. Rauch at Emory, asking for a telehealth appointment. Dr. Rauch pops up on FaceTime or Skype and conducts an initial diagnosis that same day, then runs a broader assessment of Private Garrett using predictive analytics that pulls from a large artificial intelligence dataset. Recognizing that he's showing initial symptoms of PTSD, Dr. Rauch texts Private Garrett's chain of command and sets up a video conference. Based on her digital diagnosis, she recommends they pull him off the battlefield and enroll him in an Emory telehealth program that provides prolonged exposure for primary care. Private Garrett successfully completes that program and rejoins his unit, stronger and more resilient as a result of that treatment. Dr. Rauch continues to remotely monitor Private Garrett's wearable data to ensure he has no relapses and continually updates his digital health record.

This may now just be a figurative example, but it's illustrative of the fact that we now have the technology we need to provide PTSD and other mental health treatments that are proactive, personalized, and more equitably accessible. Digital health just needs the connectivity, data interoperability, data management, and stewardship to unlock its full potential.

Dr. Feinberg: This all sounds futuristic, but how far out do you think we are before the Private Garrett scenario that we've discussed here could actually be a reality in practice?

Lt. Gen. Garrett: I'd say the future is faster than we think. The acceleration and convergence of exponential technologies will completely reshape healthcare as we know it. This technological convergence is driving a shift from a healthcare system that's retrospective, reactive, and generic to a system that is prospective, proactive, and personalized. Second, I think this technological convergence will drive a significant shift in healthcare management. Apple CEO Tim Cook recently said that Apple's greatest contribution to mankind will be in health. As technology giants like Apple and Google begin to change the overall way we manage healthcare, my best advice is don't blink. Extraordinary opportunities are ahead.

Focus on **socioeconomics**

Uncovering invisible socioeconomic risk factors can improve cancer care

Ajeet Gajra, MD, MBBS, FACP

Amy Valley, PharmD, BCOP

Social determinants of health (SDOH) – such as financial, housing, and food insecurity; social isolation; addiction; access to transportation; and patient health literacy – can significantly impact patient outcomes.

A recent survey[1] by Cardinal Health Specialty Solutions backs up this assertion. Sixty-eight percent of the 160 oncologists surveyed said that more than half of their patients are negatively impacted by SDOH. Unfortunately, the majority of the time, these SDOH – which can have such a powerful impact on patient outcomes – are largely "invisible" to providers.

Lack of resources to analyze data make SDOH difficult to identify

This lack of visibility into SDOH certainly isn't due to a lack of information or patient data. The problem is usually a lack of time and resources. Eighty-one percent of the oncologists we surveyed indicated that they don't have enough time with patients to adequately understand or address their SDOH needs over time. This isn't a surprise given that the average visit between a cancer patient and his/her oncologist lasts just 15-20 minutes – a timeframe during which more pressing discussions relative to the diagnosis, treatment plan, side effects from treatment, imaging results, and other more obvious symptoms of the disease tend to be prioritized.

While EMRs may often contain reams of seemingly endless patient data, most community oncologists have no practical, useful, or actionable way to mine EMRs for data to identify those patients most at risk of an adverse event – ranging from depression to near-term mortality.

That lack of visibility into SDOH data all too often means that oncologists are missing opportunities to prevent hospital readmissions, emergency room visits, medication noncompliance, missed patient visits, and other avoidable events that often lead to higher costs and less than optimal outcomes for patients. The ability to intervene early to support patients with SDOH risks is not only a win for patients, but it's also a win for providers who are being reimbursed based on value-based models, such as the Centers for Medicare and Medicaid Services (CMS) Merit-based Incentive Payment System (MIPS) and the Oncology Care Model (OCM).

Artificial intelligence: the key to unlocking actionable insights behind SDOH

The good news is that advances in technology and analytics, including artificial intelligence (AI) solutions, are providing a novel way to help oncologists and their teams identify patients who may be at a higher risk for adverse events due to these hidden SDOH factors so that they can provide interventional care sooner. By providing clear visibility into relevant patient-specific SDOH and recommending specific, targeted interventions, AI can empower community oncology practices to:

- prioritize which patients could most benefit from personalized case management support and interventions;
- adjust their workflows to enable rapid intervention for patients at greatest risk; and
- simplify and lessen emotional influence from challenging decisions, like palliative care.

Cardinal Health Specialty Solutions recently teamed up with clinical AI developer Jvion to deliver an AI population health tool, CORE™, that helps oncology specialists reveal hidden SDOH risk factors in their oncology patients. This AI-powered solution enables oncologists to quickly identify patients who are at risk or on an accelerated trajectory for mortality, emergency department visits, depression, avoidable and multiple admissions, and other adverse health events, so they can provide interventional care sooner to change the outcome. The decision support tool also recommends individualized interventions that can improve patient outcomes based on the clinical and SDOH levers most impactable for their them.

Some forward-looking practices are already using AI tools like CORE™ to quickly transform mountains of socioeconomic, environmental, and behavioral data into real clinical value that drives higher patient engagement, more tailored interventions, and greater alignment between need and risk. The results are better care, outcomes, and experiences for individual patients and the community as a whole and an overall reduction in cancer care costs. Here, we recap the results of two recent poster presentations at the American Society of Clinical Oncology (ASCO) 2020 annual meeting, reinforcing these assertions.

Leveraging AI to improve the use of palliative care services in oncology

Addressing SDOH in oncology has arguably never been as important as it is now, as millions of patients have deferred cancer screenings due to the COVID-19 pandemic. The resulting economic challenges have made SDOH factors even more acute for many Americans. As of June 2020, the U.S. had seen 37% fewer cancer diagnoses versus the same time point of the previous year, and experts are predicting 34,000 excess deaths in the U.S. due to reduced cancer care during the pandemic[2].

COVID-19 factors notwithstanding, managing palliative care and hospice referrals are consistently among the most challenging tasks that oncologists face. Research shows that patients are often referred too late[3], in part because oncologists struggle to determine when the time is right. As a result, many patients with terminal cancer undergo expensive and aggressive treatment late in their disease — often with little, if any, positive impact.

AI tools are helping oncology practices simplify and lessen subjectivity related to challenging palliative care decisions by identifying the patients who would benefit the most from a timely integration of hospice and/or palliative care in their final stages of advanced illness. By also recommending a personalized end-of-life care plan that is based on the individual's therapeutic needs and preferences, this functionality can help streamline the patient referral process for hospice and palliative care.

In the real world, we're already seeing that the application of AI to end-of-life palliative care decisions can be a particularly compelling opportunity to improve cancer care costs, which are highest as patients near their end of life[4].

Seattle oncology practice leverages AI to drive a 12-fold monthly increase in hospice referrals

Oncologists like Dr. Sibel Blau, a lead oncologist at Northwest Medical Specialties (NWMS) in Seattle, Washington, are finding that AI is helping their practices make difficult end-of-life care decisions – which not only reduces treatment costs but helps patients and caregivers avoid unnecessary suffering and emotional turmoil.

Cardinal Health Specialty Solutions partnered with NWMS to conduct a study to determine the extent to which the implementation of a prescriptive analytics solution, Jvion's CORE™, could help the practice better identify patients who could most benefit from palliative care or hospice referrals. The CORE™ mines publicly available and purchasable SDOH data and synthesizes it with clinical datasets, AI algorithms, and machine learning techniques to identify patients with a propensity for poor outcomes.

In this study[5], the CORE™ was tasked with scoring and risk-stratifying, weekly, patients who were at risk for mortality within 30 days. It then recommended patient-specific, dynamic, actionable insights for providers to consider as they developed a care plan. Patients identified by the CORE™ as being at risk for mortality within 30 days were referred by the practice for a supportive care visit to determine if it was clinically appropriate to provide them with a palliative care referral.

Applying this approach, NWMS – a practice with 21 providers managing over 3,000 unique patients per month – nearly doubled its number of palliative care consults in a 10-month period. During that time, it also saw a 12-fold increase in its mean monthly rate of hospice referrals.

"Referring patients for hospice or palliative care is never an easy decision but failing to do so when the patient could benefit ultimately worsens the patient's end-of-life experience," says Dr. Blau. "AI helps us to make these difficult decisions, saving not only treatment costs but also unnecessary suffering and emotional turmoil for patients with terminal cancer and their caregivers."

AI also helps improve depression care among cancer patients

In a similar study[6], we partnered with NWMS to explore the degree to which AI could be leveraged to help the practice identify cancer patients at most risk for depression – and help those patients better manage their depression. Depression is common among patients with cancer and is associated with worse cancer treatment outcomes[7]. Still, it is often underdiagnosed and undertreated because cancer clinicians are focused on the complex aspects of therapy and care coordination.

After we trained the CORE™ to identify and risk-stratify NWMS patients who were at risk of having depression within the next six months, NWMS saw a 271% increase in its rate of depression screenings, a 184% increase in patients referred for depression-related case management evaluations, and a 168% increase in the number of patients who received prescriptions for antidepressants as a result of a case management consult.

While AI tools may not be a silver bullet for addressing all cancer care challenges, forward-thinking practices are already leveraging it to better address the needs of underserved populations while also reducing avoidable healthcare costs. As the healthcare industry continues to move toward more value-based care models, AI technologies like CORE™ will become increasingly essential to oncology practices in their continued quest to deliver higher quality care to more patients at a lower cost.

About Jvion and Cardinal Health

Cardinal Health is the exclusive reseller of Jvion oncology products to community oncology practices. CORE™ by Jvion is part of Cardinal Health™ Navista™ Tech Solutions (TS), an integrated suite of tech solutions for value-based care. The AI-enabled population health technology helps oncology providers improve care and lower costs for high-risk, modifiable patients by mining unique socioeconomic and health data sets. For more information, go to cardinalhealth.com/navista.

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Focus on **oncolytics**

Real-world U.S. uptake among newly approved cancer drugs

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Therapeutic cancer drugs (oncolytics) represent an increasing proportion of the overall drug pipeline with 35.2% of the 5,697 active drugs in development dedicated to cancer in 2019.[1] Innovation in cancer drug development has been coupled with developments in the Food and Drug Administration (FDA) expedited review pathways resulting in double-digit novel mechanism-of-action, first-in-class drug approvals annually. Recently introduced FDA expedited methodologies including: accelerated approval, priority review, fast track designation, breakthrough therapy designation, and the Oncology Center of Excellence Real-Time Oncology Review all help to create efficiencies in drug approval processes that are shortening the historical 12 years for bench-to-bedside development to less than 6 years on average.[2,3] In 2018 alone, 19 oncolytic drugs gained first approval, and 22 gained expanded indications. Myriad factors, including market uptake, payer authorization, physician prescribing, patient receptivity, and healthcare costs in the weeks and months after FDA approval, is of great interest to all stakeholders, yet remains poorly tracked and described. In this article we characterize unique oncolytic drugs approved in calendar year 2018 and their uptake during calendar year 2019.

Oncolytic drugs approved for the first time in 2018

The 19 new oncolytic drug/regimen approvals in 2018 comprised 6 kinase inhibitors, 4 monoclonal antibodies, and 1 each of the following: androgen receptor inhibitor, asparagine specific enzyme, CD123 cytotoxin, hedgehog pathway inhibitor; HER2 inhibitor; isocitrate dehydrogenase-1 (IDH1) inhibitor, PARP inhibitor, peptide receptor radionuclide therapy (PRRT), and a radioactive therapeutic agent (Table 1). Four new oncololytic drug approvals in 2018 were components of combination therapies.

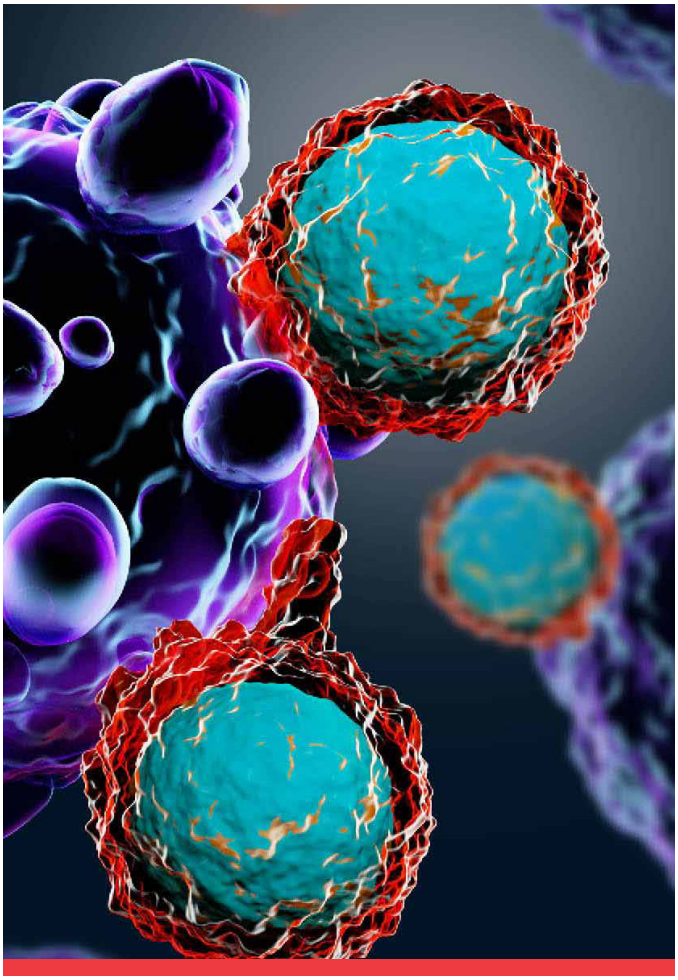
Encorafenib and binimetinib were approved in combination for the treatment of unresectable or metastatic melanoma with a BRAF V600E or V600K mutation. Glasdegib was approved in combination with low-dose cytarabine for newly diagnosed acute myeloid leukemia (AML) among those 75 years or older or who have comorbidities that preclude intensive chemotherapy use. Calaspargase pegol-mknl was approved for AML treatment as a component of a multi-agent chemotherapeutic regimen.

First-in-class approvals

Five drugs were approved with a first-in-class designation, indicating they had a novel mechanism of action for treatment.[4] As such, these innovative therapies offer new treatment options for patients and fulfill an unmet clinical need. Ivosidenib, an IDH1 inhibitor, was approved in the third quarter (Q3) of 2018 for the treatment of adult patients with relapsed or refractory (RR) AML with an IDH1 mutation. Lutetium Lu 177 dotatate, a PRRT and radiolabeled somatostatin, was approved in the first quarter (Q1) of 2018 to treat somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) making it the first PRRT approved by the FDA. The approval of lutetium Lu 177 dotatate was also supported, in part, by a real-world, single-arm, open-label study of 1,214 patients as part of the FDA's expanded access program designed to leverage non-RCT data to support drug approvals. Mogamulizumab-kpkc, a monoclonal antibody, was approved in Q3 of 2018 for the treatment of adult patients with RR mycosis fungoides or Sézary syndrome (SS). Mogamulizumab-kpkc is the first FDA approved therapy specifically for SS. Tagraxofusp-erzs, a CD123 cytotoxin, was approved in the fourth quarter (Q4) of 2018 for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adults and in pediatric patients 2 years and older making it the first drug – and first CD123-target therapy – for BPDCN. Finally, larotrectinib, a kinase inhibitor, was approved in Q4 of 2018 for the treatment of adult and pediatric patients with a neurotrophic receptor tyrosine kinase gene fusion without a known acquired resistance mutation, that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment. The approval of larotrectinib marks the second tissue-agnostic indication approval from the FDA (after pembrolizumab) and the first time a tissue-agnostic indication has been granted upon initial approval of a drug.

Other notable highlights

Apalutamide is the first drug FDA approved for the treatment of nonmetastatic castration-resistant prostate cancer (CRPC). Notably, the pivotal trial on which apalutamide's approval was based (NCT01946206) was the first to use the major efficacy endpoint of metastasis-free survival, which measures the length of time that a patient is alive and tumors did not spread to other parts of the body. Of the 19 oncolytics approved in 2018, apalutamide was one of the few that did not receive orphan drug designation given the potential size of the eligible patient population.



Cemiplimab-rwlc was approved for the treatment of patients with locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC) who are not candidates for curative surgery or curative radiation, making it the first drug and the first immune checkpoint inhibitor to be approved by the FDA specifically for advanced CSCC. Moxetumomab pasudotox-tdfk was approved as treatment for adult patients with RR hairy cell leukemia (HCL) who received at least two prior systemic therapies, including treatment with a purine nucleoside analog. The approval of moxetumomab pasudotox-tdfk marked the first approval of a drug for the treatment of HCL in over 20 years. The 2018 FDA approval of glasdegib marked the first approval of a hedgehog inhibitor for the treatment of AML. The approval of iobenguane I-131 represented the first FDA approved drug for the treatment of adult and pediatric patients aged 12 years and older with unresectable, locally advanced or metastatic phenocromocytoma or paraganglioma, requiring systemic anticancer therapy. Finally, gilteritinib was approved for the

treatment of adult patients with RR AML with a FLT3 mutation making it the first nonchemotherapy monotherapy for this indication.

Biosimilars are likely to represent an increasing percentage of new drug approvals in oncology and represent a distinctive class in this analysis as they are unique, yet similar, to an established reference brand. Although no biosimilars are FDA approved yet as interchangeable products (a biosimilar that may be substituted for the reference product without prescriber involvement; a biosimilar that has met additional requirements to show the same clinical result as the reference product and has evaluated the safety and efficacy risks of switching back and forth between the interchangeable product and the reference product), they are often treated as such in the real world.[5] Two oncology biosimilars received initial approval in 2018. Trastuzumab-pkrb was approved in Q4 as a biosimilar to trastuzumab for the treatment of patients with HER2-overexpressing breast cancer. The approval of rituximab-abbs in Q4 marked the first approval of a biosimilar to rituximab for patients with CD20-positive, B-cell non-Hodgkin's lymphoma (NHL) to be used as a single agent or in combination with chemotherapy.

Table 1: Oncology Drugs Approved for the First Time In 2018

Drug Name	Approval quarter	Class	Indication	First-line	Orphan
First-In-Class Approvals					
Ivosidenib (Tibsovo)[6]	Q3	Isocitrate dehydrogenase-1 (IDH1) inhibitor	Relapsed or refractory acute myeloid leukemia with a IDH1 mutation		X
larotrectinib (Viktrakvi)[7]	Q4	Kinase inhibitor	Solid tumors with neurotrophic receptor tyrosine kinase (NTRK) gene fusion proteins		X
Lutetium Lu 177 dotatate (Luthathera)[8]	Q1	PRRT; radiolabeled somatostatin analog	Somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs)		X
Mogamulizumab-kpkc (Poteligeo)[9]	Q3	Monoclonal antibody	Relapsed or refractory mycosis fungoides or Sézary syndrome		X
Tagraxofusp-erzs (Elzonris)[10]	Q4	CD123 cytotoxin	Blastic plasmacytoid dendritic cell neoplasm		X
Other Approvals					
Apalutamide (Erleada)[11]	Q1	Androgen receptor inhibitor	Non-metastatic castration-resistant prostate cancer		
Calaspargase pegol-mknl (Asparlas)[12]	Q4	Asparagine specific enzyme	Acute lymphoblastic leukemia		X
Cemiplimab-rwlc (Libtayo)[13]	Q3	Monoclonal antibody; programmed death receptor (PD)-1 blocking antibody	Metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC)		
Dacomitinib (Vizimpro)[14]	Q3	Kinase inhibitor	Metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations	X	X
Duvelisib (Copiktra)[15]	Q3	Kinase inhibitor	Relapsed or refractory chronic lymphocytic leukemia, small lymphocytic lymphoma, and relapsed or refractory follicular lymphoma		
Encorafenib+binimetinib (Braftovi/ Mektovi)[16, 17]	Q2	Kinase inhibitor	Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation		
Gilteritinib (Xospata)[18]	Q4	Kinase inhibitor	Relapsed or refractory acute myeloid leukemia with a FLT3 mutation		X
Glasdegib (Daurismo)[19]	Q4	Chemotherapy; hedgehog pathway inhibitor	Acute myeloid leukemia		X
Iobenguane I-131 (Azedra)[20]	Q3	Radioactive therapeutic agent	Iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma		X
Lorlatinib (Lobrena)[21]	Q4	Kinase inhibitor	Anaplastic lymphoma kinase-positive metastatic non-small cell lung cancer		X
Moxetumomab pasudotox-tdfk (Lumoxiti)[22]	Q3	Monoclonal antibody; CD22-directed cytotoxin	Relapsed or refractory hairy cell leukemia		X
Talazoparib (Talzenna)[23]	Q4	PARP inhibitor	Germline BRCA-mutated, HER2-negative, locally advanced or metastatic breast cancer		
Biosimilar Approvals					
Trastuzumab-pkrb (Herzuma)[24]	Q4	HER2 inhibitor targeted therapy; HER2/neu receptor antagonist	HER2-overexpressing breast cancer		
Rituximab-abbs (Truxima)[25]	Q4	Monoclonal antibody; CD20-directed cytolytic antibody	Relapsed or refractory, low grade or follicular, CD20-positive, B-cell Non-Hodgkin's lymphoma and previously untreated follicular, CD20-positive, B-cell NHL		

Uptake of oncolytic drugs approved for the first time in 2018

Analysis of uptake of oncolytic drugs was limited to first-in-class drugs and drugs that were the first to be approved for a particular indication. While tagraxosfusp-erzs was approved as a first-in-class drug, the rarity of the condition for which it was indicated precluded incorporation in this analysis. To characterize 2019 market uptake, a multi-payer claims-based cohort was constructed for each therapy approved in 2018 using patients with at least one claim for the therapy regardless of indication between January 1, 2019 and December 31, 2019. Data were pulled from the Symphony Health Integrated Dataverse (IDV), a large U.S. claims database containing linked longitudinal prescription, medical, and hospital claims for a broad view of healthcare delivery and patient usage patterns. The database is representative of the U.S. population across age, sex, geography, and payment type (including commercial, Medicare, and Medicaid plans) and contains claims for 280 million active unique patients, including 17 million active cancer patients, representing over 73% of specialty prescriptions, 58% of medical claims, and 30% of hospital claims volume in the U.S. Patient characteristics for IDV drug/regimen cohorts, the number of claims within each IDV drug/regimen cohort across time, and the proportion of patients in each IDV drug/regimen cohort receiving "on-label" treatment (treatment that aligns with an indication for use specified in the FDA's approved packaging label or insert) were summarized using descriptive statistics. Patients treated with each of the oncololytic drugs assessed were considered on-label if their primary disease or condition indicated by ICD-10 diagnosis code matched the broad indication for which the drug was approved. Comparisons of the demographic characteristics of the each IDV drug/regimen cohort to the corresponding patient populations from the trials that supported the FDA approval of each drug were made qualitatively.

The number of 2019 fills/administrations for first-in-class approvals ranged from 111 for larotrectinib to 1,950 for lutetium Lu 177 dotatate. Lutetium Lu 177 dotatate and larotrectinib generally maintained consistent levels of fills/administration throughout the year with slight fluctuations. Ivosidenib, saw an increase in the number of fills/administrations from Q1 to Q2 followed by a decline in the number of fills/administrations from Q2 to Q3 that plateaued into Q4. Mogamulizumab-kpkc saw a sharp increase in fills/administrations from previous quarters to Q4 of 2019 increasing from 0 fills/administrations in Q3 to 514 fills/administrations in Q4 (Figure 1).

The median ages of patients in the IDV cohorts were older than their corresponding trial populations (ivosidenib: 69 vs. 67; larotrectininb: 60.5 vs. 45; lutetium Lu 177 dotatate: 66 vs. 63.3 (mean value) and 61; mogamulizumab-kpkc: 69 vs. 63) for all 2018 first-in-class oncolytic drug approvals assessed (Table 2). The sex distribution of the IDV cohorts for ivosidenib, lutetium Lu 177 dotatate, and mogamulizumab-kpkc largely matched that of their corresponding trial populations. For larotrectinib, the IDV cohort had a greater proportion of female patients compared to its corresponding trial population (60.5% vs. 47%). The proportion of patients in the IDV cohorts receiving on-label treatment ranged from 42% (mogamulizumab-kpkc) to 100% (larotrectinib).

Apalutamide had the greatest number of fills/administrations identified in the IDV claims dataset for 2019 of all the oncolytic drugs included in this uptake analysis. Starting with 1,427 fills/administrations in Q1 of 2019, the number of apalutamide fills/administrations steadily increased throughout the year closing 2019 with 2,391 fills in Q4. Cemiplimab had 1,810 fills/administrations identified for 2019 with 99% of those occurring in Q4. Cemiplimab saw a sharp increase in fills/administrations from previous quarters to Q4 of 2019 with 4 fills/administrations in Q3 to 1,796 fills/administrations in Q4 (44,800% increase).

For apalutamide, the age and sex makeup of the IDV cohort largely matched that of the corresponding trial population. For cemiplimab the IDV cohort was older and had a greater proportion of female patients compared to its corresponding trial population. The proportion of patients in the IDV cohorts receiving on-label treatment was 82% and 29% for apalutamide and cemiplimab, respectively (Table 2).

Figure 1: 2019 Fills/Administrations for Select Oncolytic Drugs Approved for the First Time in 2018

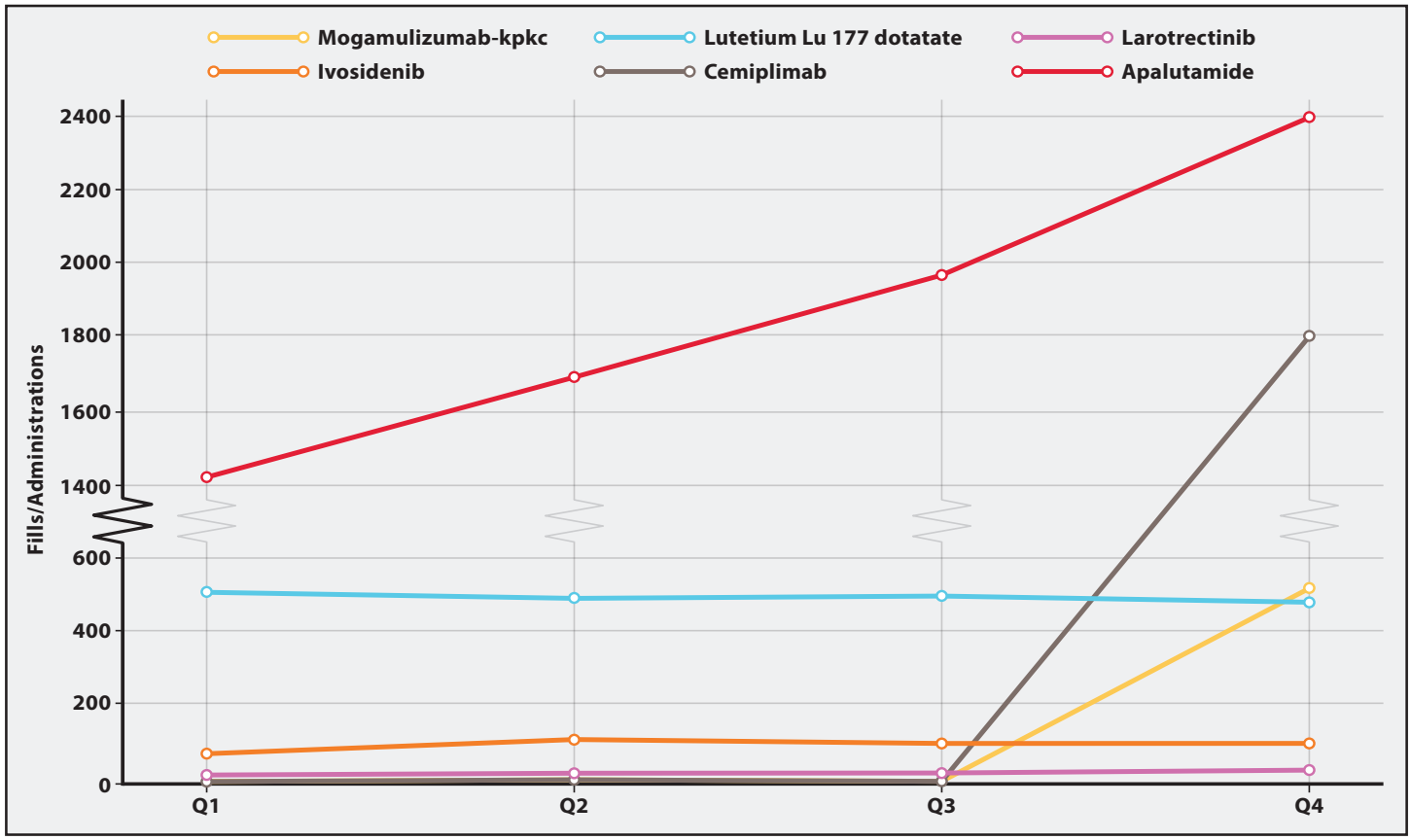


Table 2: Trial Population and IDV Cohort Demographic Characteristics and IDV Patient Receiving On-Label Treatment

Drug name	Trial patient demographics					IDV patient demographics				IDV drug cohort patients receiving on-label treatment (%)
	Trial identifier	N	Median age (range), years	Male (%)	Female (%)	N	Median age (range)	Male (%)	Female (%)	
First-in-class approvals										
Ivosidenib	Study AG120-C-001 (NCT02074839)[6]	174	67 (18-87)	51%	49%	122	69 (29-79)	49%	51%	59%
larotrectinib	LOXO-TRK-14001 (NCT02122913)[7] SCOUT (NCT02637687)[7] NAVIGATE (NCT02576431)[7]	55	45 (0.3-76)	53%	47%	38	60.5 (12-79)	40%	60%	100%
Lutetium Lu 177 dotatate	NETTER-1 (NCT01578239)[26]	116	63.3 (9.4)*	54%	46%	850	66 (5-79)	53%	47%	66%
	ERASMUS Medical Center study[8]	360	61 (25-88)	52%	48%					
Mogamulizumab-kpkc	Study 0761-010 (NCT01728805)[9]	186	63 (25-101)	59%	41%	116	69 (32-79)	57%	43%	42%
First approvals for an indication										
Apalutamide	SPARTAN (NCT01946204)[27]	806	74 (48-94)	100%	0%	1799	74 (40-79)	99.9%	0.1%	82%
Cemiplimab	Study R2810-ONC-1423 (NCT02383212)[28]	26	73 (55-88)	81%	19%	613	77 (17-79)	74%	26%	29%
	Study R2810-ONC-1540 (NCT02760498)[28]	59	71 (38-93)	92%	8%					

*Reported as mean (SD) as opposed to median (range)

Limitations/Strengths

Limitations of this analysis include those commonly associated with claims data. As claims data are collected for administrative as opposed to research purposes, it has structural limitations only allowing for the collection of fixed data points pertaining to certain events for certain people. Findings should be interpreted taking into context the potential impacts on generalizability inherent within a claims database study, especially one such as this where integrated electronic medical record (EMR) data for capture of additional clinical details such as biomarker, histology, or stage information were not available. For instance, it is likely that the proportion of patients receiving on-label treatment within the IDV cohorts for all the drugs assessed has been overestimated. The determination of on-label treatment was made based on the diagnosis codes available within the IDV, which represent diagnoses that were generally broader than the indications for use specified in the FDA's approved packaging label or inserts. A salient example is larotrectinib, which received a tissue-agnostic indication approval from the FDA for all patients of all ages who have solid tumors harboring fusions in NTRK1, NTRK2, or NTRK3. As identification data for NTRK fusion was not available in the IDV database, any patient utilizing larotrectinib for the treatment of a solid tumor cancer

was considered to be receiving on-label treatment. This resulted in 100% of the larotrectinib IDV cohort being designated as receiving on-label treatment. The lack of availability of racial/ethnic data in the IDV also precluded the comparison of IDV drug cohorts to their corresponding clinical trial populations on the basis of racial/ethnic makeup.

Factors that could potentially impact market uptake of a drug, such as burden of disease or unmet need and comparator choice, were not assessed as part of this study. Strengths of this study are that the IDV includes longitudinal data regardless of treatment facility leading to accurate capture of medical and pharmacy data, and treatment history for the patients included in the study. This study also utilizes a geographically diverse and payer-neutral data source.

Conclusion

In 2018, the FDA approved 19 oncolytic novel drugs or biosimilars for the first time, including a first approved treatment for: non-metastatic CPRC, advanced CSCC, and SS as well as a second ever tissue-agnostic indication. Demographic variances between the real-world and trial populations were notable. Apalutamide had the greatest number of fills/administrations for 2019 of all the oncology drugs/regimens approved for the first time in 2018; this was true across all quarters as well as for the total year and likely the result of a much larger target population than the advanced, relapsed or refractory indications of the other ultra-orphan cancer populations studied. As the wave of targeted therapy innovation in the oncology treatment landscape continues to grow and the FDA continues to create efficiencies in its review and approval processes, the identification and understanding of evolving drug characteristics and market forces that drive utilization patterns will be critical for the U.S. oncology drug market stakeholders.

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- Awareness and utilization of tumor mutation burden (TMB) as a biomarker for administration of immuno-oncology (I-O) therapeutics by practicing community oncologists in the United States (US)
- Racial disparity in uterine cancer treatment and survival: a matter of black women's lives
- Age-based disparities in clinical trials supporting FDA approval of therapies for solid tumors
- Postmarketing requirements for drugs approved by the Food and Drug Administration for the treatment of solid tumor cancers, 2010-2019
- Cooperative group and pharmaceutical sponsored clinical trials: perceptions of US community oncologists
- Assessment of objective response rate by investigator vs. blinded independent central review in pivotal trials of drugs approved for solid tumor indications

ISPOR Annual Meeting – May 2021

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- Preliminary estimate of the prevalence of low HER2 expression among HER2 negative metastatic breast cancer patients in US: multi-site, retrospective chart review study
- Oncologists' perceptions and utilization of therapeutic oncology biosimilars in the US

San Antonio Breast Cancer Symposium – December 2020

- Evolution of prescribing trends for HR+/HER2- metastatic breast cancer (mBC) in a post-CDK4/6i world
- Effectiveness of eribulin in poor prognosis subgroups of metastatic breast cancer (mBC) patients (elderly, African Americans, and patients with liver metastases) in the United States

ASH Annual Meeting – December 2020

- Real-world use of enasidenib in relapsed or refractory acute myeloid leukemia is associated with reduced risk of disease progression and death
- Real-world effectiveness of first-line (1L) dasatinib versus 1L imatinib in newly diagnosed patients with chronic phase chronic myeloid leukemia (CP-CML)
- Real-world investigation of spleen, symptom, and hematologic response in patients with myelofibrosis treated with first-line ruxolitinib
- Adoption of approved CAR-T therapies among US community hematologists/oncologists
- Acute myeloid leukemia/myelodysplastic syndrome (AML/MDS) associated with PARP inhibitors: a real-world analysis
- Real-world adverse events associated with tisagenlecleucel in acute lymphoblastic leukemia and large B-cell lymphoma
- Age-based disparities in clinical trials supporting FDA approval of therapies for hematologic malignancies
- Assessment of measurable residual disease (MRD) in chronic lymphocytic leukemia (CLL) and multiple myeloma (MM) among US community hematologists/oncologists (cH/O)

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- Treatment patterns of advanced or recurrent endometrial cancer following platinum-based therapy in the US real-world setting
- Patient-reported outcomes in routine oncology care: perceptions, execution, and barriers
- Linking reimbursement to patient-reported quality of life: provider perspectives
- Real-world utilization of quality of life data: perspectives from community oncology providers
- The use of validated geriatric assessment instruments among US community oncologists
- Knowledge and evaluation of geriatric assessment (GA) domains among US community oncologists/hematologists (cOH)

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