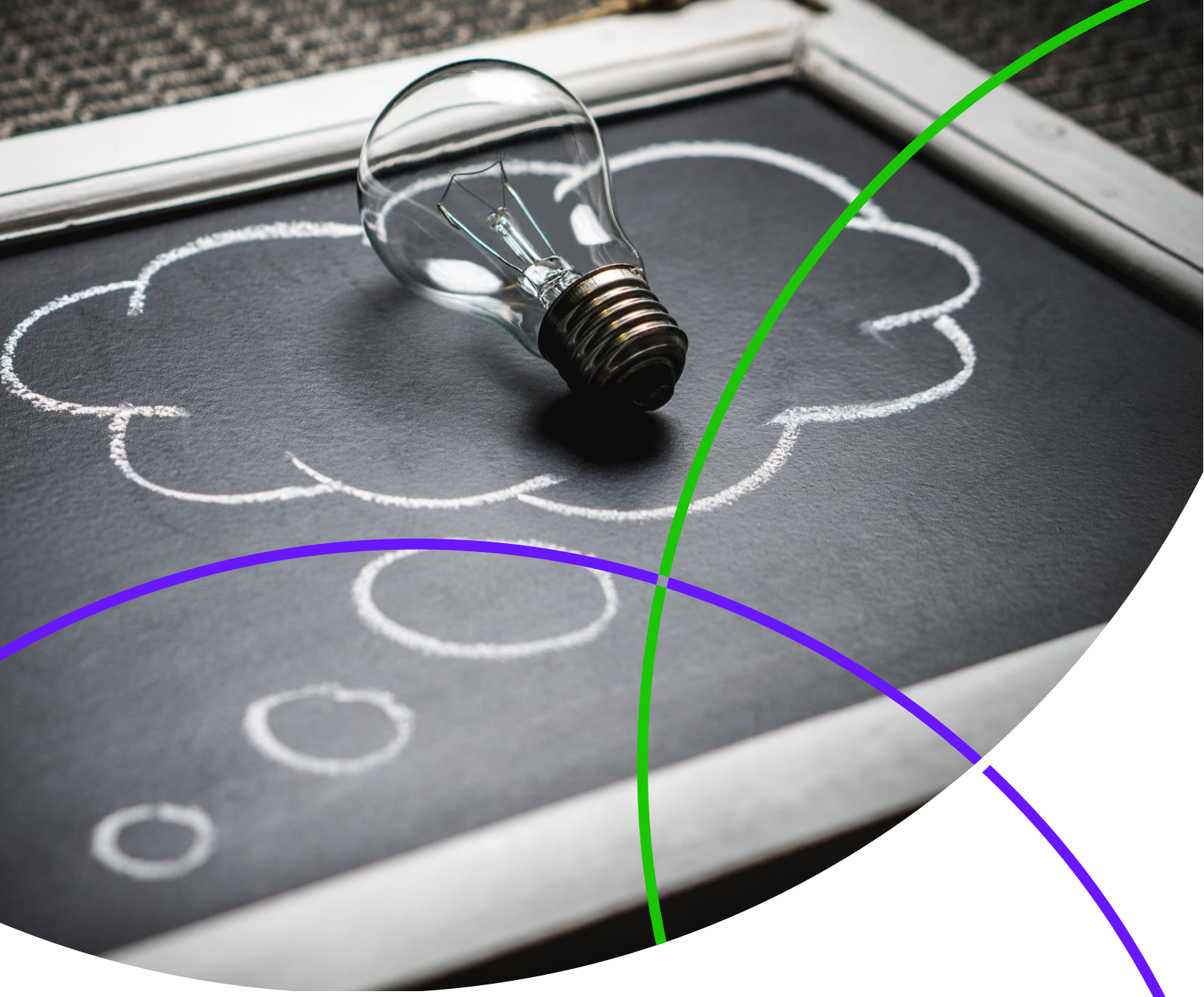

The Life Sciences Innovation Report

A data-driven view of emerging R&D trends

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Pistoia Alliance

Clarivate Analytics

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Introduction

Most people working in Biopharmaceutical R&D, or more broadly the Life Sciences industry, would agree that innovation is important. But, what is innovation? Googling "What is innovation" returns more than 1 billion hits. Focusing on the top search result, from the Google dictionary, doesn't add any more insight to clarify the question: "the action or process of innovating." However, in producing this report and the data used to create it, new perspectives were gained about how to define and identify innovation in Life Sciences. Unsurprisingly, different people have different views of innovation. So, rather than trying to establish a common definition of innovation across Life Sciences, which embraces many forms of innovation interesting to different stakeholders in different ways, we have looked at innovation through a data lens. We have used literature, patents, drug pipelines and drug targets' data sources to produce this report with the aim of: 1) producing an innovation watch that would be of interest to the various stakeholders in the Life Sciences industry, and 2) establishing a repeatable method for performing the data analysis across multiple linked sources. In each section we include ranked data on the featured topics, the data sources used and the methodology, followed by any key messages.

The process of innovating is not a single event; it's not contained in time, place, discipline or industry. It's a continuous learning process, where one discovery is built upon by another as the knowledge represented by those discoveries expands. The output of that innovation process is recorded along the way, in particular, in two important ways. First, innovation is published in the scientific literature. Those publications are subject to a peer review process to uphold the veracity and novelty of the research. Once published, the information contained in those articles can be read and interpreted, continuously feeding innovation. The second way innovation is recorded is through patents, which aim to protect that innovation, usually for some commercial or financial gain. In this analysis we relied on both the literature and patent sources, but we also used secondary sources cross-indexed with literature and patents, including drug pipeline data and drug-target-indication data, both of which also include data sourced from news, scientific conferences, government websites and financial analysts, to name a few. The scientific literature analysis focused on the top 1% of the highly cited scientific literature in biomedical and clinical sciences.

Summary of Featured Innovations

In this report we feature several innovations as measured through the scientific literature using bibliometric measures and classified based on their maturity in application to Biopharmaceutical R&D. We used a methodology called Research Fronts, described in the Methodology section. The innovations we feature in the report include:

Translation of Innovation to Pharma R&D Impact →

Emerging	Developing	Contributing
3D Printing	Cryo-electron microscopy (CryoTEM)	Exome-Wide Association Study in NASH
Adverse Outcome Pathways	Nanosensors	Comprehensive Genomic Profiling in Triple Negative Breast Cancer
Post-transcriptional RNA modification (circular RNA and RNA methylation)	Microbiome Gut-Brain Axis	EGFR and ALK receptor Inhibitors in in multiple cancers
	NAFLD/NASH disease onset and progression research	JAK-STAT pathway, gene variants, and JAK inhibitors in myeloproliferative neoplasms
	Brain Imaging (TAU PET and Gadolinium-based contrast)	PD-1/PD-L1 expression inhibitors in multiple cancers

Research Front Type: Purple = Technology, Method, Technique, Green = Disease, Diagnostic, Drugs from Therapeutic Modalities

Overall Key Messages

- There is an **acceleration in Biopharmaceutical R&D innovation**, buoyed by several contributing factors: precision medicine getting into gear in rare diseases, cancer and autoimmune diseases; immunotherapy heating up in multiple cancers; the expansion of therapeutic modalities exploiting natural and synthetic biology innovation; expedited regulatory pathways seeming to pave the way for greater New Molecular Entity (NME) output and drug launches.

- The **expanding role of academia contributing to biologics drug R&D**, and the variety of innovation across the genetic and cellular therapies with antibodies, CAR-T cells, siRNA, stem cells and CRISPR-Cas9 all leading to new approaches to potential new biological therapies.

- The **variety of multi-disciplinary innovation** globally is unprecedented as seen through the emergence and development of 3D printing, nanosensors, new imaging methods, bi-specific antibodies, antibody-drug conjugates and computational biology.

- **Whole genome studies** contributing to more refined disease understanding, diagnosis and treatment as seen in the Nonalcoholic Steatohepatitis (NASH) and triple negative breast cancer patient stratification innovations.

- The **microbiome** represents a new frontier in health and disease research.

- Machine learning, Natural Language Processing (NLP) are not only in proof-of-concept, **IT budgets are increasing to include AI predictive analytics** across R&D for deployment in decision-making, with blockchain still maturing but not as advanced.

- R&D IT is at the entry point in **adopting large-scale use of cloud-based platforms** in enterprise computing.

- **Mobile computing** is poised to support digitization of the workforce and **as digital health**, both stand-alone as therapy and in combination with drug therapy.

Innovation Around Us

Before placing attention solely on Life Sciences (Biopharmaceutical and Biotech primarily), let's consider innovation more broadly, which is today impacting the Life Sciences Industry, and will continue to do so. There are several adjacent industries to Biopharmaceutical and Biotech where innovations in those industries cross over into the same consumer space, namely (using 2016 growth rates): Consumer Products (39%), Cosmetics & Well-Being (23%), Information Technology (15%) and Medical Devices (3%). While Pharmaceuticals and Biotechnology show healthy growth in 2016 of 22% and 23% respectively, the innovation from these neighbouring industries is already contributing to the healthcare system.

Consumer Products/Cosmetics & Well-Being

The increasing consumerization of healthcare opens the door for more innovation from adjacent consumer products aimed at consumer health and disease management. Although there are legal and regulatory considerations, certain food, beverage and cosmetic innovations are already in play, placing pressure on regulators to keep consumers safe and claims in check. Example innovations and their potential relation to wellness and disease management include:

- Probiotics – microbiome ("good" microbe balance)
- Cannabinodiol – chronic pain, seizures (Dravet syndrome), and insomnia.

Information Technology

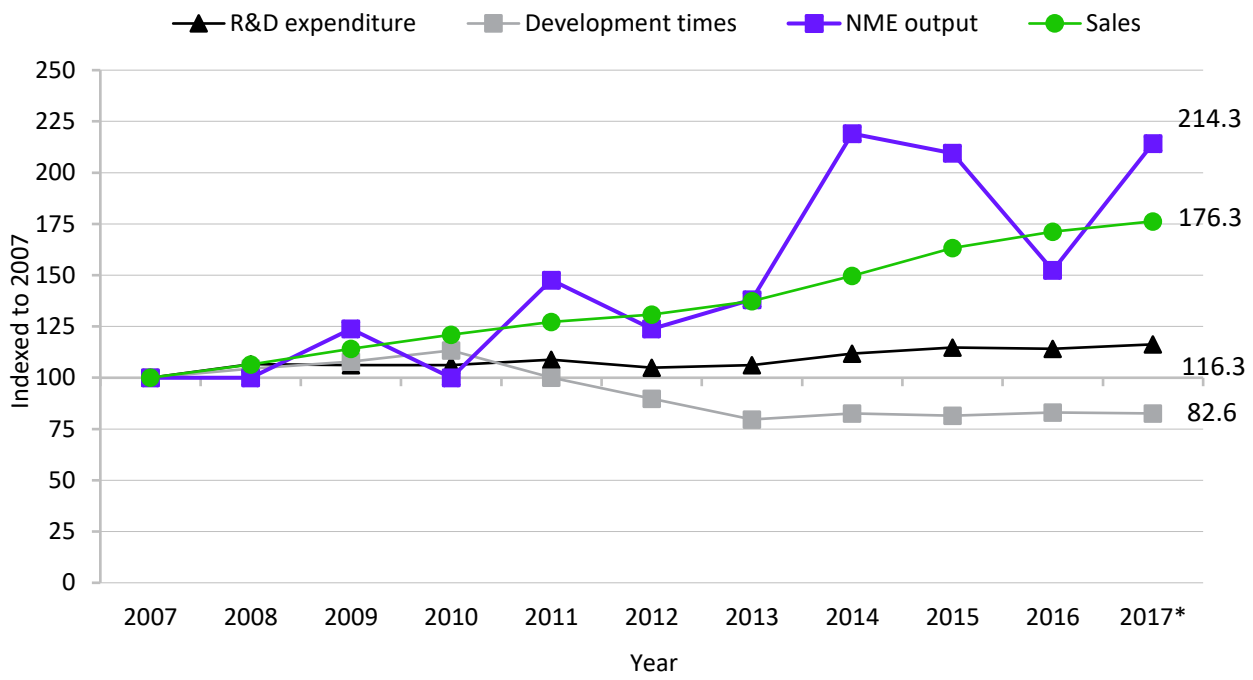
The IT industry overshadows all innovation in patents issued globally, with about one third of all global patents issued, and double-digit growth rates. So, it's not surprising that information technology is significant in Biopharmaceutical R&D, in diagnostics, and as a new modality in treatment options. In this report we look at IT's contribution through the literature (via the Research Fronts), patents, recent developments in the marketplace and regulatory trends, in the following IT categories:

- Algorithms
- Cloud-based computing
- Mobile applications and digital health.

Medical Devices

Although not a high-growth industry in recent years, the medical device industry has seen the benefits of whole genome sequencing, biomarkers, nanosensors and mobile computing. This is an industry to watch for Life Sciences as the convergence of these technologies is likely to lead to the arrival of a new class of mobile-enabled, smart medical devices used in combination with drugs, enhancing what drug-companion diagnostic combinations can deliver today.

Global Biopharmaceutical R&D Metrics



*The development times data point for 2017 includes data from 2016 and 2017 only

Source : 2018 CMR Biopharmaceutical R&D Factbook, from Clarivate Analytics : data from CMR International Performance Metrics Programme, Industry R&D Investment Programme, Annual Survey of New Molecular Entity First Launches / New Medicine Launches 2017, A Complete Guide to New Molecular Entities (NMEs) Launched World-wide. Global Biopharmaceutical sales: Sales data estimated by CMR of the data sourced from IQVIA.

Definitions

Development time: Time taken from compound registration code assigned to first world launch.

Global Biopharmaceutical sales: The revenue from global sales of ethical Biopharmaceuticals. This includes finished products, bulk sales and royalties from licensed-out ethical Biopharmaceuticals.

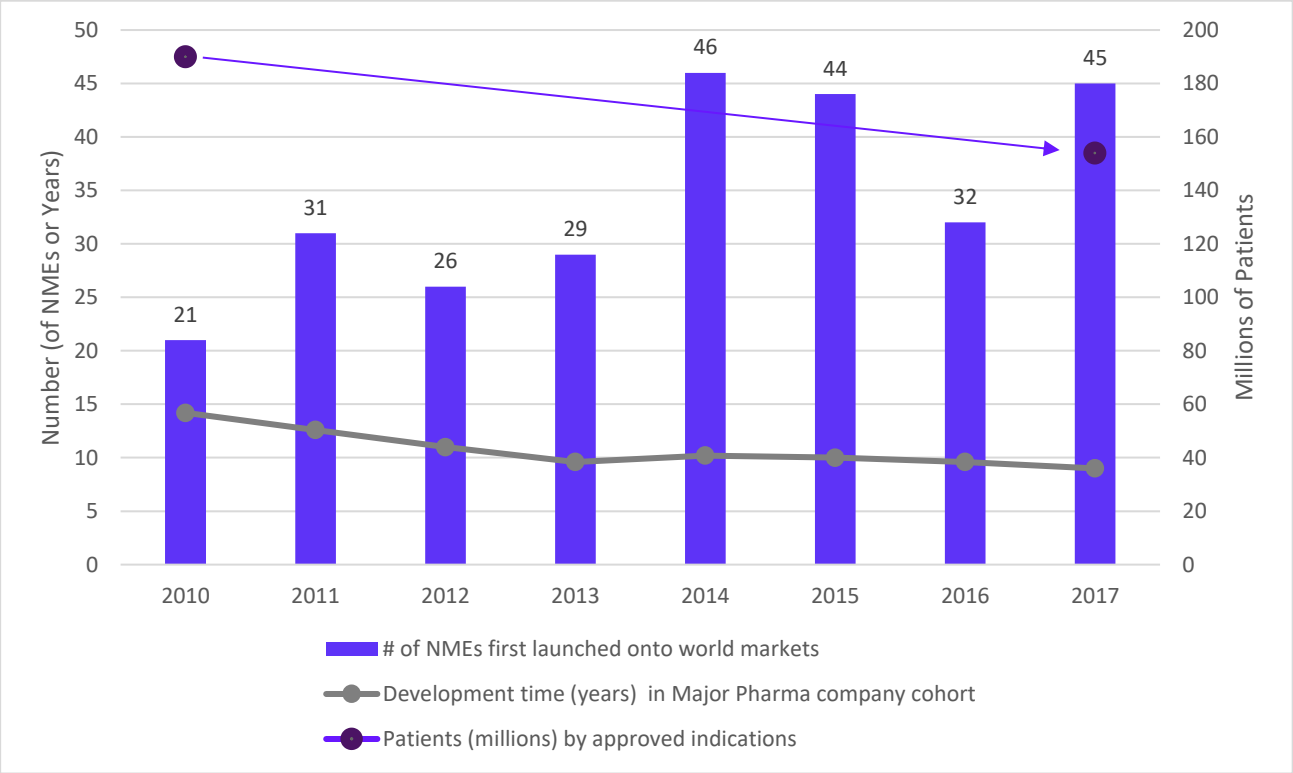
New Molecular Entity: A new chemical entity or biological (including products of biotechnology) that has not been previously available for therapeutic use in man and is destined to be made available as a "prescription only medicine," to be used for the cure, alleviation, treatment, prevention or *in vivo* diagnosis of diseases in man. Vaccines, new salts, pro drugs, metabolites and esters of existing compounds and certain biological compounds (e.g., antigens) are not classified as NMEs. Combination products are excluded from the list unless one or more of the constituents of the combination product has never been previously available

R&D expenditure: This includes salaries and all other personnel-related expenditure, expenditure related to consumable materials and supplies, and an appropriate share of overheads to cover administration, depreciation/amortization, space charges, rent, etc. The expenditure on R&D conducted by means of grants or contracts to other companies or institutions, and proportional expenditure for joint ventures should be included. This definition excludes capital R&D expenditure.

Key Messages

- Since the beginning of the decade the Biopharmaceutical industry is delivering innovation output, with NME output growth outpacing R&D expenditure and a decline in R&D development times.
- Sales look to be on an initial point of leveling off, although it's too early to tell if it's a trend.

Key Trends in Drug Development

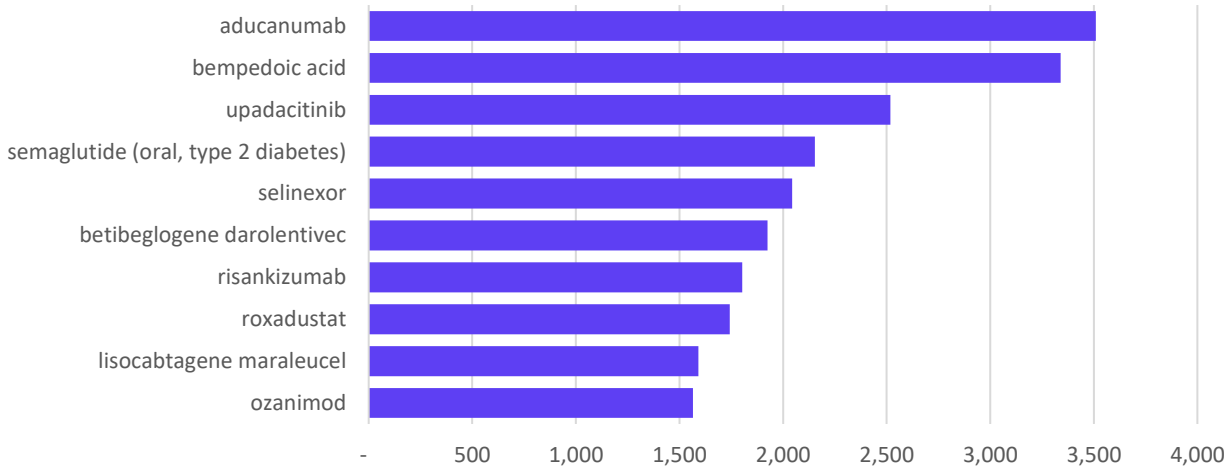


Methodology: NME launches refer to unique substances first launched anywhere in the world. Development times are measured from time of substance registration number assigned to date of launch. Patient estimates from a variety of epidemiology, literature and U.S. FDA public reference sources. **Source:** Incidence and Prevalence Database, Web of Science, 2018 CMR Biopharmaceutical R&D Factbook, all from Clarivate Analytics; U.S. FDA.

Key Messages

- Since the beginning of the decade until the end of 2017, NME launches have been trending upward, with each of the past four years higher than any of the previous four years.
- During that same time R&D development time has seen a material 37% decrease, although that decrease has leveled off since 2013.
- Comparing the number of patients treated from those launched drugs in 2010 and in 2017 reveals a decline in patients treated from 190 million in 2010 compared to 154 million in 2017, even though the number of drugs launched more than doubled. The era of precision medicine has arrived.
- Although the U.S. FDA introduced incentives for Biopharmaceutical companies to develop products for rare diseases as early as 1983 (known as Orphan Drug Designation), the FDA provided additional expedited approval guidance in May 2014, through *Guidance for Industry: Expedited Programs for Serious Conditions — Drugs and Biologics.* Those regulatory pathways may be a contributor to the increase in launches as approximately 40% of approved drugs in 2017 received expedited regulatory review under these available regulatory review pathways, with some drugs receiving multiple designations.

Late Stage Pre-Launch Drugs – Consensus Forecast 2023 Sales ($M)



Methodology: Top 10 drugs in phase III, pre-registration or registration ranked by analyst consensus forecast for 2023 sales ($M). ***Source:*** Cortellis from Clarivate Analytics

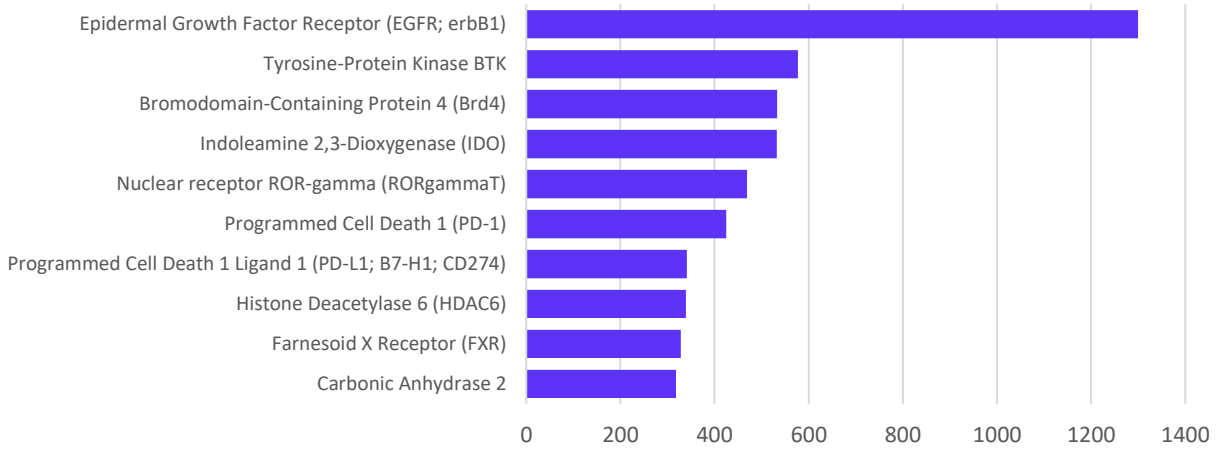
Drug Name	Active Companies	Target
aducanumab	Biogen Inc; Eisai Co Ltd	Beta amyloid
bempedoic acid	Esperion Therapeutics Inc	Niemann-Pick C1-like protein-1 inhibitor; ATP citrate lyase inhibitor; AMP activated protein kinase stimulator
upadacitinib	AbbVie Inc	Jak1 tyrosine kinase
semaglutide	Novo Nordisk A/S	Glucagon-like peptide 1 receptor
selinexor	Karyopharm Therapeutics Inc; Ono Biopharmaceutical	Exportin 1
betibeglogene darolentivec	Bluebird Bio Inc.	HBB gene
risankizumab	AbbVie Inc; Boehringer Ingelheim International GmbH	IL-23
roxadustat	Astellas Pharma Inc; AstraZeneca plc; FibroGen Inc	HIF prolyl hydroxylase
lisocabtagene maraleucel	Celgene Corp; Juno Therapeutics Inc	B-lymphocyte antigen CD19
ozanimod	Receptos Inc	Sphingosine-1-phosphate receptor-1 and 5

Key Message

- **Biogen/Eisai's aducanumab is an important Amyloid Beta hypothesis test**, since verubecestat (Merck & Co), atabecestat (Johnson & Johnson) and lanabecestat (AstraZeneca/Lilly), all BACE inhibitors, did not meet their primary endpoints in 2018. **A key phase III drug to watch.**

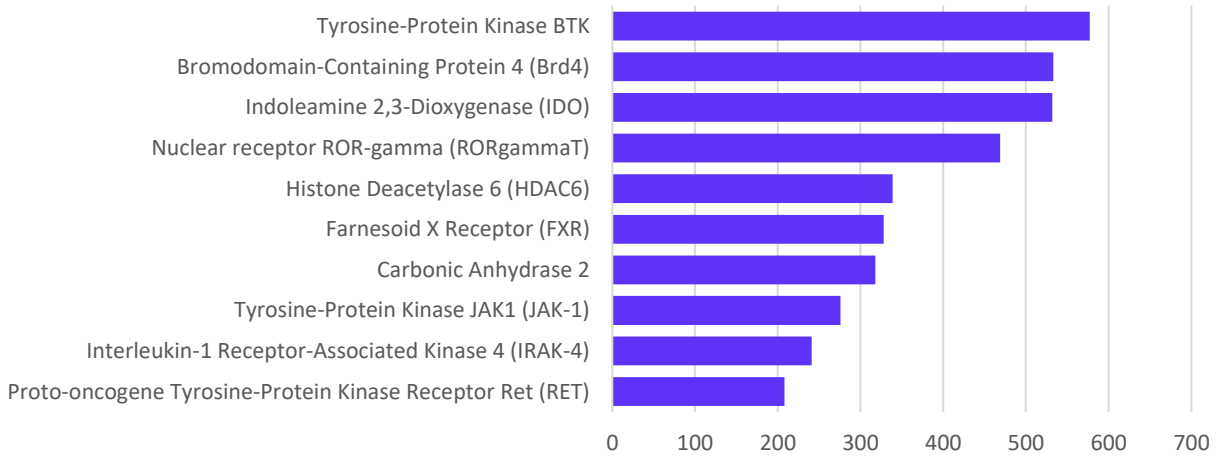
Drug Target Innovation

Top Developing Drug Targets (Small Molecule and Biologics) by Investigational Drug Count



Methodology: Top 10 targets with the greatest number of active investigational drugs under development in the last 2.5 years, and with the highest growth rate between the most recent 2.5 years vs. the previous 10 years. ***Source:*** Integrity, a Cortellis Product, from Clarivate Analytics.

Top Developing Small Molecule Drug Targets by Investigational Drug Count



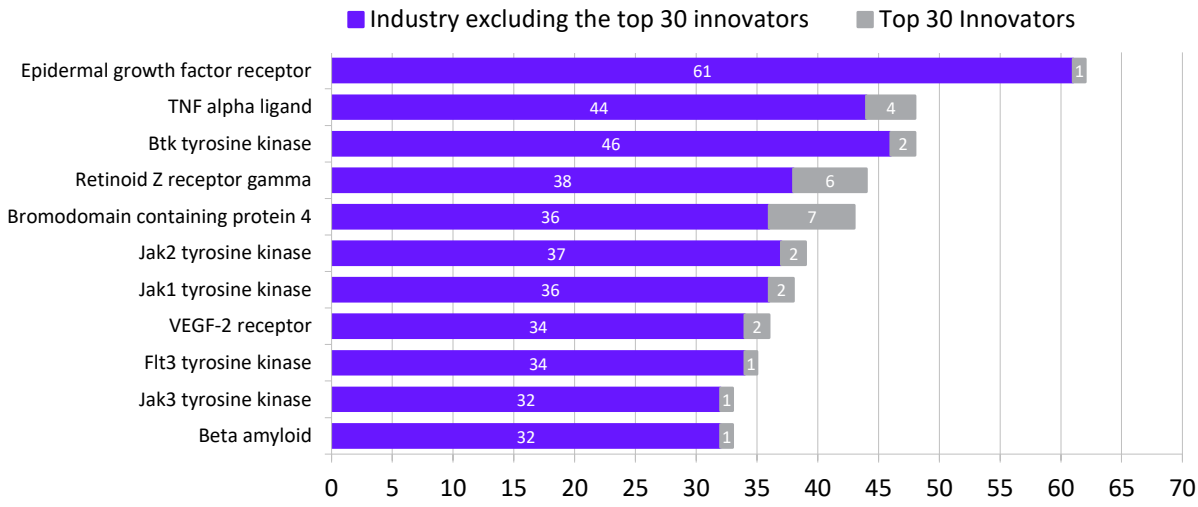
Methodology: Top 10 small molecule targets with the greatest number of active investigational drugs under development in the last 2.5 years, and with the highest growth rates between the most recent 2.5 years vs. the previous 10 years. ***Source:*** Integrity, a Cortellis Product, from Clarivate Analytics.

Key Messages

- Of the top 10 targets, 95% of the molecules under development for those targets are small molecules. PD-1 and PD-L1 are the exception, where 26% of the actively developed molecules for those targets are biologics. Those PD-1/PD-L1 investigational drugs are comprised primarily of antibodies, but also chimeric antigen receptor-T cell (CAR-T), CRISPR-Cas9, gene therapy and stem cells.
- Acetylcholinesterase (AChE), HIV-1 protease and cyclooxygenase-2 (COX-2) were on the list of most actively investigated drugs, but were replaced by RET, IRAK-4 and JAK-1 due to the growth rate of the latter targets in the past 2.5 years.

Top Small Molecule Developing Targets Patent Output by Patents Issued

For the past three years there has been only small movement in new patents issued for small molecules modulating targets where no previous patent was issued for the same target, either industry-wide or in the Top 30 Innovators (Tables of Top 30 small molecule innovators on page 10). Of the top targets where patents were issued for small molecules acting on those targets from institutions for the first time, nine of the 11 were also on the list of top targets in 2017, and eight of 11 were on the list in 2016.



Methodology: Small molecule targets by organizations (commercial and non-commercial) issued patents for novel molecules where no previous patents from the same organization for that target modulation exists. Patents issued in calendar year 2015 inclusive through May 2018. Note: The analysis includes issued patents, which lag patent submissions. ***Source:*** Cortellis, from Clarivate Analytics.

CMR Factbook Year	2018		2017		2016	
Target Name	Industry	Top 30	Industry	Top 30	Industry	Top 30
Amyloid beta A4 Protein (Abeta)	32	1	42	6	25	6
Epidermal Growth Factor Receptor	61	1	65	1	26	1
Receptor-Type Tyrosine-Protein Kinase FLT3 (FLT-3)	34	1	33	2	23	2
Retinoic Acid Receptor RXR-gamma	38	6	38	6	24	5
Tumor Necrosis Factor (TNF-alpha)	44	4	46	1	24	1
Tyrosine-Protein Kinase BTK	46	2	40	7	25	7
Tyrosine-Protein Kinase JAK1 (JAK-1)	36	2				
Tyrosine-Protein Kinase JAK2 (JAK-2)	37	2	31	3		
Tyrosine-Protein Kinase JAK3 (JAK-3)	32	1				
Vascular Endothelial Growth Factor Receptor 2 (VEGFR-2; KDR)	34	2	35	1	23	2
Bromodomain-Containing Protein 4 (BRD4)	36	7	45	3	23	3
Phosphoinositide 3-kinase					23	4
mTOR					23	4
Histone deacetylase-1			35	1		

Methodology: Small molecule targets by organizations (commercial and non-commercial) issued patents for novel molecules where no previous patents from the same organization for that target modulation exists. Patents issued in calendar years 2015, 2016, 2017. Note: The analysis covers issued patents, which lag patent submission and may lag in time of active research. ***Source:*** CMR International Biopharmaceutical R&D Factbook, 2016, 2017, 2018, from Clarivate Analytics.

Top 30 Small Molecule Innovators

Company or Institution	Small Molecule Patents
Merck Sharp & Dohme Corp	238
Bristol-Myers Squibb Co	191
F Hoffmann-La Roche AG	164
Bayer Corp	156
Hoffmann-La Roche Inc	113
GlaxoSmithKline plc	108
Genentech Inc	74
Janssen Pharmaceutica NV	71
Takeda Biopharmaceutical Co Ltd	71
Boehringer Ingelheim International GmbH	69
Pfizer Inc	65
Novartis AG	65
AbbVie Inc	58
University of California	57
Eli Lilly & Co	55
Shanghai Institute of Materia Medica of the Chinese Academy of Sciences	53
Medshine Discovery Inc	46
Sunshine Lake Pharma Co Ltd	46
Incyte Corp	43
Dana-Farber Cancer Institute Inc	43
E Merck Patent GmbH	42
WuXi PharmaTech (Cayman) Inc	40
Gilead Sciences Inc	38
Centre National de la Recherche Scientifique (CNRS)	38
INSERM	35
Syngene International Ltd	34

Shionogi & Co Ltd	34
AstraZeneca AB	33
Vanderbilt University	32
University of Michigan	32

Methodology: Top 30 institutions or companies issued patents for the first time for new small molecules for calendar year 2015 inclusive through May 2018. ***Source:*** Cortellis, from Clarivate Analytics.

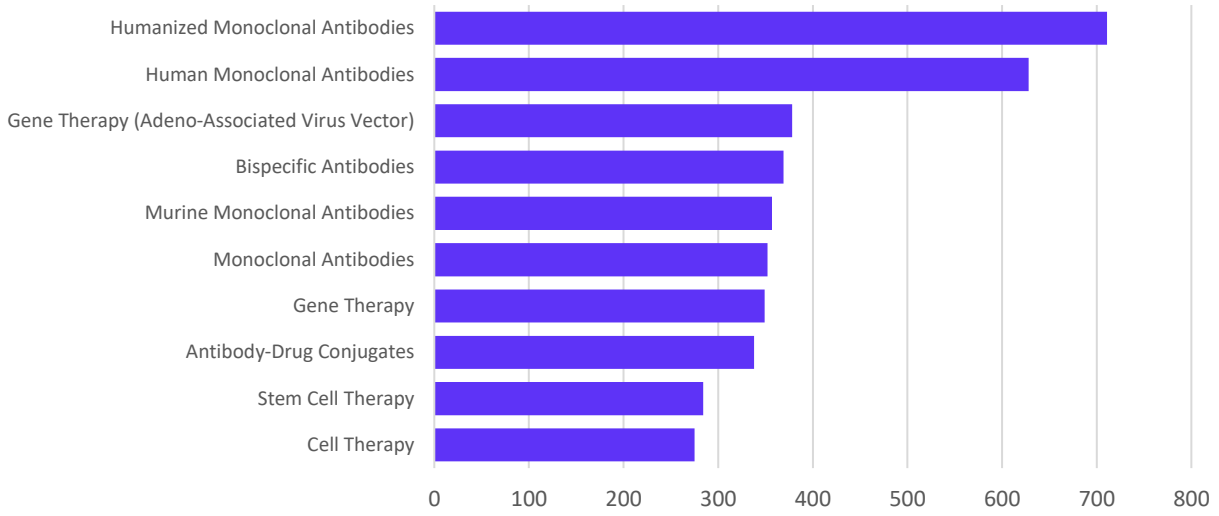
Key Messages

- Over the past three years the JAK target class is the highest emerging of the active developing targets. The number of patents issued in this period for the JAK sub-types is 105; this is far greater than the next target, EGFR, at 61 (from Industry group).
- All of the launched JAK inhibitors, including baricitinib from Lilly (licensed from Incyte), ruxolitinib from Novartis (licensed from Incyte) and tofacitinib from Pfizer are documented to have multiple JAK sub-type activity, whereas more of the JAK inhibitors advancing through the pipeline exhibit selective inhibition of one sub-type.
- Several JAK inhibitors have been granted accelerated development status, with Aldeyra Therapeutics's ganetespib receiving Fast Track designation the earliest phase, in phase I. AbbVie's upadacitinib has three separate expedited regulatory designations and looks to be next up for launch having met its phase III SELECT-NEXT primary endpoints for ACR20 in RA, and with 2023 forecast sales of $2.5B.
- Bromodomain containing protein 4 (BRD4) stands out, as interest in that target has increased more than two-fold in the focus of the Top 30, yet surprisingly has decreased industry-wide.
- Few of the BRD4 inhibitors have received accelerated development designation, with the exception of Roche's (in-licensed from Dana-Farber Cancer Institute) RG-6146 and Celgene's (in-incensed from Forma Therapeutics) FT-1101, each having received Orphan Drug designation.
- The two targets that saw the greatest drop in patent issuance, in the Top 30, were Abeta and BTK, with Abeta's decline likely due to the increasing evidence from clinical trials challenging the Abeta hypothesis in Alzheimer's disease.
- Phosphoinositide 3-kinase, mTOR and Histone deacetylase-1 also left the scene of top patented targets over the period.
- The Top 30 Innovators of these actively developed small molecule targets are led by Roche (351 across corporate entities), Merck and Bristol-Myers Squibb, with Large Pharma dominating the top third.

Biologics Targets

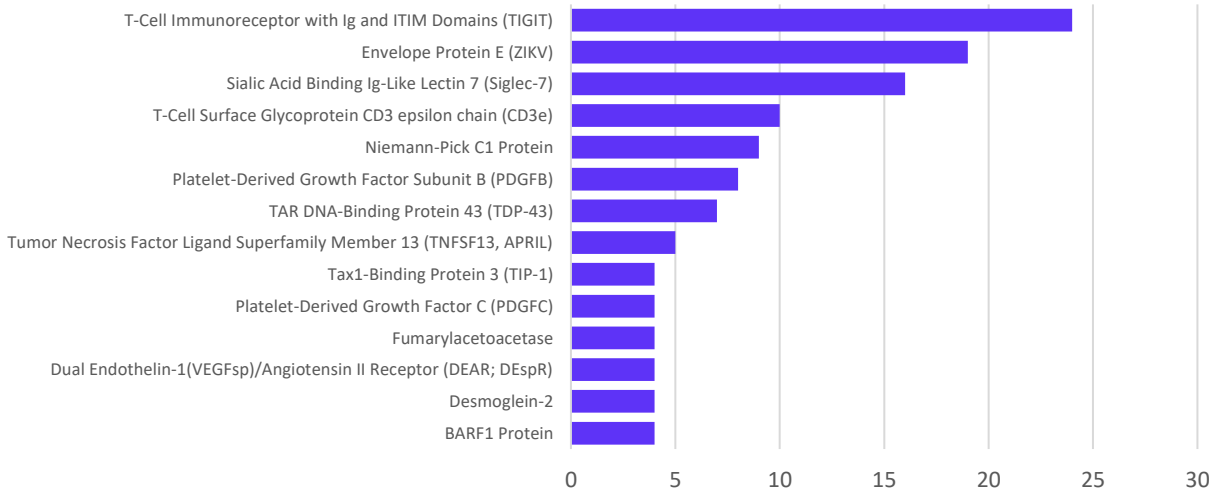
The number of antibody, cell and genetic-based therapies under active investigation is increasing, yet is still modest compared to the number of small molecules under investigation. However, the therapeutic categories in biologics are more varied than small molecules, exploiting the natural diversity of biological processes, function and structure from genes, to RNA, to proteins, to cells and to viruses. Through the application of biological knowledge, scientists are expanding the frontiers of synthetic biology, producing bi-specific antibodies and antibody-drug conjugates at a higher rate of growth than other biologics categories.

Leading Biologics Therapeutic Categories by Investigational Drug Count



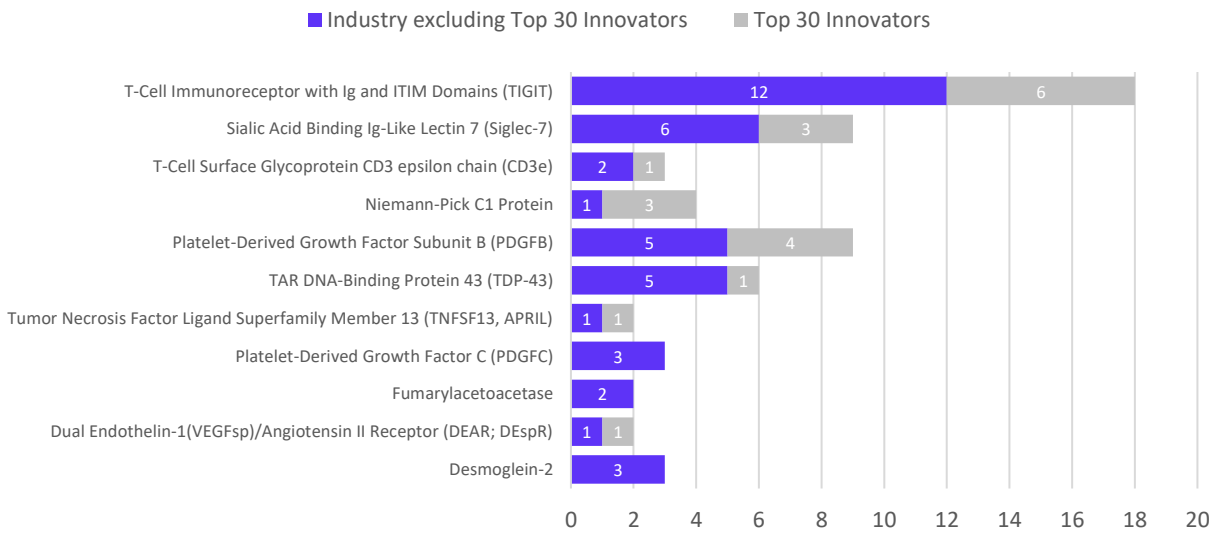
Methodology: The top 10 biologic therapeutic categories ranked by number of investigational drugs in the global pipeline. ***Source:*** Integrity, a Cortellis Product, from Clarivate Analytics.

Top Emerging Biologics Drug Targets by Investigational Drug Count



Methodology: Top 14 biologics targets with the greatest number of active investigational drugs under development in the last 2.5 years, and with the highest growth rates between the most recent 2.5 years vs. previous 10 years. ***Source:*** Integrity, a Cortellis Product, from Clarivate Analytics.

Top Emerging Biologics Drug Targets Patent Output by Issued Patents



Methodology: Biologics targets by organizations (commercial and non-commercial) issued patents for novel bioactive molecules where no previous patents from the same organization for that target modulation exists for those most actively investigated biologics targets. Patents issued in calendar year 2015 inclusive through May 2018. Note: The analysis includes issued patents, which lag patent submissions. ***Source:*** Cortellis, from Clarivate Analytics.

Key Messages

- TIGIT stands out among the biologics targets, with Top 30 also focused on Siglec-7, Niemann-Pick C1 Protein and PDGFB.
- The consistency between the emerging biologics targets and the targets subject of issued patents suggests that the top targets of TIGIT, Siglec-7, CD3e, Niemann-Pick C1, PDGFB and TAR-43 are all hot biologics targets as their growth in investigational drugs and patents is both increasing at the same time.

Top 30 Biologic Target Innovators

Company or Institution	Biologics Patents
University of California	183
F Hoffmann-La Roche AG; Hoffmann-La Roche Inc	112
F Hoffmann-La Roche AG; Genentech Inc	109
Regeneron Biopharmaceuticals Inc	99
Johns Hopkins University	91
MedImmune LLC	91
Novartis AG	78
Stanford University	77
Bristol-Myers Squibb Co	72
National Institutes of Health; US Health and Human Services Department	71
Harvard University	66
Agency for Science Technology & Research	61
Samsung Electronics Co Ltd	58

Memorial Sloan-Kettering Cancer Center	58
Texas A&M University System	54
Dana-Farber Cancer Institute Inc	52
Massachusetts General Hospital	50
Massachusetts Institute of Technology	48
University of Pennsylvania	47
Janssen Biotech Inc	47
Mayo Clinic Foundation	47
Amgen Inc	46
SNU R & DB Foundation	44
Chugai Biopharmaceutical Co Ltd	44
University of Washington	43
University of Massachusetts	39
Duke University	39
AbbVie Inc	39
University of Wisconsin-Madison	37
UCL Business PLC	37
Pfizer Inc	37

Methodology: Top 30 institutions or companies that issued patents for the first time for new biologics for calendar year 2015 inclusive through May 2018. ***Source:*** Cortellis, from Clarivate Analytics.

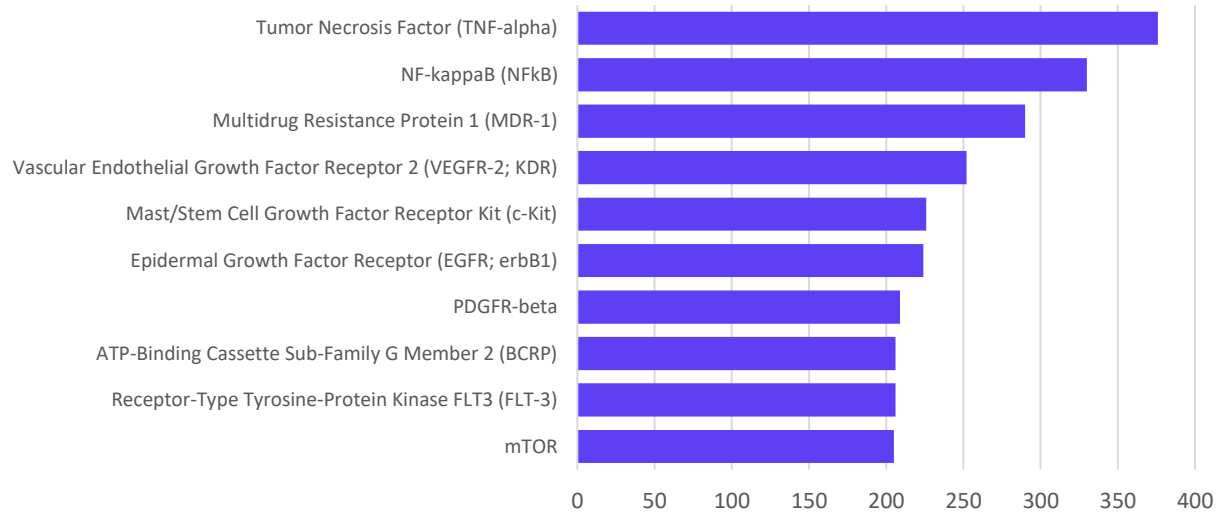
Key Messages

- Monoclonal antibodies dominate the biologics investigational drug pipeline.
- Bi-specific antibodies and antibody-drug conjugates are the fastest growing biologics category (data not shown).
- T-Cell Immunoreceptor with Ig and ITIM Domains (TIGIT), Platelet-Derived Growth Factor Subunit B (PDGFB), Sialic Acid Binding Ig-Like Lectin 7 (Siglec-7) and Niemann-Pick C1 Protein have attracted the attention of the Top 30 Innovators.
- The majority of Top 30 biologics innovators are non-commercial institutions.

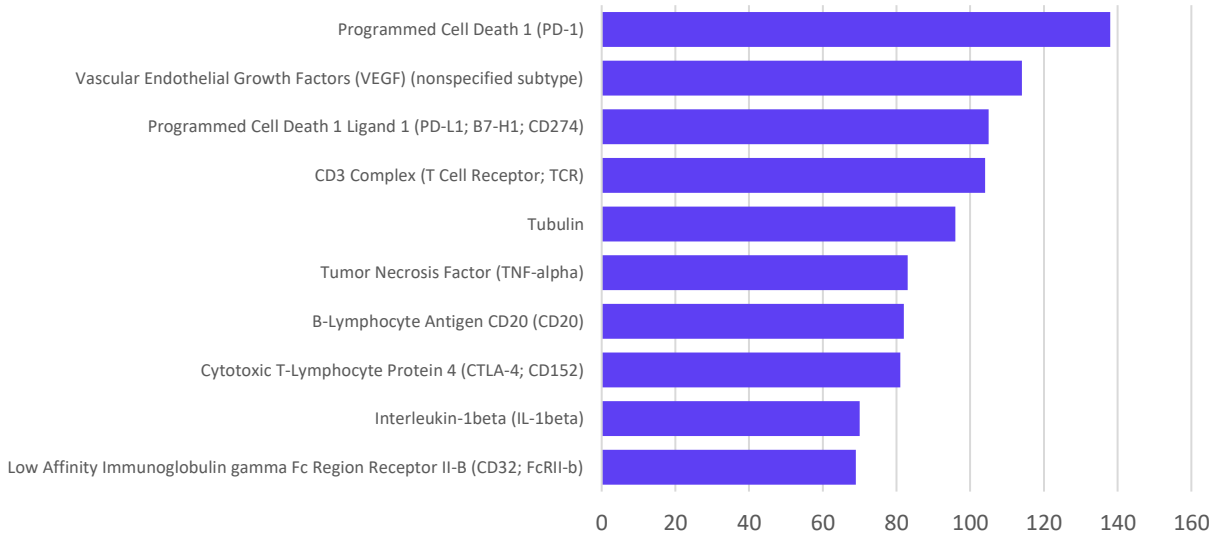
Disease Focus in Drug Development

The following disease count analysis includes the number of diseases being investigated by therapeutic category and a ranking of the top targets within those categories by number of diseases under investigation for each target. The developing and emerging disease focus is also presented.

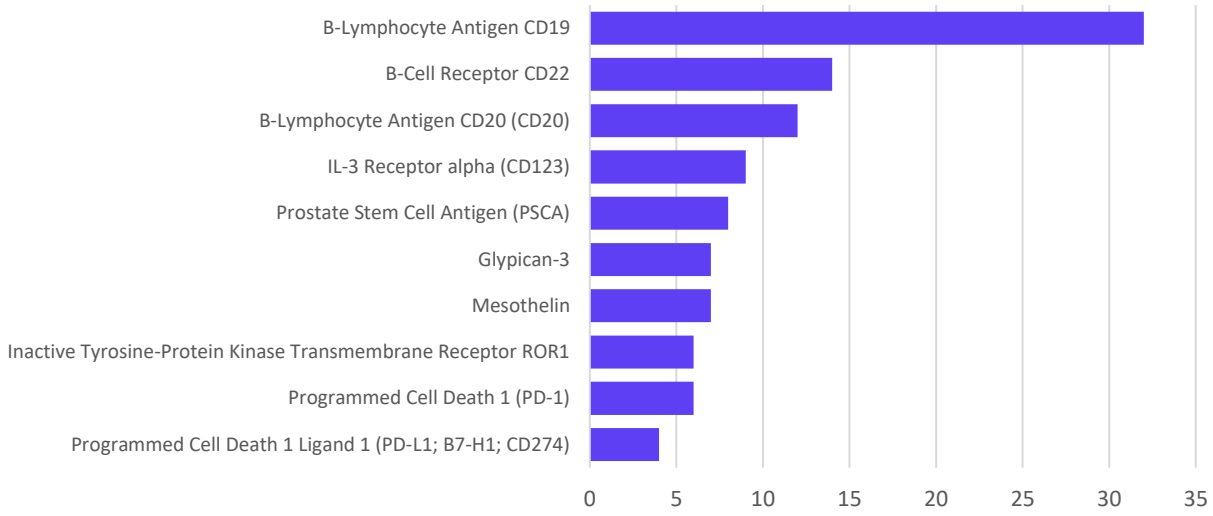
Top Small Molecule Targets by Disease Count



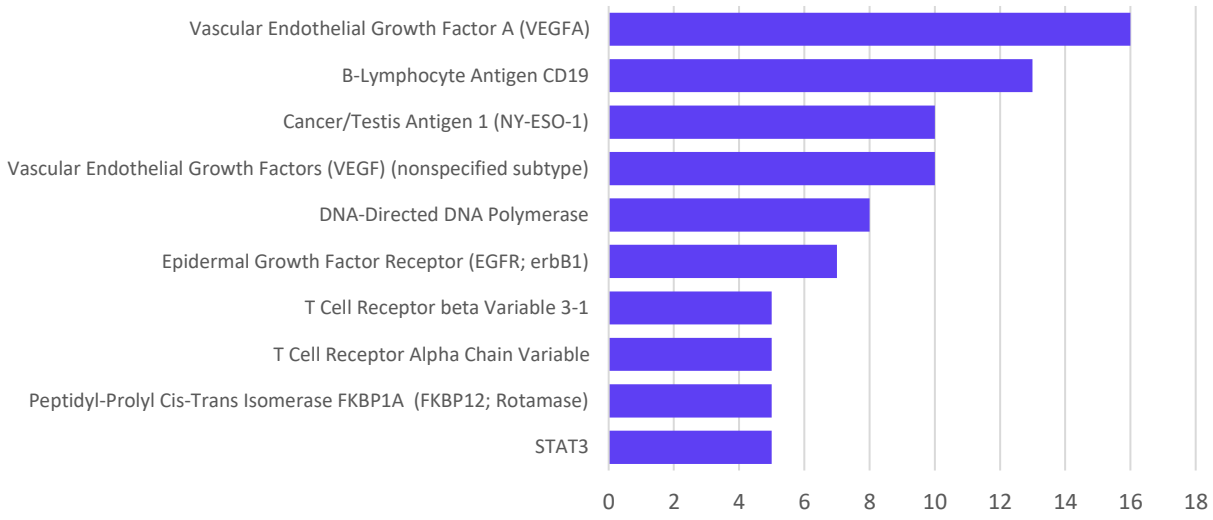
Top Antibody Targets by Disease Count



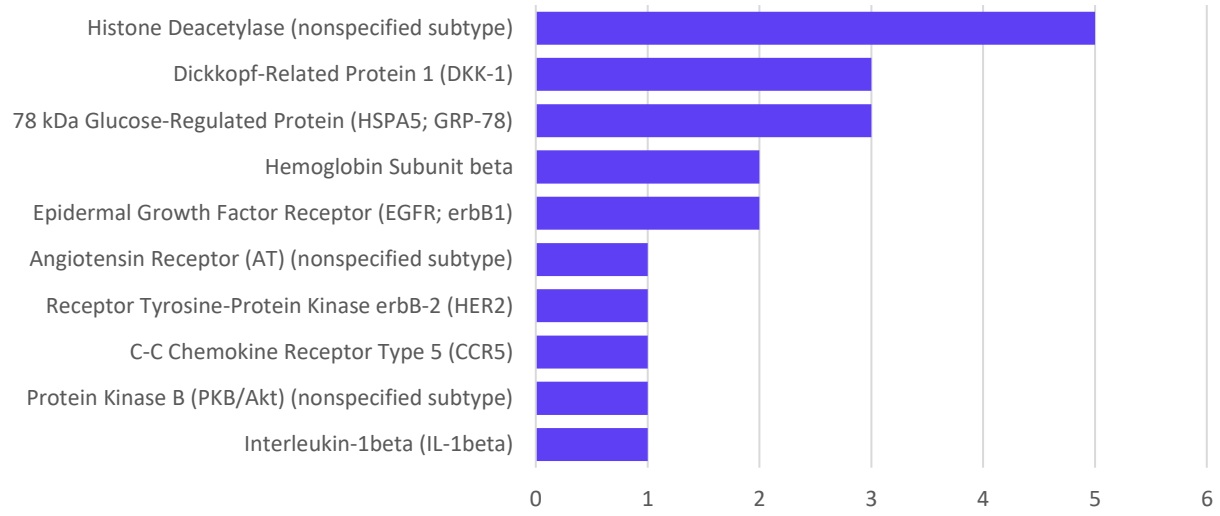
Top CAR-T Targets by Disease Count



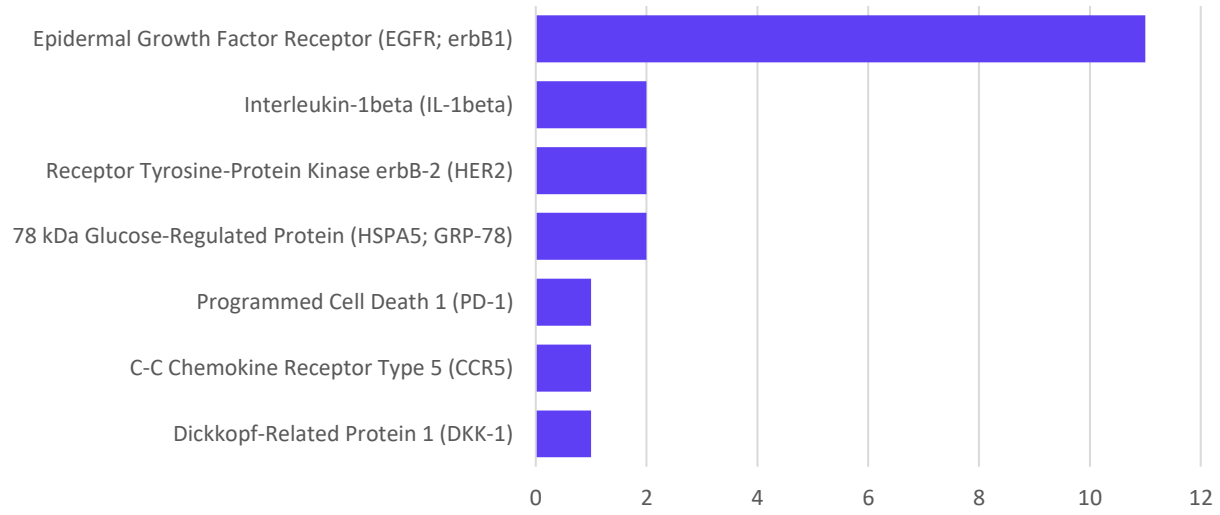
Top Gene Therapy Targets by Disease Count



Top Stem Cell Therapy Targets by Disease Count

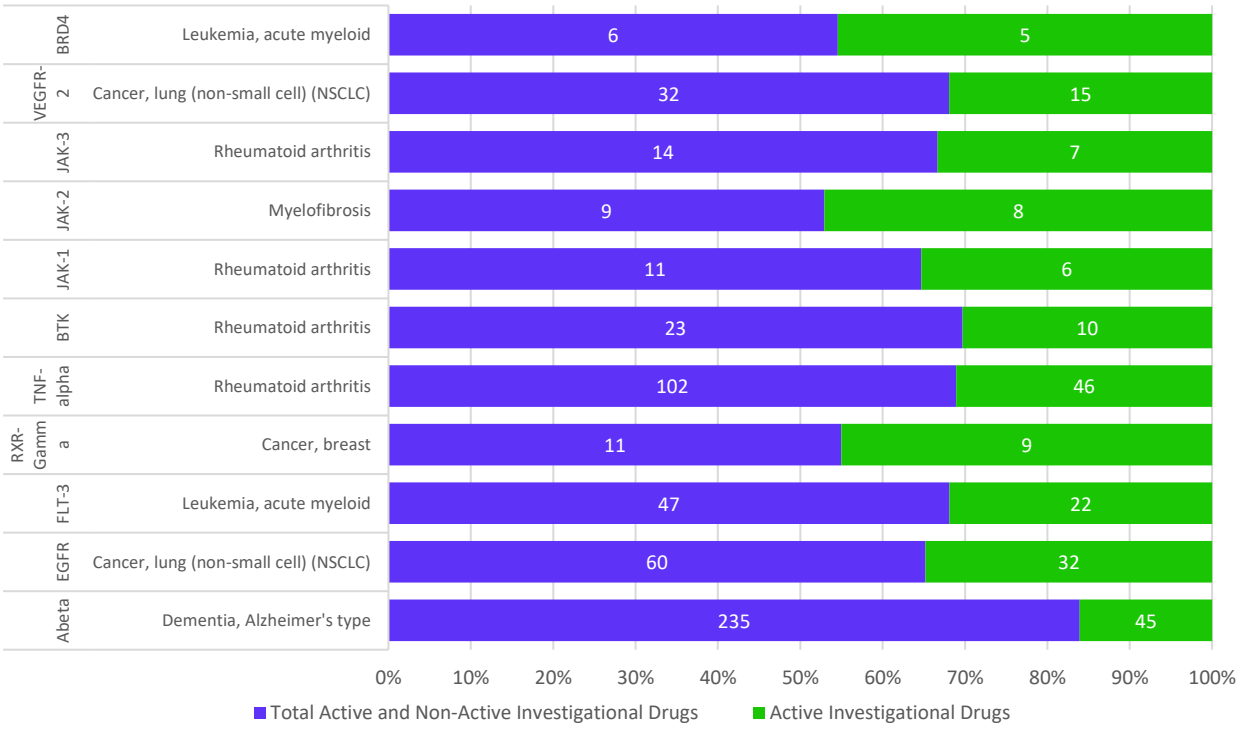


Top siRNA Targets by Disease Count



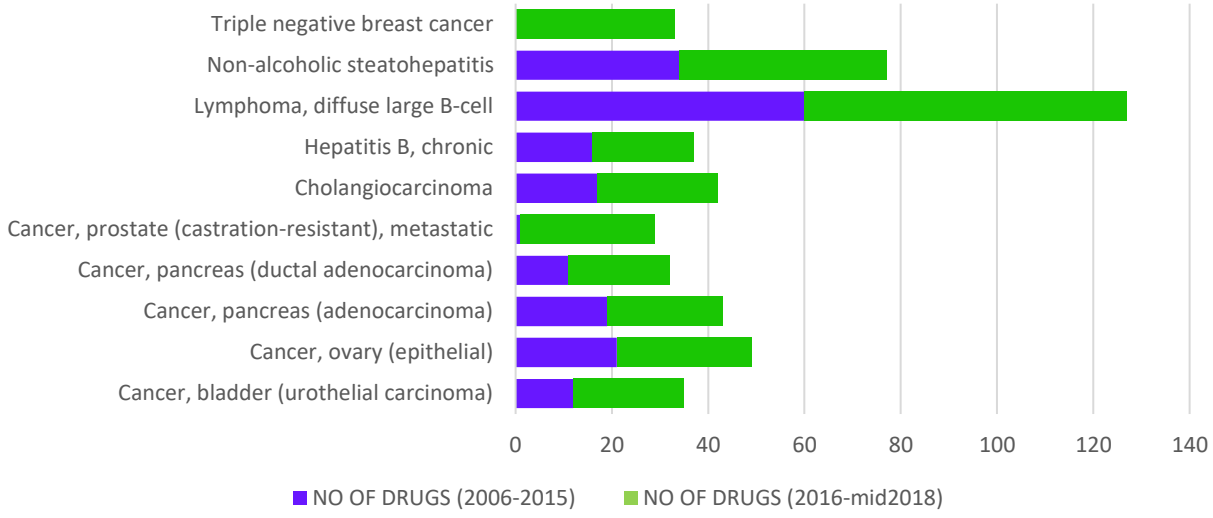
Methodology for Disease Counts: Statistics from use of the Integrity schema, and ranked by disease count for each top target for therapeutic category. ***Source:*** Integrity, a Cortellis Product, from Clarivate Analytics.

Diseases Under Investigation and Status of Activity for Developing Small Molecule Targets



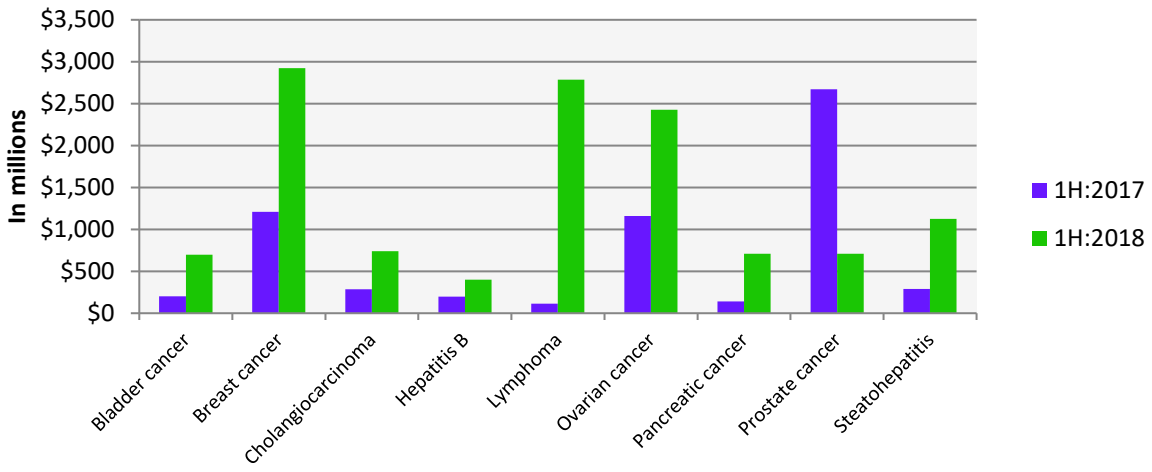
Methodology: Prioritization of the top disease under investigation against the top developing targets, with active vs. inactive drugs in the pipeline for those targets. ***Source:*** Integrity, a Cortellis Product, from Clarivate Analytics.

Emerging Disease Focus of New Drugs by Investigational Drug Count



Methodology: Diseases with more active investigational drugs in last 2.5 years compared to the previous 10 years, and > 10 active drugs in pipeline
Source: Integrity, a Cortellis Product, from Clarivate Analytics.

Biopharma Financings by Emerging Diseases



Methodology: Analysis of the news from BioWorld on financing in biotech by disease. ***Source:*** BioWorld, the daily biopharma news service from Clarivate Analytics.

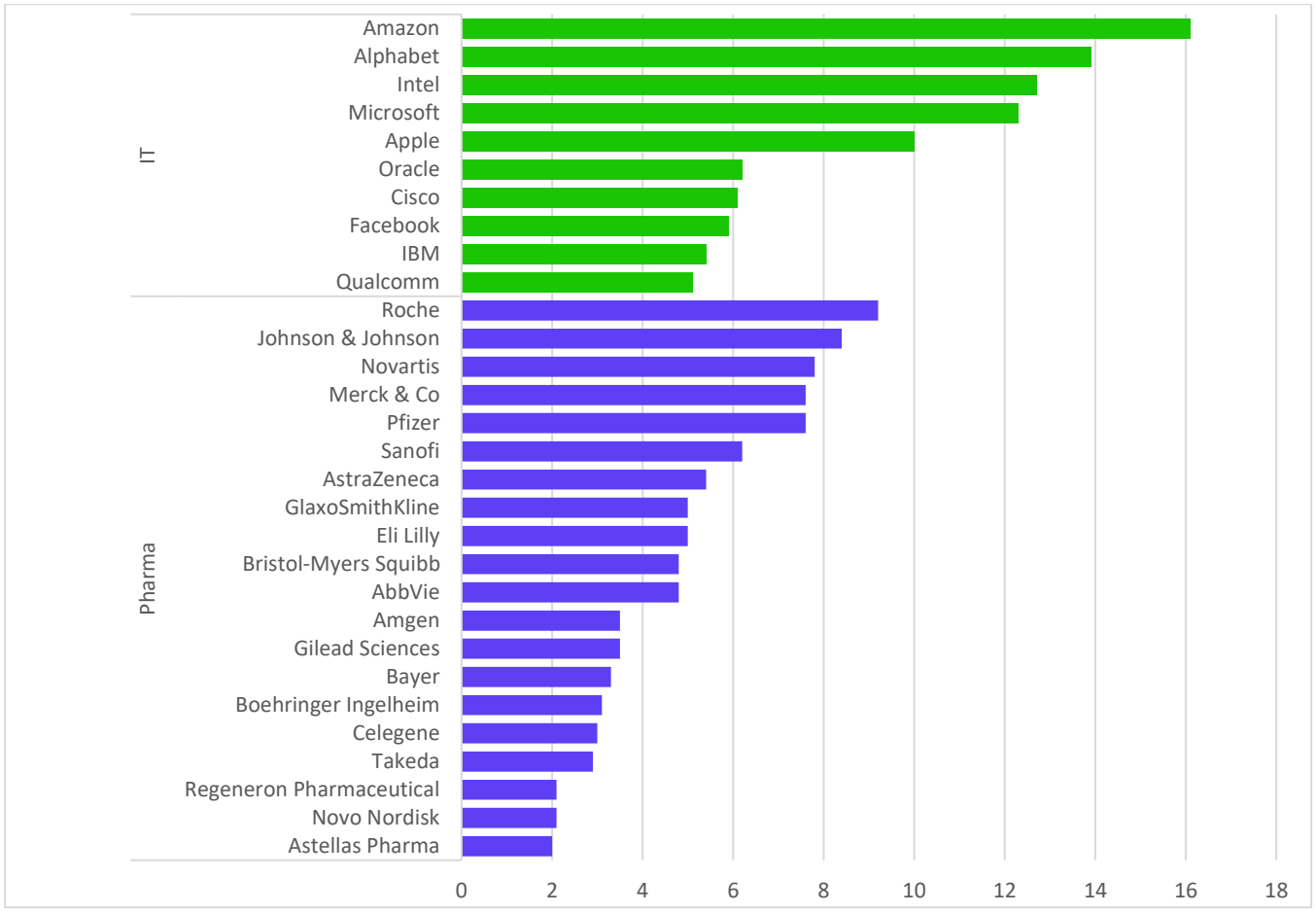
Key Messages

- Diffuse large B-cell lymphoma, NASH and triple negative breast cancer rank the highest by number of active drugs in development.
- NASH and large B-cell lymphoma met the definition, but did have several active drugs in development in the previous 10 years; however, the number of drugs in each disease has increased.
- Triple negative breast cancer and metastatic (castration-resistant) prostate cancer had the largest increase in investigational drugs vs. the prior 10 years
- The biotech financing for the emerging diseases has seen a strong increase in lymphoma, NASH and the other cancer types.
- While metastatic (castration-resistant) prostate cancer has seen high growth in drugs in the pipeline, biotech financing declined in the past year, suggesting a possible Biotech investment opportunity in the disease.

IT Innovation Trends and Developments

IT companies occupy a rising share of commercial R&D spending, with R&D budgets of the top five U.S. IT companies, Amazon, Alphabet (Google), Intel, Microsoft and Apple, all topping the leading Pharma R&D spender, Roche.

IT and Pharma R&D budgets



Methodology: 2017 R&D Spend ranking in IT and Biopharmaceutical industries ($B). ***Source:*** Factset, Evaluate Pharma

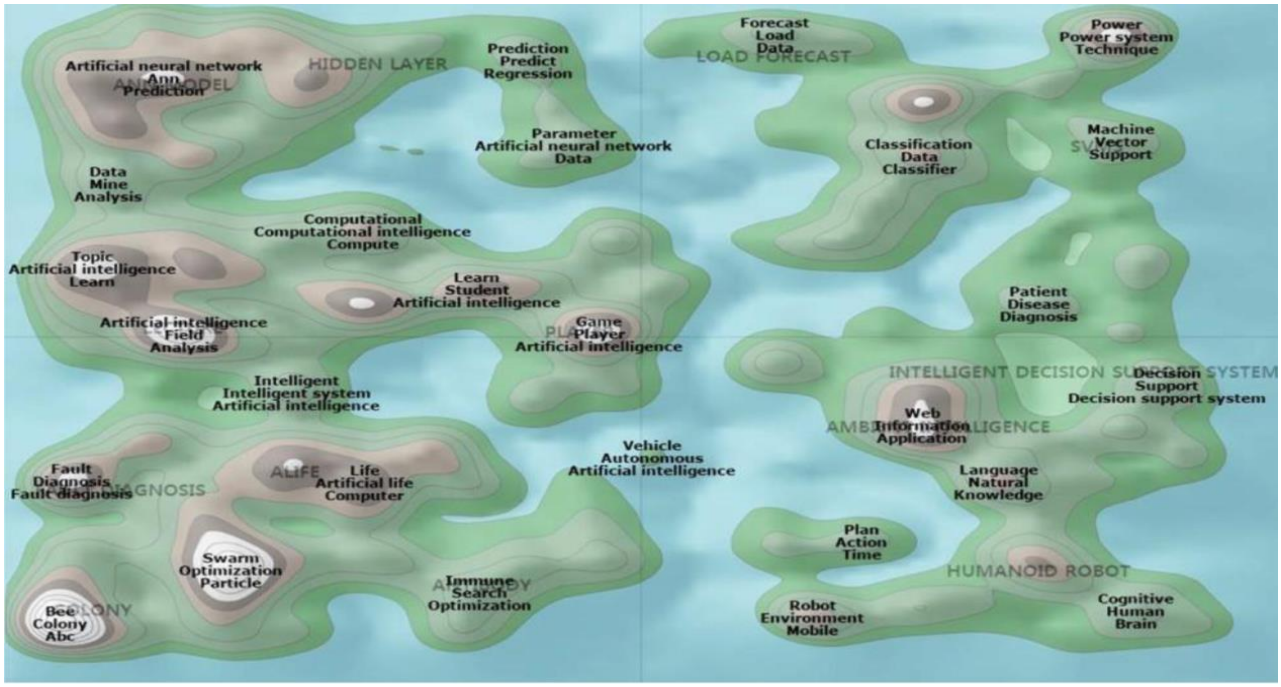
Not only do these IT companies market products for direct-to-consumer use as well as corporate R&D use, many also have initiatives aimed at becoming more embedded in the healthcare ecosystem, potentially complementing and/or competing for consumer adoption in health and disease management.

Algorithms – Artificial Intelligence (Machine Learning, Deep Learning, Natural Language Processing, Pattern Recognition) and Blockchain

Analysis of the 15,000 highly cited papers on artificial intelligence research shows hot areas of AI:

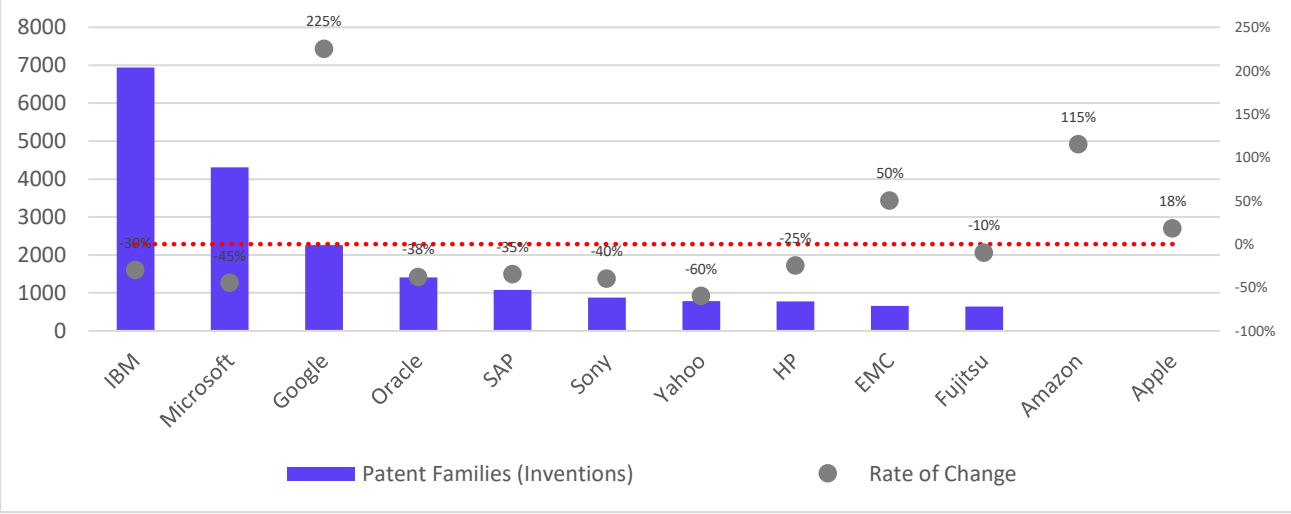
- Recognition – data classification or pattern recognition.
- Natural language processing or knowledge representation schemes.
- Intelligent robot autonomous driving
- Artificial life.
- Machine learning, artificial neural nets and fuzzy logic.

Artificial Intelligence Research Landscape



Methodology: Artificial intelligence research landscape (Top 15,000 highly cited papers from Web of Science Core Collection, 2008-2017). ***Source:*** Web of Science, from Clarivate Analytics.

Top 10 Patent Producing Machine-Learning Organizations (1996-2015)



Methodology: Machine-learning patents issued of the top 10 IT companies, 1996-2015. ***Source:*** Derwent World Patent Index, from Clarivate Analytics.

- Although Amazon and Apple did not meet the top 10 patent families issued within the period, **Google, Amazon, EMC and Apple have the highest growth rate** in patents issued for machine learning in the 10-year period.
- An analysis of IT Research Fronts (separate from the biomedical focus profiled in this report) shows a picture emerging of AI algorithms benefitting from **hybrids of previous mathematical techniques**. For example, Fuzzy Adaptive Neural Net is a hybrid of previous research on fuzzy logic, Neural net and Adaptive Systems, improving on the innovation of the previous learnings. Deepmind developed AlphaGo on the MCTS algorithm, which is a hybrid of Monte Carlo simulation developed in 1949 and Tree Search, developed in 1963. The program has now mastered Go and can beat the best players in the game.
- CIOs surveyed in the U.S. and Europe report a **doubling of spending on IT projects in AI** and networking equipment. ***Source*** Mary Meeker's Internet Trends 2018 report.
- Spending on cognitive and AI systems will reach $77.6 billion in 2022, more than three times the $24.0 billion forecast for this year. The compound annual growth rate **(CAGR) for the 2017-2022 forecast period is 37.3 percent**. ***Source*** IDC's Semiannual Cognitive AI Systems Spending Guide.
- Although **blockchain** is beginning to appear in the biomedical literature, only 31 papers covered the topic in our biomedical Research Fronts, and of those only one was highly cited, and that paper did not make the 1% most highly cited threshold.

Market Developments in Algorithms

- July 16, 2018 - AI Company Verge Genomics Snags $32 Million in Series A Funding. ***Source:*** Biospace
- 101 startups using AI in Drug Discovery. ***Source:*** BenchSci.
- **Exscientia announces 2 BioBuck style deals** with research funding and milestones to use its **AI-driven drug discovery** methods, first with Sanofi for $273 million in bi-specific molecules in metabolic disease, followed by a £33 million deal with GSK.
- A a new journal called Blockchain in Healthcare Today has started and includes useful guidance and review.
- April 12, 2018 – The FDA approves **Coralville LLC's autonomous Idx-DR system** for screening for diabetic retinopathy, an example of advances in **automated medical imaging**. ***Source:*** BioWorld, from Clarivate Analytics.
- March 12, 2018 – The FDA approves AI-based device developed by **Alivecor Inc., which turns an Apple watch into a personal electrocardiogram**. ***Source:*** BioWorld MedTech, from Clariviate Analytics.
- January 3, 2018 – The first **AI-based prescription digital therapy from Pear Therapeutics Inc. reSET** is announced. ***Source:*** BioWorld MedTech, from Clariviate Analytics.
- **Takeda Biopharmaceutical Co. Ltd. formed a multiyear agreement with Numerate Inc.,** to develop drugs for oncology, gastroenterology and central nervous system disorders using **Numerate's AI platform**. ***Source:*** BioWorld, from Clarivate Analytics.
- **AstraZeneca plc signed up Berg LLC**, of Boston, to use **Berg's Interrogative Biology AI platform** to help develop drugs to treat neurological disorders such as Parkinson's disease. ***Source:*** BioWorld, from Clarivate Analytics.
- **Recursion Biopharmaceuticals Inc., of Salt Lake City, announced a research collaboration agreement with Osaka, Japan-based Takeda** to search for drug candidates for rare diseases **using Recursion's AI architecture**. ***Source:*** BioWorld, from Clarivate Analytics.
- **Venture capital firm Menlo Ventures brought on Greg Yap as a partner to help dole out 15 percent of its $450 million Menlo XIV fund** to companies working at the intersection of computers and life sciences. ***Source:*** BioWorld, from Clarivate Analytics.

Both Machine Learning and NLP are moving into the developing phase across the R&D value chain with NLP more advanced due to the less predictive nature of the technology. NLP has been used for several years in pharmacovigilance monitoring of the literature and regulatory documents, real world metadata extraction, and monitoring adverse events from social media. Machine learning is being tested and beginning to impact decision-support across the R&D value chain today, with great promise for its predictive value. We will undoubtedly test those limits and engage in debate about the impact of machine learning and AI in the years ahead.

Enterprise Computing Adoption of Cloud-based Platforms

Over the last half century enterprise computing has come full circle, from centralized mainframe-hosted computing of the 1960s-1980s, through the decentralized personal computer revolution of the 1980s-2000s, and now back towards hosted infrastructure and applications. This time, however, the hosting is more flexible and cost-effective, with the leading Amazon Web Services, Microsoft Azure and Google Cloud platforms all offering on-demand compute and storage capacity, simplicity (remote file storage) synced to mobile or desktop operating systems, low-cost, open-source software infrastructure, hosted office productivity solutions (word processing, spreadsheets, presentation tools), GPU-based options for computer-intesive machine learning and many other flexible services. Implementations also come in a variety of forms, from public, to private, and hybrid public-private. And while Pharma has been relatively slow to adopt compared with other industries, the wide-scale adoption and transition to cloud-based R&D IT seems inevitable given the cost equation, collaboration value and overall flexibility.

- AWS per instance **price has dropped 300%** 2008-2018. ***Source*** Mary Meeker's Internet Trends 2018 report.
- Cloud-computing revenues from AWS, Microsoft and Google are **increasing 50% YOY**. ***Source*** Mary Meeker's Internet Trends 2018 report.
- Cloud infrastructure players with dominant share are Amazon Web Services, Microsoft Azure and Google Cloud, with the application implementation players including Accenture, Cloud Biopharmaceuticals, Dassault, IBM, SAS Institute, Tata Consultancy and Wuxi AppTec. Expect to see more here.

Market Developments

- September 17, 2018 – Merck, Accenture, Amazon Web Services announce collaboration to develop a cloud-based informatics research platform for drug discovery. This development would complement Accenture's Life Sciences Research Cloud already deployed for clinical applications.
- November 3, 2017 – LifeImage announced use of Google Cloud for population health and precision medicine for its medical imaging network.

Mobile Applications and Digital Health

Mobile medical applications and mobile applications in R&D are not widespread yet, but they are now beginning to appear as Pharma adopts a more enterprenurial information technology edge, and it's exciting to think about how Pharma and IT resources may be able to change dramatically the patient experience through advancing the combination of mobile apps, smart diagnostics, AI, cloud-based platforms and drugs all working in harmony.

Digital health continues to attract growing investment, research, and the collection of government approved solutions and the adoption in clinical trials is trending upward.

- **Large Pharma establishing independent incubators / accelerators** to work with technology start ups: AbbVie FT2 and Matter, Bayer iHub, GSK innovation group, J&J JLabs, Merck M2i2, Novartis joint fund with Qualcomm, Pfizer Healthcare Hub, Takeda Digital Accelerator.
- **Growing number of patents**, more than 15K annually. China and U.S. leading.
- In 2017, **$11.5 billion invested** in digital health start-ups (approximately 800 deals), up by 40% vs 2016.
- **FDA cleared 51** "connected health apps and devices" in 2017, up from 36 in 2016.
- Little **Estonia** has become a potential **model for digital health,** with 95 percent of all health data in Estonia digitized, 99 percent of prescriptions are digital and there is 100 percent electronic billing. By 2022, as many as 500,000 people will have records combining EHRs and genotypes. Yet, Estonia spends only 6% of GDP on healthcare. ***Source:*** BioWorld, from Clarivate Analytics.
- 21 out of the 25 top Biopharmaceutical companies have **established a dedicated digital health team**. ***Source***: ZS.
- 60% of Pharma companies are already **using digital health in clinical trials**, with 97% planning implementation by 2021. ***Source***: Clarivate primary market research.
- In Nov 2017 **NHS launched a digital-first mobile app** health service, "GP at Hand" from Babylon Health.

In addition to mobile medical apps for patients, mobile computing in R&D is also expanding. Mobile applications and digitization of workflows is especially apparent in teams that require the latest news and competitive intelligence anywhere, and with functions such as Regulatory Quality teams that are performing and supporting audit functions across site to ensure regulatory compliance.

Market Developments

- September 11, 2018 - The U.S. FDA grants two de novo classification requests for mobile applications to be used with the Apple Watch. Both devices are **software-only mobile medical applications** for identifying irregular heart rhythms.
- June 21, 2018 – The U.S. FDA approves first continuous glucose monitoring system with **implantable glucose sensor and compatible mobile app** for adults with diabetes.
- March 19, 2018 – The FDA approves Medtronic's Guardian Connect, a continuous glucose monitoring system, that works with Sugar.IQ. Portending to potential issues with such mobile apps, Medtronic sends physicians in July 2018 a letter warning of possible connectivity issues.
- February 2018 – Medtronic, the top innovator by issued patents in medical devices, launches its AI-based Sugar.IQ **diabetes management app**, which is powered by IBM Watson Health. Watson is expected to provide capabilities to the app that **evaluates user's blood sugar levels** in response to variables such as food intake and insulin dosing.
- In November 2017 the US. FDA approves the first drug with an **embedded sensor, Abilify MyCite,** which communicates with a **wearable patch and mobile application** to track patient drug compliance, which communicates with a physician web portal.

Innovation Profiling of the Research Fronts

The biomedical Research Fronts used in this analysis were analyzed in the following charts to identify patterns of research activity based on the impact of the research using bibliometric measures. The Research Fronts methodology is described in the Methodology section, the key point to keep in mind is that Research Fronts only represent the top 1% of highly cited research, in this case in the biomedical and clinical sciences. Two categories of Research Fronts have been included in the analysis: 1) disease research, diagnostics and drugs from therapeutic modalities; and 2) technologies, methods and techniques which we refer to herein as "R&D tools."

Featured Innovations

Translation of Innovation to Pharma R&D Impact →

Emerging	Developing	Contributing
3D Printing	Cryo-electron microscopy (CryoTEM)	Exome-Wide Association Study in NASH
Adverse Outcome Pathways	Nanosensors	Comprehensive Genomic Profiling in Triple Negative Breast Cancer
Post-transcriptional RNA modification (circular RNA and RNA methylation)	Microbiome Gut-Brain Axis	EGFR and ALK receptor Inhibitors in in multiple cancers
	NAFLD/NASH disease onset and progression research	JAK-STAT pathway, gene variants, and JAK inhibitors in myeloproliferative neoplasms
	Brain Imaging (TAU PET and Gadolinium-based contrast)	PD-1/PD-L1 expression inhibitors in multiple cancers

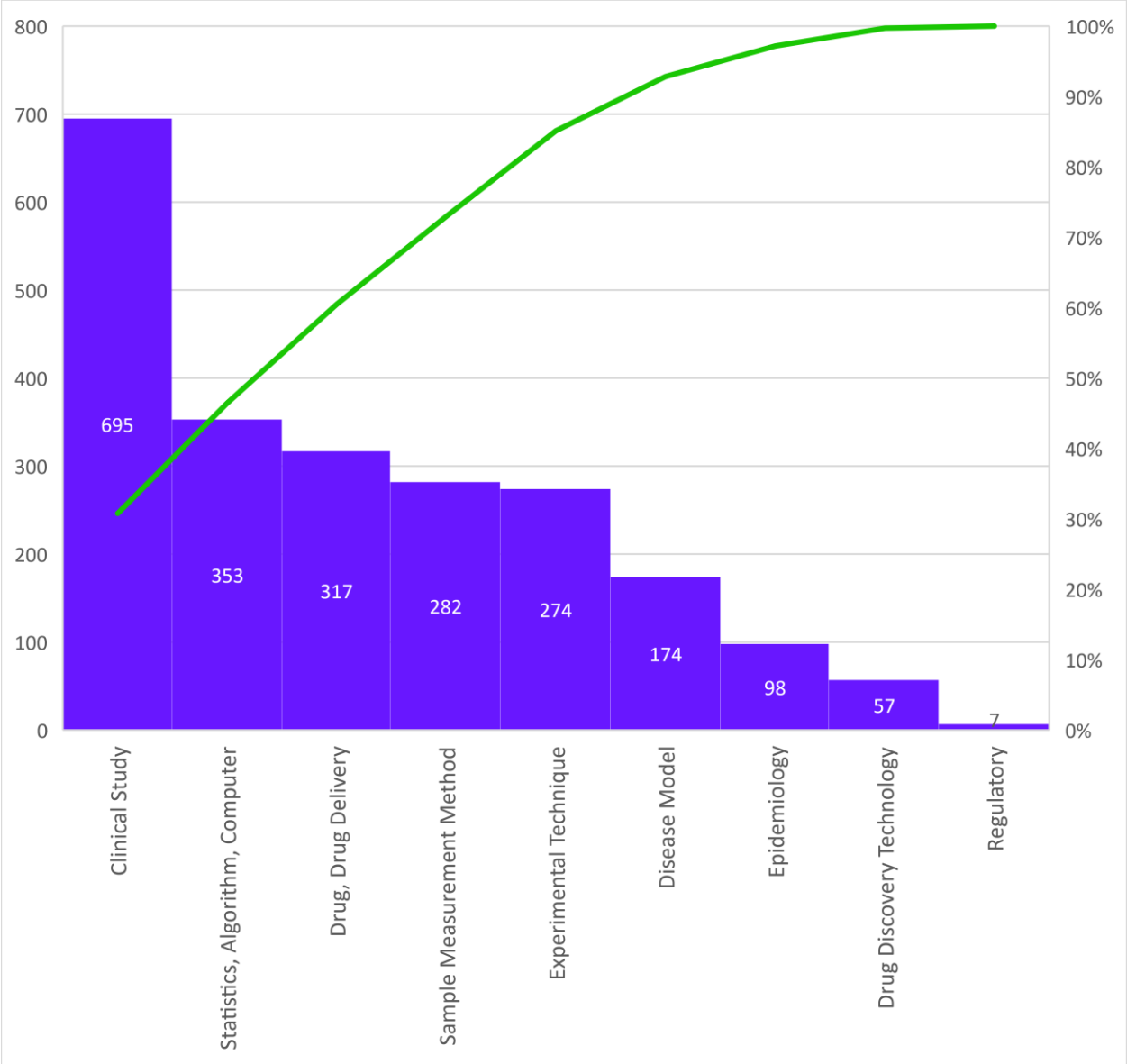
Research Front Type: Purple = Technology, Method, Technique, Green = Disease, Diagnostic, Drugs from Therapeutic Modalities

This report profiles the R&D tool innovations featured prominently in the Research Fronts. Four large clusters of research activity from the therapeutic modalities tree of MeSH were observed, including:

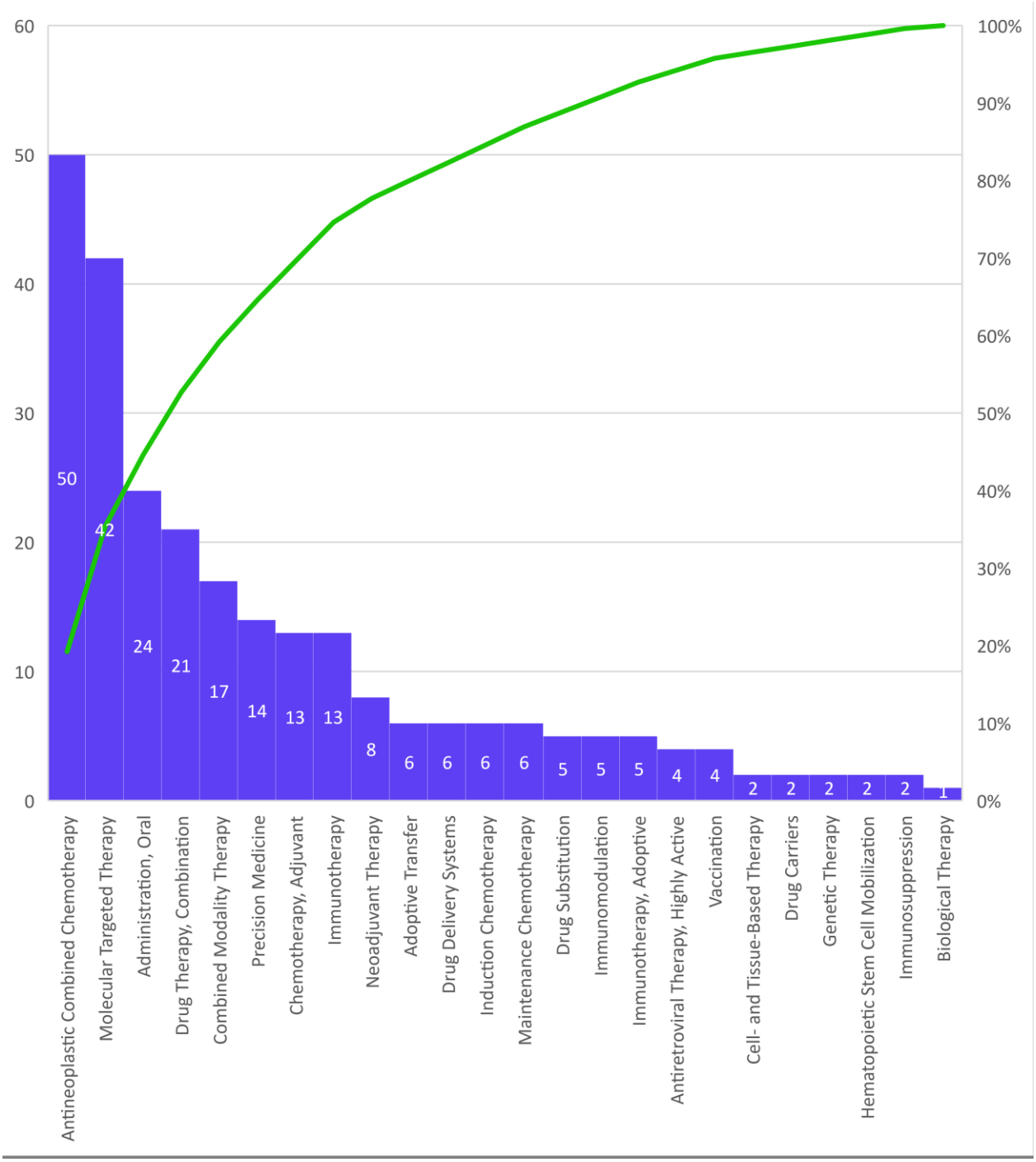
- 117 papers from studies of EGFR, ALK, JAK-STAT and PD-1, PD-L1 in **cancers.**
- 84 papers from TAU PET and Gadolinium-based contrast agents for **brain imaging** studies in Alzheimer's, traumatic brain injury, dementia and other psychiatric disorders.
- 81 papers investigating the role of circular RNA and methylated RNA, and in general the importance of **post-transcriptional RNA modification** related to biological function, health and disease.
- 44 papers studying the pathology of nonalcoholic fatty liver disease (**NAFLD**) and its relationship to non-alcoholic steatohepatitis (**NASH**), as well as investigational drugs.

To understand what is contained within the Research Fronts without reading all of the articles, the following analysis shows the hot topics in the top 1% of the most highly cited biomedical research literature.

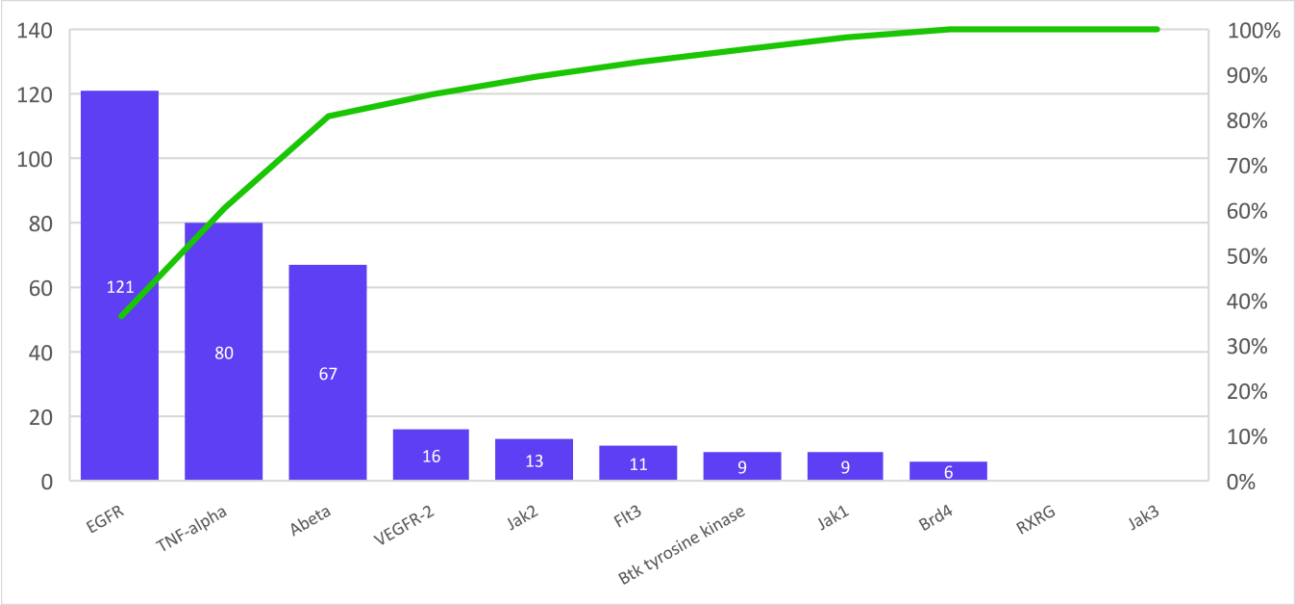
The Overall Profile of the Research Front Topics



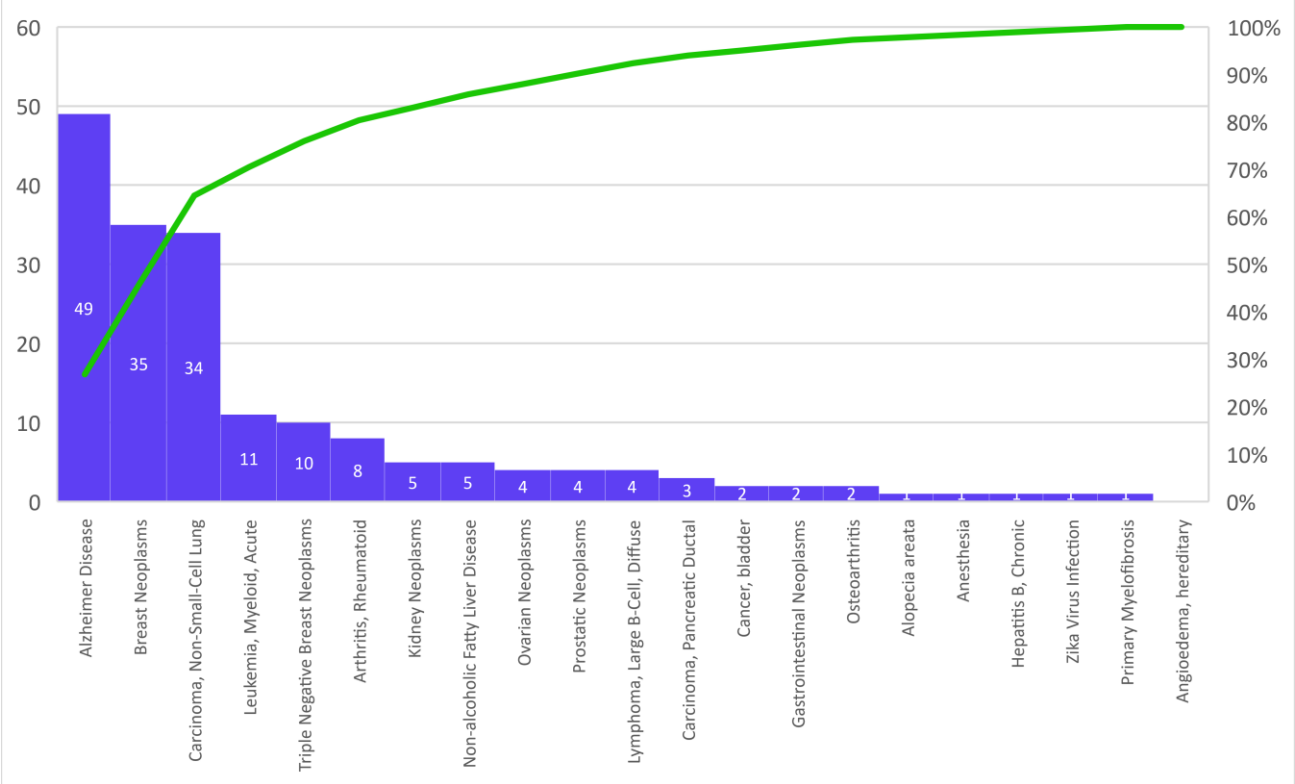
Therapeutic Category Occurrences in the Research Fronts



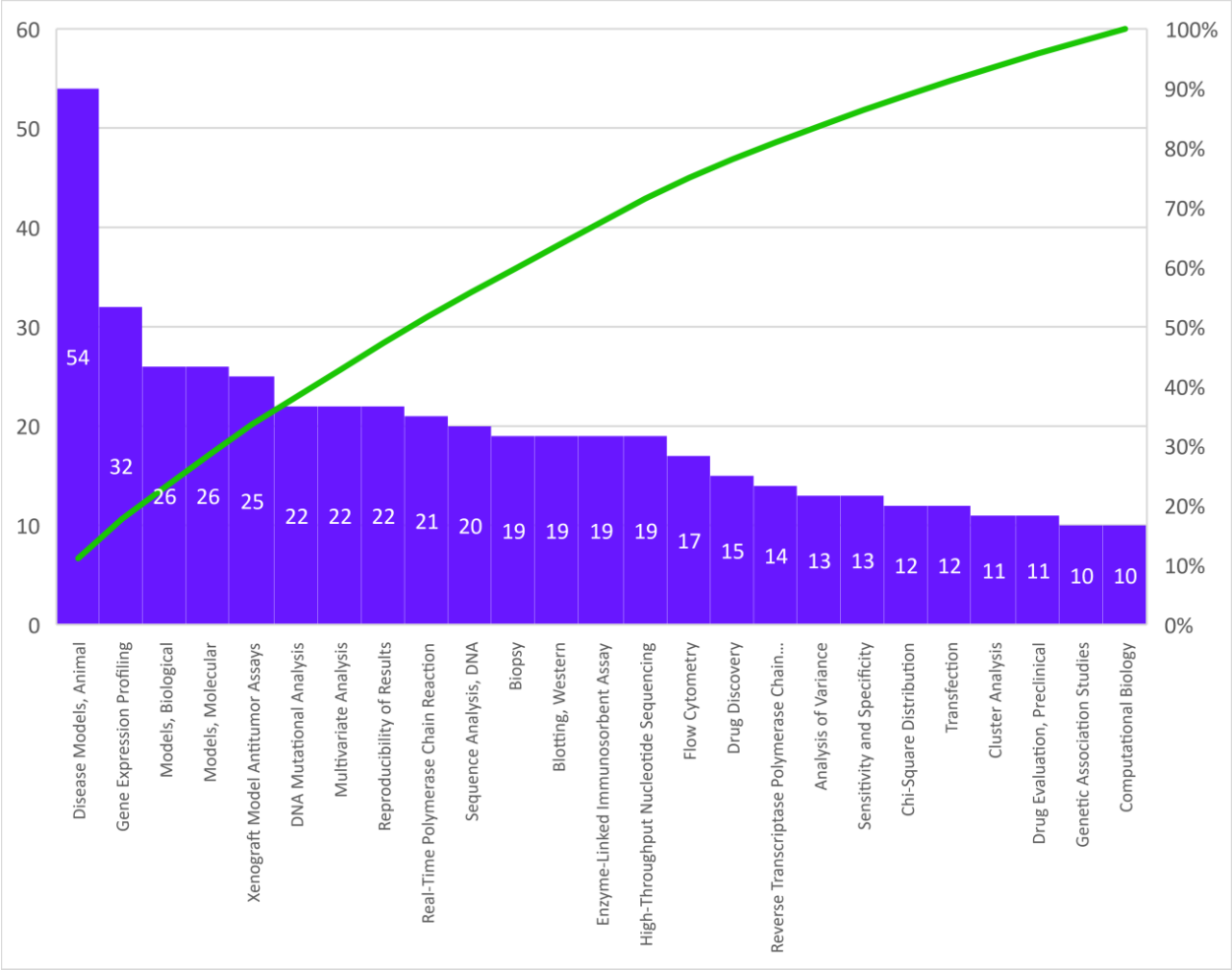
Top Developing Small Molecule Drug Target Occurrences in Research Fronts



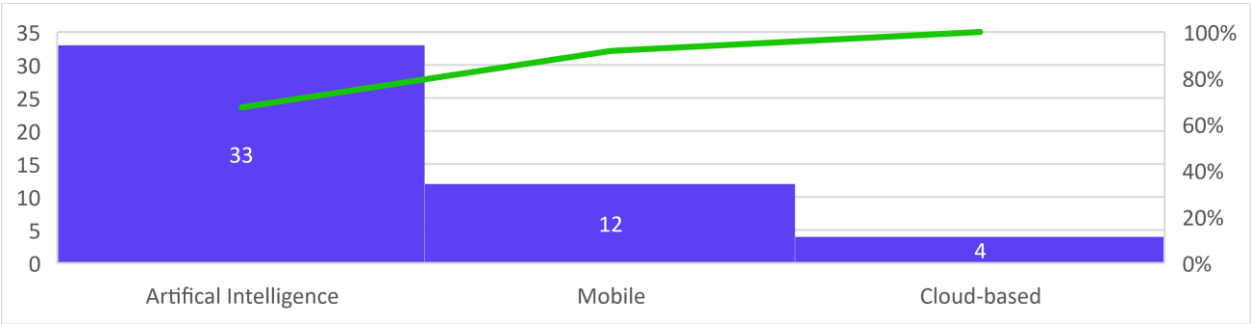
Top Disease Occurrences in Research Fronts



Top 'R&D Tools' Technology Occurrences in Research Fronts with 10 or More Occurrences



Information Technology Occurrences in Research Fronts



Methodology in all Research Front Occurrence charts: Top occurrences of keywords appearing in the Research Fronts by type of topic, using MeSH terms, plotted with a Pareto chart. Source: Web of Science, Research Fronts, Emerging Science Citation Index, from Clarivate Analytics.

Key Messages

- The top technologies abstracted from individual keywords present are **models**, comprising disease models, biological models and gene knock-down models.
- **Computational methods** are evident in computational biology, molecular modeling, gene-protein-molecule databases, and a variety of statistical analysis terms. This category was second only to clinical studies, and had double the occurrence of disease model topics.
- **Genetic analysis** features in a variety of methods, real-time PCR, GWAS, RNA sequence analysis, etc.
- Alzheimer's, non-small cell lung cancer and breast neoplasms dominate the Research Fronts, with acute myeloid leukemia, triple negative breast cancer and rheumatoid arthritis rounding out the disease results, all of the above comprising the top 80% of disease focus.
- EGFR, TNFa, Abeta and PD-1/PD-L1 are the top targets of focus in Research Fronts

Featured Innovations in Pharma R&D from Research Fronts

Using the bibliometrics analyses and through review of the results, we have selected the following featured innovations for their potential application in Life Sciences and we have classified those based on their maturity in application to Life Sciences.

Definitions: **Innovation Classification** is a qualitative measure of maturity; **Core Paper Strength** is the score above the AVG number of cited core papers contained within each Research Fronts; **Recency** is the mean date of all papers contained within each Research Front; **Interdisciplinarity** is a score representing the number of disciplines in the co-citations; **Funding** is the number of papers cited in funding acknowledgements and **Leading Countries** are the unique occurrences of the top-ranked countries of the institutions that are publishing papers.

Number	Innovation from Research Front	Innovation Classification	Core Paper Strength	Recency	Inter-disciplinarity	Funding	Leading Country Institutions (left to right)
1	**3D Printing for Tissue and Organ Fabrication**	Emerging	◕	◔	◕	◑	U.S., Saudi Arabia
2	**Adverse Outcomes Pathways**	Emerging	◔	◕	◑	◔	U.S., Italy
3	**Cryo-electron microscopy**	Developing	●	◑	◑	◑	U.K., Germany, U.S.
4	**Nanomaterial Sensors**	Developing	●	◑	◕	●	China
5	**Microbiome Gut-Brain Axis**	Developing	●	◑	◕	◑	Ireland, Canada
6	**Exome Wide Association Study in NASH**	Contributing	◔	◔	◑	◔	Italy, U.S.
7	**Genomic Expression Profiling in Triple Negative Breast Cancer**	Contributing	◔	◔	◑	◑	U.S.

Emerging Innovations

1. 3D Printing for Tissue and Organ Fabrication			
Why Selected	Highly ranked Research Front based on number of citations and potential for technologies to be applied both as therapies and drug discovery tools for microfluidics and extracellular matrix structures.		
What is Innovation Potential	3D bioprinting uses 3D printing to combine cells, growth factors and biomaterials to fabricate biomedical parts that imitate natural tissue characteristics. Generally, 3D bioprinting uses the layer-by-layer method to deposit materials known as bioinks to create tissue-like structures that are later used in medical and tissue engineering fields. Bioprinting covers a broad range of biomaterials. Currently, bioprinting can be used to print tissues and organs to help research new drugs. However, emerging innovations include bioprinting of cells and extracellular matrix deposited into a 3D gel layer by layer to produce the desired tissue or organ to be used as a new therapeutic modality.		
# of Core Papers in Research Front	35		
Mean Publication Year	2014.3		
Top Country Contributors	**Rank**	**Contributor (Publishing Institution Countries)**	
	1	U.S.	
	2	Saudi Arabia	
	3	South Korea, Netherlands	
Top Core Paper Funders (and Papers)	**Rank**	**Core Funder**	**Papers**
	1	National Institutes of Health (NIH) – U.S.	17
	2	National Science Foundation	11
	3	European Union	6

Featured Core Paper: Strategies and Molecular Design Criteria for 3D Printable Hydrogels

2. Adverse Outcome Pathways			
Why Selected	Selected for the recency of the published articles in the Research Fronts and the application to drug development as a new predictive toxicology approach.		
What is Innovation Potential	An adverse outcome pathway (AOP) is structured representation of biological events leading to adverse effects and is considered relevant to risk assessment. The AOP links, in a linear way, existing knowledge along one or more series of causally connected key events between two points — a molecular initiating event and an adverse outcome that occur at a level of biological organization relevant to risk assessment. The linkage between the events is described by key event relationships that describe the causal relationships between the key events.		
# of Core Papers in Research Front	7		
Mean Publication Year	2015.6		
Top Country Contributors	**Rank**	**Contributor (Publishing Institution Countries)**	
	1	U.S.	
	2	Italy	
	3	United Kingdom, Canada, Germany, Italy, Netherlands, Bulgaria, Ireland, Finland, Austria, Switzerland, Norway, France, Belgium	
Top Core Paper Funders (and Papers)	**Rank**	**Core Funder**	**Papers**
	1	U.S. Environmental Protection Agency	3
	2	American Chemistry Council, BioDetection Systems, Environment Canada, Human Toxicology Project Consortium, International Life Sciences Institute – Health and Environmental Science Institute, Research Council of Norway, U.S. Army Engineer Research and Development Center	2

Featured Core Paper: How Adverse Outcome Pathways Can Aid the Development and Use of Computational Prediction Models for Regulatory Toxicology

Developing Innovations

3. Cryo-Electron Microscopy (also known as CryoEM)			
Why Selected	Highest number of core papers in Research Fronts		
What is Innovation Potential	Cryoelectron microscopy is a method for imaging frozen-hydrated cellular and tissue specimens at cryogenic temperatures by electron microscopy. Specimens remain in their native state without the need for dyes or fixatives, allowing the study of fine cellular structures, viruses and protein complexes at molecular resolution. It's a tool comparable to and potentially superior to traditional x-ray crystallography techniques, the past workhorse in structural biology.		
# of Core Papers in Research Front	47		
Mean Publication Year	2015.0		
Top Country Contributors	**Rank**	**Contributor (Publishing Institution Countries)**	
	1	United Kingdom	
	2	Germany	
	3	U.S.	
Top Core Paper Funders (and Papers)	**Rank**	**Core Funder**	**Papers**
	1	National Institutes of Health (NIH) – U.S.	21
	2	Medical Research Council - UK	12
	3	Wellcome Trust	6

Featured Core Papers: The development of cryo-EM into a mainstream structural biology technique; Breaking Cryo-EM Resolution Barriers to Facilitate Drug Discovery

4. Nanosensors	
Why Selected	Ranked second in cited research in Research Fronts, and the promise of the technology for rapid diagnostic in multiple indications and as a drug delivery technology.
What is Innovation Potential	Nanosensors are sensors with active elements that include nanomaterials. Nanomaterial-based sensors have several benefits in sensitivity and specificity over sensors made from traditional materials. Nanosensors can have increased specificity because they operate at a similar scale as natural biological processes, allowing functionalization with chemical and biological

	molecules, with recognition events that cause detectable physical changes.		
# of Core Papers in Research Front	45		
Mean Publication Year	2015.1		
Top Country Contributors	**Rank**	**Contributor (Publishing Institution Countries)**	
	1	China	
	2	Pakistan	
	3	U.S.	
Top Core Paper Funders (and Papers)	**Rank**	**Core Funder**	**Papers**
	1	National Natural Science Foundation of China	44
	2	China Postdoctoral Science Foundation	20
	3	Economical Forest Cultivation and Utilization of Collaborative Innovation Center in Hunan Province	19

Featured Core Paper: Current Progress in Gene Delivery Technology Based on Chemical Methods and Nano-carriers

5. Microbiome Gut-Brain Axis		
Why Selected	Ranked third in cited research in Research Fronts, and potential role the microbiome may play in effecting disease onset, progression, drug absorption and response to therapy.	
What is Innovation Potential	The gut–brain axis is the biochemical signaling that takes place between the gastrointestinal tract (GI tract) and the central nervous system (CNS). The term "gut–brain axis" is occasionally used to refer to the role of the gut flora in the interplay as well, whereas the term "microbiome–gut–brain axis" explicitly includes the role of gut flora in the biochemical signaling events that take place between the GI tract and CNS.	
# of Core Papers in Research Front	43	
Mean Publication Year	2014.9	
Top Country Contributors	**Rank**	**Contributor (Publishing Institution Countries)**
	1	Ireland

	2	Canada	
	3	U.S.	
Top Core Paper Funders (and Papers)	**Rank**	**Core Funder**	**Papers**
	1	Science Foundation Ireland	11
	2	National Institutes of Health (NIH) - U.S.	9
	3	European Union	6

Featured Core Paper: Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the hosts metabolism

Contributing Innovations

6. Exome-Wide Association Study in NASH			
Why Selected	An individual paper within the broader Research Front related to genetic variants increasing risk of NAFLD and NASH, with 252 citations.		
What is Innovation Potential	A method for studying disease-gene associations using whole exome sequencing, an alternative method to gene-disease association studies by SNP-based GWAS methods. It is estimated that 85% of disease-related gene variants exist in the human exome, even though it is a small portion of the total human genome. This method substantially lowers costs in gene-disease association studies over large specimen collections.		
# of Core Papers in Research Front	11		
Mean Publication Year	2014.5		
Top Country Contributors	**Rank**	**Contributor (Publishing Institution Countries)**	
	1	Italy, U.S., Sweden	
Top Core Paper Funders (and Papers)	**Rank**	**Core Funder**	**Papers**

	1	ALF/LUA, Academy of Finland, Associazione Malattie Metaboliche del Fegato ONLUS, Clinical Senior Lectureship Award from the Higher Education Funding Council of England, National Institutes of Health (NIH) – U.S, Novonordisk Foundation Excellence Grant in Endocrinology, Ricerca Corrente Condazione Ca Grande IRCCS Policlinico of Milan, Swedish Heart-Lung Foundation, Swedish Research Council	2

Featured Core Paper: Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease

7. Comprehensive Genomic Profiling in Triple Negative Breast Cancer			
Why Selected	An individual paper within the overall Research Front related to refinement of triple negative breast cancer molecular subtypes.		
What is Innovation Potential	This method of genetic profiling uses Next Generation Sequencing to identify different types of genetic alterations across hundreds of genes known to drive cancer. It is applicable for use across any type of cancer. Using comprehensive genomic profiling, it is possible to map an individual's unique genomic profile across all four types of genetic alteration (base substitution, insertions/deletions, copy number variation and rearrangements), spanning several hundred different types of mutations. These insights provide invaluable information to physicians which can help them determine the best possible treatment for each patient. Likewise, the integration of these new data sources on a large-scale aid's discovery of more targeted cancer treatments, in this case for triple negative breast cancer patient segments.		
# of Core Papers in Research Front	7		
Mean Publication Year	2014.3		
Top Country Contributors	**Rank**	**Contributor (Publishing Institution Countries)**	
	1	U.S.	
Top Core Paper Funders (and Papers)	**Rank**	**Core Funder**	**Papers**
	1	Susan G. Komen Breast Cancer Foundation	3
	2	National Institutes of Health (NIH) – U.S.	2
	3	AMC Cancer Fund	1

Featured Core Paper: Comprehensive Genomic Analysis Identifies Novel Subtypes and Targets of Triple-Negative Breast Cancer

Regulatory Perspectives on the Featured Innovations and Information Technology Topics

3D Bioprinting Regulatory Topics

FDA:

1. The FDA plans to review the regulatory issues related to the bioprinting of biological, cellular and tissue-based products in order to determine whether additional guidance is needed beyond the recently released regulatory framework on regenerative medicine medical products.
2. In November 2017, the FDA announced comprehensive regenerative medicine policy framework with two new final guidance documents and two draft guidance documents
    a. Final Guidance 1: provides greater clarity around when cell and tissue-based products would be excepted from the established regulations if they are removed from and implanted into the same individual within the same surgical procedure and remain in their original form.
    b. Final Guidance 2: helps stakeholders better understand how existing regulatory criteria apply to their products by clarifying how the agency interprets the existing regulatory definitions "minimal manipulation" and "homologous use."
    c. Draft Guidance 1: building off the regenerative medicine provisions in the 21st Century Cures Act, addresses how the FDA intends to simplify and streamline its application of the regulatory requirements for devices used in the recovery, isolation and delivery of regenerative medicine advanced therapies (RMATs), including combination products. The guidance specifies that devices intended for use with a specific RMAT may, together with the RMAT, be considered to comprise a combination product.
    d. Draft Guidance 2: describes the expedited programs that may be available to sponsors of regenerative medicine therapies, including the new Regenerative Medicine Advanced Therapy (RMAT) designation created by the 21st Century Cures Act, Priority Review and Accelerated Approval.

South Korea:

3. In December 2016 South Korea published two guidelines:
    a. Guideline 1: to provide information on safety and performance testing of biodegradable scaffolds for tissue regeneration
    b. Guideline 2: blood vessel regeneration that were manufactured with a 3-D printer

Topic	Link
1.	https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm585345.htm (FDA)
2a.	https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM419926.pdf
2b.	https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585403.pdf
2c.	https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585417.pdf
2d.	https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585414.pdf
3a.	https://www.cortellis.com/intelligence/report/ri/regulatory/238579
3b.	https://www.cortellis.com/intelligence/report/ri/regulatory/238579

AOP Adverse Outcome Pathway Regulatory Topics

NIEHS:

1. In 2017, the National Institute of Environmental Health Sciences (NIEHS) Superfund Research Program (SRP) held a series of three seminars, focused on adverse outcome pathways (AOPs).

OECD (Organization for Economic Cooperation and Development):

2. OECD supports international standardization of testing methods to assess substance toxicity. In this role, the OECD is actively supporting AOP development.
3. In July 2017, the OECD published a revised guidance document on developing and assessing adverse outcome pathways.
4. In addition, OECD published a User's Handbook supplement to the guidance document for developing and assessing adverse outcome pathways.

Topic	Link
1.	https://www.niehs.nih.gov/research/supported/centers/srp/events/riskelearning/aop/index.cfm
2.	http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm
3.	http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2013)6&doclanguage=en
4.	https://www.oecd-ilibrary.org/environment/users-handbook-supplement-to-the-guidance-document-for-developing-and-assessing-adverse-outcome-pathways_5jlv1m9d1g32-en

Cryo-EM Regulatory Topics

1. U.S. FDA

In FY2016, the FDA developed a collaborative research program with the FDA Advanced Characterization Facility (ACF) at the Office of Science and Engineering Laboratories (OSEL) and the Center for Devices and Radiological Health (CDRH) through which physicochemical characterization of several emulsion and liposome drug products are being conducted. Advanced analytical methods such as cryo-electron microscopy (cryo-EM) enable FDA researchers to image these nano-sized drugs in a frozen hydrated state to better understand their unique structural properties. Collaborative projects in this area advance the FDA's understanding of the use of nanotechnology in developing generic drug products. Despite the increasing number of nano-sized products on the market, compendial or bio-relevant *in vitro* drug release assays for these complex dosage forms are in short supply. This shortage, along with complexities in physicochemical properties, pose a significant challenge to science-based policy development as well as the regulatory review of this product category.

Topic	Link
1	https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm549163.htm

Microbiome Regulatory Topics

1. The U.S. **FDA** held a workshop on Sept. 18 in Rockville, MD, titled "Science and Regulation of Live Microbiome-Based Products Used to Prevent, Treat, or Cure Diseases in Humans."
   - The purpose of the public workshop was to exchange information with the scientific community about the clinical, manufacturing and regulatory considerations associated with live microbiome-based products, when administered to prevent, treat or cure a disease or condition in humans. The public workshop brought together government agencies, academia, industry and other stakeholders involved in research, development and regulation of live microbiome-based products for such uses.
2. In June 2018, National Center for Toxicological Research (NCTR) scientists presented at The Gut Microbiome: Markers of Human Health, Drug Efficacy and Xenobiotic Toxicity workshop convened by the Health and Environmental Sciences Institute (HESI).
3. The FDA in parallel with other government agencies developed a working group tasked to develop a five-year interagency strategic plan for microbiome research.

Topic	Link
1	https://www.eventbrite.com/e/science-and-regulation-of-live-microbiome-based-products-used-to-prevent-treat-or-cure-diseases-in-tickets-44649072578
2	http://hesiglobal.org/event/the-gut-microbiome-workshop/
3	https://science.energy.gov/~/media/ber/pdf/workshop%20reports/Interagency_Microbiome_Strategic_Plan_FY2018-2022.pdf

Nanotechnology (Nanosensors) Regulatory Topics

1. U.S. FDA:

In 2007, the FDA created a taskforce to determine regulatory approaches that would enable the continued development of innovative, safe and effective FDA-regulated products that use nanoscale materials.

From that task force several guidelines were published covering safety in cosmetics, food and animals. The final guidance below describes FDA's current thinking on determining whether FDA-regulated products involve the application of nanotechnology. The guidance is intended for manufacturers, suppliers, importers and other stakeholders.

In December 2017, the FDA published a draft guidance on the development of human drug products, including those that are biological products, in which a nanomaterial (as explained in this section) is present in the finished dosage form.

2. NCTR:

The National Center for Toxicological Research (NCTR) recently held a subcommittee review of cutting-edge technology being conducted at the FDA.

3. EMA:

The EMA provides guidance in four areas: block co-polymer micelles, iron-oxide, liposomal formulations, and coating for nanotechnology-incorporating products.

4. The Ministry of Health, Labour and Welfare (Japan) and EMA

In 2013, MHLW and EMA developed a working group to consider the regulatory requirements for nanomedicine. The working group published a paper on the development of block copolymer micelle medicinal products.

5. Therapeutic Goods Administration (Australia)

In October 2016, the TGA published a presentation on the regulation of nanomedicines.

Topic	Link
1a.FDA Final Guidance on Nanotechnology	https://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm
1b. FDA Draft Guidance	https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM588857.pdf
2. NCTR	https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/ToxicologicalResearch/UCM595579.pdf
3. EMA	http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2017/12/WC500240112.pdf
4. MHLW and EMA	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/02/WC500138390.pdf
5. TGA:	https://www.tga.gov.au/sites/default/files/tga-presentation-nanoparticle-therapeutics-2016-20-october-2016.pdf

Information Technology

In addition to the regulatory perspectives of the seven profiled innovations, the following regulatory topics in information technology are included to provide a perspective on the regulatory trends related to artificial intelligence, cloud-based platforms and mobile medical applications.

Artificial intelligence (Machine Learning, Natural Language Processing) Regulatory Topics

U.S. FDA

1. 2018: The FDA approves 2 artificial intelligence products through the de novo premarket review pathway
   a. The first approval was for IDx-DR, a software program that uses an artificial intelligence algorithm to analyze images of the eye taken with a retinal camera. This product was also given a Breakthrough Device designation.
   b. The second approval was for OsteoDetect which analyzes wrist radiographs using machine learning techniques to identify and highlight regions of distal radius fracture during the review of posterior-anterior (front and back) and medial-lateral (sides) X-ray images of adult wrists.
2. FDA researchers are developing computational approaches to use deep learning, a form of artificial intelligence (AI), to extract standard MedDRA terms automatically from large-scale free-text documents.
3. Center for Devices and Radiological Health (CDRH) is working the Medical Device Innovation Consortium (MDIC), a public–private partnership among federal agencies, industry, nonprofits and patient organizations, to facilitate computer modeling and simulation as a validated and accepted part of clinical trials.

EMA

4. May 2018: EMA held its third meeting between regulators and representatives of industry stakeholder organizations to address all areas of product development support, from scientific advice, to specifics for pediatric and orphan medicines, and to needs for innovation support.

South Korea

5. December 2017: South Korea published a Guideline on Evaluating Clinical Efficacy of AI Based Medical Devices.
6. November 2017: South Korea published a Guideline on Approval and Review for Medical Devices with Big Data and AI Technology.

Canada

7. April 2018: Under the "Regulatory Review of Drugs and Devices" initiative, Health Canada is establishing a new division within the Therapeutic Products Directorate's Medical Devices Bureau to allow for a more targeted pre-market review of digital health technologies, to adapt to rapidly changing technologies in digital health,

and to respond to fast innovation cycles. This includes Artificial Intelligence and mobile applications.

AdvaMed

8. August 2018: Xavier University in partnership with FDA officials and industry representatives developed a publication as a starting point for sharing considerations and best practices when developing Clinical Laboratory Science applications in healthcare.

Topic	Link
1a.	https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm604357.htm
1b.	https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm608833.htm
2.	https://www.fda.gov/Drugs/ScienceResearch/ucm616420.htm
3.	https://www.fda.gov/AboutFDA/CommissionersPage/ucm614772.htm
4.	http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2018/09/WC500255521.pdf
5.	https://www.cortellis.com/intelligence/report/ri/regulatory/267144
6.	https://www.cortellis.com/intelligence/report/ri/regulatory/264927
7.	https://www.cortellis.com/intelligence/report/ri/regulatory/273447
8.	https://www.advamed.org/sites/default/files/resource/perspectives_and_good_practices_for_ai_and_continuous_learning_systems_in_healthcare.pdf

Blockchain Regulatory Topics

U.S. FDA

April 2018: The INFORMED (Information Exchange and Data Transformation) Initiative - Launched in collaboration with the U.S. Department of Health and Human Services's (HHS) Innovation, Design, Entrepreneurship and Action (IDEA) Lab, INFORMED is a decentralized, multidisciplinary science and technology incubator for collaborative oncology regulatory science research focused on supporting innovations that FDA officials believe will enhance its mission of promotion and protection of the public health.

1. Through INFORMED, the FDA is investigating the utility of blockchain technology with IBM Watson Health. Blockchain can be a scalable, decentralized mechanism for patients to directly share their data with researchers, regulators, data aggregators and the drug development community. Large volumes of data can be shared securely via Blockchain, with mechanisms put in place to ensure patient privacy

EU

2. May 2017: A European observatory on Blockchain technologies is planned, to map and monitor developments, build expertise and promote use cases.

DIA

3. New Collaboration Models with Regulators and Patients discusses the rapid growth of technology including the use of Blockchain

Topic	Link
1.	https://www.cortellis.com/intelligence/report/ri/regulatory/273873
2.	https://www.cortellis.com/intelligence/report/ri/regulatory/279816
3.	DIANewCollaborationModel

Cloud Computing Regulatory Topics

South Korea

1. November 2017: South Korea published a Guideline on Approval and Review for Medical Devices with Big Data and AI Technology.

China

2. December 2017: China issued technical guideline on mobile medical devices. For mobile medical devices, cloud computing services can be regarded as off-the-shelf software. Cloud service providers can be regarded as suppliers rather than medical device manufacturers.

DIA

3. The adoption of a new technology paradigm that instruments the cloud for continuous measurement of both risk and integrity.

Topic	Link
1.	https://www.cortellis.com/intelligence/report/ri/regulatory/264927
2.	https://www.cortellis.com/intelligence/report/ri/regulatory/267046
3.	https://www.diaglobal.org/en/resources/news#article=b5be230f-26a3-4487-9818-618ce3849734

Mobile Medical Applications Regulatory Topics

U.S. FDA

1. In February 2015, the FDA issued the Mobile Medical Applications Guidance document, which superseded the previous version from September 2013.
2. The FDA created MedWatcher mobile medical app. MedWatcher is the only app that allows you to report side effects directly to the FDA to make medical products safer for everyone.
3. September 2018: Statement from FDA Commissioner Scott Gottlieb and Center for Devices and Radiological Health Director Jeff Shuren on agency efforts to work with tech industry to spur innovation in digital health.

UK

4. In June 2018, MHRA published a revised version of the Guideline: Medical device stand-alone software including apps (including IVDMDs). The intent of the guideline is to provide an updated guidance to help identify the health apps which are medical devices and make sure they comply with regulations and are acceptably safe.

Canada

Health Canada is establishing a new division within the Therapeutic Products Directorate's Medical Devices Bureau to allow for a more targeted pre-market review of digital health technologies, to

adapt to rapidly changing technologies in digital health, and to respond to fast innovation cycles.

5. April 2018: Canada's Scientific Advisory Committee on Digital Health Technologies announces it will hold its first meeting, sometime in the fall of 2018.

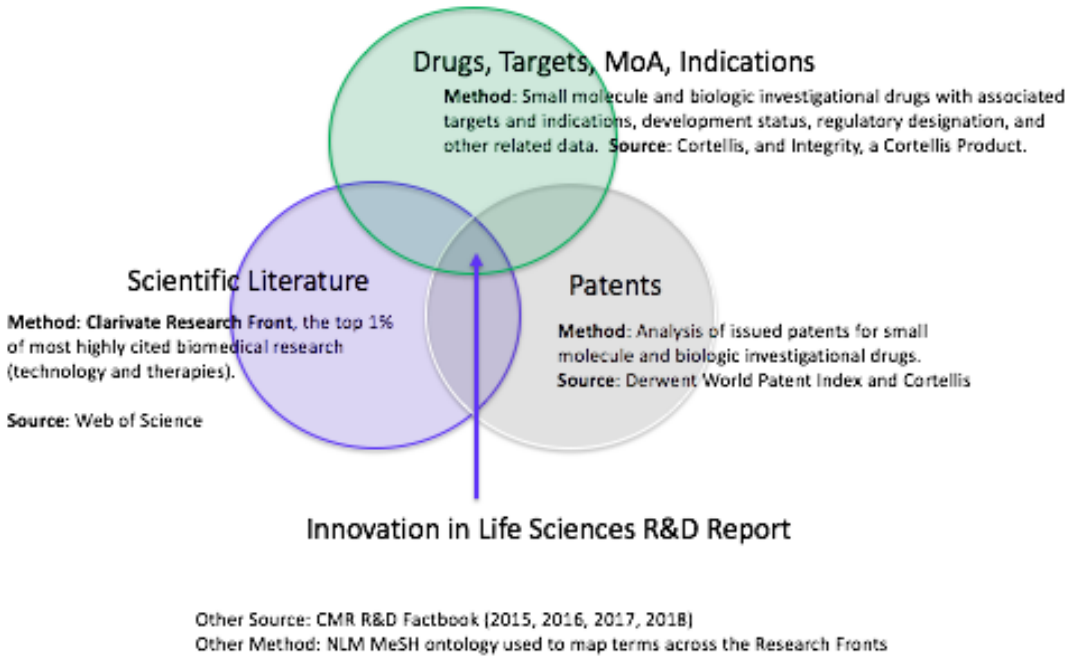
EU

6. In February 2018, the EU published On Consultation: Transformation Health and Care in the Digital Single Market. The report provides an analysis of the results of consultation activities carried out by the European Commission in preparation of a Communication on the Transformation of Health and Care in the Digital Single Market.

Topic	Link
1.	https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366.pdf
2.	https://www.fda.gov/MedicalDevices/Safety/ReportaProblem/ucm385880.htm
3.	https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620246.htm
4.	https://www.cortellis.com/intelligence/report/ri/regulatory/278133
5.	https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/activities/announcements/notice-digital-health-technologies.html5
6.	https://www.cortellis.com/intelligence/report/ri/regulatory/269831

Methodology

This innovation report has used scientific literature, patents, and drug pipeline, and drug targets-indications to support the data with the aim of providing insight into the intersection of those sources.



Other Source: CMR R&D Factbook (2015, 2016, 2017, 2018)
Other Method: NLM MeSH ontology used to map terms across the Research Fronts

Research Fronts Methodology

A Research Front consists of a collection of highly cited "core" papers (i.e., those in the world's top 1% of most frequently cited papers) that have been frequently cited together (co-cited). Research Fronts represent the highly cited cores of research topics at the leading edge of the fields to which they relate. The 302 Research Fronts used in this analysis were selected using biomedical and clinical science keywords from 8,819 Research Fronts in the Web of Science across all disciplines. The 302 Research Fronts contain 2,193 individual papers. The average publication year for the papers in these Research Fronts is 2014.9. They were cited a total of 258,966 times, or 857.5 citations per Research Front or 118.1 citations per paper. This link leads to a more detailed description of Research Fronts.

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