SCORR MARKETING

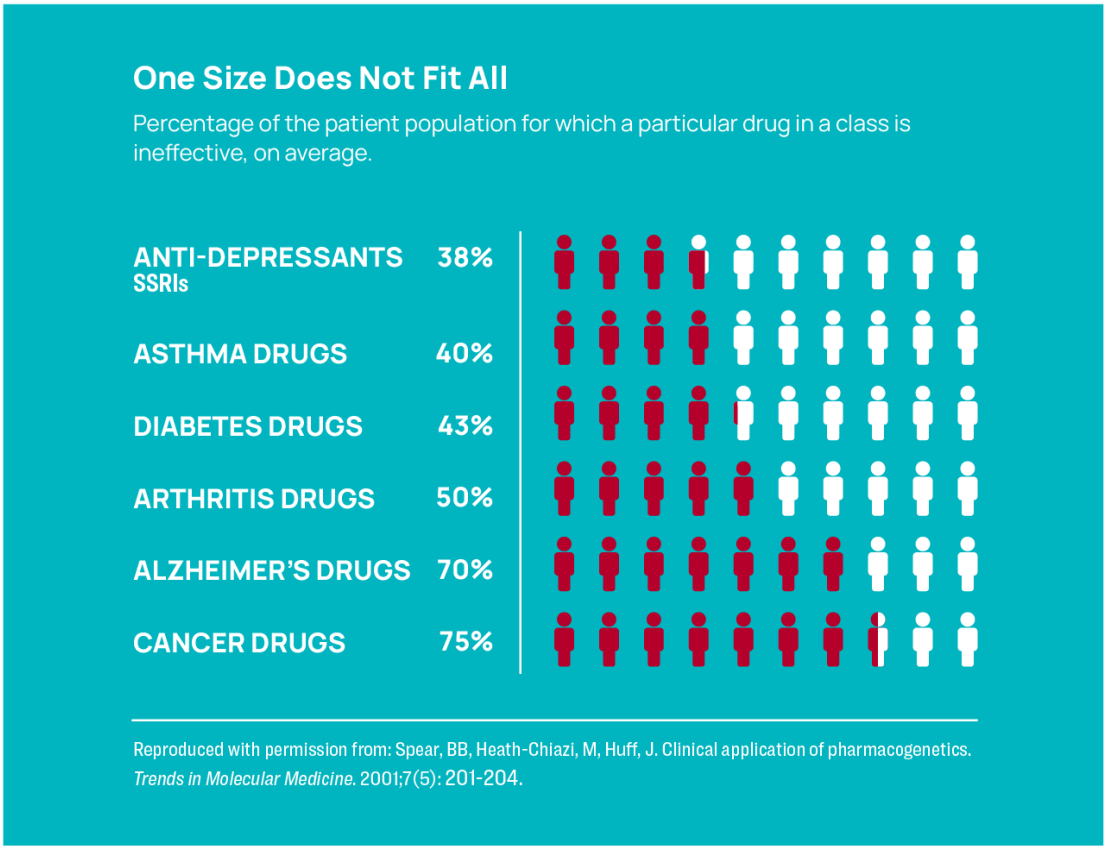
A QUICK GUIDE TO PRECISION MEDICINE IN CLINICAL RESEARCH

October 2021

CONTENTS

INTRODUCTION

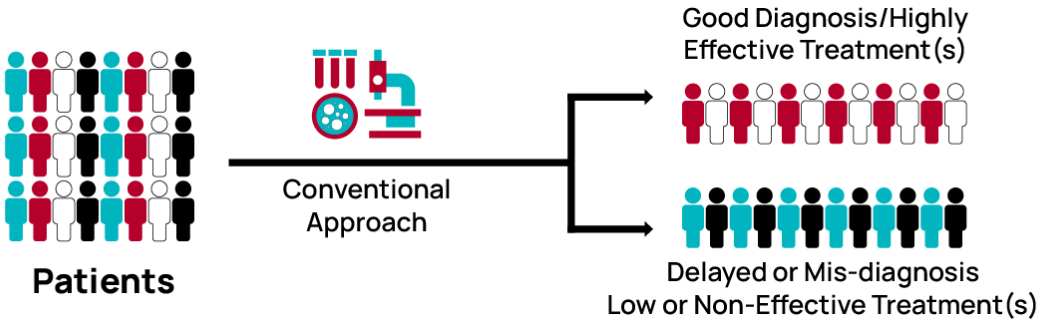
Currently, the industry predominantly treats pharmaceuticals as if they will work similarly across a broad population. However, the data of drugs in use contradicts this approach. According to the Personal Medicine Coalition, citing a 2001 study published in Trends in Molecular Medicine, 38% of antidepressants and 40% of asthma drugs are ineffective in patients.[1] These numbers are even more disturbing for Alzheimer's and cancer drugs, which are ineffective in 70% and 75% in each population, respectively.



Source: Personalized Medicine Coalition, "The Personalized Medicine Report: 2020 – Opportunity, Challenges, and the Future," November 2020

The conventional approach to drug prescription is to diagnose a disease, then prescribe the most common medication used to treat that disease. The patient and physician then wait to see if the patient is a responder or if the treatment is ineffective.

Conventional Medicine



Precision medicine deviates from this approach by predicting responses. Some experts predict that it will be the next major leap forward in biopharmaceutical development and disease treatment.[2] The fundamental promise of precision medicine is to use a patient's genetics, lifestyle, and environment to predict which treatments are likely the most optimal for that individual.[3]

High Definition Medicine

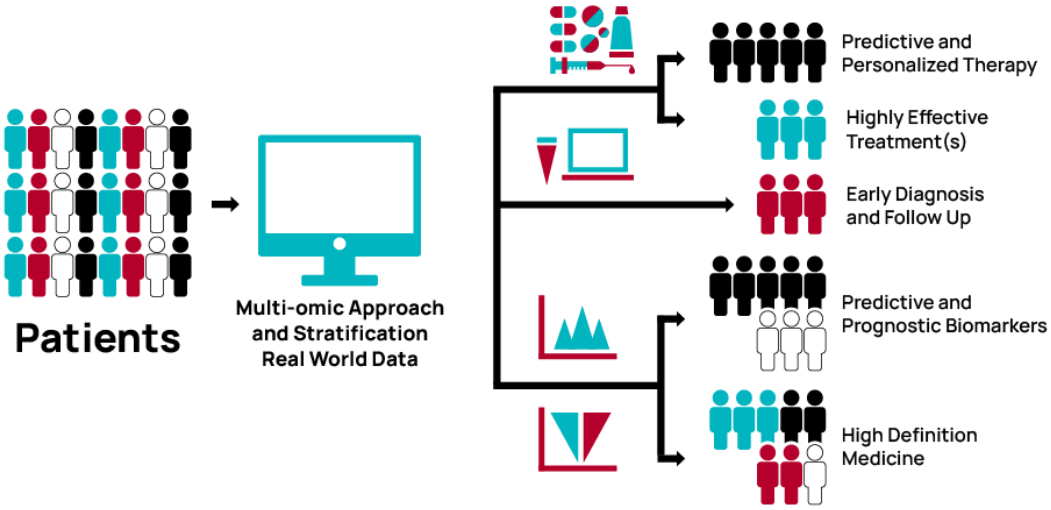


Figure 2. Schematic comparison of high-definition medicine with conventional approaches.

Source: Journal of Personalized Medicine, "Translational Research in the Era of Precision Medicine: Where We Are and Where We Will Go," March 18, 2021

"Personalized health care has the capacity to detect the onset of disease at its earliest stages, preempt the progression of disease, and, at the same time, increase the efficiency of the health care system by targeting treatments to only those patients who will benefit."
– Precision Medicine Coalition

How precision medicine will be practiced in a real clinical setting is still in flux. One could imagine that a physician orders a panel of molecular diagnostic tests to detect biomarkers from an individual patient. Combined with lifestyle, environment, and health history information, these could be combined to decide which therapies and preventive measures are more likely to be impactful on the patient's disease.

The core of precision medicine is the data from patients collected before administering treatment, especially biomarkers.[4] The most familiar of these would be genomics, or DNA sequencing. DNA sequencing is becoming more common and well-known, even among the general public. But for personalized medicine, genomics alone does not provide enough information. Instead, each patient would require a "multi-omic" panel — of their RNA, proteins (proteomics), metabolism (metabolomics), and more.[5] Only patients that are likely to have therapeutic benefit will receive treatments, based on their personal data, potentially even preempting the development of disease.

Multi-omics Approach

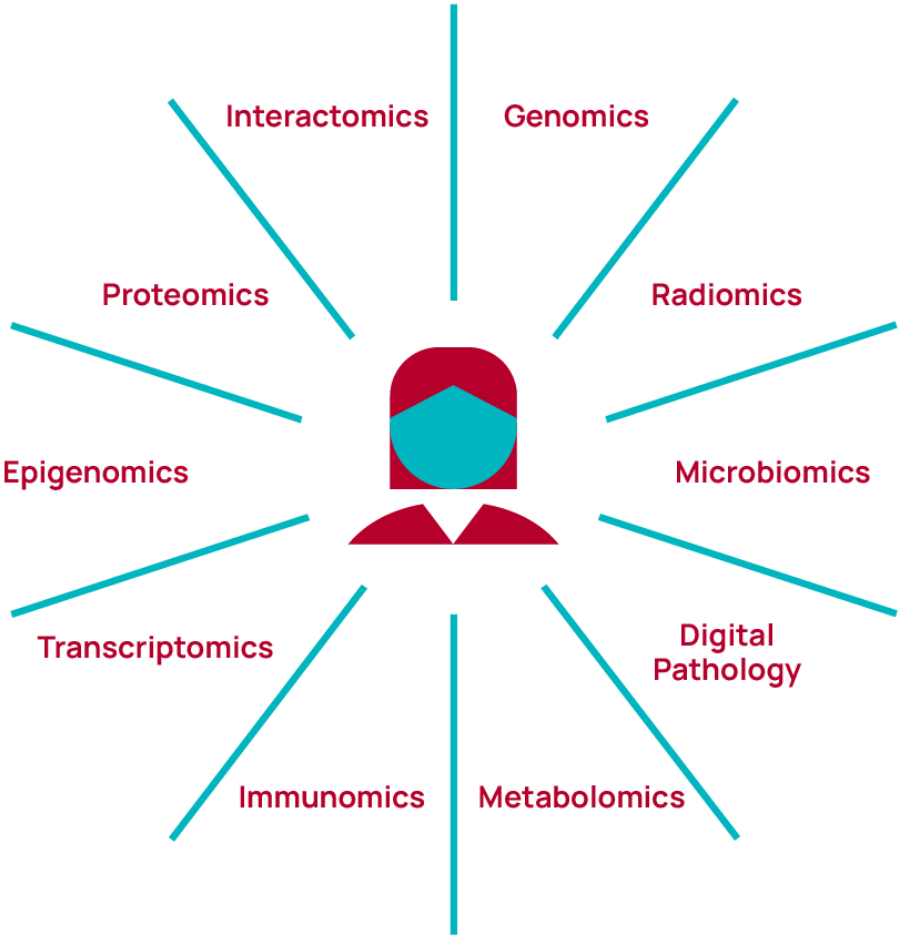


Figure 1. Scheme of "MultiOmics" approach(es).

Source: Journal of Personalized Medicine, "Translational Research in the Era of Precision Medicine: Where We Are and Where We Will Go," March 18, 2021

"Biomarkers can improve the clinical trial success rate for pharma and biopharma drug developers by allowing for the selection of patients more likely to respond to a potential new therapeutic, by enhancing safety, and by serving as surrogate clinical endpoints."

– Amanda Finan, PhD, Head IHC/Histology R&D and Clinical Validations at Cerba Research

With more individualized approaches to prescribing medicine, clinical trials could transform. Instead of attempting to approve every drug for large swaths of the population, clinical trials could reduce their size to a targeted population. These trials would require fewer participants and proceed faster, ultimately leading to better outcomes for patients. We already have a model in rare disease clinical trials for how to do smaller clinical trials, leading many in the biopharmaceutical industry to support the development of precision medicine trials.

Current and future work in the field focuses on the primary problem represented by multi-omics: huge amounts of data.[6] Researchers are developing artificial intelligence (AI) and analytical methods to sift through the extraordinary amount of data produced by these approaches. As these solutions become increasingly more digital, so, too, do their problems. Data privacy, information security, and health record access are already challenges. The vast amount of sensitive information collected for precision medicine creates even greater vulnerabilities. Even if personalized medicine is proven to be technically feasible, social factors surrounding data privacy remain a major concern preventing widespread adoption of the technology.

DEFINITIONS

Precision medicine is a developing field that is still undergoing changes. The exact definition remains in flux; below are several definitions proposed by different organizations.

Organization	Definition of Personalized Medicine
Personalized Medicine Coalition	The use of new methods of molecular analysis to better manage a patient's disease or predisposition to disease.
American Medical Association	Healthcare that is informed by each person's unique, clinical, genetic, and environmental information.
European Union	Providing the right treatment to the right patient, at the right dose, at the right time.
NHS England	A move away from a "one size fits all" approach to the treatment and care of patients' health and toward targeted therapies to achieve the best outcomes in the management of a patient's disease or predisposition to disease.
National Cancer Institute (NCI)	A form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease.

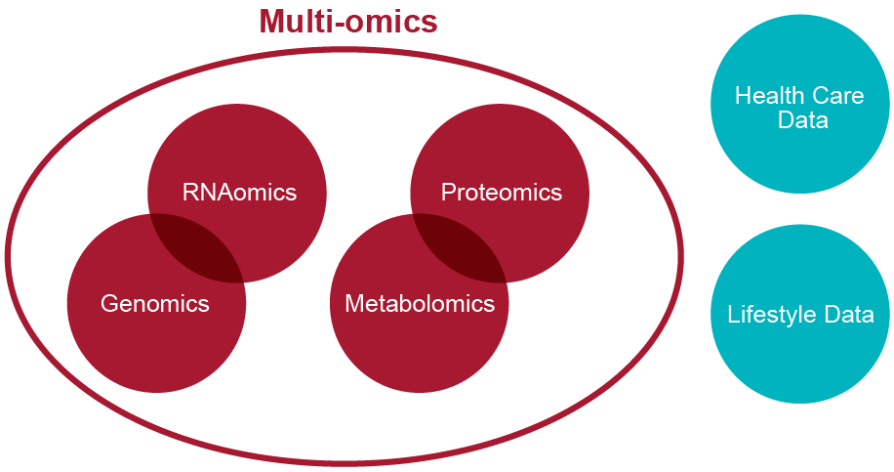
Source: GlobalData, "The State of Personalized/Precision Medicine." October 2019

For the purposes of this primer, personalized medicine is currently used interchangeably with precision medicine. The field is moving toward this interchangeable usage.[7]

Notably, there was a period when precision medicine was considered superior nomenclature. Precision medicine was adopted because there was a concern that "personalized" implied that each individual would have a uniquely developed cure.[8]

While it is a unique discipline, pharmacogenomics is considered a field under the larger umbrella of precision medicine.[9] The term pharmacogenomics is meant to reflect the study of how a patient's genes predict drug efficacy.

Precision Medicine

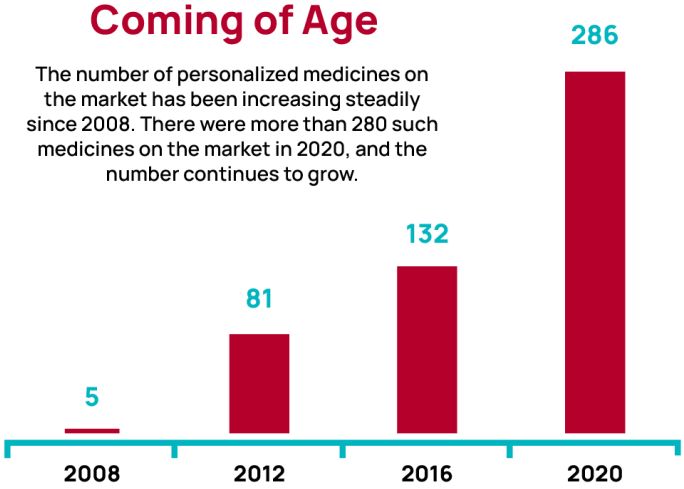


Multiple terms related to precision medicine follow a similar pattern to pharmacogenomics. For example, genomic medicine is "using an individual patient's genetic information in their clinical care."[10] Again, a portion of precision medicine, but not all-encompassing. Beyond genomics, multi-omics includes RNA analysis, proteomics, and metabolomics from patients, but not their health care or lifestyle data.

The term P4 medicine encapsulated the promise of precision medicine by offering health care that is predictive, preventive, personalized, and participatory.[11] The idea of P4 medicine was the predecessor to precision medicine. While P4 medicine has not been implemented in the way that its purveyors hoped, it formed the critical intellectual backbone that allowed for the widespread adoption of personalized medicine campaigns. This term may come back into vogue as precision medicine becomes more common.

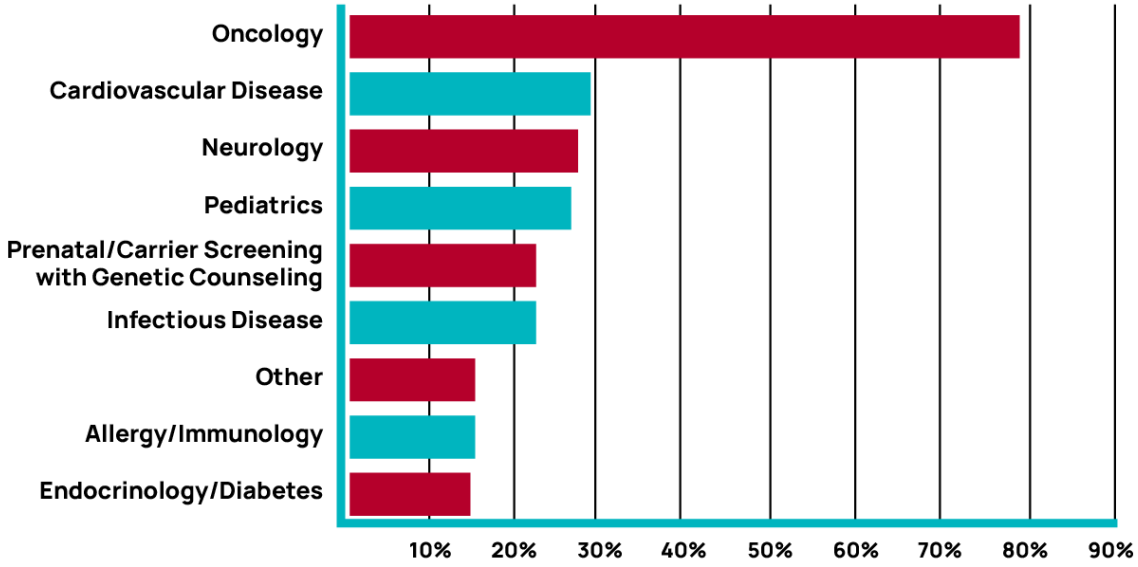
MARKET OVERVIEW

The total "Precision Medicine Market" size exceeded $52 billion in 2020 and is expected to grow at a CAGR of 11.5% by 2027, according to Global Market Insights.[12] As of 2020, 286 personalized medicines were available, a rapid growth considering that only five personalized medicines were accessible in 2008.[13]



Source: Personalized Medicine Coalition, "The Personalized Medicine Report: 2020 – Opportunity, Challenges, and the Future," November 2020

Modern personalized medicine's rise was mainly in oncology, where 70% of treatments are ineffective.[1] Therefore, researchers have developed treatments to target cancer based on personal and tumor genetics. The primary approach of using underlying genetic profiles had promise beyond cancer. In fact, precision medicine brings a long-needed path forward for rare diseases, which are notoriously difficult to study and treat.[14] Oncology remains the largest focus of precision medicine; however, interest is growing in nearly every major discipline of patient care.[15]



Source: Oracle/GenomeWeb, "Trends in Precision Medicine Adoption," 2018

PROMINENT PRECISION MEDICINE DRUGS

Below is a selection of prominent precision medicine drugs, their sponsors, and the indications they treat.

Drug Name	Sponsor	Indication
Opdivo®	Bristol Myers Squibb	Cancer
Keytruda®	Merck	Cancer
Herceptin®	Genentech	Cancer
Gleevec®	Novartis	Cancer
Tagrisso®	AstraZeneca	Cancer
Symdeko®	Vertex	Cystic Fibrosis
Vosevi®	Gilead	Hepatitis C
Isentress®	Merck	HIV

RESEARCH ORGANIZATIONS

Below are some research organizations that address personalized/precision medicine in some way on their websites.

Organization	How Precision Medicine Is Addressed on Website
ALTASCIENCES	Personalized Medicine - Genetics, Genomics, and What They Mean to You (blog post)
biorasi™	Precision Medicine: What can we learn from precision oncology clinical trials? (white paper)
CATO SMS Partnering from Strategy to Approval	Precision Medicine and the FDA
Frenova Renal Research	Data-Driven Precision Medicine: Building the World's Largest Kidney-Disease Focused Genomic Registry With Kurt Mussina (video)
FRONTAGE	Precision medicine and companion diagnostics (panel discussion – gated)
ICON	Precision Medicine - Looking ahead: The future of device developers in precision medicine (white paper)
IQVIA	Supporting Precision Oncology: Targeted Therapies, immuno-oncology, and predictive biomarker-based medicines (report)

LabCorp	Precision Medicine
MEDPACE	Personalized Medicine in Oncology and the Implication for Clinical Development (white paper)
parexel	Precision Medicine
Pharm-Olam	Cancer clinical trials: Recent oncology studies in review (blog post)
PRC CLINICAL RIGHT FOR YOUR RESEARCH	How Can Precision Medicine Change Our Approach to Clinical Trials? (blog post)
PPD	PPD Laboratories Biomarker Lab
Rho	Targeted Product Development: Personalized Medicine and Orphan Product Development (presentation)
Syneos Health syneract BRINGING CLINICAL TRIALS TO LIFE	Targeted Therapies - Understanding the Challenges of Precision Medicine Successful Study in Precision Medicine

HOW CLINICAL TRIALS ARE AFFECTED

It is no secret that clinical trials are prohibitively expensive. From the initial discovery of a potential drug to commercialization, it takes a minimum of 10 years to go through development.[16] Six to seven of those years are consumed by the clinical trial process. This length contributes substantially to costs, but so do a myriad number of other factors, including the type of therapeutic and phase of the trial.

Assumptions on costs, attrition rates, & cycle times per phase used in the P2I v.2 model

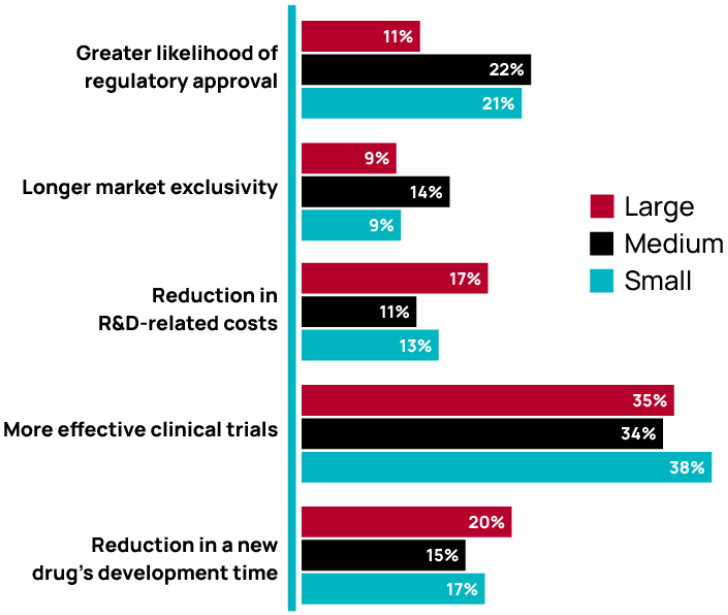
Archetype	Cost per phase ($, millions)				Length of phase (years)			
	Preclinical	Phase 1	Phase 2	Phase 3	Preclinical	Phase 1	Phase 2	Phase 3
Simple vaccine	6.7	2.2	13.2	201.0	3.4	1.6	2.2	2.3
Complex vaccine	16.6	2.5	13.9	223.0	3.3	2.0	3.7	3.5
Unprecedented vaccine	16.6	2.5	13.9	223.0	3.3	2.0	3.7	3.5
Simple NCE	5.0	2.2	5.8	32.8	2.5	1.8	3.4	3.2
Simple NCE for TB	5.0	2.2	5.8	32.8	2.5	1.8	3.4	3.2
Complex NCE	10.0	7.4	6.4	36.1	2.9	1.9	3.5	2.8
Simple repurposed drug	5.0	2.2	5.8	17.6	2.3	1.6	2.1	2.1
Complex repurposed drug	5.0	2.2	5.8	17.6	2.3	1.6	2.1	2.1
Simple biologic	6.7	2.2	13.2	122.0	3.4	1.6	2.2	3.1
Simple biologic for TB	6.7	2.2	13.2	122.0	3.4	1.6	2.2	3.1
Complex biologic	16.6	2.5	13.9	126.0	3.3	2.0	3.7	2.8

Source: Gates Open Research, "Developing New Health Technologies for Neglected Disease: A Pipeline Portfolio Review and Cost Model," February 19, 2020

The total cost of bringing a new medicine through approvals to market is estimated to be about $2.6 billion, according to a Tufts Center for the Study of Drug Development's 2016 analysis.[17] For research and development expenses, it is estimated that $985 million is the median capitalized price per product, according to JAMA.[18] However, these costs are highly variable between the needs unique to each study. A Phase III oncology trial might only recruit a few hundred patients, while another disease may require over 1,000. Such variance in participation leads to significant deviations in costs.[19] Still, the industry standard is to expect a cost of $4 million, $13 million, and $20 million respectively for Phase I, II, and III trials.

One reason for this is the reluctance of clinical trial organizations to update their methodologies. According to HHS/ASPE, "[t]he clinical trial business model has not kept pace with potential for efficiency gains through technological advances or centralized coordination."[20] While there are undoubtedly efficiencies to be realized from multiple avenues, personalized medicine offers a unique opportunity.

Top Advantages Personalized Medicine Could Bring to Drug Developers — Differences Between Organization Size



Source: GlobalData, "The State of Personalized/Precision Medicine," October 2019

From the perspective of a biopharmaceutical company, personalized medicine clinical trials offer both a less costly and shorter alternative to classic clinical trial design. Currently, precision medicine promises to remove weeks to months of time from the 10-year process of clinical trials. The efficiency gains of using precision medicine clinical trials are expected to be even more drastic in the future, as shown in the graph above.[21] This is an intuitive expectation as the drug developers are using a smaller target population with a highly specified product, which results in a faster path to market than large-scale trials.

IMPACT ON CLINICAL TRIAL DESIGN

Randomized clinical trials (RCTs) are considered the gold standard in clinical protocol design.[22] The major feature of RCTs include randomly allotting patients to control or experimental groups, strict criteria for allowing or excluding patient participation, placebo or standard of care control group against which the intervention is tested, blinding (especially double-blinding), and standardization of the protocol used.

Precision medicine offers an alternative to the dominant RCT model. In a personalized medicine clinical trial, only the specific cohort of patients is relevant, allowing for much smaller patient enrollment. We already have a model for how these smaller protocols should operate in the form of rare disease clinical trials, whereby nature the patient populations are small and potentially geographically distant.[23]

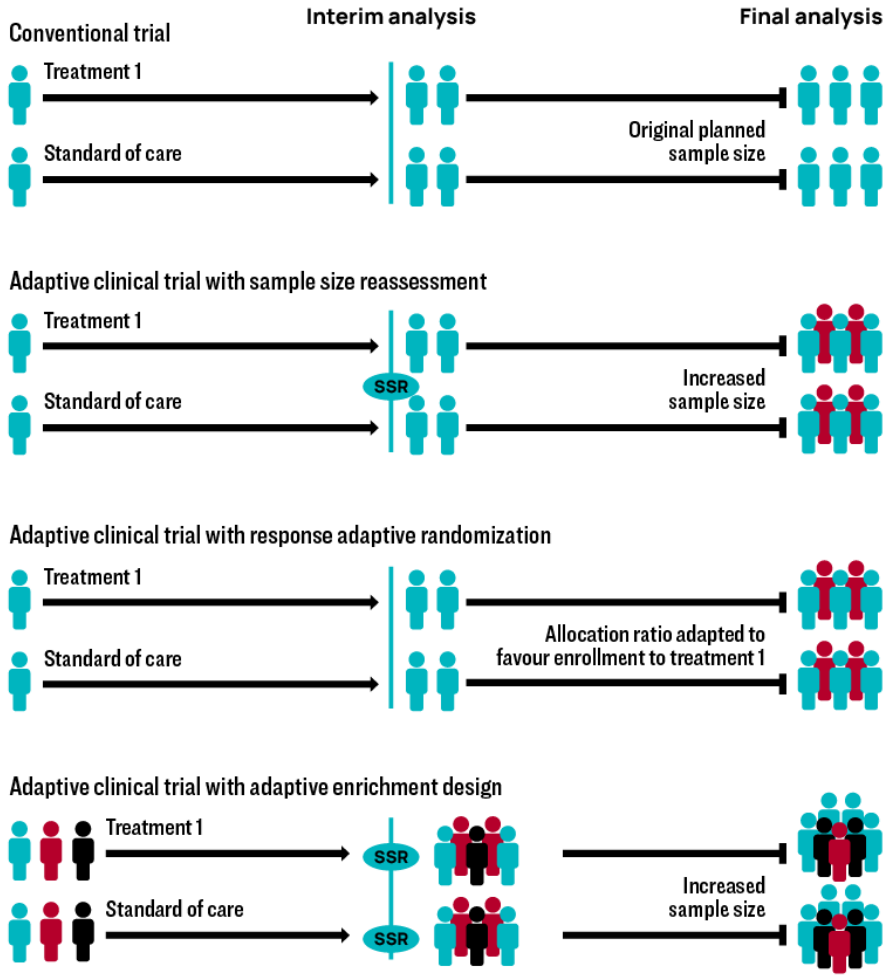
"Constantly evolving clinical trial designs for precision Medicine will require a high degree of agility, as novel endpoints and collaborative frameworks to investigate medication efficacy will be critical for the success of these studies."

– Adam Gottlieb, Manager, Creative – Marketing, Biorasi

This means that trial types beyond RCTs that mimic rare disease trial approaches are the most appropriate. With a small number of patients to enroll, the design must be far more flexible than a traditional clinical trial.

Because precision medicine trials have fewer potential patients to draw from, their trial design needs to allow for this as well as be more flexible than what is traditional for randomized controlled clinical trials. Some trial designs that are used for precision medicine studies include the following: adaptive with sample size reassessment, adaptive with response adaptive randomization, adaptive with adaptive enrichment design, platform, basket, and umbrella trials.

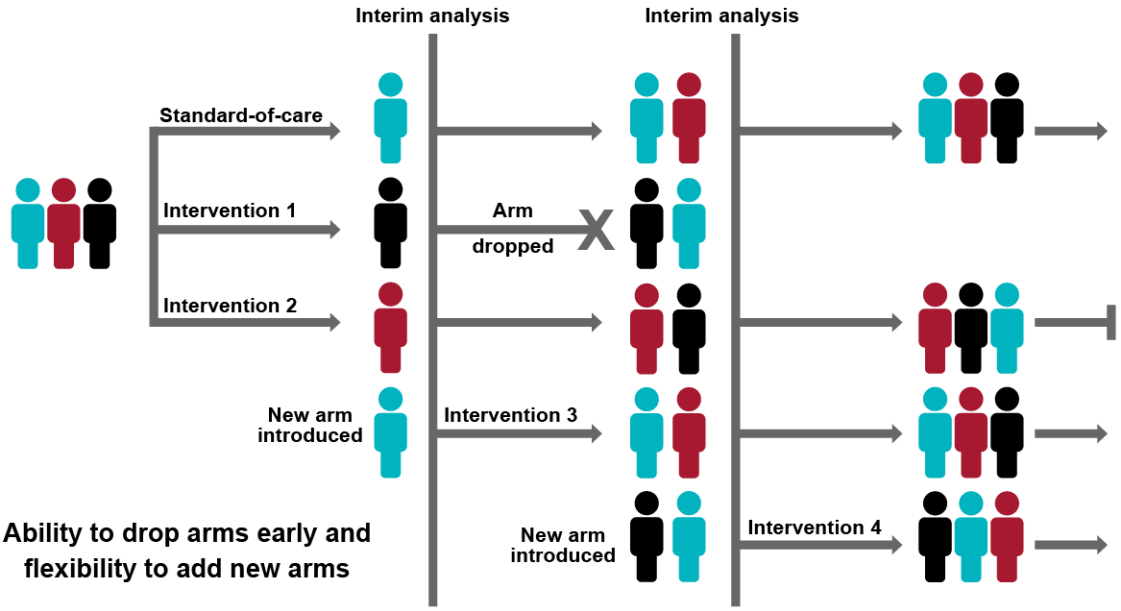
Design Considerations for Adaptive Clinical Trials: A Primer for Clinicians



Source: "Key Design Considerations for Adaptive Clinical Trials: A Primer for Clinicians," (The BMJ – 3/8/18)

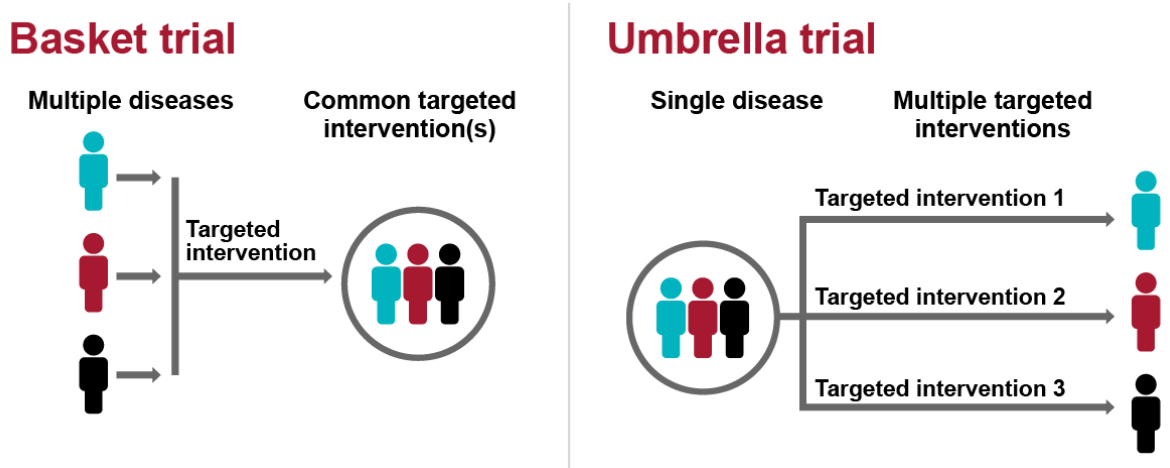
Adaptive trials are so-called because they change in process, purposefully deviating from the original protocol when certain thresholds are reached.[24] This allows the trials to be dynamic when initial data arrives from the trial to maximize the opportunity. The type of trial determines which form of adaptation will occur.

Platform Trial



Source: "An Overview of Platform Trials with a Checklist for Clinical Readers," (Science Direct – September 2020)

The platform trial is another process with interim evaluations, just like the adaptive trials.[25] These are, in fact, a subcategory of adaptive multiarmed, multistage trials. Their unique feature is the addition of new intervention during the course of the trial, along with dropping arms of the protocol based on interim data.



Source: "Systematic Review of Basket Trials, Umbrella Trials, and Platform Trials: A Landscape Analysis of Master Protocols," (BioMed Central – 9/18/19)

Basket trials are different from most clinical trial forms because more than one disease is tested by a single intervention.[26] By batching related diseases together, the patient pool is expanded. Indeed, in

the context of precision medicine, the basket trial allows those patients whose disease would normally exclude them from participating to become contributing patients in a trial.

An umbrella trial can be thought of as the inverse of a basket trial. In the umbrella design, a set of patients suffering from a single disease is stratified and subjected to different interventions.[26] Similarly, the patients are subgrouped based on their risk factors or biomarker status.

Each modality provides an alternative to the standard RCT design. The onus is on the investigator to choose the appropriate design for their potential precision medicine therapeutic, as a standard has not yet emerged in the field.

IMPACT ON CLINICAL TRIAL RECRUITMENT AND RETENTION

The development of precision medicine is inextricably linked with the rise of technology's use in clinical trials. It is difficult to define what parts of clinical trial innovation are specific to precision medicine and which technological methods would have been adopted in its absence.

The first building block of all precision medicine is a large real-world dataset. To that end, companies have entered into the realm of AI with continuous learning algorithms trained on their clinical research data.[27] As data is collected and processed, precision medicine can then be used to hasten timelines and increase productivity for drug developers.

Similarly, patients' electronic medical records provide a source of data to feed algorithmic decision-making.[28] More information about patient disease progression, combined with other information, ultimately should result in the recommendation of the most optimal interventions.

As for running a clinical trial, precision medicine studies can take advantage of recent innovations in the field. In particular, the rich data and newer health technologies facilitate workflows that help increase and maintain patient enrollment.[29] These include early diagnostic data and information centralization. Counterintuitively, the centralization of information has fueled the growth of decentralized clinical trials.[23] These are particularly important for diseases with a diffuse population, as they can use online patient portals, mobile vans, home visits, and eSourcing solutions to capture data electronically away from a trial site and route it to researchers.[23] This eases access to diagnostics before and during a trial, such as genetic testing a large patient population.[30] It also allows penetration into the hitherto neglected rural populations of the world.

"Applying eSource solutions to the conduct of Clinical Trials allows sponsors flexibility when it comes to their study design. Whether its direct collection of data from patients at their home, office, in a mobile research van or over a telemedicine visit – eSource solutions make this a reality. eSource solutions, because of their offline and online capabilities and their ability to collect data, audio, video and photographs, allows for any number of possible study designs to be applied in a clinical trial, therefore embracing a "meet patients where they are" mentality."

– Jonathan Andrus, Chief Strategy Officer, Clinical Ink

More pharma-related groups are partnering together than ever. CROs are creating relationships and connections to find the patients that can enroll in their precision studies.[23] This includes finding patient registries, disease advocacy groups, and nonprofit organizations to communicate more effectively with patients that may benefit from their trials.[31] On the other side of the arrangement, companies have the resources to offer allied groups diagnostics like genetic testing to find specific patient characteristics. Sometimes this means including a third organization if a CRO does not yet have an internal genetic testing program.[30] Together, these partners have the people, expertise, and capability to start on the journey through a precision medicine clinical trial.

"We know by looking at other disease areas that precision medicine improves patient outcomes. In response, we've launched My Reason to create the world's largest collection of genomic and clinical data in support of research in kidney disease. My Reason will help researchers better understand underlying genetic causes of impaired kidney function and develop truly novel and personalized therapies."

– Kurt Mussina, MBA, President, Frenova Renal Research, and Senior Vice President, Global Medical Office, FMC

While precision medicine trials have lower total recruitment numbers and therefore predict higher retention, the practice is still relatively new and evolving, indicating that major shifts could still happen within the industry, positively or negatively.

"Because precision medicine trials are new and developing, early patient engagement in trial design, collaboration with patient advocacy groups, and ongoing systematic research into patient-burden, specifically accessibility of precision medicine trial sites to diverse patient populations, will be key factors in patient retention."

– KimberLee Heidmann, Vice President, Patient Services, Scout Clinical

CHALLENGES

Reimbursement remains an issue within the world of precision medicine. Currently, it ranks as the No. 1 deterrent to the development of personalized medicine.[32] Why?

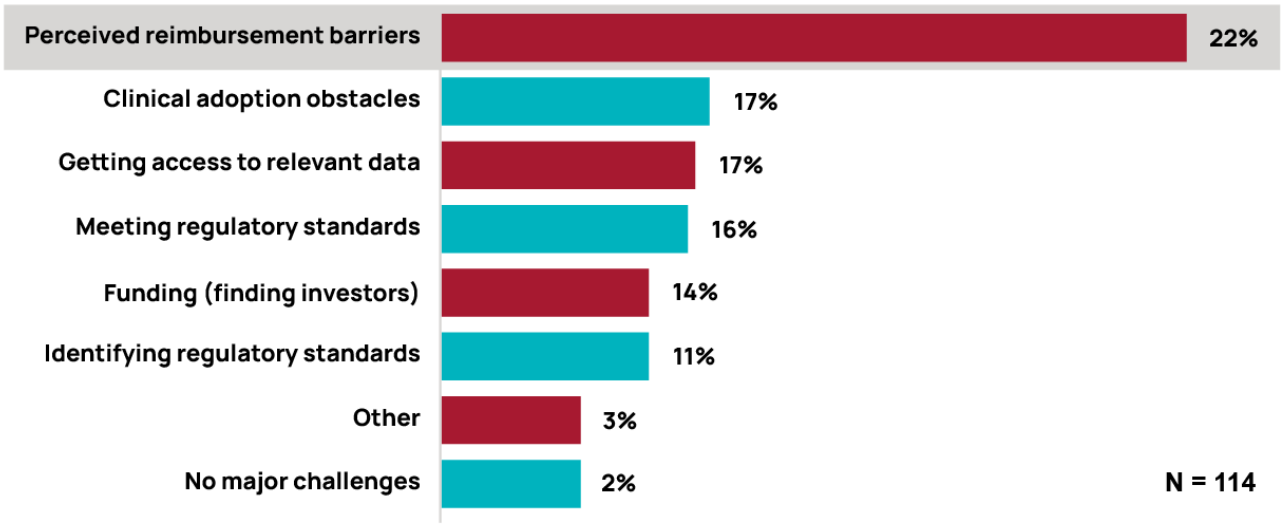
The common model of reimbursement for a particular drug or service is intended to be used on a large population. Precision medicine, by its nature, is targeting ever smaller populations with more specific interventions that are not generalizable, making it difficult to price. This uncertainty either requires higher upfront costs to patients which are rejected by payers (like American health insurance companies), or the biopharmaceutical companies that made the medicine will not generate enough revenue to continue creating new treatments.[32] In addition, it is unclear how payers should value the diagnostic tests, data collection, and data analysis needed for precision medicine.[33]

However, just as innovation has been important in developing precision medicine, it is also changing the much-maligned health care reimbursement model. New models, such as outcome-based repayment, have seen some success in rare disease treatments that suffer the same

limited population issues as precision medicine.[34] Installment plans, like a mortgage for expensive treatments, have been initiated, though they are still too new to see if they will be successful within the industry.[35] As for diagnostic tests, clinicians and hospitals are unequipped to deal with the amount of information inflowing from multi-omic panels, nor do they know how to value them, preventing adoption.[36] Currently, precision medicine is in chaos in most clinical care settings, with most physicians waiting for directions from payers.

Notably, companies pursuing precision medicine have found that focusing on the value of their treatments has created knock-on effects that, when accounted for, make it a profitable investment.[37] This belief — somewhat controversial within the field — is not shared by all.[37]

Perceived Reimbursement Barriers Are a Major Challenge Associated with Developing Personalized Medicine



Source: GlobalData, "The State of Personalized/Precision Medicine," October 2019

Regulatory

Regulatory guidance has been variable for precision medicine.[13] While using a similar model for rare disease trials to facilitate FDA approval of a given therapeutic, personalized medicine includes more than that. FDA guidance less clearly defines assays necessary to define patient populations, data analytic techniques, and collection methods. Historically, the FDA regulates some diagnostic tests as medical devices. The alternative is the Centers for Medicare & Medicaid Services, which has jurisdiction over laboratory-developed tests.

For an outside company, knowing which federal department will be reviewing is opaque, while both have separate requirements for review. Precision medicine is based on a number of diagnostic panels and tests, and unclear regulatory guidance has inhibited innovation in this space. Currently, pharmaceutical companies are advocating for more clear guidance as precision medicine is a growing opportunity for them.

Data

With the advent of big data, so too has come the time of truly massive data management issues, the first of which is patient data privacy concerns.[6] Hospital and frontline clinical settings are not known for their data security methodologies. Naturally, patients are resistant to having their data collected and analyzed in an environment that has no track record when it comes to data security. The future of precision medicine will be informed by the growing conversations around data access and privacy.[38]

Often overlooked, physical infrastructure is an issue.[6] Clinical settings have every computer needed for clinical work and billing, but there is not an isolated second system for big data servers. To truly use machine learning, they would also have to significantly increase the total processing capacity available at their location in addition to the hardware.

The final barrier is clinical translation. Precision medicine and data will be disruptive to the clinical environment.[6] This means disrupting the everyday workflow of nearly every clinical team member and altering the patient experience drastically. For precision medicine to be adopted, practitioners must adapt it into preexisting workflows as much as possible, which is already providing difficulty. Here, greater automation may be the key to remove at least some decision-making from physicians, to simplify the information they receive to actionable advice.[6]

FUTURE IMPLICATIONS

Artificial Intelligence

The amount of data that will be generated for precision medicine is too large for the human mind to comprehend. The only path forward is through the use of artificial intelligence systems.[39] In particular, machine learning, where a computer is trained on a dataset for a very specific task, will be essential. This approach is already being used in fields with a large amount of image analysis like radiology and pathology with levels of accuracy soon to exceed human ability.[40]

However, the promise is beyond replacing current disciplines. High-powered computing techniques can find patterns in datasets that are not obvious, cross-referencing all details, even if they do not seem germane.[41] For example, an image analysis program looking at skin biopsies would also have access to blood pressure information that could be used to find a hitherto unknown connection in health. As more of these connections are made, precision medicine will become more predictive than our current retrospective datasets, allowing for better interventions earlier, with the promise of preventing disease before full presentation.[39]

Blockchain

Blockchain technology enjoys a reputation as a solution in search of a problem. Primarily associated with cryptocurrencies, blockchain is a sophisticated database technology.[42] A blockchain structures itself into groups, or blocks, connected together, with each new block connected to a previously filled block. The chain has no technical end, indicating a functionally infinite amount of storage. However, a blockchain is decentralized, meaning no individual has control over the data. It is held in a public ledger, securing it from interference.

Blockchain technology has two features that make it promising for hosting biomedical information. First, it is secure.[43] To date, no major blockchain has ever successfully been hacked. Second,

blockchain is transparent. Cryptography can be implemented in the blockchain to anonymize data, but that data is still available and transparent for researchers and clinicians to use.
It seems that blockchain technology is the answer to balancing data security and privacy, but the biomedical community has not adopted it. The reasons remain unclear, though lack of familiarity and a lack of technical prowess among physicians, researchers, and insurers are leading candidates.

Digital Therapeutics

Digital therapeutics exist somewhere between diagnostics and precision medicines.[44] Current use of digital health care technologies focuses mainly on mimicking traditional interventions. However, the future of precision medicine in the digital world is adaptive. The same AI and machine learning that goes through large data could monitor an individual human's behaviors and what predicts their responses. Especially when it comes to lifestyle interventions, digital therapeutics have the promise of creating a truly individualized and effective therapeutic.[44]

SUMMARY

Precision medicine is an exciting new field promising better-targeted therapeutics to patient populations that will find them more effective. By collecting a large amount of data, including multi-omic panels, lifestyle, and environmental information, then analyzing it, the industry can better predict the efficacy of biopharmaceutical interventions in specific populations. This is meant to reduce the number of drugs that are prescribed but ineffective in patients. For example, in oncology, >70% of cancer patients fail to respond to their therapeutics, indicating a dire need for better medical interventions.

How Clinical Trials Are Affected

Clinical trial companies are slow to alter their approach or to innovate in the space. However, precision medicine can use small-scale trials for a targeted population, which promises to increase clinical trial efficiency, along with an aggregation of marginal but positive effects.

Impact on Clinical Trial Design

RCTs have been the apex of clinical trials. However, the practical needs of precision medicine trials are pushing the industry to use trial designs created for rare disease protocols. Some trial designs that are used for precision medicine studies include the following: adaptive with sample size reassessment, adaptive with response adaptive randomization, adaptive with adaptive enrichment design, platform, basket, and umbrella trials.

Impact on Clinical Trial Recruitment and Retention

Precision medicine trials are the primary beneficiaries of clinical trial innovation. The digital tools necessary for large decentralized clinical trials can also be applied to personalized medicine protocols. The sheer amount of data, processing capacity, and patient access needed to run these trials are forcing companies to partner with each other, nonprofit groups, and patient advocacy groups. However, the smaller population size needed creates the opportunity for better patient enrollment and retention. The field is still new enough that there may be innovations or setbacks that change these dynamics.

Challenges

Payer reimbursement plans remain the No. 1 issue with precision medicine. Still, regulatory burdens are unclear with opaque federal decision-making mechanisms, which need to be clarified. Finally,

learning how to integrate truly massive datasets into existing workflows is the major rate-limiting step of clinical adoption.

Future Implications

Patients using integrated digital therapeutics as an adaptive tool to promote health will likely be the future of precision medicine. Currently, the development of ever-better artificial intelligence promises a drastic increase in the quality of personalized medicine. As with all digital information, data security will only grow in importance, with blockchain representing a promising solution.

Precision medicine holds the promise of increasing the efficacy of almost all medical interventions, by combining patient data to predict the best outcomes. However, the field is still new and growing, with many questions surrounding how it will be integrated effectively in clinical research practice.

If researchers and physicians can overcome the various hurdles, varying from regulatory to technological, precision medicine has a bright future in improving the lives of patients.

REFERENCES

[1] Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. Trends Mol Med. 2001 May;7(5):201-4. doi: 10.1016/s1471-4914(01)01986-4. PMID: 11325631. https://pubmed.ncbi.nlm.nih.gov/11325631/

[2] Joshua C. Denny and Francis S. Collins. Precision medicine in 2030—seven ways to transform healthcare. Cell Commentary. March 18, 2021. 184:6, P1415-1419. DOI: https://doi.org/10.1016/j.cell.2021.01.015 https://www.cell.com/cell/fulltext/S00928674(21)000581?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867421000581%3Fshowall%3Dtrue

[3] "What is Precision Medicine?" Medline Plus, U.S. National Library of Medicine. September 2020. https://medlineplus.gov/genetics/understanding/precisionmedicine/definition/

[4] Vargas, A., Harris, C. Biomarker development in the precision medicine era: lung cancer as a case study. Nat Rev Cancer 16, 525–537 (2016). https://doi.org/10.1038/nrc.2016.56. https://www.nature.com/articles/nrc.2016.56#citeas

[5] Olivier M, Asmis R, Hawkins GA, Howard TD, Cox LA. The Need for Multi-Omics Biomarker Signatures in Precision Medicine. Int J Mol Sci. 2019;20(19):4781. Published 2019 Sep 26. doi:10.3390/ijms20194781. https://www.mdpi.com/1422-0067/20/19/4781

[6] Hulsen T, Jamuar SS, Moody AR, Karnes JH, Varga O, Hedensted S, Spreafico R, Hafler DA and McKinney EF (2019) From Big Data to Precision Medicine. Front. Med. 6:34. doi: 10.3389/fmed.2019.00034. https://www.frontiersin.org/articles/10.3389/fmed.2019.00034/full

[7] "The Shift From Personalized Medicine to Precision Medicine and Precision Public Health: Words Matter!" Muin J Khoury, Director, Office of Public Health Genomics, Centers for Disease Control and Prevention. April 21, 2016. https://blogs.cdc.gov/genomics/2016/04/21/shift/

[8] "What is the difference between precision medicine and personalized medicine? What about pharmacogenomics?" MedlinePlus, U.S. National Library of Medicine. September 2020.

[9] "What is pharmacogenomics?" MedlinePlus, U.S. National Library of Medicine. June 2021.

[10] Manolio TA, Chisholm RL, Ozenberger B, et al. Implementing genomic medicine in the clinic: the future is here. Genet Med. 2013;15(4):258-267. doi:10.1038/gim.2012.157. https://www.nature.com/articles/gim2012157

[11] Flores M, Glusman G, Brogaard K, Price ND, Hood L. P4 medicine: how systems medicine will transform the healthcare sector and society. Per Med. 2013;10(6):565-576. doi:10.2217/pme.13.57. https://www.futuremedicine.com/doi/10.2217/pme.13.57

[12] "Precision Medicine Market Size By Product Type (Diagnostics {Genetic Tests, Biomarker Based Tests}, Therapeutics), By Application (Oncology, CNS, Immunology, Respiratory), By End-use (Hospitals, Diagnostic Centers, Research & Academic Institutes), COVID-19 Impact Analysis, Regional Outlook, Growth Potential, Price Trends, Competitive Market Share & Forecast, 2021 – 2027" Global Market Insights, June 2021. https://www.gminsights.com/industry-analysis/precision-medicine-market

[13] "The personalized medicine report: opportunity, challenges, and the future. The Personalized Medicine Coalition. November 17, 2020. https://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/PMC_The_Personalized_Medicine_Report_Opportunity_Challenges_and_the_Future.pdf

[14] Brian Delavan, Ruth Roberts, Ruili Huang, Wenjun Bao, Weida Tong, Zhichao Liu, Computational drug repositioning for rare diseases in the era of precision medicine. Drug Discovery Today. 23:2 p. 382-394. 2018. https://doi.org/10.1016/j.drudis.2017.10.009. https://www.sciencedirect.com/science/article/abs/pii/S1359644617301587

[15] "Research Report: Trends in Precision Medicine Adoption," GenomeWeb, 2017. https://www.oracle.com/a/ocom/docs/industries/healthcare/research-report-genomeweb-trends-precision-medicine.pdf

[16] "Biopharmaceutical Research & Development: The Process Behind New Medicine," PhRMA, 2015.

[17] "A Tough Road: Cost To Develop One New Drug Is $2.6 Billion; Approval Rate for Drugs Entering Clinical Development is Less Than 12%," Thomas Sullivan, Policy & Medicine, May 21, 2019. https://www.policymed.com/2014/12/a-tough-road-cost-to-develop-one-new-drug-is-26-billion-approval-rate-for-drugs-entering-clinical-de.html

[18] Olivier J. Wouters, Martin McKee, and Jeroen Luyten. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. JAMA. March 3, 2020. 2020;323(9):844-853. doi:10.1001/jama.2020.1166. https://jamanetwork.com/journals/jama/fullarticle/2762311

[19] "How Much Does a Clinical Trial Cost?" Sofpromed, January 2, 2020. https://www.sofpromed.com/how-much-does-a-clinical-trial-cost/

[20] "Examination of Clinical Trial Costs and Barriers for Drug Development," Office of the Assistant Secretary for Planning and Evaluation. Jul 24, 2014. https://aspe.hhs.gov/reports/examination-clinical-trial-costs-barriers-drug-development-0

[21] "The State of Personalized/Precision Medicine, 2019 Market Study," Research And Markets, December 03, 2019. https://www.researchandmarkets.com/reports/4858719/the-state-of-personalized-precision-medicine?utm_source=dynamic&utm_medium=GNOM&utm_code=rswmhp&utm_campaign=1327253+-+The+State+of+Personalized%2fPrecision+Medicine%2c+2019+Market+Study&utm_exec=joca220gnomd

[22] Harald O. Stolberg, Geoffrey Norman, and Isabelle Trop. Randomized Controlled Trials. American Journal of Roentgenology 2004 183:6, 1539-1544. https://www.ajronline.org/doi/full/10.2214/ajr.183.6.01831539

[23] "Biorasi: precision medicine trials call for specialized approach," Jenni Spinner, Out-Sourcing Pharma, August 19, 2020. https://www.outsourcing-pharma.com/Article/2020/08/19/Precision-medicine-trials-call-for-specialized-approach

[24] Thorlund K, Haggstrom J, Park J J, Mills E J. Key design considerations for adaptive clinical trials: a primer for clinicians BMJ 2018; 360 :k698 doi:10.1136/bmj.k698. https://www.bmj.com/content/360/bmj.k698

[25] Jay J.H. Park, Ofir Harari, Louis Dron, Richard T. Lester, Kristian Thorlund, Edward J. Mills, An overview of platform trials with a checklist for clinical readers. Journal of Clinical Epidemiology. 2020. 125 p. 1-8. https://doi.org/10.1016/j.jclinepi.2020.04.025. https://www.sciencedirect.com/science/article/pii/S0895435619309874

[26] Ravi R, Kesari HV. Novel Study Designs in Precision Medicine - Basket, Umbrella and Platform Trials. Curr Clin Pharmacol. 2021 Mar 16. doi: 10.2174/1574884716666210316114157. Epub ahead of print. PMID: 33726655. https://www.eurekaselect.com/192306/article

[27] "Clinical Trials In The Era Of Precision Medicine: What Needs To Change?" Clinical Leader, July 11, 2019. https://www.clinicalleader.com/doc/clinical-trials-in-the-era-of-precision-medicine-what-needs-to-change-0001

[28] "Ask the Experts: advancing real-world data in the precision medicine era," OncologyCentral, July 1, 2020. https://www.oncology-central.com/ask-the-experts-advancing-real-world-data-using-biospecimens-in-the-precision-medicine-era/

[29] "Busting Patient Recruitment Bottlenecks in Oncology Trials," Applied Clinical Trials, Applied Clinical Trials-06-01-2020, Volume 29, Issue 6. May 31, 2020. https://www.appliedclinicaltrialsonline.com/view/busting-patient-recruitment-bottlenecks-oncology-trials

[30] "The Right Precision Medicine Partner Is Essential For Trials And Patients," Ed Miseta, Clinical Leader, July 20, 2021. https://www.clinicalleader.com/doc/the-right-precision-medicine-partner-is-essential-for-trials-and-patients-0001

[31] "How Precision Medicine Will Revolutionize Trial Recruitment," Justin Grossman, PharmExec.com, March 19, 2019. https://www.pharmexec.com/view/how-precision-medicine-will-revolutionize-trial-recruitment

[32] "Reimbursement, regulation, resistance to change remain provider barriers to precision medicine," Susan Morse, Healthcare Finance, May 8, 2019. https://www.healthcarefinancenews.com/news/reimbursement-regulation-resistance-change-remain-provider-barriers-precision-medicine-adoption

[33] "The future of precision medicine part 4: diagnosing the diagnostic problem," Life Sciences Intellectual Property Review, February 14, 2019. https://www.lifesciencesipreview.com/contributed-article/the-future-of-precision-medicine-part-4-diagnosing-the-diagnostic-problem

[34] "Pioneering cancer drug, just approved, to cost $475,000 — and analysts say it's a bargain," Damin Garde, StatNews, August 30, 2017. https://www.statnews.com/2017/08/30/novartis-car-t-cancer-approved/

[35] "Bluebird endorses plan for installment-based payments for costly gene therapy," Natalie Grover, Endpoint News, January 9, 2019. https://endpts.com/bluebird-endorses-plan-for-installment-based-payments-for-costly-gene-therapy/

[36] Geoffrey S. Ginsburg and Kathryn A. Phillips. Precision Medicine: From Science To Value. Health Affairs Vol. 37, no. 5. May 2018. https://doi.org/10.1377/hlthaff.2017.1624. https://www.healthaffairs.org/doi/full/10.1377/hlthaff.2017.1624

[37] "The future of precision medicine part 6: reimbursement," Life Sciences Intellectual Property Review, August 8, 2019. https://www.lifesciencesipreview.com/contributed-article/the-future-of-precision-medicine-part-6-reimbursement

[38] "Precision Medicine: 'Big Data' Security, Privacy Concerns," Marianna Kobasuk McGee, GovInfo Security, October 1, 2015. https://www.govinfosecurity.com/interviews/precision-medicine-big-data-security-privacy-concerns-i-2935

[39] Uddin, M., Wang, Y. & Woodbury-Smith, M. Artificial intelligence for precision medicine in neurodevelopmental disorders. npj Digit. Med. 2, 112 (2019). https://doi.org/10.1038/s41746-019-0191-0. https://www.nature.com/articles/s41746-019-0191-0#citeas

[40] Daniel S. Kermany, Michael Goldbaum, Wenjia Cai, Carolina C.S. Valentim, Huiying Liang, Sally L. Baxter, Alex McKeown, Ge Yang, Xiaokang Wu, Fangbing Yan, Justin Dong, Made K. Prasadha, Jacqueline Pei, Magdalene Y.L. Ting, Jie Zhu, Christina Li, Sierra Hewett, Jason Dong, Ian Ziyar, Alexander Shi, Runze Zhang, Lianghong Zheng, Rui Hou, William Shi, Xin Fu, Yaou Duan, Viet A.N. Huu, Cindy Wen, Edward D. Zhang, Charlotte L. Zhang, Oulan Li, Xiaobo Wang, Michael A. Singer, Xiaodong Sun, Jie Xu, Ali Tafreshi, M. Anthony Lewis, Huimin Xia, Kang Zhang. Identifying Medical Diagnoses and Treatable Diseases by Image-Based Deep Learning. Cell 172:5. P. 1122-1131.e9. 2018. https://doi.org/10.1016/j.cell.2018.02.010. https://www.cell.com/cell/fulltext/S0092-8674(18)30154-5?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867418301545%3Fshowall%3Dtrue

[41] Poplin, R., Varadarajan, A.V., Blumer, K. et al. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. Nat Biomed Eng 2, 158–164 (2018). https://doi.org/10.1038/s41551-018-0195-0. https://www.nature.com/articles/s41551-018-0195-0#citeas

[42] Tsung-Ting Kuo, Hyeon-Eui Kim, Lucila Ohno-Machado. Blockchain distributed ledger technologies for biomedical and health care applications, Journal of the American Medical Informatics Association, Volume 24, Issue 6, November 2017, Pages 1211–1220, https://doi.org/10.1093/jamia/ocx068. https://academic.oup.com/jamia/article/24/6/1211/4108087?login=true

[43] "The Data-Powered Patient: Precision Medicine Enabled by Decentralized Identity and Blockchain," David Houlding, The Journal of Precision Medicine, 2021. https://www.thejournalofprecisionmedicine.com/the-journal-of-precision-medicine/the-data-powered-patient-precision-medicine-enabled-by-decentralized-identity-and-blockchain/

[44] Palanica A, Docktor MJ, Lieberman M, Fossat Y: The Need for Artificial Intelligence in Digital Therapeutics. Digit Biomark 2020;4:21-25. doi: 10.1159/000506861. https://www.karger.com/Article/FullText/506861#

ABOUT THE AUTHOR

Alex Generous, Ph.D., a scientific writer at SCORR Marketing, earned his Ph.D. in biomedical sciences from Mayo Clinic and B.A. in biochemistry, cell and molecular biology from Drake University. He served as a science writer for Mayo Clinic's Research Communications and subsequently as associate director of science communication for the National Cattlemen's Beef Association. He is currently a member in good standing of the National Association of Science Writers.

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