



Disruption is Personal: RWE and AI changing the game for Personalized Medicine

Arnab Goswami

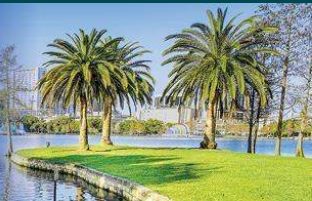
ICON DOCS, Bangalore , India



March 8th-11th
Renaissance Orlando at
SeaWorld Florida

US 2020

The Clinical Data
Science Conference



Biography of Author

Arnab Goswami is a seasoned life science industry professional with 14+ years of experience and has been working in the clinical programming arena for last 11 years. His therapeutic area experience includes respiratory diseases, neurological disorders, diabetes, ophthalmology, oncology, vaccines etc. His primary expertise is in statistical programming and he has detailed exposure in implementing CDISC standards. Currently working as Senior Statistical Programmer II in ICON DOCS, Arnab efficiently handles multicultural environments, interacts cross-functionally and manages global resources and projects.

Arnab obtained his MSc in Microbiology from University of Kalyani, India. He has published multiple papers across organizations and pharma journals. Very enthusiastic about changing paradigm of medicine development, he is a regular presenter for many conferences including PhUSE, CONSPIC etc.

Arnab lives in Bangalore, India with his family and loves travelling and listening music. An avid biker, he spends his free time in trekking, playing cricket---and to mention, playing with his 4-year old son whatever the younger one likes!!



Abstract of the paper

- Conventional clinical trial approach deals with data from patients enrolled in a designated trial and represents a small portion of the actual patient population. Real world evidence (RWE) is developed using Real world data (RWD) that reflects use of broader, more heterogeneous populations and utilize variety of sources like clinical data, administrative/claims data, patient-generated/reported data, and emerging data sources including social media.
- Personalized medicine based on RWE adopts a data-driven approach and aims to design the best treatment option tailored to individual patients, using predictive analytics from a large data set. Artificial Intelligence tools like Neural Network and Deep Learning algorithms can act in tandem to generate more decisive outcomes than the traditional stratified approach, as every patient is different. Linking real-world clinical, healthcare and genomic data with the help of Deep Genomics and next-gen cognitive assistance can create study populations that provide generalizable evidence for precision medicine interventions.



Introduction

- Very few drugs are actually effective when considering broader patient population globally. They either act on a subset of population, or work in different ways on different people. Reasons include the difference in genetic makeups (genome), proteins in our body (proteome), metabolites (metabolome) and microbial flora (microbiome) amongst different individual. At this age of personalization, medicine is also poised to become more patient-specific.
- To accomplish that specificity --- the cost and time to develop drugs can increase due to delays in creating patient pools, difficulty in finding patients with the right genetic makeup, and the need to increase the length of trials to find drugs that will work for greater portions of the population. Changing the way of design and administering treatment trials, using real-world big data to bring personalized medicine to drug trials and research, has the potential to reduce costs, faster development of new drugs, and improve outcomes.
- At this crux, Deep learning, Artificial Intelligence, Internet of Things and Blockchain technologies can create amazing wonder if used properly. Ultimately, this procedure holds possibility of faster drug development with lesser risk and can create win-win situation for pharmaceutical companies and patients alike .



Part I:
The path to
Personalization

Present scenario---one size fits all!!

Current Medicine: "One Size Fits All" Healthcare



The problem is, we are all very different!

- Most medical therapies administered to large groups of patients only help a subset of the patients; frequently, we do not know why a particular treatment did not work in a given patient.
- Common diseases can have many different causes, and the effectiveness of a particular therapy may depend on the specific disease pathology in an individual patient.

Paul Ehrlich and Magic Bullets



- Paul Ehrlich was a Nobel prize-winning German-Jewish physician and scientist who worked in the fields of hematology, immunology, and antimicrobial chemotherapy. He is credited with finding a cure for syphilis in 1909.

The Magic Bullet is a scientific concept developed by German Nobel laureate Paul Ehrlich in 1900. Ehrlich formed an idea that it could be possible to kill specific microbes (such as bacteria), which cause diseases in the body, without harming the body itself. He named the hypothetical agent as Zauberkegel, the magic bullet. He envisioned that just like a bullet fired from a gun to hit a specific target, there could be a way to specifically target invading microbes.

Are we re-visiting the idea of Magic Bullets?

General vs Customized/Personalized



Personalized Medicine:

- An emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment and lifestyle for each person [NIH].

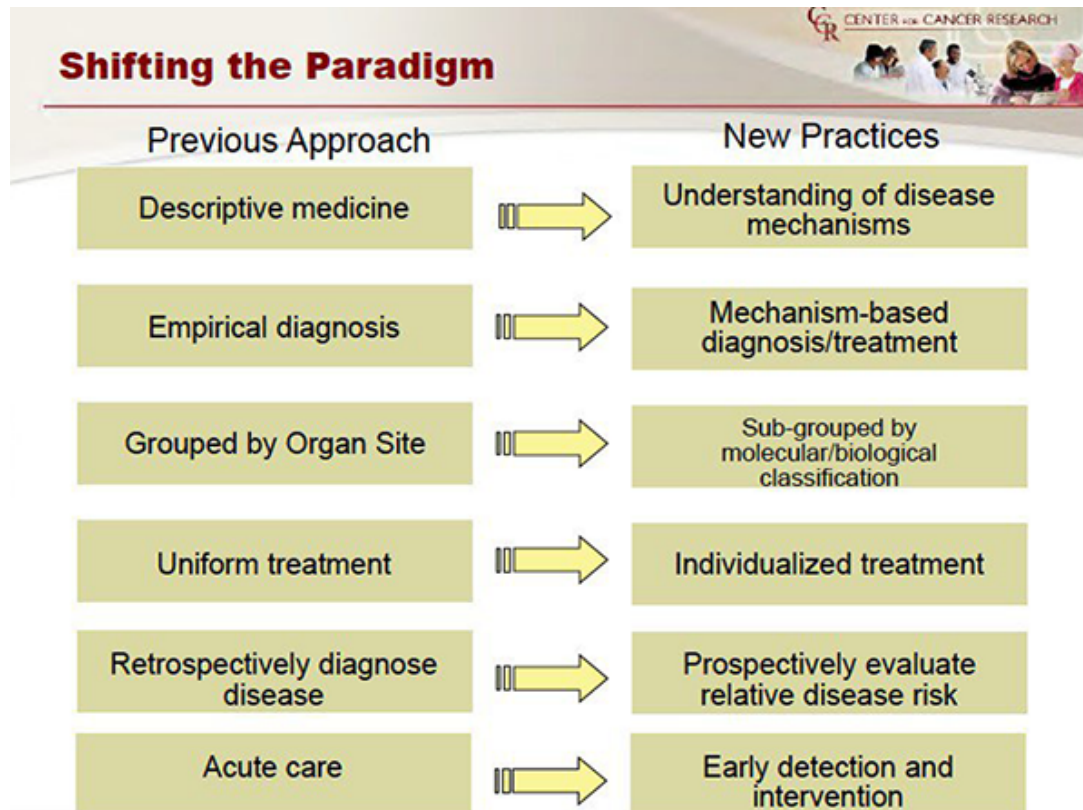
Heralding a new era



We have entered a remarkable era in which it is now possible to address:

- 1) The ubiquity of accessible information;
- 2) Massive increase in ability to store data; and
- 3) A revolutionary change in the ability to align computing to organize, curate, and analyze data with exponential improvements in speed and efficiency.

Shift to control



Traditional vs. Personalized medicine

TRADITIONAL MEDICINE **vs.** **PRECISION MEDICINE**

Traditionally, radiation, chemotherapy, and surgery were the only means by which doctors could treat cancer.

With precision medicine, doctors use a patient's genes to uncover clues for treating the disease.

RADIATION

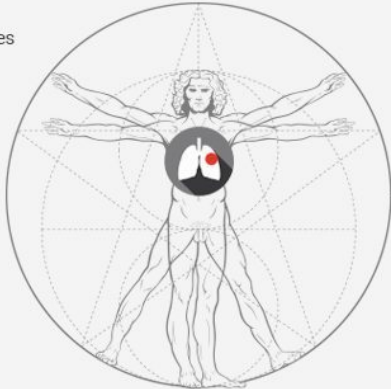
- High-energy particles damage or destroy cancer cells

CHEMOTHERAPY

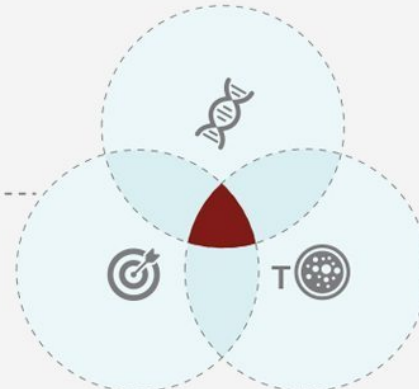
- Chemicals attack cancer

SURGERY

- Operate on part of the body to diagnose or treat cancer



Advanced
Personalized
Treatment



GENETICS

- Gene sequencing
- Locate cancer-causing genes

IMMUNOTHERAPY

- Identify ways to customize treatment
- Find ways to turn immune system on
- Personalize treatment with immune-activating drugs

TARGETED THERAPIES

- Drugs turn specific genes on or off

+ TRADITIONAL THERAPIES

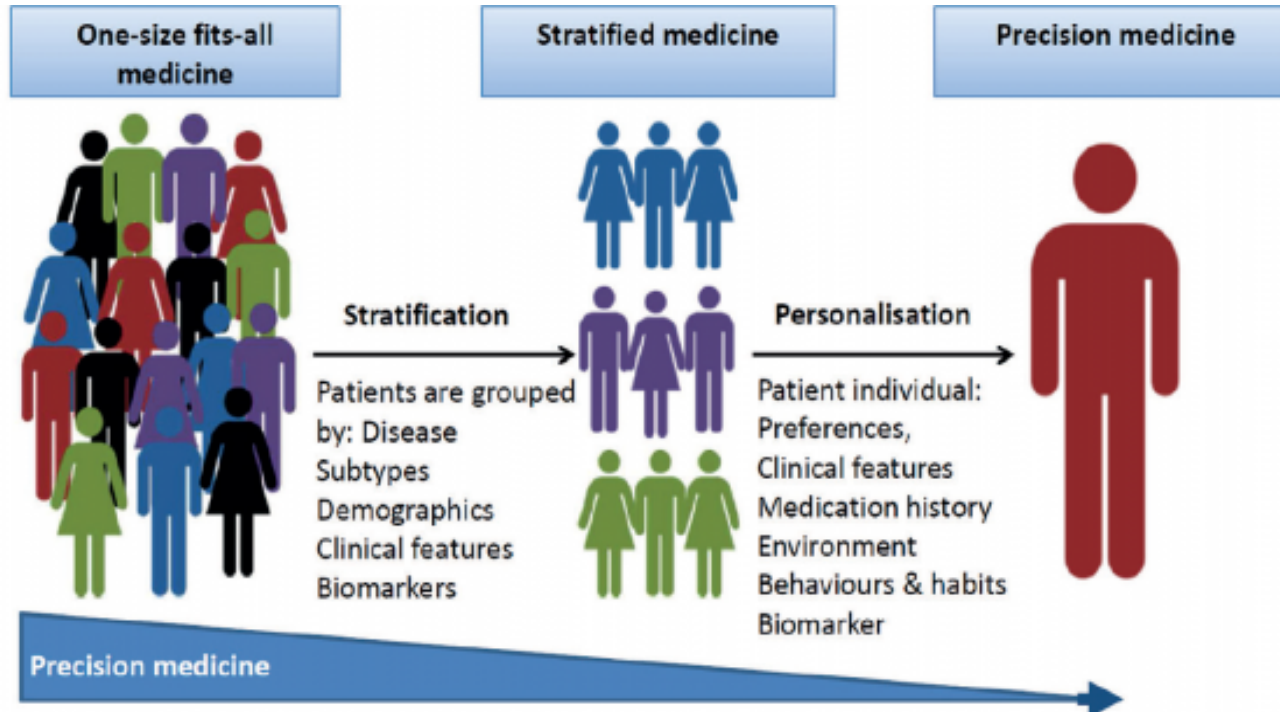
Example of targeted treatment in Oncology

What Are the promised benefits of Precision Medicine over traditional?

Precision medicine has following benefits over traditional medicine:

- It can do more. The primary aim of traditional medicine is to treat symptoms of a disease once they start. The goals of precision medicine are to predict, prevent, and treat disease.
- It's more accurate. Drugs and other traditional medicine treatments are created for and tested on large groups of people. Because they're prescribed so broadly, they don't work for everyone. The average prescription drug may not work well for all the people who take it. Precision medicine can predict which treatment will work best for you because it's targeted to your condition and genes. So a precision drug is far more likely to be effective against your disease than a drug that treats everyone in the same way.
- It makes side effects less likely. Any drug you take has risks. What makes precision medicine better is that targeted drugs act directly on the disease. They don't affect your entire body. And because you're more likely to find the right drug the first time, you won't have to take as many medicines. The fewer drugs you take, the lower the odds of side effects.

Path towards precision



Hitting the targets

- In many ways medicine has always been personal – a physician makes decisions based on their experiences and interaction with a patient. Truly personalized medicine though, is more revolutionary. With personalized medicine we can target treatments to those people we know will benefit the most. This will reduce waste, and lead to better outcomes for patients



Source: ignitedata.co.uk

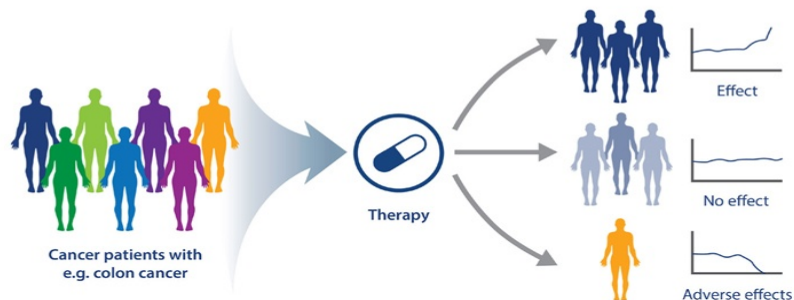
How Personalized Medicine can help?

- **Learning the disease risk.** Testing your genes can reveal which conditions run in your family and how likely you are to get them.
- **Prevent disease.** Once you know you carry a certain gene, you may be able to make lifestyle changes or get medical treatment so you don't get sick. For example, women who carry the BRCA1 or BRCA2 gene mutation are at higher risk for breast cancer.
- **Find disease.** If you know you're at risk for a certain disease, you can get tested for it. The earlier you find diseases like cancer, the easier they are to treat.
- **Target treatments.** Your genetic makeup can help guide your doctor to the drug that's most likely to work for you and cause the fewest side effects. Precision medicine can even help you decide what dose of a drug you should take.
- **Monitor your response.** Doctors can use precision medicine techniques to see how well your condition responds to a treatment.

What's in the future?

Current Medicine

One Treatment Fits All



Future Medicine

More Personalized Diagnostics



Part II:

It's all about Data

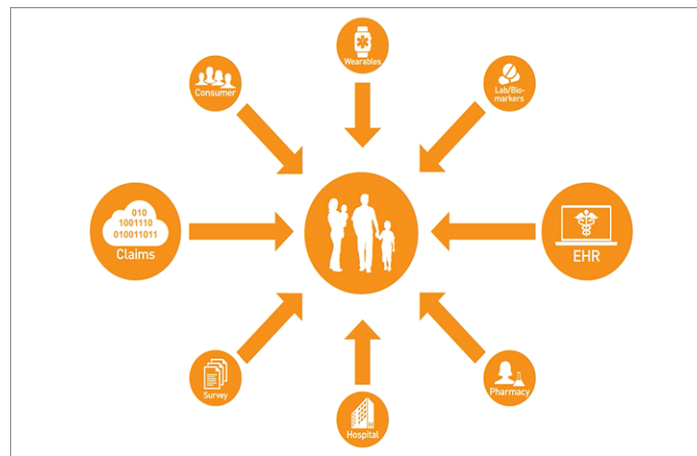
Entering the Real World

Real-World Data (RWD) :

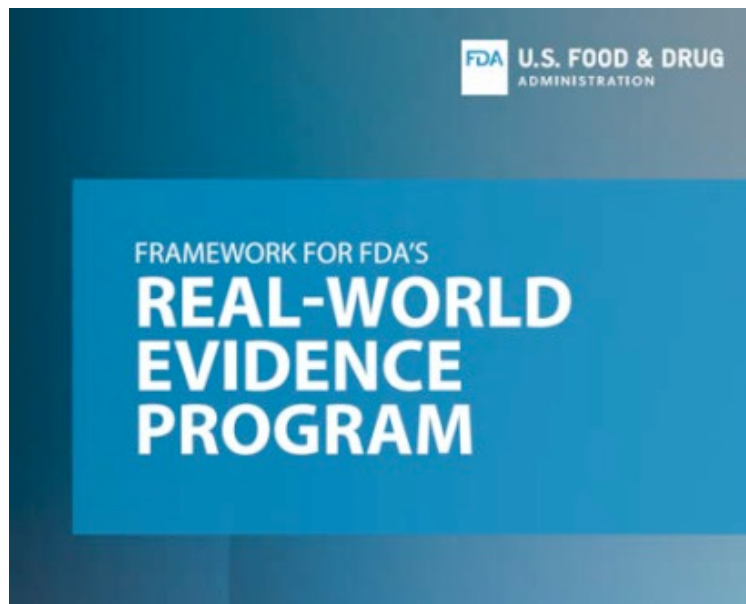
- RWD is the raw data being generated in the real world in healthcare system, outside of controlled setup of clinical trial. This can be in an electronic medical record data set, a claims data set, self-reported data, data coming from wearable and other medical devices.

Real World Evidence (RWE):

- RWE is the downstream insight that comes from analyzing RWD.



Regulatory focus on RWE



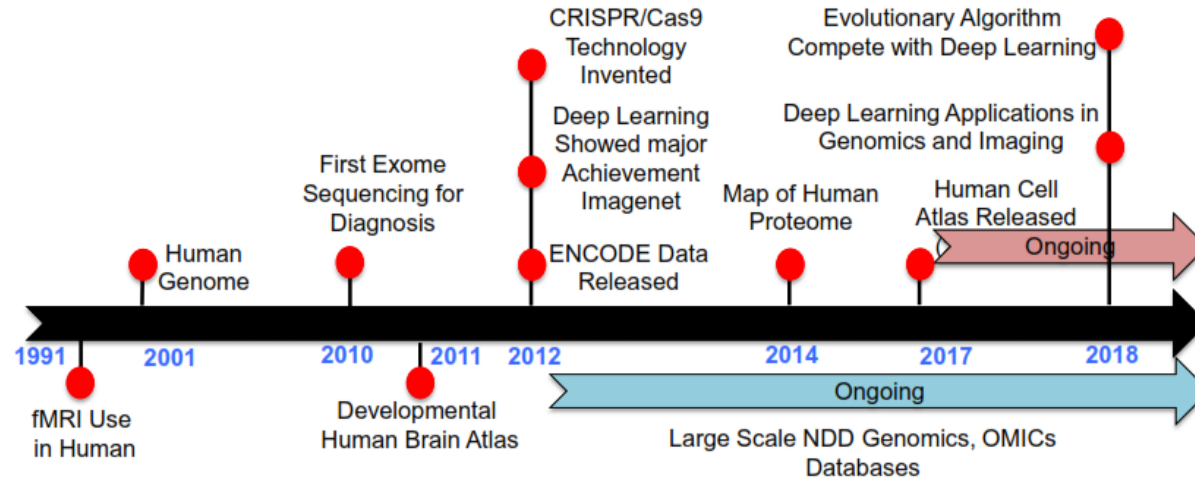
Why RWE is important for Personalized medicine

Data is the foundation for patient-centric, precision medicine clinical trials. The life sciences industry has historically relied almost exclusively on randomized controlled clinical trials for data, while making little use of real-world data (RWD) from patients and deep-diving the RWE.

- In some ways, existing patient data is essentially huge for a complete clinical trial. This data can be normalized to facilitate the search retrospectively for benchmarks and trends that can be leveraged to improve care. By collecting, organizing, and extracting from existing data sets, clinicians and researchers can assess how specific sets of patients reacted over several years.
- Data can also be utilized from direct and indirect sources to achieve a more holistic perspective on each patient, so there is now an enormous volume of qualitative and quantitative data for advancing precision medicine.
- In recent years, RWE has been used to speed up the approvals process – this is the most common application of RWE in the pharma world currently. Recent example : Avelumab by Merck . Approval achieved within 3 years after filling IND. (2014-2017).
- Over the coming years, RWE could be used as a control arm in trials. This would reduce the burden of cost that clinical trials bring, and accelerate them too. Eventually, that can lead to speeding up and cheapening trials.



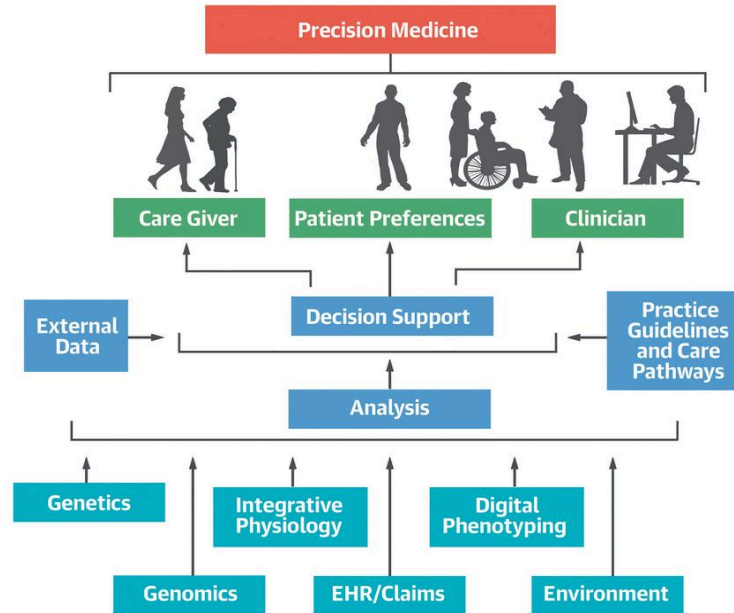
Milestones which helped personalized medicine concept



Source: npj Digital Medicine (2019) 112

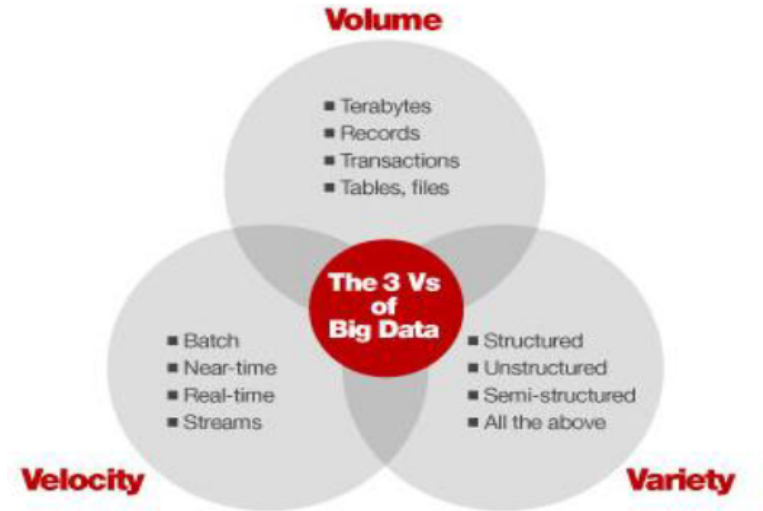
The complexity of reach

CENTRAL ILLUSTRATION: Precision Medicine

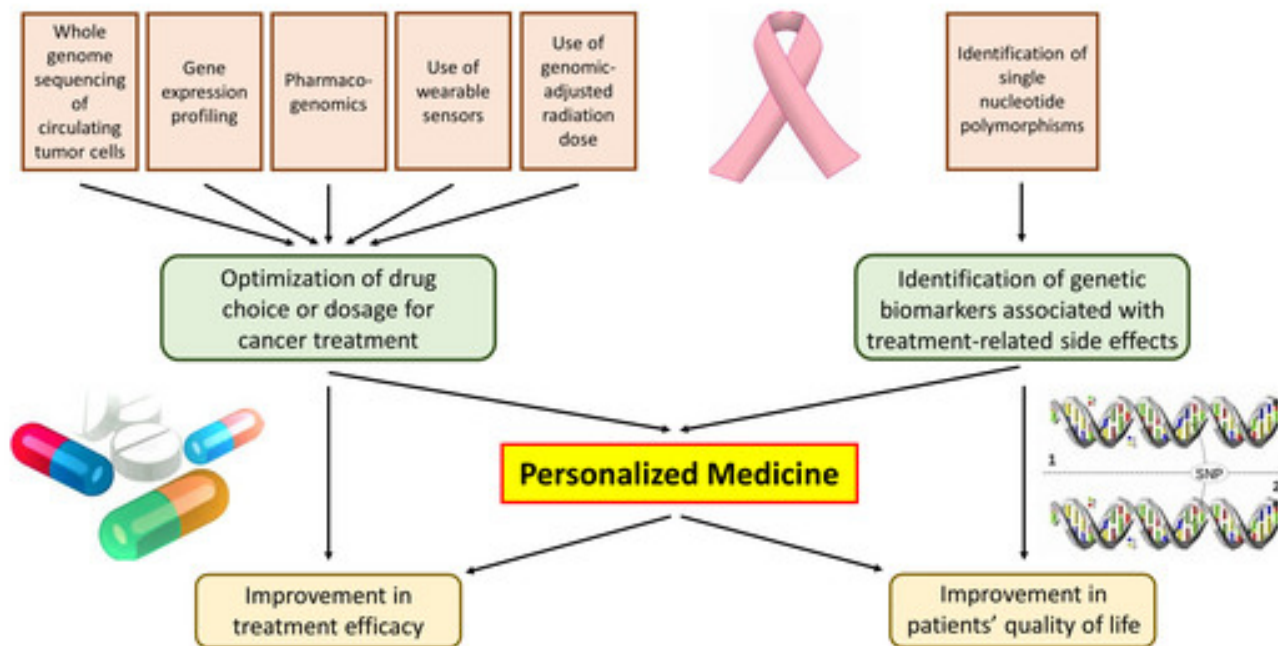


Califf, R.M. J Am Coll Cardiol. 2018;72(25):3301-9.

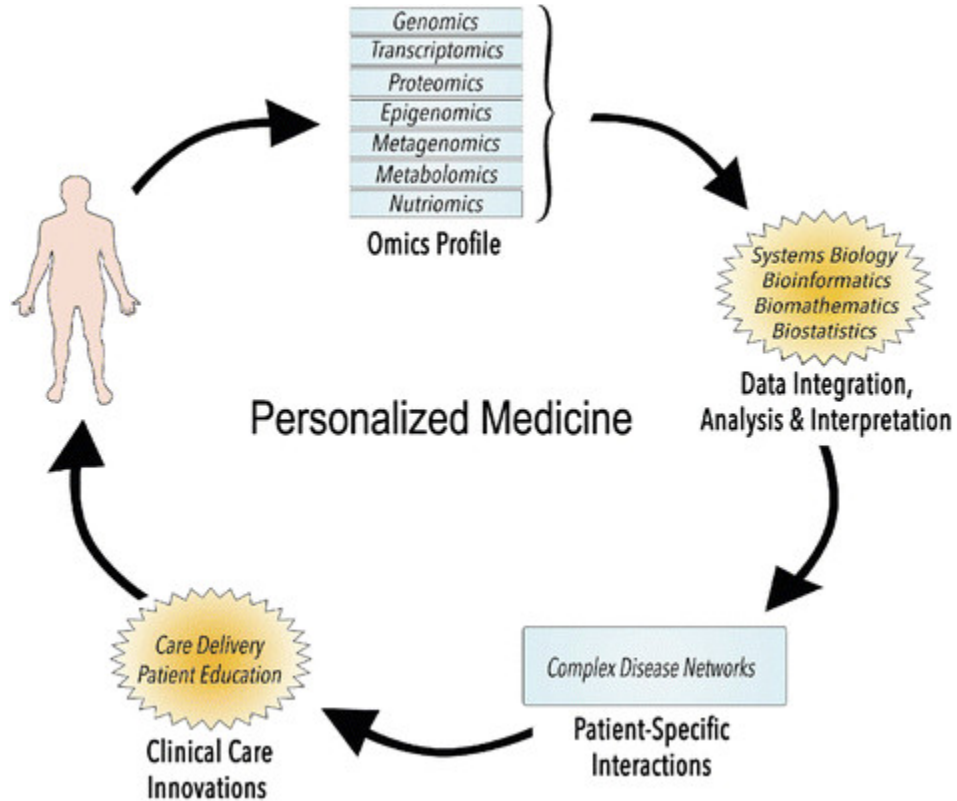
Real-World, Big Data



The parts and parcels



It's all about “-omics”

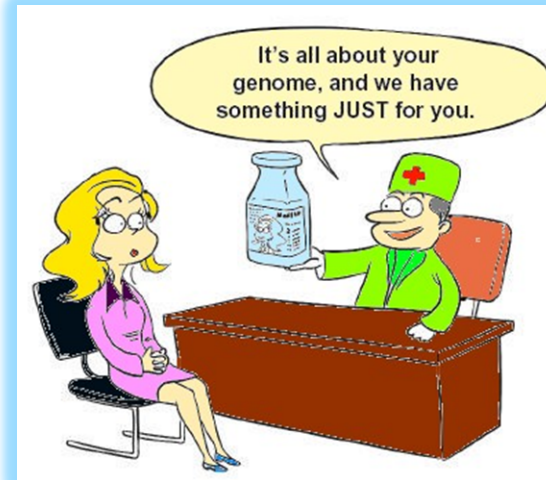


Genomics in action: Towards accuracy

When researchers compare the genomes of people taking the same drug, they may discover that a set of people who share a certain genetic variation also share a common treatment response, such as:

- A greater risk of side effects
- The need for a higher dose to achieve a therapeutic effect
- No benefit from the treatment
- A greater or more likely benefit from the treatment
- The optimal duration of treatment

This kind of treatment information is currently used to improve the selection and dosage of drugs to treat a wide range of conditions, including cardiovascular disease, lung disease, HIV infection, cancer, arthritis, high cholesterol and depression.



An example for targeted therapy with the help of genomics

Thiopurine methyltransferase (TPMT) testing for people who are candidates for thiopurine drug therapy:

- Thiopurine drugs are used to treat some autoimmune disorders, including Crohn's disease and rheumatoid arthritis, as well as some types of cancer, such as childhood leukemia.
- The TPMT enzyme helps break down thiopurine drugs. People who are TPMT deficient don't break down and clear out these drugs quickly enough. As a result, the drug concentration in the body is too high and increases the risk of side effects, such as damage to the bone marrow (hematopoietic toxicity).
- Genetic testing can identify people with TPMT deficiency so that their doctors can take steps to reduce the risk of serious side effects — by prescribing lower than usual doses of thiopurine drugs or by using other drugs instead.



Part III: Artificial Intelligence in Action

NEWS

[Home](#)[Video](#)[World](#)[Asia](#)[UK](#)[Business](#)[Tech](#)[Science](#)[Stories](#)[Entertainment & Arts](#)Technology

Artificial intelligence-created medicine to be used on humans for first time

By Jane Wakefield
Technology reporter

🕒 30 January 2020

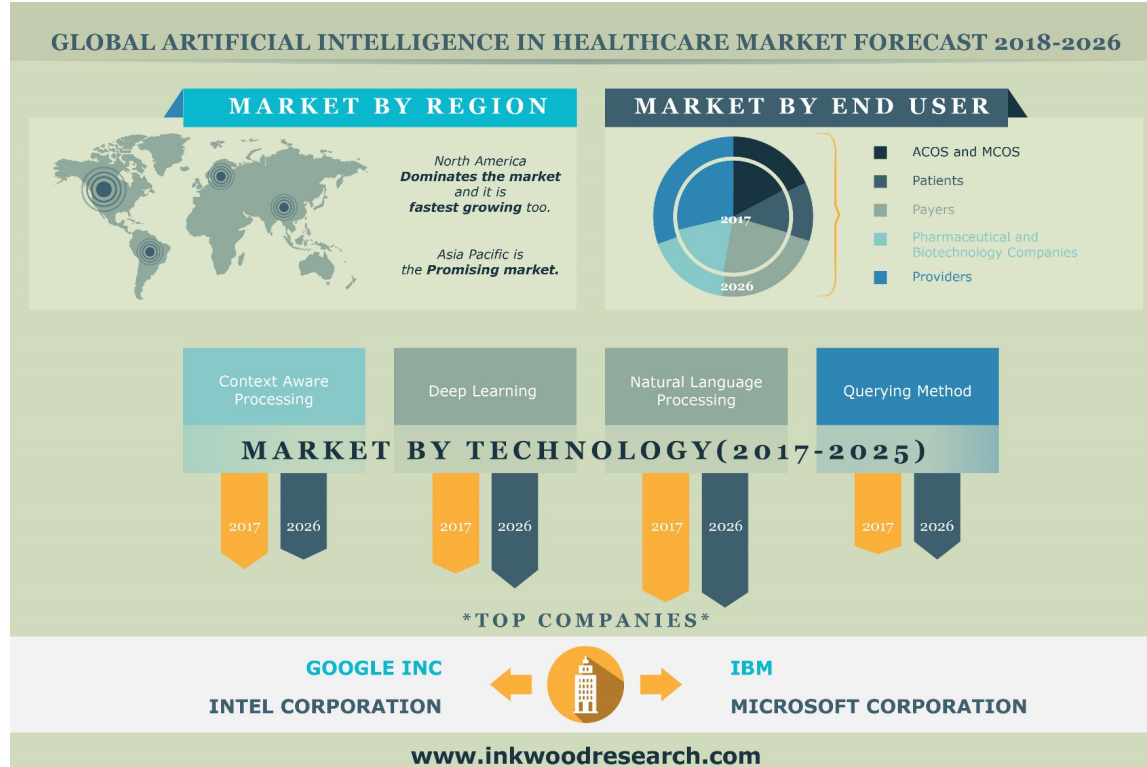


Share

A drug molecule "invented" by artificial intelligence (AI) will be used in human trials in a world first for machine learning in medicine. It was created by British start-up Exscientia and Japanese pharmaceutical firm Sumitomo Dainippon Pharma. The drug will be used to treat patients who have obsessive-compulsive disorder (OCD).

Typically, drug development takes about five years to get to trial, but the AI drug took just 12 months.

Global Healthcare Market share of AI

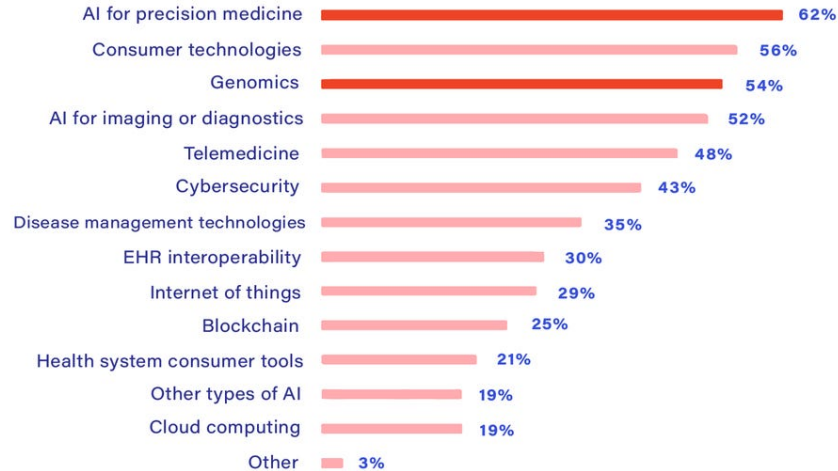


AI powered personalized medicine is impactful



Most US Health Systems Think **AI-Powered Precision Medicine** Will Be High Impact Within 5 Years

“ Which five categories of health IT do you anticipate will have the most impact on health systems five years from now? ”



Source: Center for Connected Medicine, n=63 C-level execs at US health systems, 2019

BUSINESS INSIDER
INTELLIGENCE

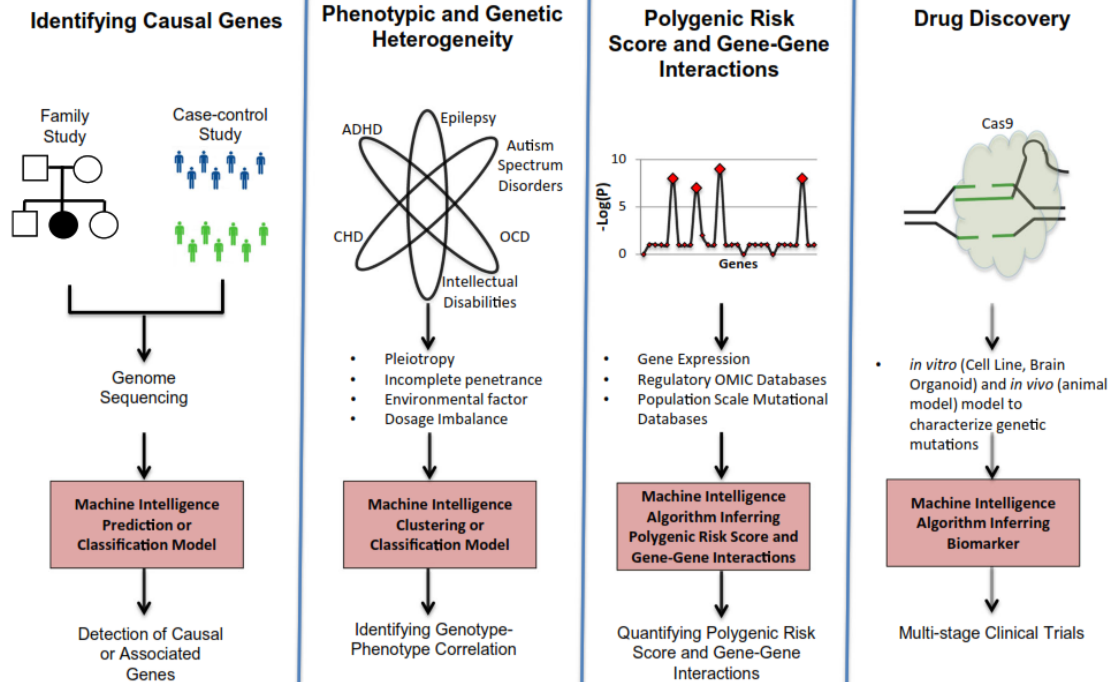
Source : Business Insider

The AI Effect

- With AI, the ability to not only predict outcomes but also be able to predict future patients' probability of having diseases is a major benefit for precision medicine.
- By better understanding why diseases may occur and in what environments they are more likely to occur, artificial intelligence can help in the education of medical professionals to know what to look for before a disease is showing symptoms. To be able to evaluate the risk of disease in patient populations is revolutionary for healthcare and the lives of many.
- AI can interpret and aggregate imaging, text, handwritten notes, test results, sensor data, and even demographic and geo-spatial data. This helps speeding up data acquisition, segregation and store better.
- AI will be able to cross reference data, find commonalities and draw insights that were previously impossible due to data silos or the sheer amount of time it would take for a human to crunch the numbers.
- It can also consider seemingly unrelated or outside factors that doctors and researchers may not immediately see as relevant. For example, environmental factor, such as elevation, humidity and proximity to certain dense mineral deposits, factories or agriculture
- This ability to rapidly analyse data, and potential correlations, creates a more comprehensive and holistic view into a patient's health.



Machine Learning in medicine development



Focus of AI technologies for personalized medicine

- AI-enabled digital transformation can improve patient selection and increase clinical trial effectiveness, through mining, analysis and interpretation of multiple data sources, including electronic health records (EHRs), medical imaging and 'omics' data.
- Next few slides will focus on use of AI for the improvement of trial efficiency through better patient recruitment, cohort design, improvement of monitoring and cognitive computing efficiency.

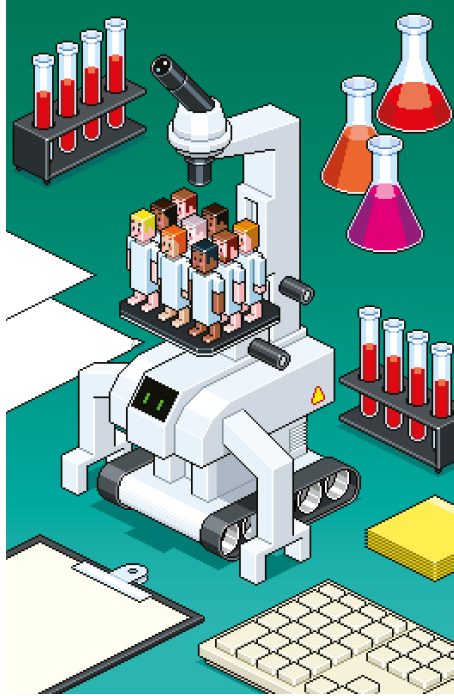


Patient recruitment challenges



According to a 2016 study, 18% of cancer trials that launched between 2000 and 2011 as part of the US National Cancer Institute's National Clinical Trials Network failed to find even half the number of patients they were seeking after three or more years of trying, or had closed entirely after signing up only a few volunteers. An estimated 20% of patients with cancer are eligible to participate in such trials, but fewer than 5% actually do.

Improvement of patient recruitment through AI



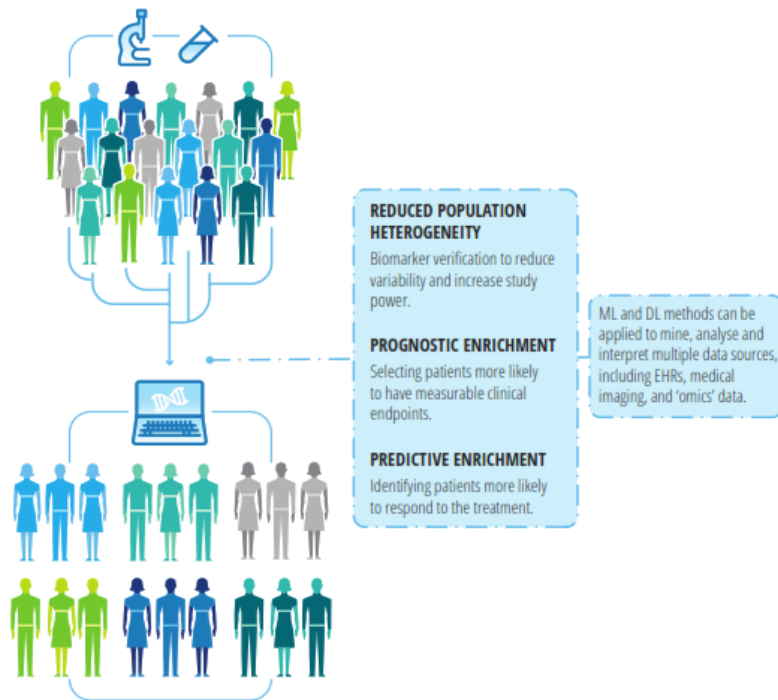
Source: Nature, Vol. 573.(2019)

- Natural language processing (NLP), enables computers to analyze the written and spoken word. This can limit the actual patient travel/visits to the site.
- ML and in particular deep reinforcement learning empowers systems to automatically analyze EHR and clinical trial eligibility databases, find matches between specific patients and recruiting trials, and recommend these matches to doctors and patient for participating in a given clinical trial.
- Utilizing social media analytics is also a preferred method for finding and recommending trial participants. These can potentially enhance reach and efficiency of the trial recruitment, and expedite targeted medicine development.

Heterogeneity of trial

How AI technologies can help deliver clinical trial enrichment strategies highlighted in FDA guidance

Trial enrichment strategies



Source: Deloitte analysis.

Prognostic enrichment:

Choosing patients who are more likely to have a measurable clinical endpoint.

Predictive enrichment:

Identifying a population more capable of responding to a treatment.

More eyes on trial: Monitoring improvement

Connected devices have huge potential to make clinical trials more patient centric and generate endpoints which are viewed to have greater value.

- Wearable sensors and video monitoring can be used to automatically and continuously collect patient data, thereby relieving the patient of this task.
- Wearables can provide real-time information on activity levels (exercise, sleep patterns) and vital signs (heart rate, blood pressure, breathing, blood-sugar levels) that allow for early detection of problems and personalized interventions.

Wearables offer promise in clinical trials and healthcare more generally with the potential to:

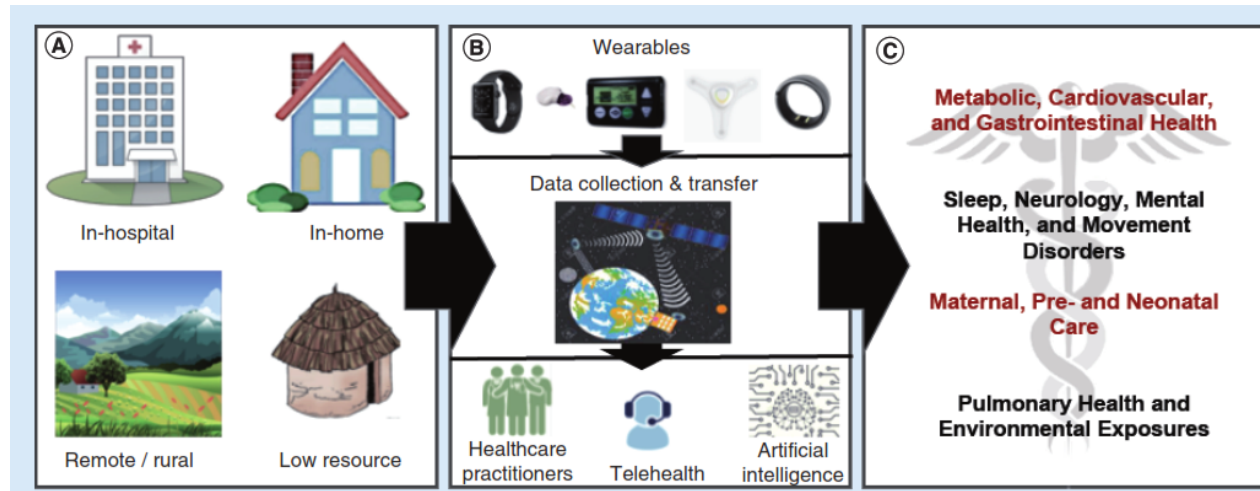
- provide richer baseline information
- contribute to understanding the safety and tolerability profile
- Novel endpoints and/or objective measures of subjective outcomes



Some devices even nudge users to take healthy actions, like going for a brief walk if they've been sedentary too long, or de-stressing with a mindful moment. It creates a truly personalized health improvement.

AI for efficiency

- ML, and particularly Deep Learning (DL) models can be used to analyze data in real-time for detecting and logging events of relevance.
- AI also has an important role to play in image-based endpoint detection. ML technologies hold potential for rapid detection of diseases from medical images and can also reduce the cost associated with image-based studies.
- AI and ML methods may also be used to dynamically predict the risk of dropout for a specific patient, to detect the onset of patient behavior that suggest difficulty to adhere to the trial protocol. The use of deep reinforcement learning algorithms help simulating the optimal treatment dose at reduced toxicity to have desired treatment effect, and thereby it can reduce the risk of patient dropout and in turn can increase trial efficiency.



AI for Connected devices

- Algorithms for analyzing, and continuously correlating, contextualizing, and filtering raw data in real-time directly at the point of sensing, will be necessary to extract actionable information. Deep learning (DL) models in combination with on-sensor data pre-processing and curation systems allow this task to be accomplished.
- To run DL algorithms continuously in real-time at the point of sensing, ultra-low-power consumption mobile processors are needed. Advances in developing both novel AI hardware and AI software techniques over the years have led to several versions of such AI-tailored mobile processing solutions now being available for real-life use.



Investing in sensors

Table 1. Examples of common consumer, clinical and research-grade wearable sensors.						
Manufacturer	Model	Market	Cost (USD)	Form factor	Sensors	US FDA status
Abbott	Libre	Ambulatory diabetes monitoring	149.98 (cost for reader and 10-day sensor)	Semi-invasive	CGM	Approved
AliveCor	Kardia Band	Consumer	199	Wristband	ECG	Cleared
Apple	Watch Series 3	Consumer	329	Watch	Accel, ambient light sensor, BALT, Gyro, PPG HR, GPS	Precertified
Ava Science, Inc.	Ava Wristband	Consumer	249	Wristband	Accel, EDA, PPG HR, temperature sensors	Approved
BACtrack	Skyn	Pre-Market	–	Wristband or watch	Transdermal	–
Bloomlife	Smart Pregnancy Tracker	Consumer (rental)	20/week	Abdominal patch	Accel, 3-channel AFE	–
Dexcom	G5 Mobile	Ambulatory diabetes monitoring	1016 (cost for transmitter, receiver, 4-pack of replaceable sensors)	Semi-invasive	CGM	Approved
Empatica	Embrace	Consumer	249	Watch	Accel, EDA, Gyro, peripheral temperature sensor	Approved
Fitbit	Charge	Consumer	149.95	Watch	Accel, PPG HR	Precertified

Accel: Accelerometer; AFE: Analog front end; BALT: Barometric altimeter; CGM: Continuous glucose monitor; ECG: Electrocardiography; EDA: Electrodermal Activity; EMG: Electromyography; GPS: Global positioning system; Gyro: Gyroscope; HR: Heart rate; PPG: Photoplethysmography; Therm: Thermometer.

Source: Personalized Medicine (2018) 15(5)

Digital biomarkers

Table 2. Digital biomarkers of disease developed from wearable sensor data.

	Lyme disease	Respiratory viral infection	Insulin resistance	Atrial fibrillation
Wearable device sensors	Resting HR (PPG)	Resting HR (PPG)	Diumal HR difference (PPG)	HR (AliveCor ECG)
	Skin temperature (Thermopile)	Skin temperature (Thermopile)	Physical activity (accelerometer)	HR (PPG)
	SpO ₂ (Pulse Oximeter)			
ML algorithm	Peak detection; logistic regression	Sliding window peak detection; logistic regression	Multiple regression	Deep neural network
HR: Heart rate; PPG: Photoplethysmography.				

Source: Personalized Medicine (2018) 15(5)

Conclusion

- Personalized medicine development can take advantage of a myriad of disruptive technologies to be utilized for developing treatments, practicing medicine, and delivering care.
- Currently, large amount of multi-omics data, imaging, medical devices and EHR data collected from large-scale cohorts and population studies have the potential to be implemented in personalized medicines discovery. Advanced machine learning techniques like deep learning and platforms for cognitive computing represents the future toolbox for data driven analysis of biomedical big data. With artificial intelligence, it takes precision medicine to the next level and increases the accuracy and prediction of outcome for patients.
- However, infusing innovation that changes established processes is a difficult task and it should be approached and implemented with caution. Usable AI technology first needs to be tested alongside the existing technology which it aims to complement or replace, and the benefit must be demonstrated in an explainable, ethical and scalable way – to users as well as to regulatory bodies. This approach may ensure AI adoption into the clinical trial ecosystem, making trials faster and holding the potential to lowering failure rates and R&D costs.
- It may not be an exaggeration to say that we have lot of data and diverse technologies at hand, but suitable amalgamation of them is still at nascent stage, considering biomedical data. RWE is a stepping-stone or link for data to medicine, and integration of disruptive technologies with RWE will curve the future path of personalized, precision medicines and herald a new dawn in healthcare.

Bibliography

1. P.Shah et al. (2019): Artificial Intelligence and Machine Learning in Clinical Trial Development: A Translational Perspective. npj Digital Medicine (2019) 2:69.
2. D, Cirrilo, A.Valencia (2019): Big Data analytics for Personalized Medicine. Current Opinion in Biotechnology 2019, 58: 161-167
3. V, Agarwala et al. (2018): Real-World Evidence In Support of Precision Medicine. Health Affairs 37, No. 5 (2018): 765–772
4. Harrer, S. et al. (2019): Artificial Intelligence for Clinical Trial Design. Trends in Pharmacological Sciences, August 2019, Vol. 40, No. 8
5. Marcus, Woo (2019): Trial by Artificial Intelligence. Nature, Vol. 573.
6. Bartalan, Mesko (2017): The role of artificial intelligence in precision medicine. Expert Review of Precision Medicine and Drug Development, 2017, Vol. 2, No. 5, 239–241
7. Romero, K. et al. (2015): The future is now: model-based clinical trial design for Alzheimer's disease. Clinical Pharmacology and Therapeutics. 97, 210–214
8. Fogel, D (2018): Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review. Contemporary Clinical Trial Communications 11(2018) 156-164
9. Asif, U. et al. (2019) SeizureNet: a deep convolutional neural network for accurate seizure type classification and seizure detection. arXiv Published online March 8, 2019. <https://arxiv.org/abs/1903.03232>
10. Comments from article “The best approach to maximize RWE Technology Platform output through the use of advance computing” by Bruce Capobianco, Real World Evidence Strategy and Analytics, ICON.
11. Also publicly available information through various search engines, published reports etc.



tusind tak
dankjem vám
ありがとう
ngiyabonga
dziękuję
merci
baie dankie
धन्यवाद
molte grazie
suksema
danke
gracias
obrigada
obrigado
teşekkür ederim
tack så mycket
thank
you
tak
gràcies
tānan
dank u
mahalo
teşekkür edire
mahalo



Contact:

Arnab Goswami

DOCS, a Division of ICON (ICON DOCS)
Address: ICON Clinical Research India Private Limited
Indiqube Zeta, 4th Floor, Kaikondanahalli, Varthur Hobli,
Bengaluru East Taluk, Sarjapur Road, Bengaluru - 560035
Karnataka, India
Work phone: 080 4039 4018

E-mail: Arnab.Goswami@docsglobal.com

E-mail: Arnab.g80@gmail.com