Chapter II

2018

The Current State of The Longevity Industry

- Global Longevity Industry Landscape 2018
- Key Persons
- Top 100 Longevity Companies
- Top 100 Venture Firms
- The Business of Longevity Technology Overview
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- Mind Map 124 P3 medicine technologies
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    - *Health / Fitness apps*
    - *Telemedicine*
    - *Virtual / Augmented Reality*
    - *Digital Health Records*
    - *Blockchain / NextGen Databases*

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-Geroprotectors
-Regenerative Medicine
-Gene therapy
-Cell therapy
-NeuroTech
-Prosthetics
-Nutraceuticals
-Microbiome
-AgeTech
-Scientifically-validated lifestyle recommendations

- Biomarkers of Aging

GLOBAL LONGEVITY INDUSTRY LANDSCAPE 2018

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“ The fourth industrial revolution is still in its nascent state. But with the swift pace of change and disruption to business and society, the time to join in is now. ”

~ Gary Coleman, Global Industry Advisor, Deloitte Consulting

The previous chapter provided a broad history of geroscience and its evolution into a fully fledged longevity industry. Two disparate disciplines were introduced: biomedical gerontology and regenerative medicine. These did not intersect until recently, when a possible synergy in the form of rejuvenation biotechnology presented itself to technologists.

The following chapter describes the state of progress today and identifies additional fields of possible future relevance currently reaching fruition, along with the longevity implications of each, some of which may not be immediately obvious.

It provides an overview of the techniques that could slow or reverse age-related ill health and the P3 approach to medicine. It summarises the diversification of uses for AI, from drug discovery to wearable devices to hospital management, the refinement of gene therapy and stem cell therapy, the decline and possible rescue of biopharma, advances in bionics, prosthetics, geroprotective drugs and regenerative medicine. It is argued that, currently, the most market-ready technologies are prognostics and diagnostics, and that the technologies which will achieve some degree of true rejuvenation will emerge in the next 3 to 10 years (a point that will be further justified in chapter 4, which deals with market-readiness in depth).

It begins with a rundown of companies and investors currently driving the fledgling industry forward, offering overviews of the current state of progress in each of its many converging strands, shining a spotlight on relevant technologies that are either already implemented, or on the cusp of implementation later this year. For further details on any of the entities referenced, please see Appendices I (Top 100 Longevity Industry Companies Profiles) and II (Top 100 Longevity Industry Investor Profiles).

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Key Longevity Industry Influencers

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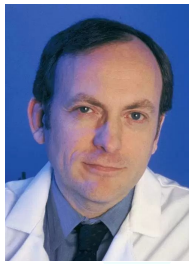
Longevity Scientists


Michael West


Eric Verdin


Cynthia Kenyon


Aubrey de Grey


Steve Horvath


Joao Pedro de Magalhães

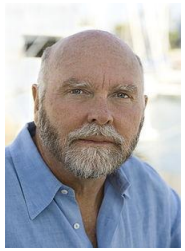

David Sinclair


Nir Barzilai


George Church


Brian Kennedy

Longevity Influencers


J. Craig Venter

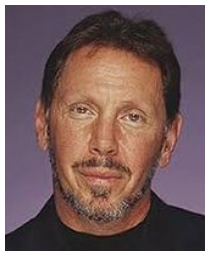

Larry Page


Sergey Brin


Ray Kurzweil


Alex Zhavoronkov


Nathaniel David


Larry Ellison


Martine Rothblatt

Longevity Investors


Dmitry Kaminskiy


Bryan Johnson


Peter Thiel


Jeff Bezos


Jim Mellon


Finian Tan


Sam Altman

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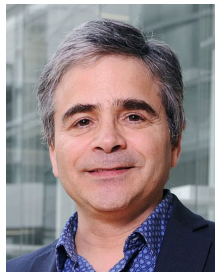
Top Longevity Scientists and Influencers


Anthony Atala


Joon Yun


Adam Antebi


Elizabeth Blackburn


Nursultan Nazarbayev


Bill Faloon

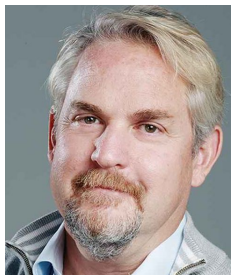

Peter Diamandis

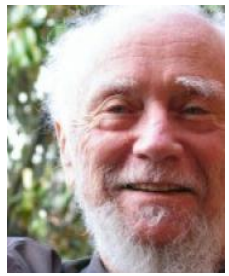

Sally Greengross


Michael Kope


Stephen Johnson

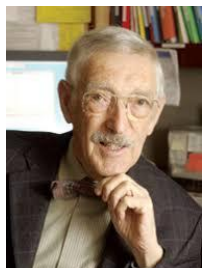

Maria Blasco

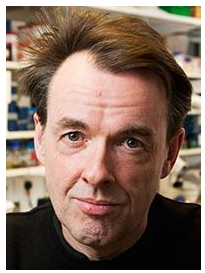

Andy Conrad


David Finkelstein

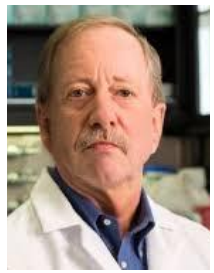

David Botstein


John D. Furber

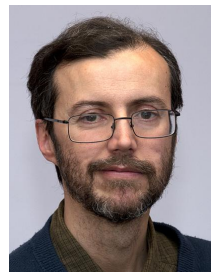

Bruce Ames


David Gems


Denham Harman


Steven Austad


Robert Freitas


Alex Freitas

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Key Longevity Influencers

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Top Longevity Scientists and Influencers


Vitalik Buterin


Alexey Moskalev


Ilia Stambler

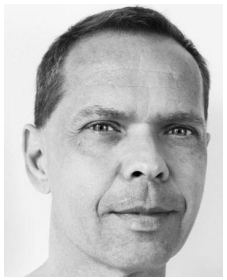

Edwina Rogers


Robin Farmanfarmaian


Christine Peterson


Linda Partridge


Bill Maris


Michael Greve

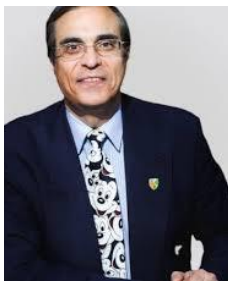

Maria Konovalenko


Calvin Harley

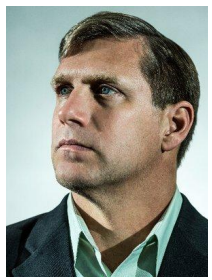

Leonard Guarente

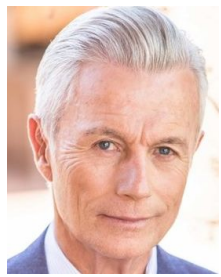

Thomas Langer


Nils-Göran Larsson


Jose Cordeiro


Dmitry Itskov


Zoltan Istvan


James Strole


Bernadeane


Robert Young


Kevin Perrott

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Top Longevity Scientists and Influencers


Arthur Bilger


Laura Carstensen


Henry Cisneros


Pinchas Cohen


Catherine Collinson


Joseph Coughlin


Fernando Torres-Gil


William Dow

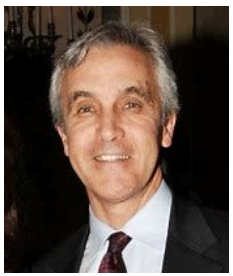

Ken Dychtwald


Marc Freedman


Linda Fried


Lynn Goldman


Christopher Herbert


Michael Hodin


Jo Ann Jenkins


Yves Joanette


Becca Levy


Freda Lewis-Hall


Robin Mockenhaupt


Philip Pizzo


Andy Sieg

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Youngsook Park


Keith Comito


Alexey Turchin


David Wood


Arielle Burstein


Rita Beamish


Paul Irving


Rodney Slater


Trent Stamp

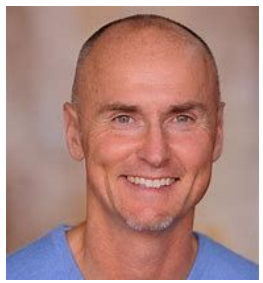

Dana Ardi


Errol Barnett


Arthur Bilger


Fred Jonske


Alexander Klabin


Chip Conley


Richard Eisenberg


Chris Farrell


Sherry Lansing


Campbell Gerrish


Taimur Hyat


Robert Johnson

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David Amess


Laura Deming


John Bell


Helen R. Griffiths


Martin Green


Paul Thornalley

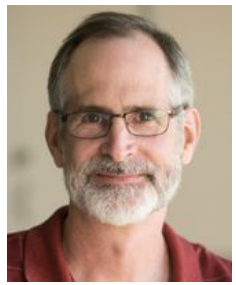

Janet Thornton


Malcolm Jackson


Tom Kirkwood


Andrew Krentz


Ilora Gillian Finlay


Joel Parker


Richard Barker


Richard Faragher


Joao Passos


Narendra Patel


Paul Keith Potter


Julia Neuberger


John Speakman


Aisling Burnand


Anne McArdle

Top 10 Lists

Top 10 Reg Med Companies

Top 10 Longevity Companies

Top Gene 10 Therapy Companies

Top 10 Longevity Venture Funds

Top 10 P3 Medicine Companies

Top 10 Research Institutions

Top 100 Longevity Companies

1. Aeonian Pharmaceuticals
2. AgeX
3. Alkahest
4. Antoxis
5. AstraZeneca
6. Athersys
7. AxoGen
8. Avalon AI
9. BGI
10. BIOAGE Labs
11. BioLife Solutions
12. BioMarin
13. BioMarker Pharmaceuticals
14. BioTime
15. BrainPatch
16. Bluebird Bio
17. Calico
18. Canada Cancer & Aging Research Laboratories (CCA-RL)
19. Cell
20. CellAge
21. Celularity
22. Centagen
23. Centrillion Technologies
24. Chipscreen
25. Chronos Therapeutics
26. CohBar
27. Color Genomics
28. Cyfuse Biomedical
29. Cytori
30. DeepWave Technologies
31. Definigen
32. Editas Medicine
33. Elysium Health
34. Emulate
35. Epitracker
36. Eterly
37. Everist Health
38. Everon Biosciences
39. Evox Therapeutics
40. Fronteo
41. Genedrive
42. Genescient Corp
43. Genos
44. GenSight Biologics
45. Genzyme Corporation
46. Geron
47. Harbour Biomed
48. Hua Medicine
49. Human Longevity Inc.
50. Ichor Therapeutics
51. Inception Sciences
52. Insilico Medicine
53. Juvenescence AI
54. Juventas Therapeutics
55. Kailos Genetics
56. Leadhexa Biotechnologies
57. LifeGen
58. Longevity Biotech
59. MacuCLEAR
60. Mesoblast
61. Metabomed
62. Mitobridge
63. Mitotech
64. Navitor
65. Nemaura
66. NovaDip Biosciences
67. NuSirt
68. Oisin Biotechnologies
69. NOX Technologies
70. Orig3n
71. Osiris Therapeutics
72. Oxstem
73. PHIGENIX
74. Pluristem
75. Population Bio
76. Prana Biotechnology
77. Proteome Sciences
78. Proteostasis Therapeutics
79. PureTech Health
80. Retrotope
81. Quark Pharmaceuticals
82. Quincy Bioscience
83. Rapamycin Holdings
84. ReThink Pharmaceuticals
85. Revance Therapeutics
86. RondinX
87. Samumed
88. Semma Therapeutics
89. Signum
90. Silene Biotech
91. Sierra Sciences
92. SIWA Therapeutics
93. TauRx Therapeutics
94. Unity Biotechnology
95. Universal Cells
96. Vault
97. Vericel Corporation
98. Veritas Genetics
99. Visgeneer
100. Youth Laboratories

Company Landscape

Regenerative Medicine

P3 Medicine

Gene Therapy

Geroscience

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Top 100 Venture Firms

1. ABN AMRO
2. Accuitive Medical Ventures
3. Advantech Capital
4. Alexandria Venture
5. Ally Bridge Group
6. ALS Finding a cure
7. AME Cloud Ventures
8. Amino Capital
9. Ann Arbor SPARK
10. ARCH Venture Partners
11. Arkin Holdings
12. Aspire Capital Partners LLC
13. ATEL Ventures
14. BRCC
15. Brainchild Holdings
16. Cardinal Partners
17. Casdin Capital
18. Celgene
19. CIRM
20. Cyberdyne
21. Deep Knowledge Life Sciences
22. Deerfield Partners
23. DeNovo Ventures
24. DFJ
25. Easton Capital
26. EcoR1 Capital
27. Eight Roads Ventures
28. Emerson Collective
29. Essex Woodlands Health Ventures
30. F-Prime Capital Partners
31. Ferghana Partners
32. Fidelity Investments
33. First Analysis
34. Flagship Pioneering
35. Forbion Capital Partners
36. Formation 8
37. GE Capital
38. GE Ventures
39. General Catalyst
40. GV
41. Harvest Global Investments
42. Horizon Ventures
43. Illumina
44. Integrale Advisors
45. Inventages Capital Investment inc
46. Jennison Associates
47. Juno Therapeutics
48. Juvenescence Limited
49. Khosla Ventures
50. LabCorp
51. Legend Capital
52. LYZZ Capital
53. Magic Stone Alternative
54. Mayo Clinic Ventures
55. Merck Ventures
56. NanoDimension
57. Nazem and Company
58. New Science Ventures
59. Nivelinvest
60. Odey Asset Management
61. Odey Swan
62. Omega Funds
63. OrbiMed
64. OS Fund
65. Oxford Finance Corporation
66. Oxford Sciences Innovation
67. Partners Innovation Fund
68. Piper Jaffray Private Capital Group
69. Polaris Partners
70. RA Capital Management
71. Ramius Advisors
72. Sanofi-Genzyme BioVentures
73. Shibuya Kogyo
74. Silicon Valley Bank
75. Sino-Alliance International LTD
76. S.R.I.W
77. Sphera Funds Management
78. Springboard Capital
79. StartUp Health
80. Sutter Hill Ventures
81. SWMF Life Science Fund
82. Syno Capital
83. Synthetic Genomics
84. T. Rowe Price
85. Tan Thay
86. Techammer
87. Techno Venture Management
88. Testudo Funds
89. The Thiel Foundation
90. Third Rock Ventures
91. Toray Engineering
92. TVM Capital
93. TYLT Ventures
94. Venrock
95. Versant Ventures
96. Vertex Ventures
97. Viking Global Investors
98. Vives Fund
99. Warburg Pincus
100. WuXi Healthcare Ventures

Venture Firm Landscape

Regenerative Medicine

Geroscience

P3 Medicine

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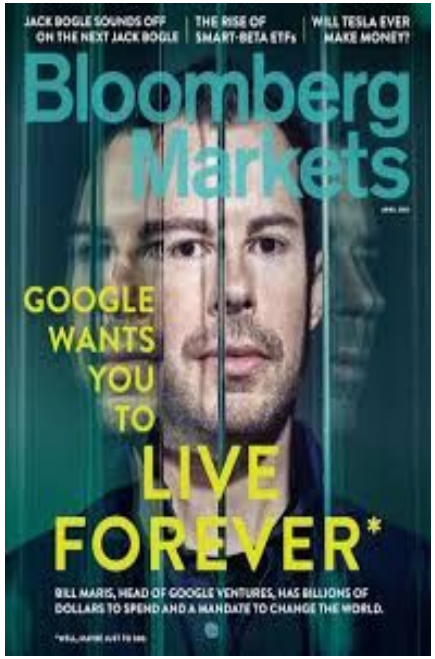
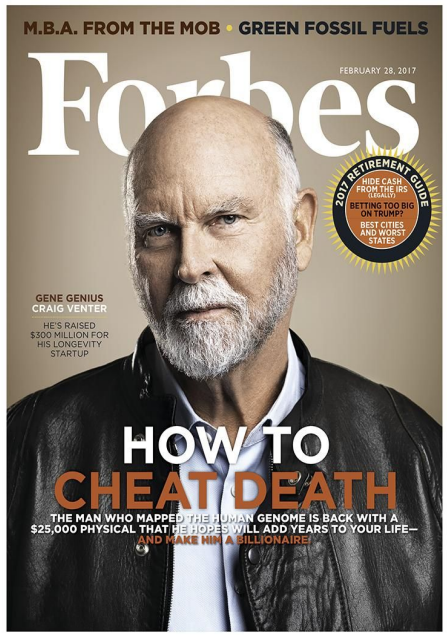
Landmark Longevity Conferences

Basel Life Sciences Aging Forum

World Economic Forum

Grand Brands in Support of Longevity





Landmark Longevity Conferences

The Economist: The Business of Longevity and Ageing Societies

Master Investor Conference 2017 Organized by Jim Mellon & Mann Bioinvest in London

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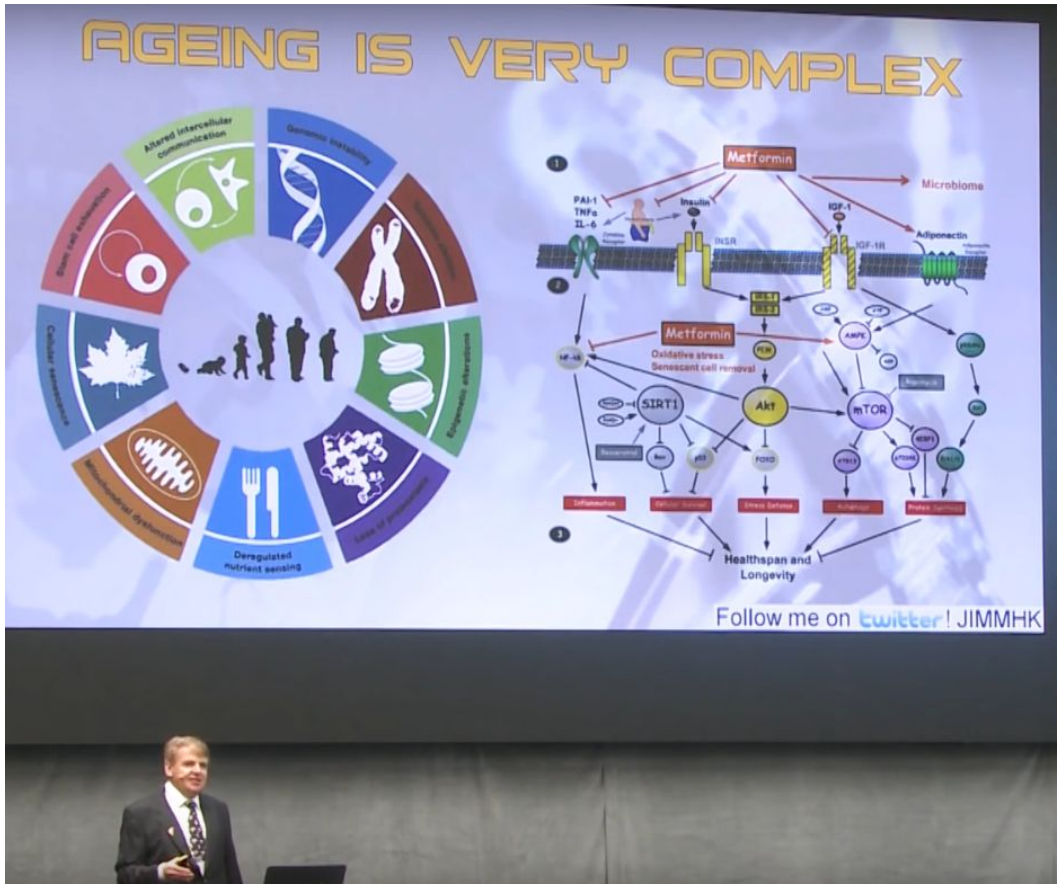


The Business of P3 Medicine Technology Overview

Whereas geroscience involves researching the biology of the human **species** and the developing technologies for intervening therein, P3 medicine in involves assessing the biology of the human **individual**, with a view to applying geroscience knowledge more bespoke manner, and to a more preventative effect.

- Digital Health
  - Wearables
  - Health / Fitness apps
  - Telemedicine
  - Virtual / Augmented Reality
  - Digital Health Records
  - Blockchain / NextGen Databases
- Biomarkers
- Artificial Intelligence
- Geroprotectors
- Regenerative Medicine
- Gene therapy
- Cell therapies
- NeuroTech
- Prosthetics
- Nutraceuticals
- Microbiome
- AgeTech
- Scientifically-validated lifestyle recommendations

Introduction to P3 medicine

P3 medicine is an emerging approach to medicine that moves away from traditional, simple, generalisable symptom-and disease-focused angle to healthcare, and into the three Ps: **precision, preventive and personalised.**

Precision medicine employs various technologies such as biomarker analysis to **tailor** treatments to individuals based on detailed health data.

Preventive medicine focuses on maintaining a given state of good health, and implicitly decreasing the probability of any disease developing as long as the state is monitored and kept within its **healthy parameters** e.g. blood glucose levels or any sub-pathological levels of biomarkers.

Personalised medicine refers to acknowledging the **individual differences** between patients in terms of genetic predispositions, genetic and metabolic regulation, cellular and tissue environment, drug response, etc. and tailoring the predictive and preventive measures to them personally. For example, there are treatments and lifestyle factors that **affect certain individuals greatly** in terms of losing or gaining weight, developing certain types of cancer or responding to certain therapies against cancer, while **the same measures may elicit little or no response** in other individuals.

As Google co-founder Larry Page pointed out, the P3 approach to medicine is empowering and requiring people to become intimately involved in their own healthcare. People, therefore, may become the fourth P in the acronym, making it P4 (Carlson, 2010).
Although there aren't many personalized interventions available presently, there are many technologies for preventive and personalized diagnostics and prognostics. Additionally, a framework for distinguishing the areas where P3 operates in as opposed to the realm of **geroscience** specifically, as well as the **longevity industry** is necessary in order to accurately track the progression and convergence of various subfields in each. As these are very complex e.g. in geroscience, it is imperative to draw the boundaries for where one begins and another one ends.

23andMe and thriva offer services that enable a P3 approach to diagnostics and prognostics.

By finding out one's individual genomic profile relating to drug response, heritable traits and diseases, as well as current profile for multiple blood markers, medicine can provide a tailored, proactive and insightful take on staving off disease and optimising health and wellbeing.

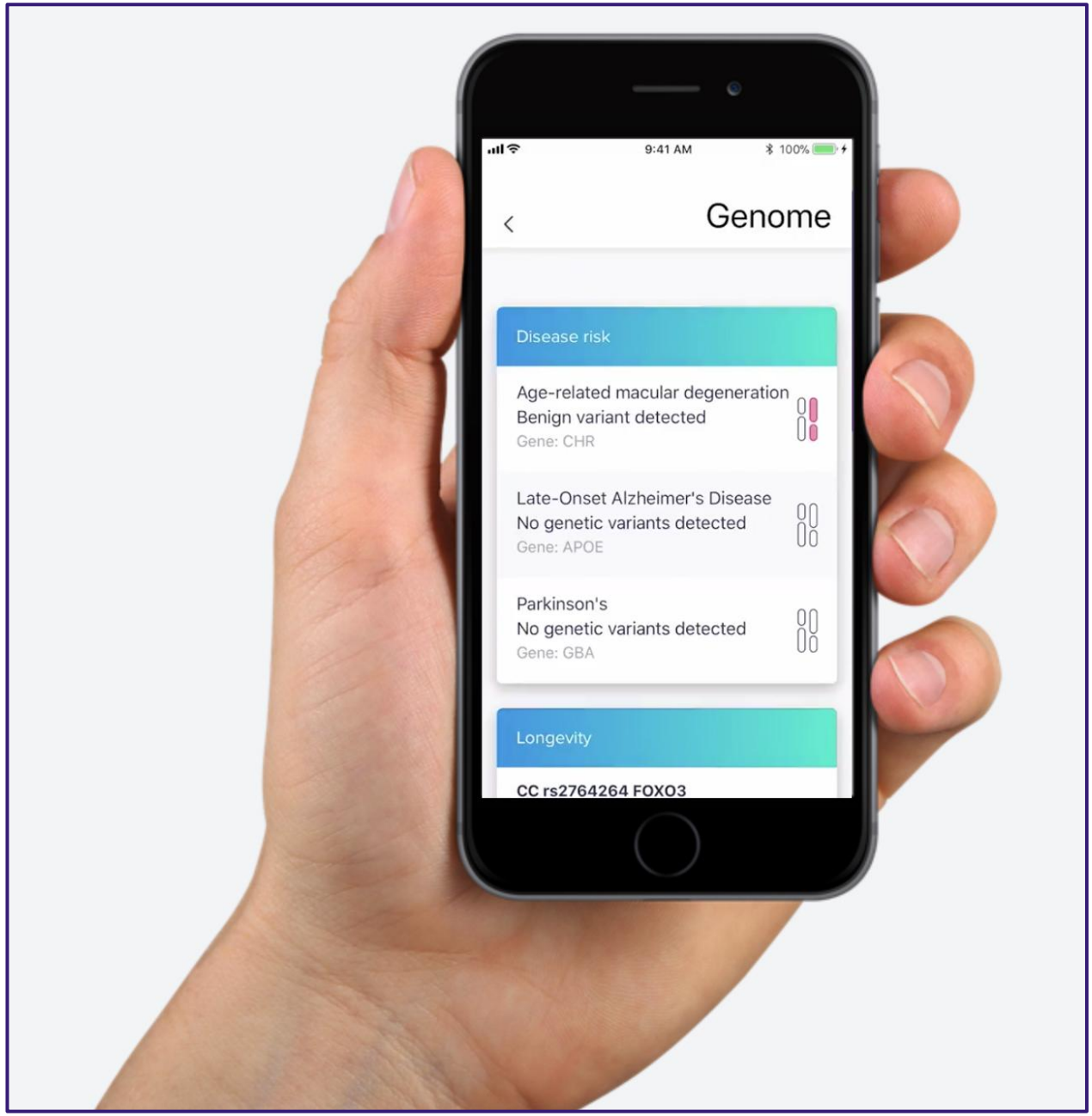
References:

Carlson, B., 2010. P4 Medicine Could Transform Healthcare, but Payers and Physicians Are Not Yet Convinced. Biotechnol. Healthc. 7, 7–8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2957728/

Doc.ai is another approach that uses harvested user data and applies AI to enable precision medicine. The platform collects health data from users, structures it in a meaningful way for scientists to dig through using AI powered predictive models.

In addition to enabling patient centric diagnosis, the platform will also lead to new ways of disease qualifications and improvement in drug efficacy.

When users submit data, servers will monitor and determine whether a target dataset is sufficient for training a neural network model. When the server determines that there are enough peers for a particular study, it will initiate a proposal to research scientists and institutions.



THE BUSINESS OF PROGRESSIVE MEDICINE *PRACTICAL APPLICATIONS*

Top 120+ Technologies & Therapeutics TRL 8-9

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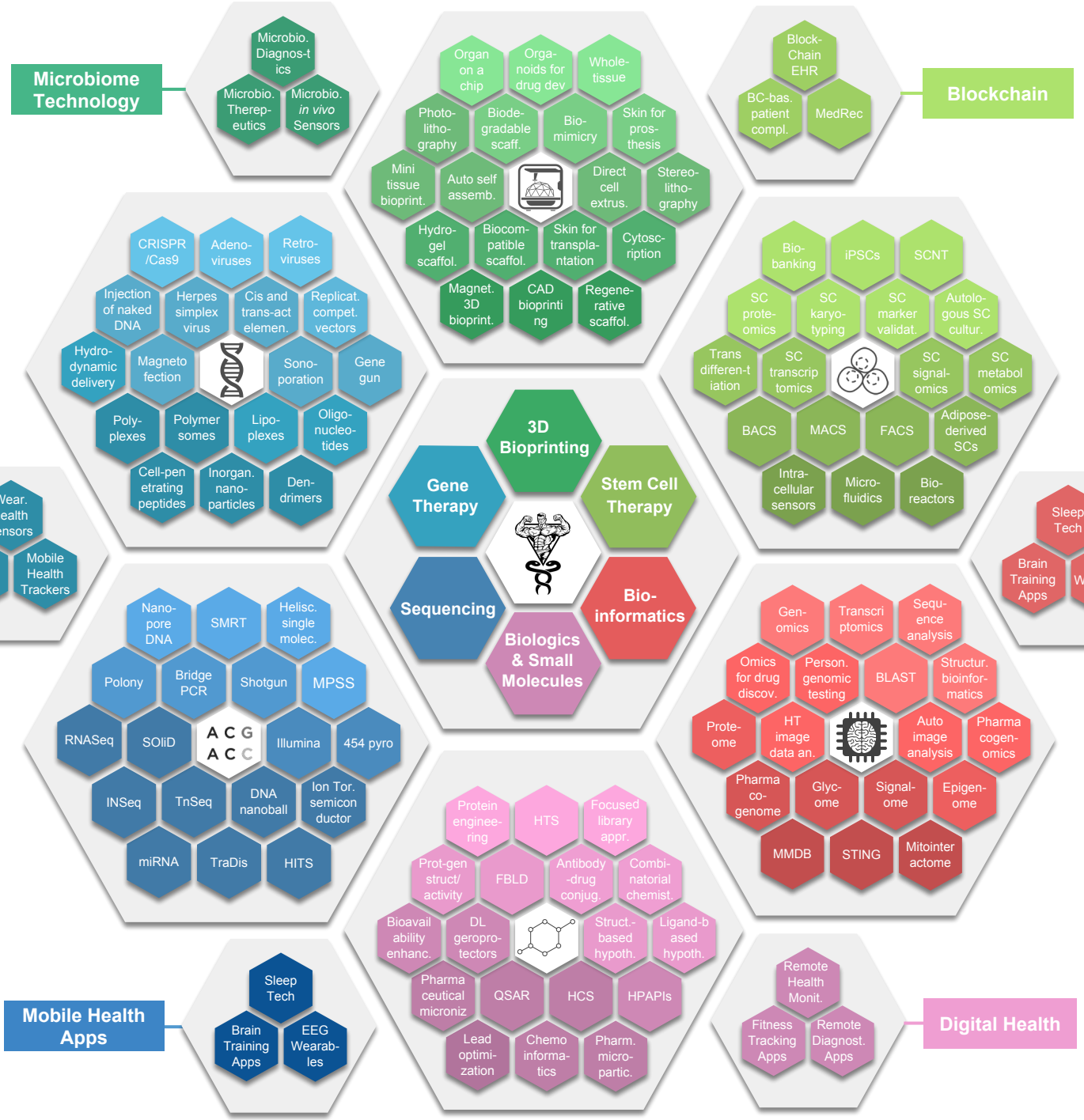

Technology Readiness Level (TRL)

9	Commercialized
8	Pre-Production
7	Field Test
6	Prototype
5	Bench/Lab Testing
4	Detailed Design

Technology Readiness Levels (TRL) are a common measure of how close a technology is for practical use, used in many engineering disciplines.
By applying it to progressive medicine, we can forecast how long it will take a given therapeutic or technology to witness practical applications in the clinic or home. The darkness of each hexagon represents its TRL, with darker colors indicating a low TRL and brighter colors indicating a high TRL.
All technologies and therapeutics shown here have a TRL between 8-9.

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THE SCIENCE OF PROGRESSIVE MEDICINE LANDSCAPE

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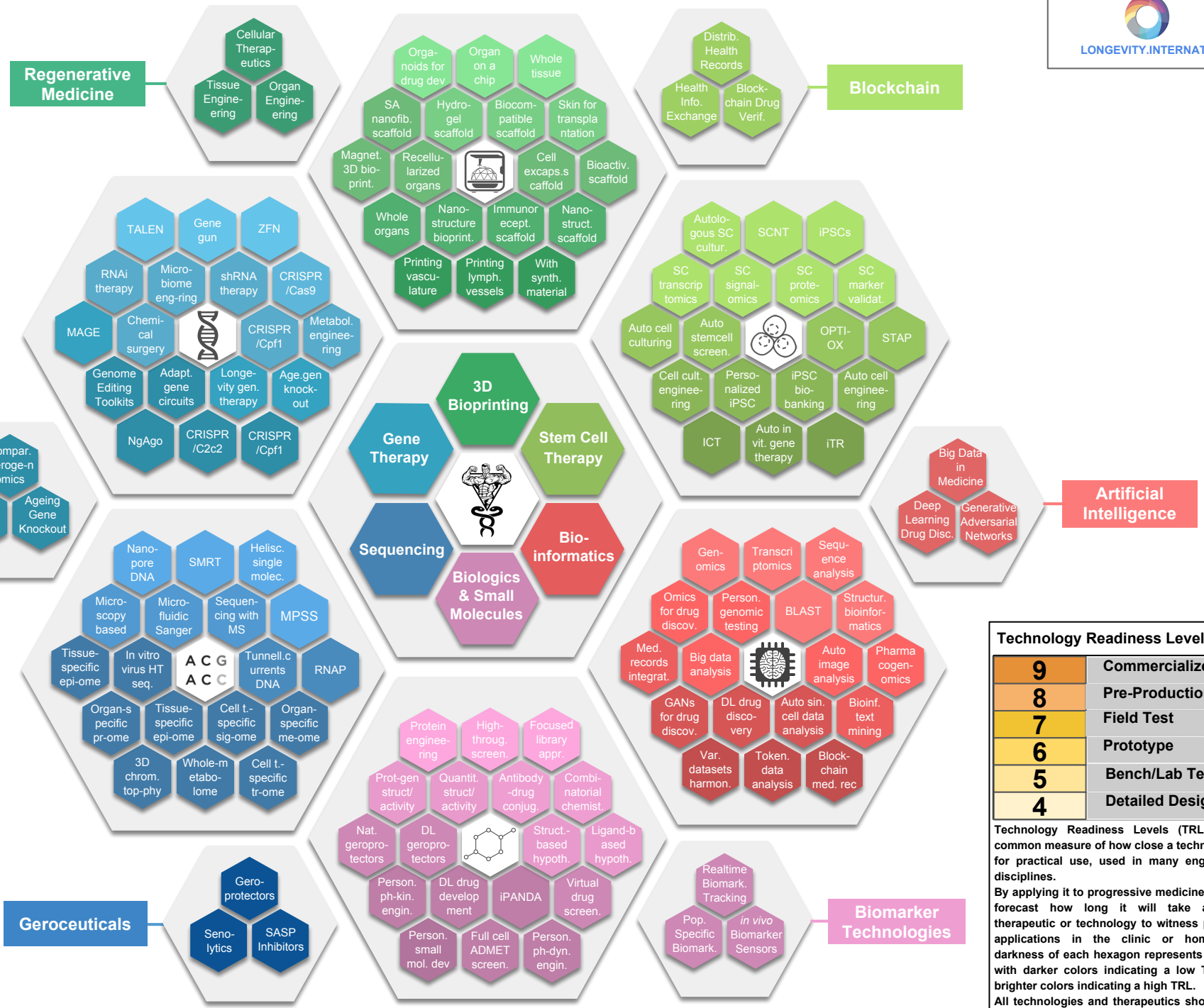
Top 120+
R&D Topics
TRL 4-7



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Technology Readiness Level (TRL)

9	Commercialized
8	Pre-Production
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6	Prototype
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Technology Readiness Levels (TRL) are a common measure of how close a technology is for practical use, used in many engineering disciplines.
By applying it to progressive medicine, we can forecast how long it will take a given therapeutic or technology to witness practical applications in the clinic or home. The darkness of each hexagon represents its TRL, with darker colors indicating a low TRL and brighter colors indicating a high TRL.
All technologies and therapeutics shown here have a TRL between 4 – 7. Technologies surpassing a TRL of 8 are transferred to the practical applications of progressive medicine landscape overview.

Digital Health

With the convergence of information technology in the **digital revolution** and the rapid increase in healthcare data in the **genomic revolution**, digital health is the emerging middle ground which is fertile in new applications, in both the hardware and software realms.

A diverse range of fields make up digital health, such as mobile health, wireless health, health 2.0, eHealth, health IT, big data, health data, cloud computing, e-Patients, quantified self, wearable computing, gamification, telehealth, telemedicine, precision and personalised medicine and connected health (Sonnier, 2013).

References: Sonnier, P., 2013. Definition of Digital Health - Paul Sonnier. Paul Sonnier - Story Digit. Health. https://storyofdigitalhealth.com/definition/

Wearables

Wearables, as the name suggests, are items worn on the body that **store, record or communicate** with the wearer or a professional information related to health. As such, they come in varied form factors and can perform varied functions depending on context and wearer.

Socio-economic context plays a key role in the way wearables can affect health and longevity in different demographics. For example, in developing areas such as Udaipur, Rajasthan, the immunisation records of infants were stored in pendants worn around the neck. These were read by local clinicians in a pilot which took place in 100 villages via NFC (near field communication) technology. Taking account of the local culture, which involves having small children wear pendants around their neck for spiritual protection, the wearable, dubbed Khushi Baby, integrates seamlessly while enabling professionals to assess local epidemiology and protect children's health in developing regions (Kharara, 2015).

For sportspeople, wearables can provide activity data to physiotherapists and prevent injuries. Such products come in vest or bra form. The wearables that have attained the greatest popularity to date fall into the **technology** category (Apple Watch), **fitness** category (Fitbit) or **condition-specific** category e.g. blood pressure monitoring, heart function monitoring, and so on.

Available measurements taken through wearables include sleep activity (Pebble Time smartwatch), different types of physical activity (Gymwatch fitness tracker), brain activity (Muse headband), stress (PIP, a device which measures skin conductivity) and weight (Fitbit Aria) (Mesko, 2016).


Fitbit


Muse


Khushi Baby

Currently, the many different wearables and their respective platforms, apps, software or accompanying professionals, such as physiotherapists or doctors, are relegated to **niche activities** such as sport or monitoring specific health conditions, while those that have come the closest to mainstream usage (such as Apple Watch) are too **limited in their sensory potential** to become the powerful, everyday, connected and actionable tool required to have a considerable impact on health and longevity.

References:
Kharara, S., 2015. Medical record necklace Khushi Baby wins UNICEF's Wearables for Good challenge [WWW Document]. Wareable. URL https://www.wareable.com/saves-the-day/necklace-khushi-baby-unicefs-wearables-for-good-challenge-1938 (accessed 1.31.18).
Mesko, B., 2016. Top 10 Healthcare Wearables For A Healthy Lifestyle. Med. Futur. http://medicalfuturist.com/top-healthcare-wearables/

Wearables hold an inherent advantage over conventional monitoring devices and methods. They are able to track physiological parameters in real time and their shrinking size does not constrain use to a specific location. Consequently, they can drastically shorten response time to critical health episodes and, more importantly, detect any of a number of alarming vital signs that occur prior to a life threatening occurrence, think seizures or a heart attack. The connectivity features mean that they act immediately, alerting the user, a family member, a doctor, a caretaker, or a hospital, or, perhaps most importantly, summon an ambulance automatically.

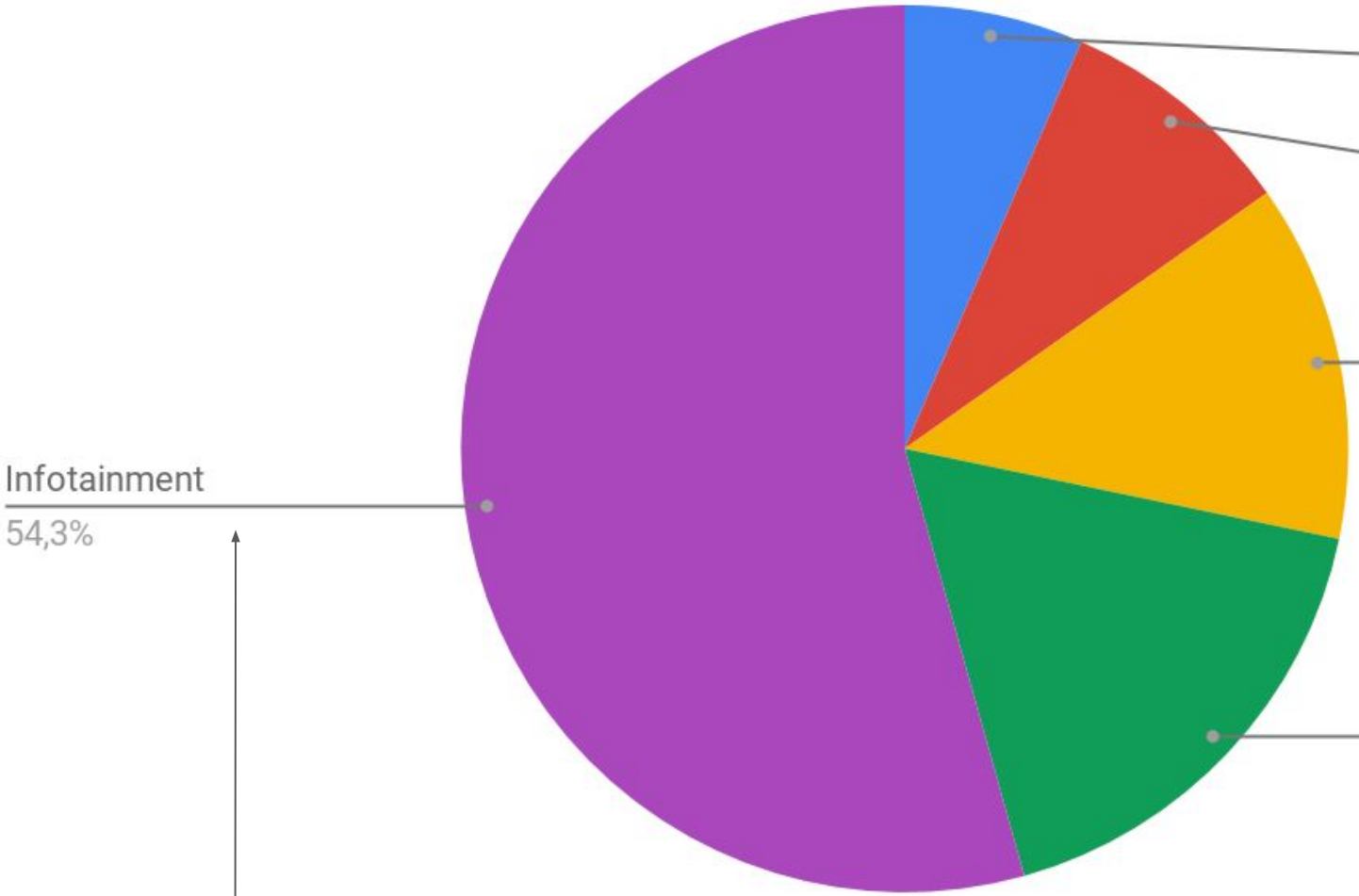
Right now heart rate, blood pressure and the number of steps a person takes are the most common readings that a wearable device can detect, but in the future, we are likely to see wearables that are more flexible in terms of their tracking capabilities, incorporating different types of sensors that would enable them to do more diverse and user specific readings.

Wearables can also be beneficial in less urgent health matters, helping users lead an active, healthy and life prolonging lifestyle. Sensors that detect motion for instance can track a person's behavior - whether they've been sitting down too long or whether they haven't been getting enough exercise - and nudge them towards healthier habits.

The almost immediate detection time and the automation of tasks afforded by wearables are even more prominent when the elderly demographic is in question. For instance, with the help of algorithms, accelerometers would be able to tell if a person fell or collapsed and respond accordingly. Wearables can also act as personal assistants, sending reminder alerts for scheduled medication.

The data collected can also be seamlessly integrated with a doctor's records system, making a visit to a physician much more efficient and accurate with historical data. Perhaps we will one day be able to trust wearables to alter dosages based on the readings that they gather.

IMS Research - World Market for Wearable Technology - Revenues by Application-Mid-range Forecast

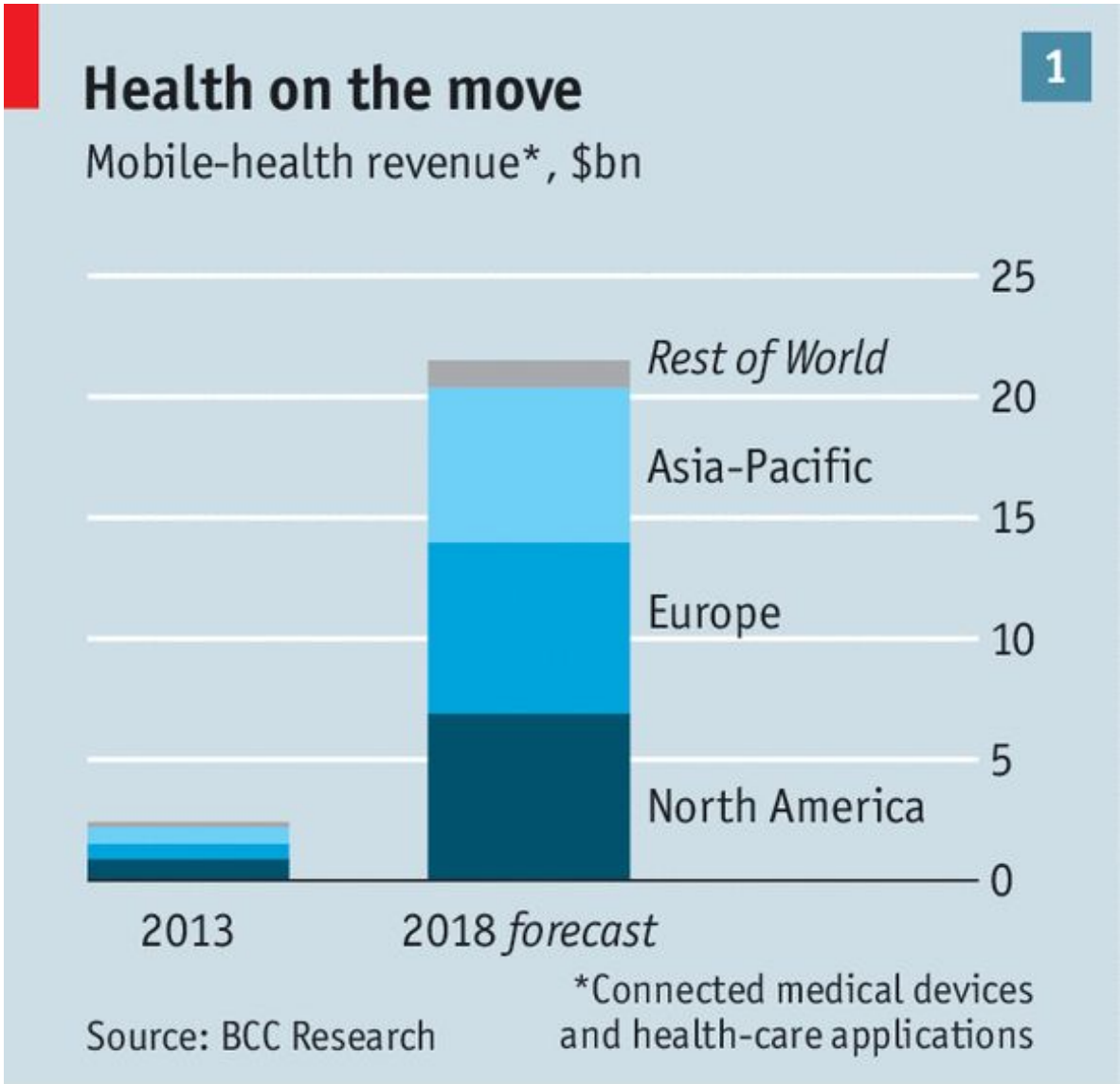


Activity Monitors to account for more than 13.0% of the Fitness and Wellness market in 2016

Smart Watches are expected to drive growth in the Infotainment segment over the review period

Continuous Glucose Monitoring (CGM) to remain the largest product category in the Healthcare and Medical market in 2016

Health/Fitness Mobile Apps

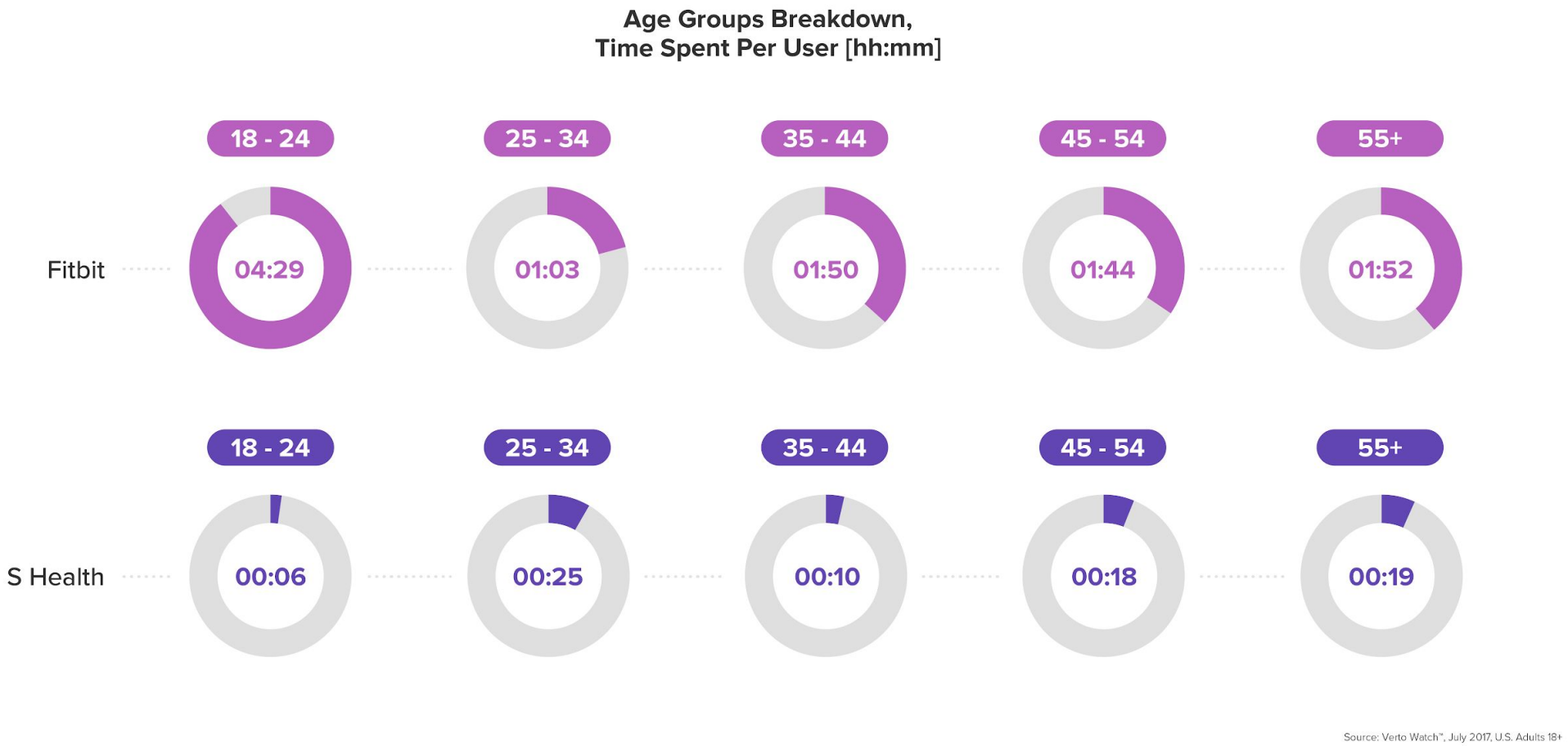


Health and fitness apps usage grew by more 330% in the last three years according to research by Flurry Analytics. Advances in artificial intelligence currently allows apps to understand individual cases and respond to questions from users with relevant follow up queries. Fitness and nutrition apps follow caloric intake and activity. Integration with wearables expand their capabilities dramatically.

Health and fitness apps show very high retention rates. According to the research by Flurry Analytics, over 75% of active users open their health and fitness app at least two times a week, and more than 25% of users access their fitness apps more than 10 times a week. The high frequency of usage drives up engagement, which, for app developers, presents an attractive opportunity to increase monetization. What's more, health and fitness app users are loyal, with 96% of them sticking to only one app. But that also means that new incumbents will find it difficult to acquire users.

verto index

Demographics Comparison: Fitbit vs. S Health



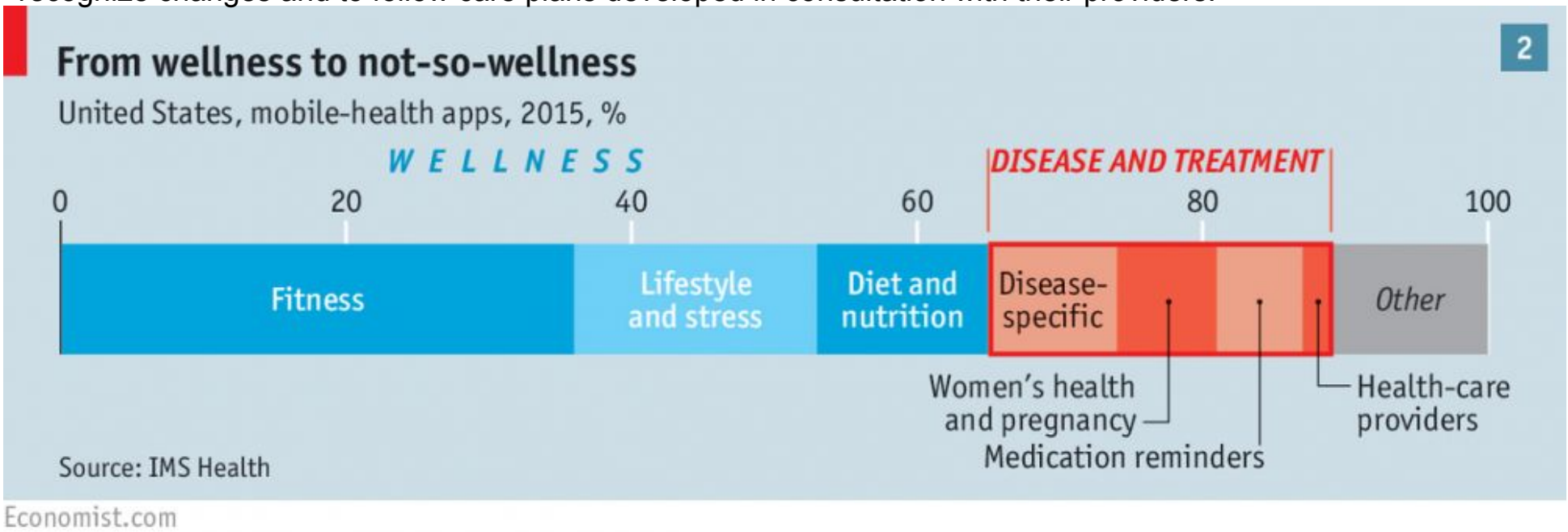
The senior demographic is relatively active on fitness apps. According to the Verto Index, a demographic comparison between the two top apps on its index, Fitbit and S Health, show that the age group 55 years and older, ranked second among the different age groupings in terms of time spent using the app.

Precision medicine necessitates that patients and healthy people participate in partnership with clinicians and researchers.

Central to this process is the technology used to monitor and provide relevant health-related data about individuals: Devices and instruments that capture physiological data. These technologies include a rapidly expanding array of consumer products and wearables, as well as complex clinical care platforms in academic medical centers.

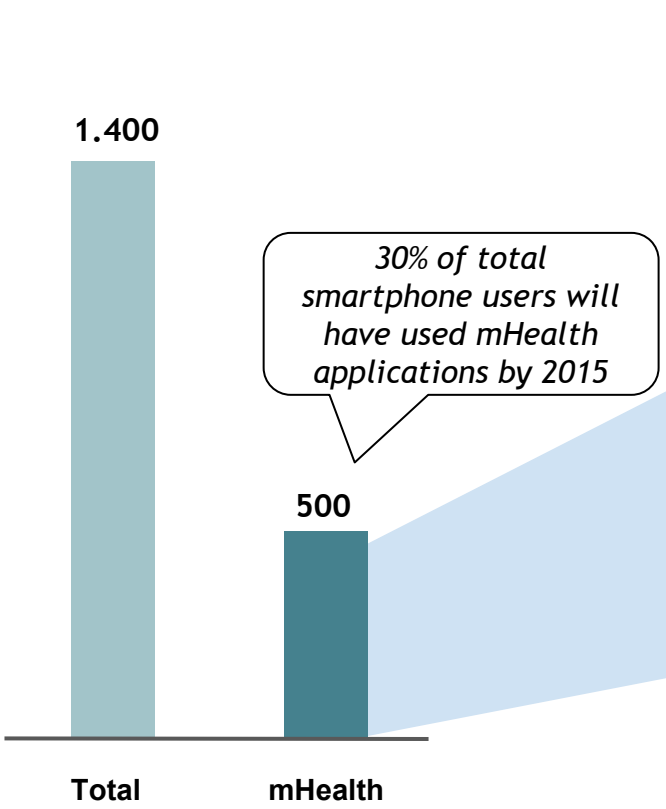
For patients, this might mean collecting data with an FDA-approved mobile device or app, such as a continuous glucose monitor or a mobile heart monitor app.

Such data can provide a practitioner immediate information about a patient, and when collected from large numbers of people, can reveal patterns and trends that are clinically useful. Data collection by patients gives them "ownership" of the process; they become more motivated to track and adjust their behavior to prevent disease, to recognize changes and to follow care plans developed in consultation with their providers.



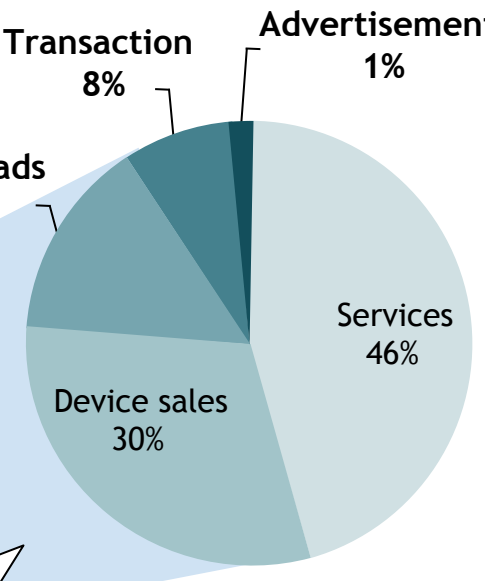
mHealth market 2015: 500m people will be using healthcare smartphone applications

Smartphone user base in 2015 (million)



30% of total smartphone users will have used mHealth applications by 2015

Share of mHealth revenue sources of total mHealth market opportunity in 2010-2015 (%)



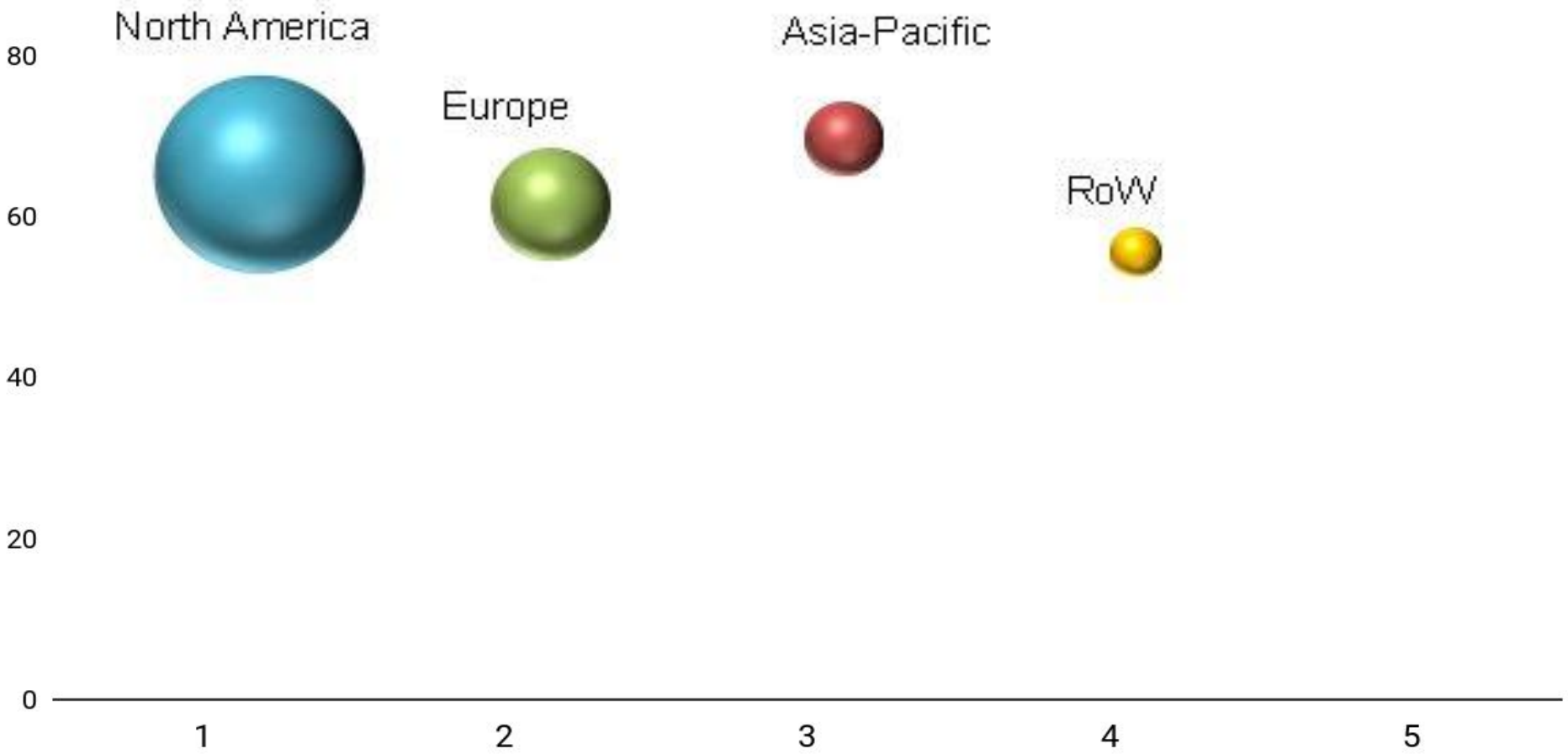
Those mHealth users will mainly pay for services and devices

Smartphone applications will become the killer applications for mobile health solutions.

research2guidance
the app market specialists

Source: https://research2guidance.com/500m-people-will-be-using-healthcare-mobile-applications-in-2015-2/

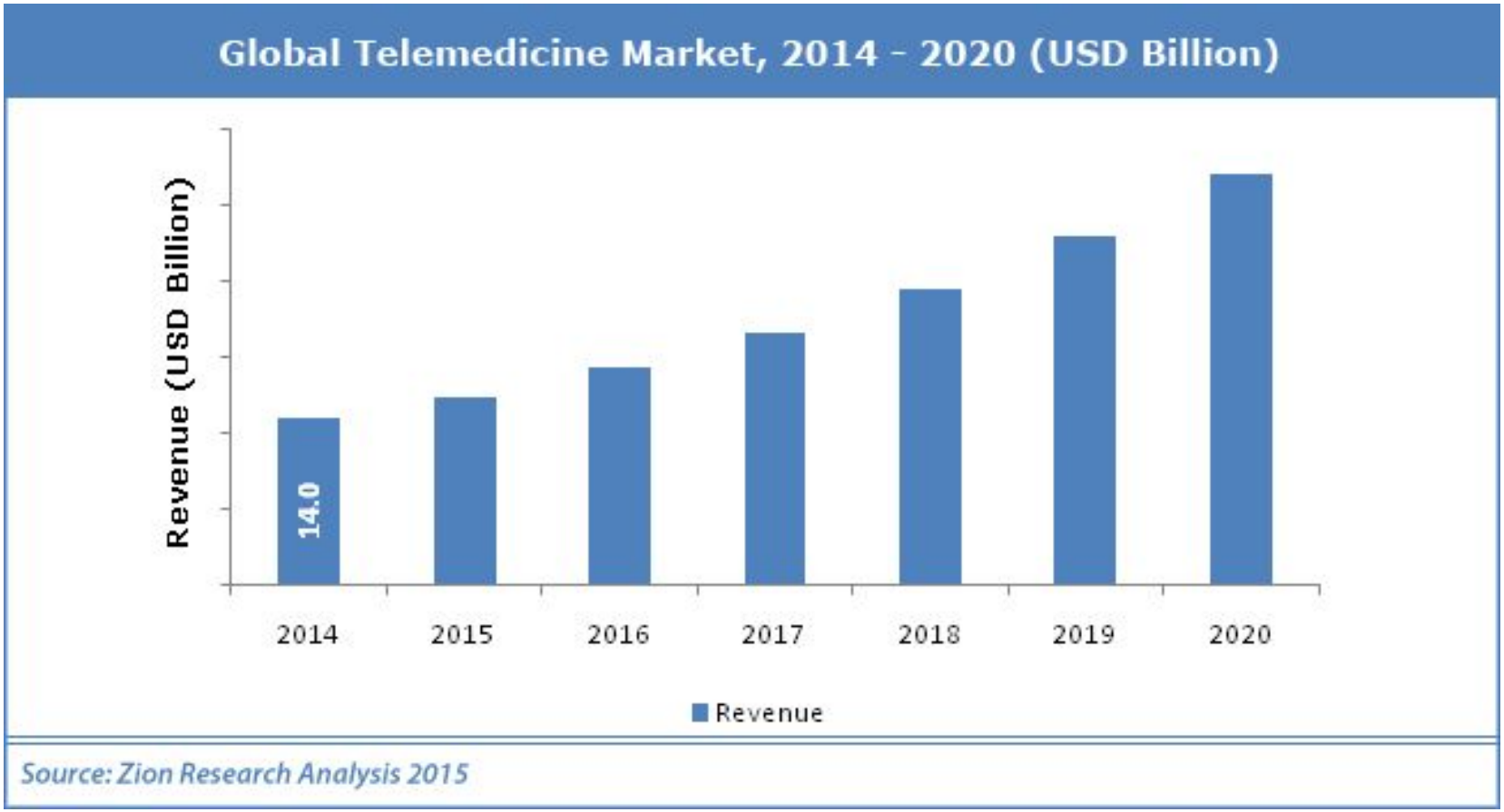
Global Telehealth Market, by Region, 2016 (USD Million)



Note: The size of the bubble depicts market size (USD million) in 2016

Source: https://www.marketsandmarkets.com/Market-Reports/telehealth-market-201868927.html

The global telemedicine market is projected to be worth almost $30 billion in 2019, a doubling from just 5 years prior in 2014. The future expansion of this market is modelled to be taking off exponentially through 2020 with global revenues approaching $40 billion.



Source: http://www.marketresearchstore.com/news/global-telemedicine-market-set-for-rapid-growth-to-118

The purpose of HealthTech apps are to increase access to healthcare and health-related information (particularly for hard-to-reach populations), improve users' ability to diagnose and track diseases, and expand access to ongoing medical education and training for health workers.

In 2016 the global number of mHealth apps has reached 259,000 apps. Today there are over 59,000 mHealth apps on the main app stores worldwide, and the trend is only rising. In fact, the healthcare mobile app development industry is one of the fastest growing today.

The global mHealth app market grows at a tremendous rate of 32.5% CAGR, and by the end of 2017 will reach $26 billion in revenue. The global market for mobile medical apps is projected to reach $102.43 billion by 2022. The mHealth app market size was valued at USD 4.19 billion in 2016 and is projected to grow at a CAGR of 44.2% over the next 5 years.

- 66% of Americans use mobile platforms to manage their health issues. 79% use a wearable device (Pulse of Online Health, 2015);
- Almost 100K health-related apps have been added by 13K new publishers to the market since 2015. At that moment, there had already been 259,000 medical apps in major app stores (Research2Guidance Annual mHealth Report, 2016);

The motivation behind the development of mHealth apps arises from two factors. The first factor concerns the myriad constraints felt by the healthcare systems of developing nations. These constraints include high population growth, a high burden of disease prevalence, small healthcare workforces, large numbers of rural inhabitants, and limited financial resources to support healthcare infrastructure and health information systems.

The second factor is the recent rapid rise in mobile phone penetration in developing countries to large segments of the healthcare workforce, as well as the population of each country as a whole. With greater access to mobile phones to all segments of a country, including rural areas, the potential of lowering information and transaction costs in order to deliver healthcare improves.

Sources: http://www.information-age.com/top-7-trends-healthcare-app-development-123468014/
https://medium.com/@Adoriasoft_Com/healthcare-mobile-app-development-and-mhealth-apps-in-2017-eb307d4cad36

Accordingly to our analysis of the industry, all existing HealthTech mobile apps can be devided into two broad categories: first generation apps which are focused on metrics/measurements, and second generation apps which include the ability to personalise output accordingly to the analysis of personalized data of each user. Apps which include personalized medicine and AI assistance are undoubtedly the key to a productive future in this arena. The HealthTech mobile apps available today generally display a low-to-medium level of sophistication, with many providing limited benefits for patients, doctors and consumers. However, there are examples of more sophisticated apps in the market, and our analytical department have made this report in order to provide tangible metrics for assessing the market and forecasting major trends and developments, both broadly and in specific subsectors, so as to give industry players, including business analysts, investors, entrepreneurs and corporate decision makers an optimized framework for quantified market forecasts, projections, assessments and valuations.

The years 2016-2017 saw basic apps lacking data analysis, insured data privacy, chatbots and AI interactions or recommendation systems. The leading edge of the current state of HealthTech mobile apps offer all these features. Previously, any HealthTech mobile app was inherently considered novel (**First Generation which is now outdated**), but in 2017 it became clear that apps needed to integrate a sufficient level of personalisation and AI analysis with a basic chatbot and other elements - i.e., which is considered at the current level as mHealth state-of-the-art solutions. This now represents a **Second Generation** of HealthTech mobile apps.

The **Third Generation is set to rise in 2018-2019**, where the aforementioned features will become basic and expected - certainly by the end of the year, and will be marked by the synergistic convergence of data analysis, insured data privacy, chatbots and data science driven sophisticated solutions empowered by AI.

If there is no AI, an app can be categorized as first generation. If an app has integrated AI and/or blockchain features, it can be classified as 2nd generation. If it uses advanced MarTech, gamification engagement technologies, Data Science, AI and blockchain in a synergistic manner, it can be classified as 3rd generation. The distinguishing features of these emerging apps through the next 6-12 months are: data science algorithms and big data analysis embedded into the system, self-teaching and self-improvement capabilities, increasing amounts of analysis of data patterns, and the ability to provide highly personalised feedback and analysis. These features will be supported by AI, making an AI team on the HealthTech mobile app development group essential.

Source: https://www.grandviewresearch.com/press-release/global-mhealth-app-market

What Distinguishes 1st Generation of HealthTech Apps from 2nd and 3rd Generations of HealthTech Apps?

Those mobile apps which are today considered as next generation HealthTech mobile apps will become the de facto standard by the end of 2018 and beginning of 2019; integration of AI, blockchain, data ownership, and engagement/gamification are the main features of the nextgen apps. These apps will be distinguished by their high level of user personalization, enhanced engagement and gamification and their use of advanced MarTech, which underpins and allows for the collection and analysis of increasing amounts of user data to further improve the efficiency of predictive AI and to tune user recommendations in a much deeper personalised and precise manner.

	Technologies	Wearables	Engagement & MarTech	Chatbot	Data Science & AI	Data Ownership	Blockchain	AI	Longevity
2010 - 2017	1st Generation	+	+	-	-	-	-	-	-
2017 - 2018	2nd Generation	+	+	+	+	-	-	+	-
2018 - 2019	3d Generation	+	+	+	+	+	+	+	+

The table above assesses and categorises current HealthTech mobile apps according to the presence of specific features and elements that our analysts have concluded will become the major hallmarks for HeathTech mobile apps over the course of the next 2 years. The table also shows which of these elements are most likely to become hallmarks by the end of the current fiscal year, and which ones will become integrated into mobile apps first, as low-hanging-fruit within the industry, as well as which ones will take longer to become standard features of HealthTech mobile apps. As can be seen above, our market analysis predicts that all eight hallmarks will become the de facto standard for competitive and state-of-the-art HealthTech mobile apps by the end of 2019.

Data Science & AI: crucially, this growth will be enabled by the reinforcement loop of a growing user base providing more data for the systems to use and improve their predictions for the user. The more data is provided, the better recommendations will be; meanwhile, the better the AI-enabled guidance, the more it will incentive users to join and submit their data. The more data users provide, the better services they get for themselves.

Chatbots: the AI chatbot will act as a personal coach and a guide for each user according to their personal requirements. More and more types of mobile applications will direct themselves towards the chatbot model. In the context of healthcare, this will most often take the form of a personal trainer adjusted to the user precisely, even in terms of the emotional and psychological state of the user at a given time.

Ownership of the data: user data should belong to the user, especially considering the risks of data privacy breaches (for example the large debacle surrounding Cambridge Analytica); it will become the norm that data will belong to users, and that if the data is used by third parties the user will need to give consent, and will be compensated or remunerated (if the third parties generate profit from this). Significant emphasis will be placed on cloud storage and cybersecurity, in order to aid this goal.

Blockchain: blockchain technologies allow the immutable, secure and decentralized storage of information. When applied to user health data, it allows storage of data in a fully anonymized yet transparent, and distributed yet secure fashion. A blockchain back-end is the foundation upon which user control of data can be realized, and it represents one of the major elements that will mark the industry standard of 3rd generation HealthTech apps.

Engagement: since mobile applications are a mass market product, they should have top tier design, but at the same time maximum engagement and maximum gamification to incentivize users to use these mobile apps, not just for monitoring their health, but also to improve it, neutralizing any detrimental behaviours and promoting positive patterns of health and lifestyle.

Longevity: another rising trend already making waves in the mHealth sector is Longevity, which means that applying on mobile apps current technologies, methods and scientifically backed recommendations soon will become the norm in regards to preventive medicine and extension of healthy period of life . The convergence of AI, Blockchain, MarTech for Longevity will be at the heart of the next generation of HealthTech mobile apps.

Case Study: Longevity United and Eterly Mobile App

Modern Health care apps, which for example are created by Longevity United, are creating a marketplace with a blockchain back-end that will host data acquired from medical institutions, research centres, and longevity experts. That data combines with user data through the integration with Eterly's front-end mobile app, allowing the app to produce personalised health plans and make recommendations to users about how to live the healthiest lives possible.

The system will also use the latest medical research on commercially available supplements, treatments and drugs of benefit to the user. Longevity United will use novel CryptoEconomic strategies and tokenization technologies; Longevity Tokens will be issued to users as a reward for completing health and fitness plans successfully, to sponsor the work of scientists and researchers, and to bring investment into the platform from leading healthcare and mobile app investors and strategic partners. Users will be able to "spend" their Longevity Tokens on premium services offered within the Longevity United marketplace.

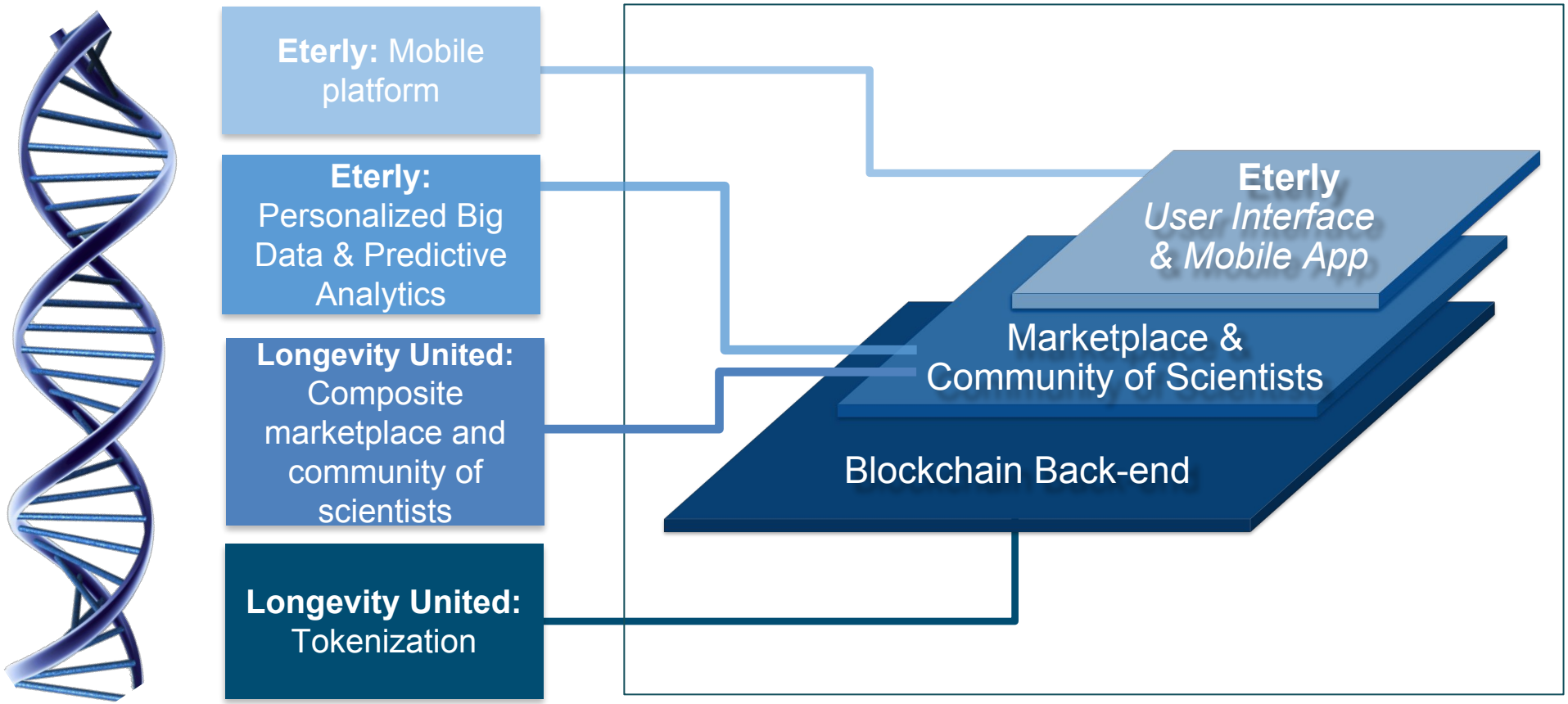
It is for these reasons that the joint venture between Eterly and Longevity United serves as an excellent case-study of what can be considered as the third generation of HealthTech mobile apps. Separately, they are both clearcut examples of second-generation HealthTech mobile apps -- ones which employ AI, big-data analysis, and which use a blockchain backend to store and access user data in secure, transparent, immutable and anonymized manner. As the fruits of their joint venture develop, in half a year they are excellently poised to unleash the third generation of HealthTech mobile apps, which combine the above features with gamification and next generation MarTech to enhance community engagement.

Eterly and Longevity United, separately, can be considered as 2nd generation mHealth apps. When they combined their forces through their recently-announced joint venture, they could be considered as being halfway toward the standard of 3rd generation solutions.

This joint venture serves as an excellent case-study of the right combination of technologies with the potential to evolve into the 3rd generation of mHealth mobile app. All the necessary elements are there, and it is just the optimal, synergistic assembly of those elements required to realise this 3rd generation of mHealth mobile app, and one of the only apps in the longevity side of mHealth in particular.

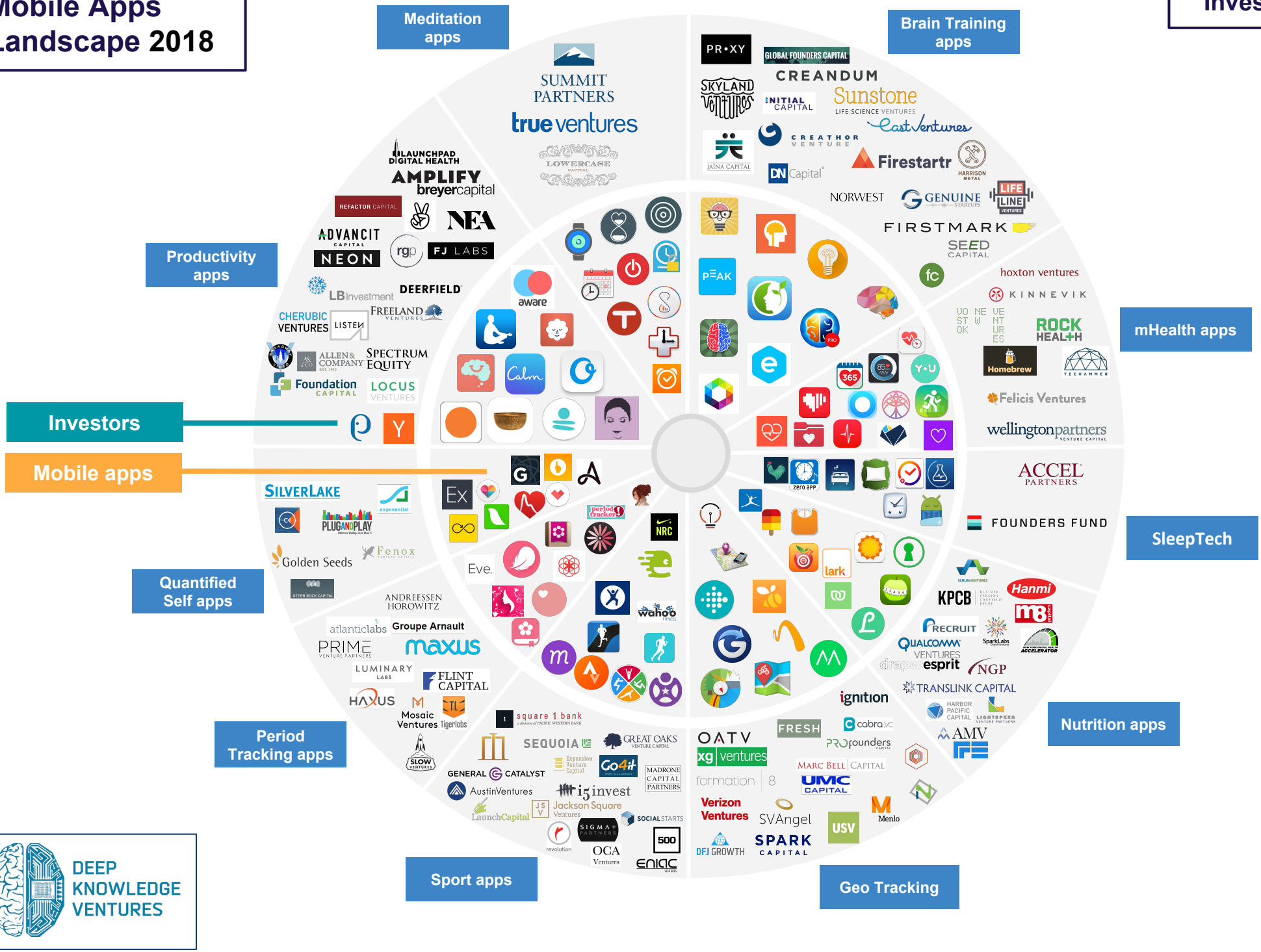
Cutting-edge mobile healthcare technologies are going to be based on following layers:

- **Open Marketplace** - A marketplace that provides recommended products, services, clinics, and doctors for a healthy life, life extension, and longevity, using an internal currency and tokenization.
- **Mobile Application** - A seamless and innovative mobile applications with an easy to use interface.
- **Blockchain Back-end** - All personal information is stored securely on the blockchain backend.
- **AI & Big Data Analysis** - Continuous monitoring, assessment and analysis, including optimized recommendations, diagnosis, and prognostics through forecasting using artificial intelligence.

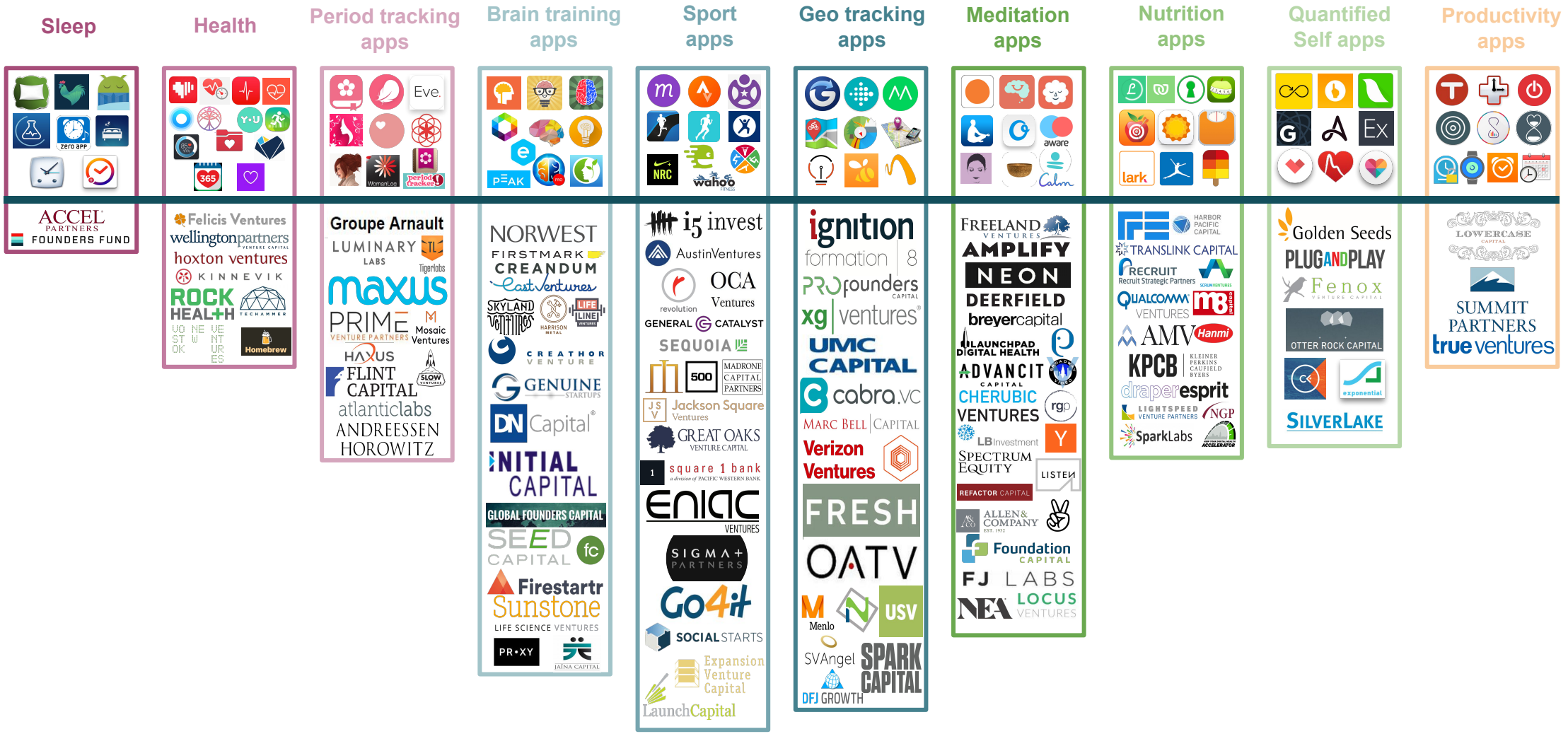


Health Tech Mobile Apps Landscape 2018

Mobile Apps - 100
Investors - 120



Apps



Investors

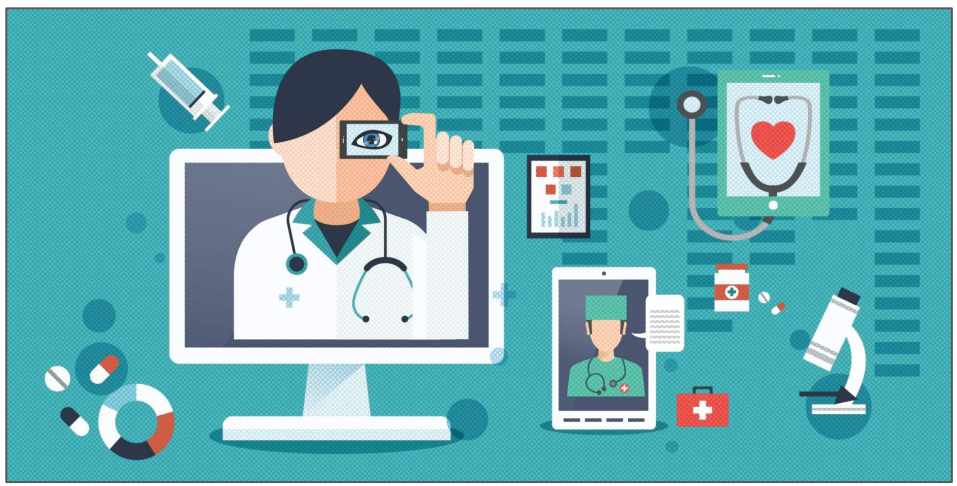
DEEP KNOWLEDGE VENTURES

Telemedicine

The costs of healthcare increase, often dramatically, with old age. As such, Telemedicine is poised to be an effective tool in geriatrics. The benefits of telemedicine for seniors include remote monitoring, which is particularly important for chronic conditions. The technology also reduces the number of routine in-person visits, which can be costly and difficult for seniors; it allows for better monitoring - telemedicine technologies can be utilized to keep track of sugar levels and blood pressure, which lead to a lower chance of hospitalization; and it grants patients a greater access to specialists.

These benefits, while particularly relevant to seniors, extend to every demographic.

Statistical reports that the global telemedicine market size will surpass 41 billion dollars in 2021. Some of the factors that are stemming the growth are the increases in technological innovation related to remote patient monitoring and treatments that require long follow-ups. It will be critical to educate doctors in the use of telemedicine; the majority of those around the world are in their mid-forties or fifties and lack experience with new technologies, having only used conventional means to treat patients. Another unfavorable factor for Telemedicine is substandard infrastructure in emerging countries, an area where telemedicine is disproportionately needed.



Some healthcare providers are integrating predictive analytics technology with telemedicine to collect data. The data is collected through physician/patient video conferences, emails, and internet of things monitoring. Identifying patients at elevated risk and spotting irregular vital signs has resulted in the reduction of rate of repeated readmissions, particularly of the emergency kind, lowering costs for patient.

Telemedicine and predictive analytics can be especially effective in administering care in rural areas. A reduced need for in person visits with medical providers and remote medical consultation with specialists are some of the benefits of telemedicine. Combining the continuous and precise monitoring of patients' health with personal data analysis means that illnesses can be diagnosed and treated early before they become life-threatening.

The process can be largely automated as well. For example, a diabetes patient can have his critical vital signs actively monitored remotely and receive personalized information about treatment.

To truly enable the convergence of telemedicine and predictive medicine, we must seamlessly integrate various digital health records systems between hospitals and clinics and make all medical devices interoperable.

VR/AR

Virtual reality (VR) and **augmented reality** (AR) are emerging realms of communication that involve immersing a participant into a digital experience via **complete 3D** audio-visual content that responds to the user's movement via **sensors** (VR) or **superimposing** digital 3D content onto the real world (AR) without isolating the participant from it, as VR does.

As an infant type of technology, its applications to date are experimental and varied. In the field of medicine, the main ranges of use include **diagnosis** e.g. analysing cancerous breast tissue in 3D to investigate the shape of different microstructures present (Douglas et al., 2016); improving the **accuracy** of routine techniques such as blood drawing e.g. visualising patient veins with AccuVein devices (Carson, 2015); and **education** e.g. by streaming 3D surgery (Mesko, 2016) and using AR to label anatomy specimens (Carson, 2015).

Other experiments in healthcare are more mind-based: pain relief through VR (Sulea et al., 2014), which enables doctors to understand their elderly patients' struggles and empathize with them (Mesko, 2016); and improving recovery outcomes in physiotherapy for stroke patients by providing a visualised feedback on their movements (Laver et al., 2015; McEwen et al., 2014).

Source:
http://www.vrtherapynews.com/goldman-sachs-predicts-vr-healthcare-market-will-5-1-billion-2025/

From patient entertainment and rehabilitation to livestreaming surgery in 3D, VR and AR hold great potential as emerging communication technologies to improve education and healthcare for both patients and professionals

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VR/AR Virtual Reality / Augmented Reality in Digital Health

Augmented and virtual reality have taken the gaming world by storm. There is also huge potential for AR and VR in healthcare. The global market is expected to reach USD 5.6 billion by 2022 according to a report by Key Market Insights.

Looking at augmented reality, some of the novel applications include being able to access much needed information at a glance during operations using head mounted displays, such as Google Glass or Microsoft's Hololens. Head mounted displays could also drastically cut down any administrative chores, leaving the doctor to focus on the patient rather than immersing himself in a computer to pull out health records. Automatic documentation using NPL also mean that doctors would have more time on their hands to deal with more patients daily. QR codes can be hung next to a patient's bed, so that a simple glance by the doctor could immediately reveal all the necessary information about that particular patient. Medical health records have come a long way to being digitized, but so far are still static - we've simply moved them from papers to computers - but AR seems poised to revolutionize that.

A recent study by the Mayo Clinic however has found a strong correlation between the digital parts of doctoring and burnout, while other studies have shown that burnout leads to greater risk of doctors making major medical errors. Furthermore, medical records have been reproached for dehumanizing patients: according to Dr. Suzanne Koven, "a medical record that abandons narrative in favor of a list does more than dehumanize our patients. It also hampers a clinician's diagnostic abilities." In light of this, we can clearly see the importance of automating administrative tasks as well reshifting the focus on the human interaction with the patient, and this is where AR comes into play.

Looking at a few examples of AR in healthcare: The AED4EU app allows any person with a cell phone to scan their surrounding and look for a defibrillator. And in the not so distant future, surgeons might be able to gain X-ray vision and view accurate reconstructions of tumors through the skin of their patients. This is a world envisioned and currently being tested by a company called Medsights Tech.

Early in 2017, a VR startup, Rendever, won the MIT Sloan Healthcare Innovations Prize competition grand prize. Their system tracks movement which helps in early diagnosis of dementia: VR simulations immerse ask elderly individuals in a virtual world full of distractions and asks them to perform tasks, which helps doctors make diagnoses.

RENDEVER

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Digital Health Records

Digital health records (also known as electronic health records or EHR) consist of the storage and management of patient data digitally, away from the traditional paper form.

The push to transfer over and start using digital health records in national and private healthcare systems has seen the **support of governments** in countries including the US under president Obama (Speed, 2013) and the UK. The latter consisted of a high-profile failure to progress quickly enough, resulting in a cease of funding and rethinking the strategy entirely (under the Conservative-Liberal Democrat coalition government) after burning through billions of British pounds.

Despite the clear benefits of going digital, the process of moving over such vast amounts of data has proven surprisingly challenging. The main issues revolve around **cost, compatibility and security** (Clarke, 2011).

In the UK, the guidelines and deadlines set for going digital are still in place, with GP practices slowly adopting new systems such as TPP's SystmOnline (https://www.systmonline.tpp-uk.com) where patients can view their record, order medication, book appointments and more, depending on the settings chosen by each individual practice. As such, the level at which each practice operates digitally can be extremely **varied from place to place**.

While digital health records have already prevented countless errors such as prescription medication errors, the difficulty of implementing them fully has caused errors in itself occasionally. For example, faulty drop-down menus and staff learning to use the new systems have caused errors in the dosage of medication prescribed (Speed, 2013).

Another overarching challenge of implementing digital health record in practices is **workflow redesign**. Beyond the quality of the digital solution itself, the training of staff, rescheduling of various work activities surrounding the digital system, and integration with existing equipment or software mean the entire process of how work takes place might require redesigning to provide optimal efficiency (Pickett, 2011).

Despite some drawbacks (listed above), digital health record systems improve healthcare quality in several areas, leading to a decreased rate of adverse medication events, and benefits for pre-operative assessment. Computer-aided diagnosis also benefit from the data derived from DHR systems.

While most clinical research is still currently based on data collected by dedicated clinical trials, the troves of data of DHR are a huge boon for medical research. So in addition to making personalized medicine more seamless, analytics can reveal trends in specific demographic groupings, including age groups, such as the elderly.

Universality is of utmost importance to a successful digital health records platform. Its success will largely hinge on its ability to integrate health records from the largest number of health institutions. Fragmentation in this industry is hugely detrimental. The success also rests on a number of other critical factors. First, the system must be safe and secure enough to inspire trust, a critical factor that will largely affect the appetite of both health institutions and patients to jump on board. Secondly, the business model must be cracked. So far attempts at granting access to health records has proven to be costly.

https://15543-presscdn-0-47-pagely.netdna-ssl.com/wp-content/uploads/2016/06/digital-health-advisor.jpg

Digital health records hold tremendous potential to unlocking P3 medicine. By definition, P3 medicine promises personalized care. As such, having an accurate and comprehensive record for each patient is critical to the application of P3 medicine. The more comprehensive the data, the more personalized, and consequently, effective, care can be. Similarly, prediction and prevention rest on incorporating individual variabilities and history. Doctors can only be enabled to deliver personalized medicine using ready-made tools, systems and software. If successfully implemented, P3 medicine could be used for targeted treatment and side-effect minimization.

There are a number of challenges that plague this area however. For P3 to be truly effective and fulfill its full potential, the access to patient data must be as universal as possible. And here lies the problem: various record platforms don't use the same formats or protocols. This puts a lot of strain on hospitals and medical institutions to be able to integrate patient data in their systems.

Another problem is the type of data stored. Many health records are not granular enough. Some for instance do not account for the exact start time of a disease of treatment. The discrepancy between each system's variables usually results in data loss. Global standardization is paramount.

When El Camino Hospital in San Francisco experienced a rise in patient falls, they used AI to mine data from EHR and combined it with data from nurse call lights bed alarms. The AI system was able to predict patients at risk and prescribe treatment. This was possible because El Camino performs and documents a fall risk assessment in its electronic health record.

Few researchers advocate for the inclusion of the population perspective (an additional P). Recently, topological analysis of a population of 11,200 individual electronic medical record and genotype patient data helped identify subgroups of of type 2 diabetes. Machine learning techniques can be employed to for precision medicine related predictions. There are problems here too, namely the data gathered can be incomplete, and finding a good sample size of patients with similar kind of phenotype is difficult too.

eHealth Ireland Strategy

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Clarke, L., 2011. Challenges of Electronic Medical Records Implementation [WWW Document]. Health Guide Info. URL http://www.healthguideinfo.com/health-informatics/p105056/ (accessed 2.2.18).

Pickett, J., 2011. What are the biggest challenges in implementing an electronic medical record? URL https://www.quora.com/What-are-the-biggest-challenges-in-implementing-an-electronic-medical-record (accessed 2.2.18).

Speed, J.R. 2013-06-25T16:01:38Z-C.E.P., 2013. Digital Health Records' Risks Emerge as Deaths Blamed on Systems. Bloomberg. https://www.bloomberg.com/news/2013-06-25/digital-health-records-risks-emerge-as-deaths-blamed-on-systems.html

Blockchain / Next Generation Databases

Blockchain technology has the potential to add tremendous value within the healthcare industry. One of the areas within healthcare where blockchain can have the biggest impact is in Electronic Health Records. First, it builds trust by giving users the ability to control the contents of health records and verify if records have been altered. Secondly, it is secure, allowing only authorized personnel to access information. Thirdly, it facilitates interoperability, allowing multiple approved parties to append information to the record.

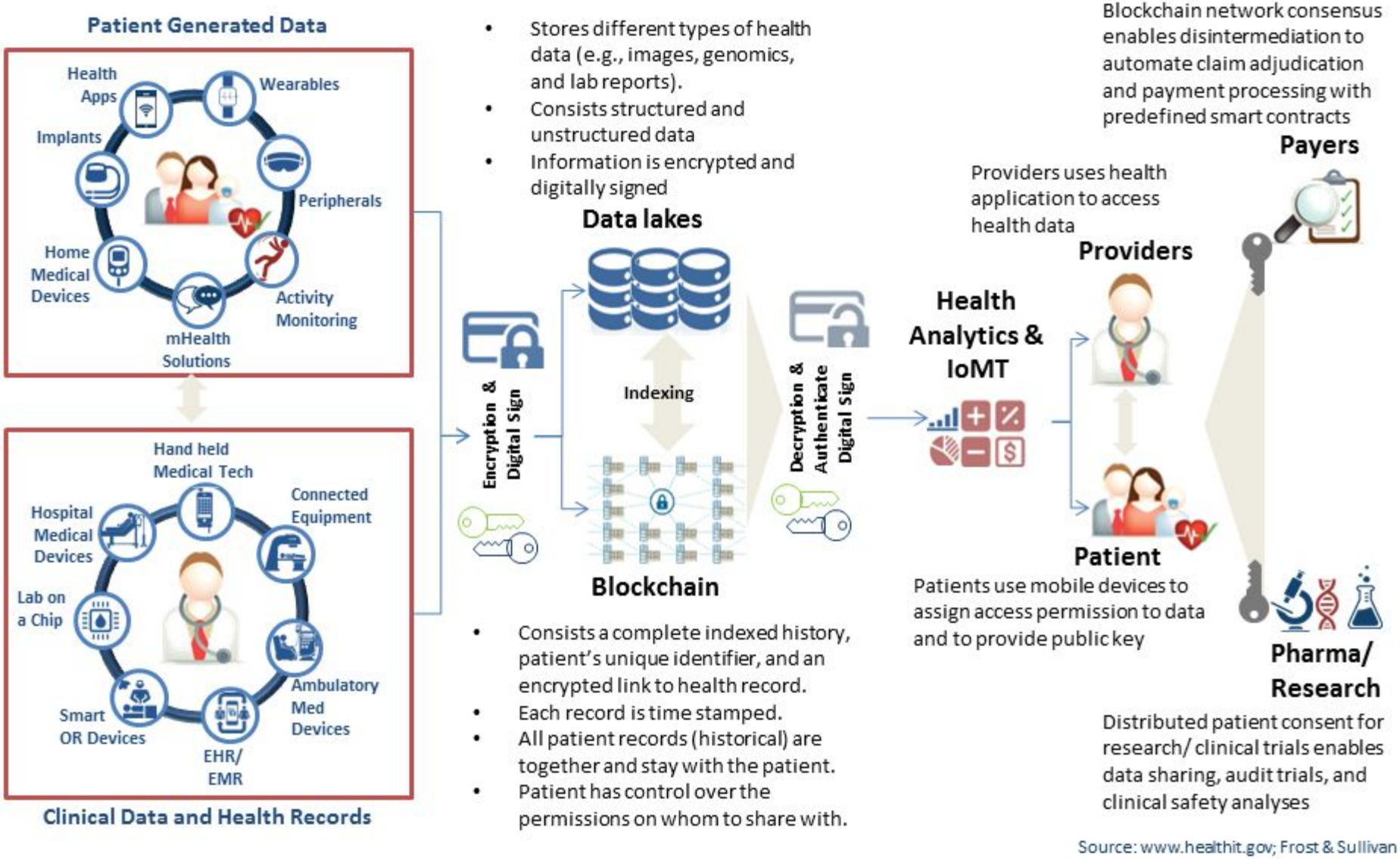
Three of Blockchain's building blocks - security, immutability, and anonymity - gives it the potential to build a global precision-medicine ecosystem. Providers can leverage two key attributes of blockchain technology - safety and trust - to enable collaboration between participants, researchers and themselves to develop individualized care.

Three potential applications of blockchain technology in healthcare are:

1. A chain-of-custody log for integrity in the drug supply chain.
2. Enhanced efficiency in clinical trials by reducing incidents of fraud and error.
3. Immutable records of trials and results potentially decreasing outcome switching, data snooping and selective reporting.

Blockchain improves security of medical data which will be increasingly important especially in light of the Internet of Medical Things.

Blockchain Technology – Promising Use Cases for Healthcare Industry



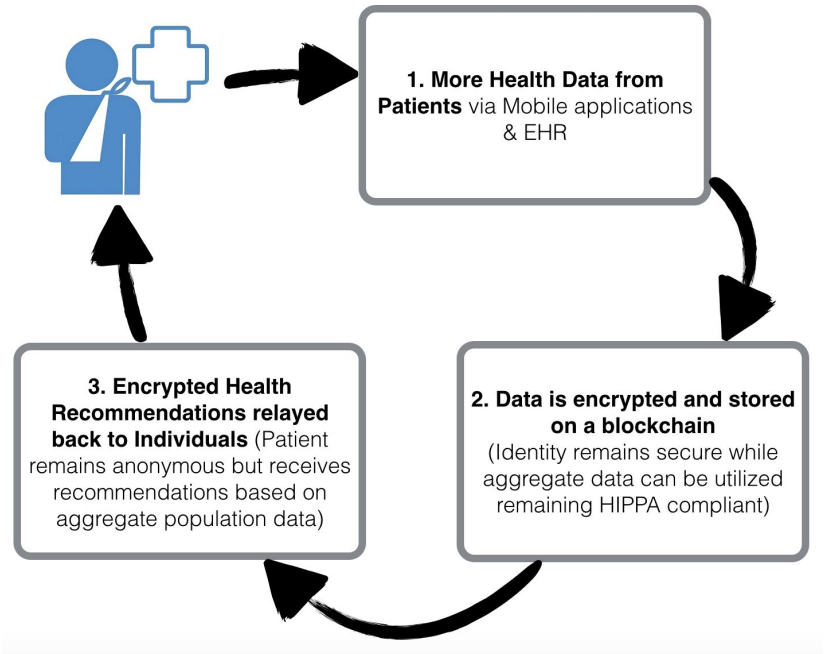
Source: https://www.forbes.com/sites/reenitadas/2017/05/08/does-blockchain-have-a-place-in-healthcare/#604b49a61c31

Lack of patient incentive, concerns over privacy, the siloing of data, and the lack of public awareness around the merits of genome mapping are the main factors P3 hasn't really taken of yet.

Looking at privacy concerns, secure tools already exist and are embedded everywhere in our lives. But the same methodologies are not fully implemented when it comes to health data. Enter blockchain.

Here again we turn our attention to digital health records. P3's success will largely depend on the successful implementation of systems that inspire trust in patients when it comes to their data.

Aside from security, blockchain technology offers a plausible system to streamline the sharing of medical records. For that, a technical infrastructure must be constructed, a health-care blockchain' so to speak.



A potential scenario for synergy between EHR, mobile health applications, blockchain technology, and preventative care.

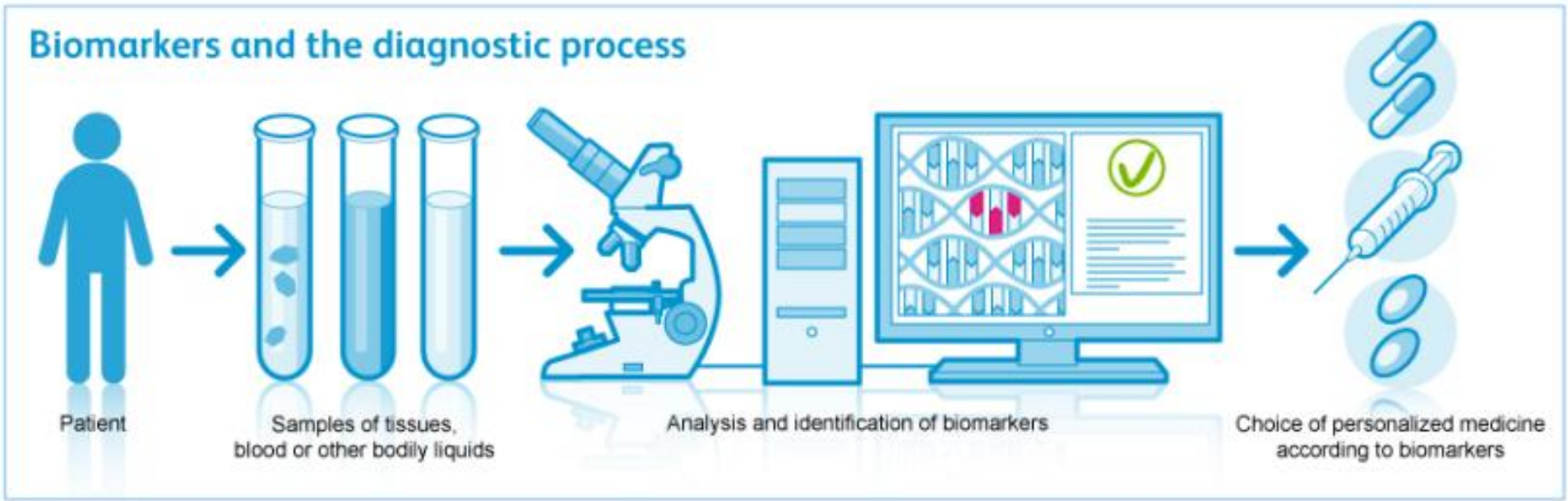
Source: https://rywalk.wordpress.com/2014/11/10/healthcare-and-the-blockchain/

Biomarkers of Aging

Biomarker technology is one of the keys that enable the transformation of the current healthcare system into the P3 Medicine system. Each biomarker is a trait of an organism such as blood pressure or presence of a specific type of antibodies that can indicate emerging diseases and other adverse processes.

While genetic tests can show the risk of acquiring a specific disease, they are static and do not reflect the state of the organism. However, the technique that allows continuous monitoring of the patient in real time is the requirement for the P3 Medicine to work.

Classical biomarkers are inadequate for the healthcare paradigm shift and many companies and non-profit institutions are now racing to develop new and efficient biomarkers to face the challenges presented by the contemporary healthcare landscape changes.



Source: https://futurism.com/were-about-to-enter-a-new-era-in-parkinsons-disease-treatments/

These new biomarkers will be essential for the longevity industry given the importance of the P3 Medicine in fighting aging. Today mainstream healthcare lacks a accurate and reliable means for monitoring the aging process.

This problem is currently being solved by various organizations, most notably SENS Research Foundation, as well as for-profit organizations.

Some strive to discover new markers by carefully studying aging processes and developing methods for direct measurement of molecules.

Others use new technologies and reimplement methods that are already used in healthcare to indirectly measure aging processes, thus making the shift to the P3 Medicine much easier. The most prominent technology implemented this way is artificial intelligence.

Chronological Age

- Measures how many times you, in this body, have revolved around the sun
- Cannot be altered by mind/body approaches
- Has little relevance to how you feel and function

Biological Age

- Measures how well your physiological systems are functioning
- Can be reversed by attending to your health
- Is the most important component of the aging process

It is becoming ever more important to develop preventative strategies to monitor and maintain health, as well as therapies that directly address the various aging processes to delay or prevent the onset of age-related diseases.

One of the ways we can do this is by developing more effective ways to measure how someone is aging; this means developing high quality aging biomarkers.

A biomarker is an indicator used to measure the state of a biological condition or process.

As aging is an especially multifarious degenerative condition, assessing progress and success therefore requires a diverse range of scientifically validated biomarkers.

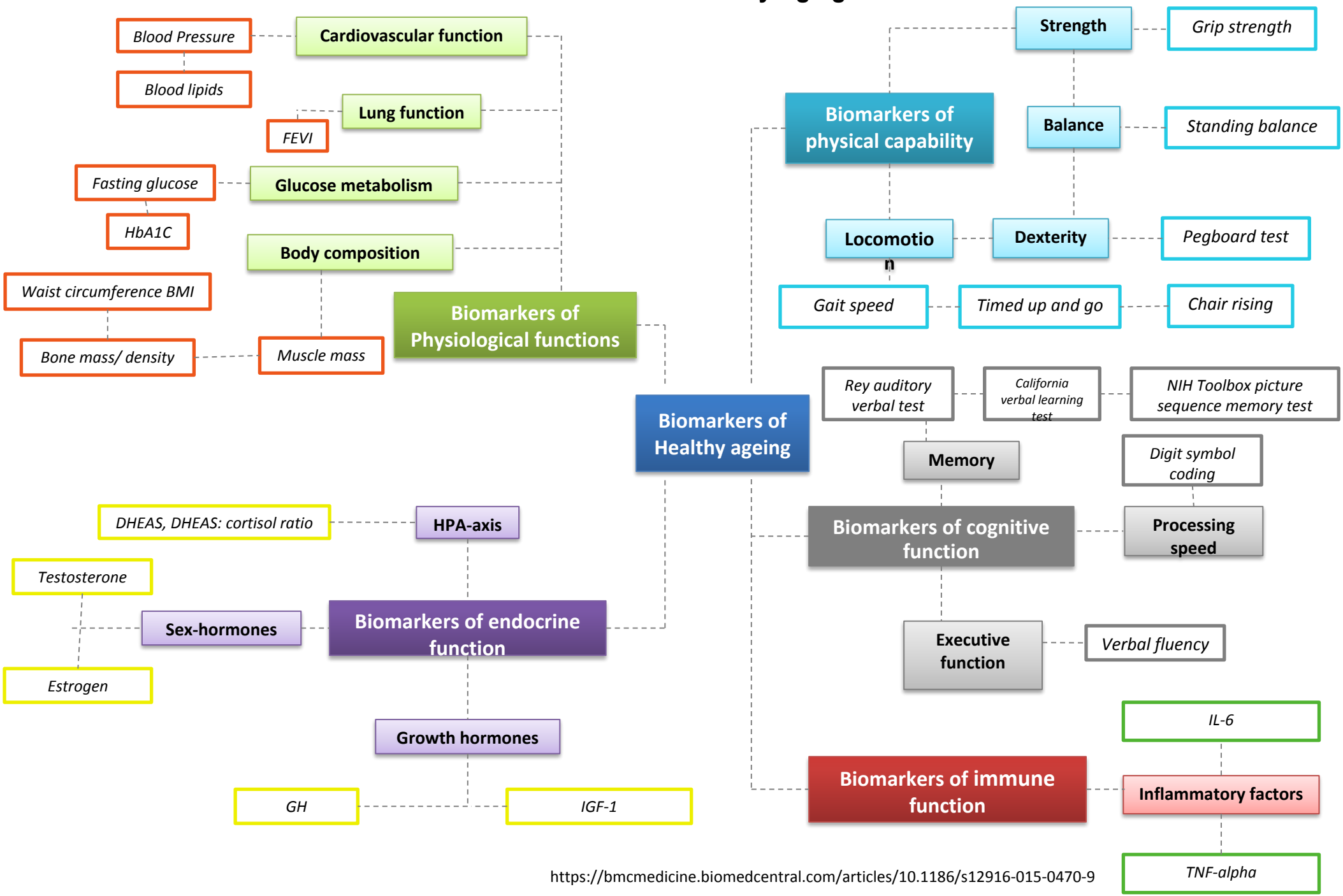
Biomarkers of aging serve as a better indicator of functional decline than chronological age.

Biomarkers of aging could therefore be thought of as scientifically validated detailed descriptions of “biological age” rather than chronological age.

Validated biomarkers of aging would allow for testing interventions to extend lifespan, because changes in the biomarkers would be observable throughout the lifespan of the organism.

Although maximum lifespan would be a means of validating biomarkers of aging, it would not be a practical means for long-lived species such as humans because longitudinal studies would take far too much time. Ideally, biomarkers of aging should assay the biological process of ageing and not a predisposition to disease, should cause a minimal amount of trauma to assay in the organism, and should be reproducibly measurable during a short interval compared to the lifespan of the organism.

Biomarkers of Healthy Aging



https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-015-0470-9

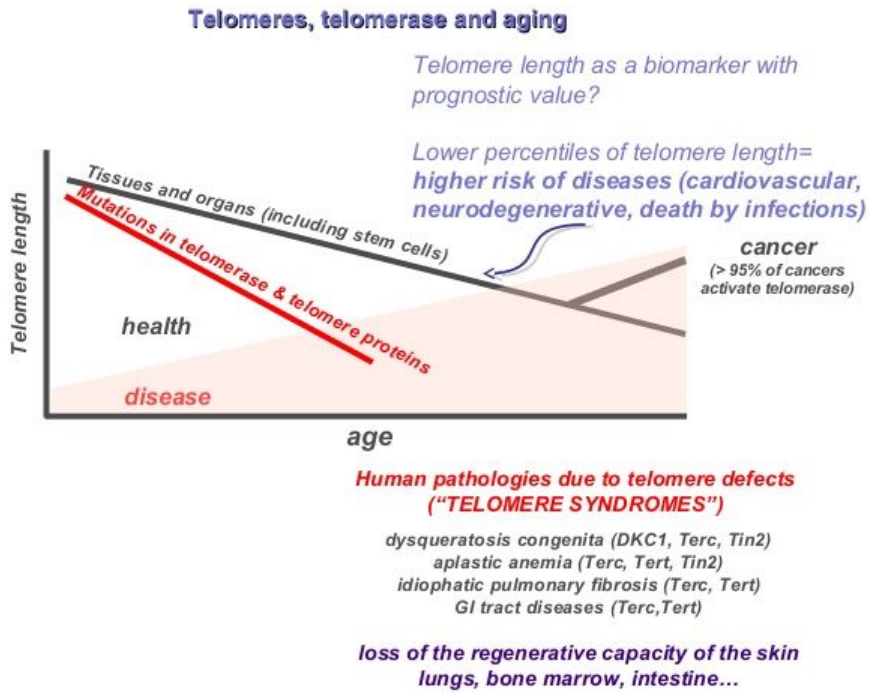
So for example, although graying of hair increases with age, hair graying cannot be called a biomarker of ageing. Similarly, skin wrinkles and other common changes seen with aging are not better indicators of future functionality than chronological age. Biogerontologists have continued efforts to find and validate biomarkers of aging, but success thus far has been limited. Levels of CD4 and CD8 memory T cells and naive T cells have been used to give good predictions of the expected lifespan of middle-aged mice.

Advances in big data analysis have allowed for three new types of "aging clocks" to be developed. The epigenetic clock is a promising biomarker of aging and can accurately predict human chronological age. Basic blood biochemistry and cell counts can also be used to accurately predict the chronological age. It is also possible to predict the human chronological age using the transcriptomic aging clocks.

Chronological age is a poor indication of how someone might be aging and is not a good way to ascertain an individual's risk factor for various age-related diseases.

This is simply because everyone ages differently and at different rates. Whilst everyone ages due to the same processes, the speed at which these different processes occur can vary between individuals. Whilst individual biomarkers are good for measuring certain aspects of aging in a very focused way, and indeed they are useful in this capacity, they do not give an overall picture of how someone is aging and where to focus preventative efforts.

One popular biomarker of aging is the measurement of telomeres. However this has some limitations, depending on the particular method used. Indeed some studies have investigated its validity as an aging biomarker, and argue that whilst useful it is not really an aging biomarker in the strict sense.



Slide: Dr. Maria Blasco

A system analysis approach to aging biomarkers

In order to get the bigger picture, we need to move beyond this simple approach to a systems analysis approach that examines multiple biomarkers at once.

A number of approaches to this issue have been proposed and even tested. Arguably one of the most well-known methods for ascertaining biological age is the DNA methylation clock developed by Horvath, it can in many ways be considered the gold standard for aging biomarkers.

Approaches that consider multiple biomarkers have also been proposed; such systems evaluate a number of biomarkers to give a 'score' as an overall indication of aging rate. More recently a package of 19 biomarkers has been suggested as another approach to evaluating age.

There are numerous similar proposals in literature to evaluate aging using a wider set of biomarkers, and one does not have to search far to find them.

There is an urgent need to not only develop more accurate biomarkers, but also to package them into a systems analysis approach. This would allow researchers developing drugs and therapies that target the aging processes to ascertain efficacy to a much greater degree. It could also allow better monitoring of an individual's health state and allow physicians to identify and address areas of concern to a far greater degree of accuracy.

The development of better biomarkers and systems capable of packaging them into compact solutions is very important to aging research. The rising popularity of health wearables and other personal health monitoring equipment also has the potential to allow the average person to take more control over their health too.

Such approaches could be combined with other functional aging tests such as the H-Scan or the updated version being developed as part of a fundraising project at Lifespan.io.

The development of biomarkers and systems that deliver them efficiently and at an affordable cost should therefore be a high priority.

The American Federation for Aging Research (AFAR) proposed that for biomarkers of ageing to be valid:

- They must predict the rate of aging. They should be able to tell exactly where a person is in their total lifespan and it must be a better predictor of lifespan than chronological age.
- They must monitor basic processes that underlie the aging process, not the effects of disease.
- They must be able to be tested repeatedly without harming the person. For example, a blood test or an imaging technique.
- They must work in humans and in laboratory animals, such as mice, so that it can be tested on laboratory animals before being validated in humans.

Biomarkers fulfilling all of the above AFAR criteria are unlikely to exist. Several candidate biomarkers of ageing have emerged in the past few decades but none has proved universally suitable for, or robust in, measuring or predicting the degree of ageing at either the population or individual levels.

afar american federation for aging research

AI in Healthcare

Artificial intelligence will revolutionize the healthcare industry. Indeed healthcare will be leading the Fourth Industrial Revolution, and a major catalyst for change is going to be artificial intelligence (AI).

AI in health represents a collection of multiple technologies enabling machines to sense, comprehend, act and learn so they can perform administrative and clinical healthcare functions. Unlike legacy technologies that are only algorithms and tools that complement a human, health AI today can truly augment human activity.

AI has already found several areas in healthcare to revolutionize, starting from the design of treatment plans through the assistance in repetitive jobs to medication management or drug creation. And it is only the beginning.

The number of startups entering the healthcare AI space has increased in recent years, with over 50 companies raising their first investment rounds since January 2015. Deals to healthcare-focused AI startups went up from less than 20 in 2012 to nearly 70 in 2016.

The field of AI has been actively growing since 2015. But 2017 became year of the ‘cambrian explosion’ of AI in healthcare.

This market is primarily being driven by factors like the rise of personalized medicine in tests for clinical decision-making, big data in the healthcare industry, and the growing adoption of AI in genetics. Also, AI created a real-time monitoring system, and wearables are playing a crucial role in digital healthcare monitoring.

AI in Healthcare:

- Drug Discovery
- Wearables
- Medical Imaging and Diagnostics
- Research
- Mental Health
- Lifestyle Management
- Digital Health Monitoring
- Patient Data and Risk Analytics
- Virtual Assistants
- Surgery
- Hospital Management

AI for Drug Discovery, Biomarker Development and Advanced R&D Landscape / 2018 Q1

Companies - 70
Investors - 180
Corporations - 25

Investors
AI Companies
Corporations

DEEP KNOWLEDGE VENTURES

AI for Drug Discovery, Biomarker Development and Advanced R&D Landscape / 2018 Q1

Companies - 70
Investors - 180
Corporations - 25

USA

Investors

AI Companies

Corporations

UK

EU

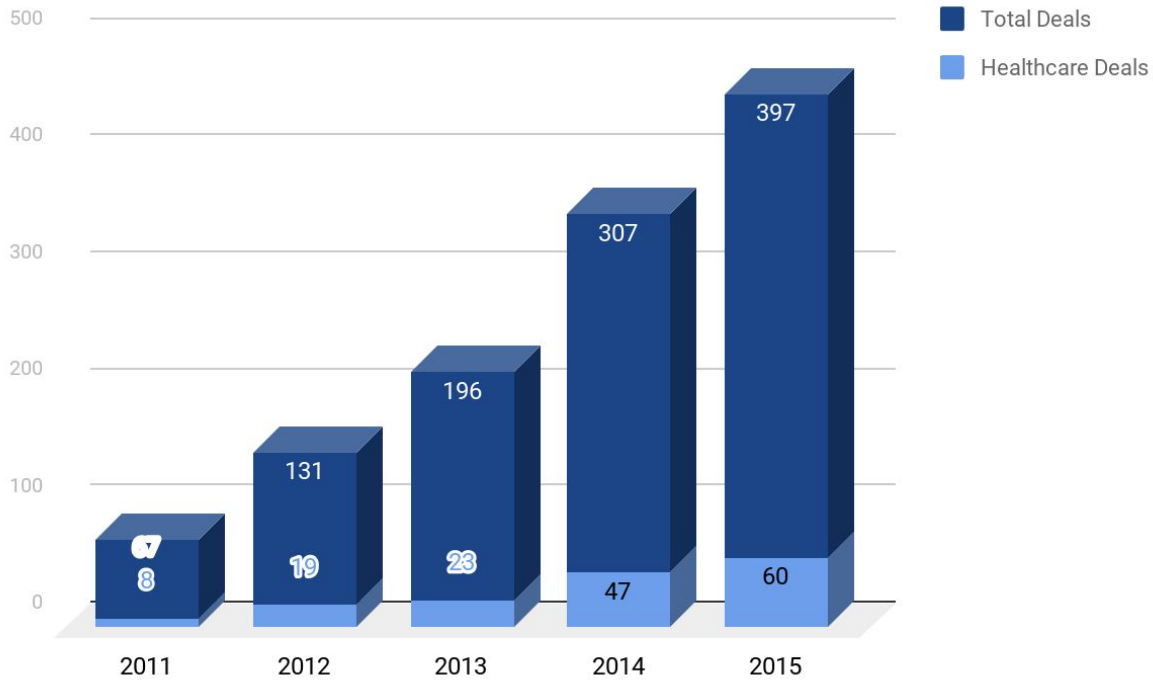
Asia

Other Regions

DEEP KNOWLEDGE VENTURES

Artificial intelligence is becoming a of modern life. In recent years, machine learning scientists have made astonishing progress implementing AI into various industries in a short span of time. From stock trading to project management, AI is now a crucial part in the normal functioning of the world economy: a study conducted in Oxford shows that 47% of all existing jobs can be automated with artificial intelligence technologies. It is natural that AI is rapidly developing in a modern healthcare system. NPOs, government organizations, and enterprises alike include algorithms to enhance their therapies.

The prospects of AI implementation in the longevity industry is closely tied to its implementation in the healthcare industry. Machine learning is an important technology that enables personalized medicine and revolutionizes drug discovery landscape, bringing us closer to the preventive, longevity-focused healthcare system. Healthcare is considered to be the top area of investment in by AI by CB Insights analytical agency



Growing healthcare AI market compared to the overall AI market. Source: https://www.slideshare.net/galengrowthasia/cb-insights-ai-in-healthcare

Although AI implementation in the longevity industry is in its infancy, the impact it will eventually make on modern biogerontology will be greater than any other innovation in this industry.

Judging from the number of new disruptive startups emerging in the field, as well as AI-mediated healthcare projects in larger companies, it's clear that machine learning will become both a leading trend in the field, and one of the most successful markets.

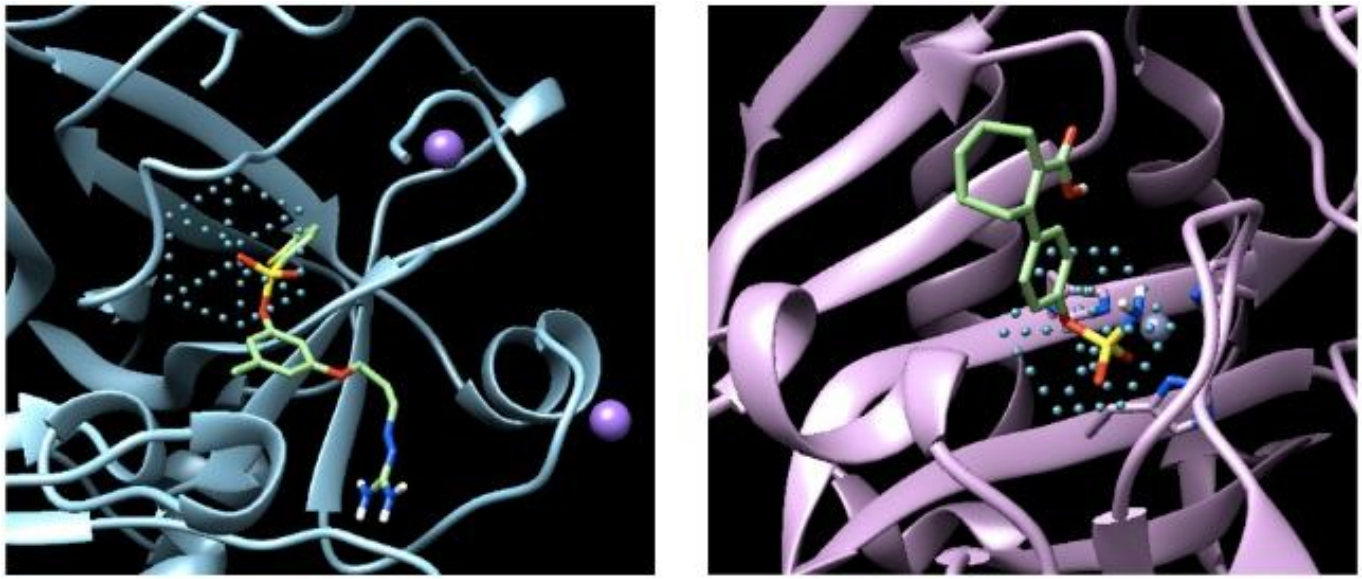
One of the notable examples of AI integration into the P3 Medicine comes from Insilico Medicine. The company has launched the http://aging.ai/, an AI-powered software that allows tracking aging using only the data from the common blood test. Having already released three versions of the Aging AI, Insilico is bringing the viable and reliable aging biomarkers closer to the industry. This is only one example of how AI can greatly benefit the P3 Medicine, being one of the most important technologies to influence the industry

Atomwise
Better medicines faster.

A leading example of the use of AI in **drug discovery** is Atomwise, which recently raised $45M to continue their work.

Instead of having to produce all drug candidates for testing, their AI (*AtomNet*) enables circumvention of this costly step by determining the most promising candidates digitally.

For example, their systems have been able to teach themselves chemistry and begin recognising key chemical groups such as sulfonyls - central to many antibiotics. Indeed, their lead molecule against Ebola has shown promise and is lined up for animal trials.



AtomNet learning to recognize sulfonyl groups – a structure often found in antibiotics.

http://www.atomwise.com/introducing-atomnet/

Some downstream challenges still exist (namely drug delivery, metabolism and side effects), but the simplification of this first stage of drug candidate screening already promises to slash the phenomenal price of finding new drugs.

Their announcement of raising $45M was attached to a claim of becoming “The Preferred Artificial Intelligence Partner for the Global Pharmaceutical Industry”.

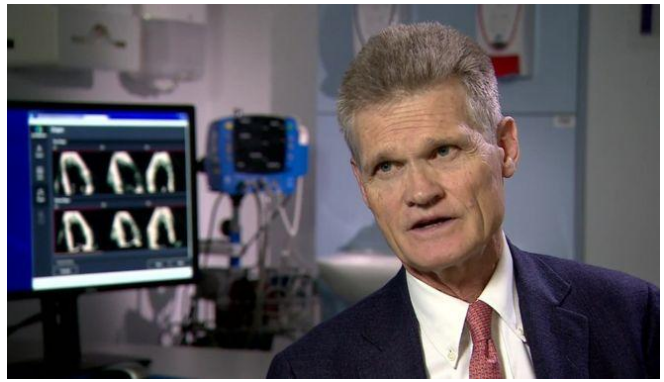
http://www.atomwise.com/atomwise-series-a/

AI in Healthcare is Supported by the UK Government

The UK government's healthcare tsar, Sir John Bell, has told BBC News that AI could "save the NHS".

John Bell said that NHS patient records are uniquely suited for driving the development of powerful algorithms that could transform healthcare and seed an “entirely new industry” in AI-based diagnostics.

“*What Google’s doing in other sectors, we’ve got an equivalent unique position in the health space*” he said. “*Most of the value is the data. The worst thing we could do is give it away for free.*”



Researchers at an Oxford hospital have developed artificial intelligence (AI) that can diagnose scans for heart disease and lung cancer. This heart disease technology will start to be available to NHS hospitals for free this summer.

"There is about £2.2bn spent on pathology services in the NHS. You may be able to reduce that by 50%. AI may be the thing that saves the NHS," he said.

The system will save billions of pounds by enabling the diseases to be picked up much earlier.

Taking this example and applying it more generally to a wider array of diseases, the NHS could create significant cost savings by better diagnosing and treating patients with the assistance of machine vision of X-rays, MRIs, cell culture results, epidemiological data crunching, and so forth.

Source: bbc.co.uk

A lot of work is currently done by expensive, error-prone humans that need not be.

- AI in Healthcare is growing very fast. There have been several deals worth tens to hundreds of millions of dollars in the past few months alone
- As this trend in AI continues it will mostly be used by existing IT giants, with the exception of areas such as electronic health records and digital pathology where these do not have access to the data
- Progress will outstrip even the most optimistic projections, outperforming even the AI development exhibited by the big IT giants of today - Google, Facebook, NVIDIA, Baidu, etc.
- A convergence of software development, the rise of the sharing economy, the distribution and processing power of AI, along with the convergence of all these niches creates a propitious environment for healthcare and BioPharma, prompting key players to switch focus from niche areas to a much more holistic and inclusive approach
- One of the most important emerging uses for AI is drug discovery, where it holds the most disruptive potential. AI has already begun to penetrate into Big Pharma's drug discovery departments.

https://www.navedas.com/real-world-examples-of-ai-and-healthcare-in-action/

AI for advanced R&D & The broken model of biopharma

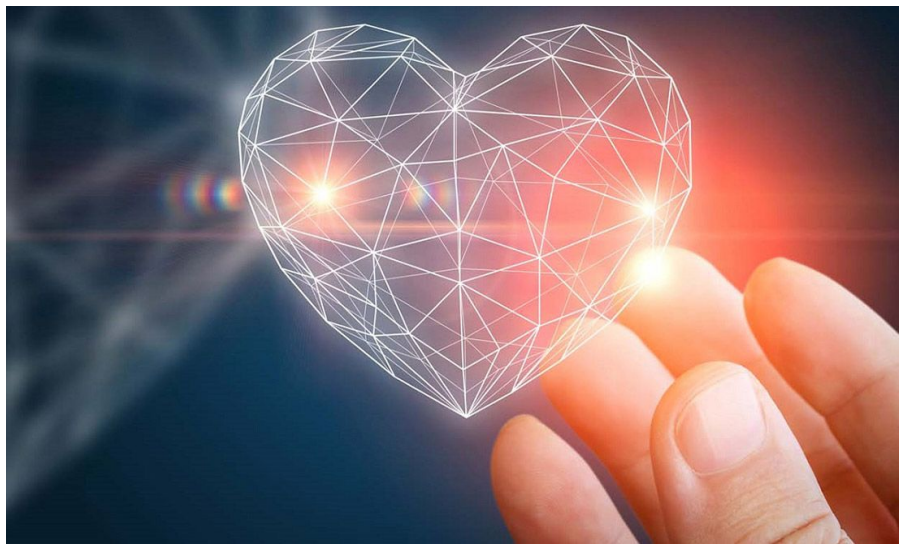
The broad field of AI in Healthcare has already experienced a significant rise during 2016, especially in the application of computer vision, text analysis and chatbot technologies. These techniques, first developed in the IT sector, were repurposed for the healthcare sector.

However, the use of AI in advanced R&D is limited to companies and researchers with very high levels of expertise. This creates a specific scarcity for AI specialists in this niche. 2018 is expected to become the year in which AI will be recognized as the most powerful driver of progress in solving the crucial challenges of the most advanced sectors of science and R&D in the healthcare and Biotech industries.

The use of AI in advanced R&D, biomarker development and for drug discovery will make the most disruptive impact on the business model of the Pharma and entire Biotech industry. This is why the players in the AI for drug discovery market can become new game changers and significantly influence the capitalization of pharma companies.

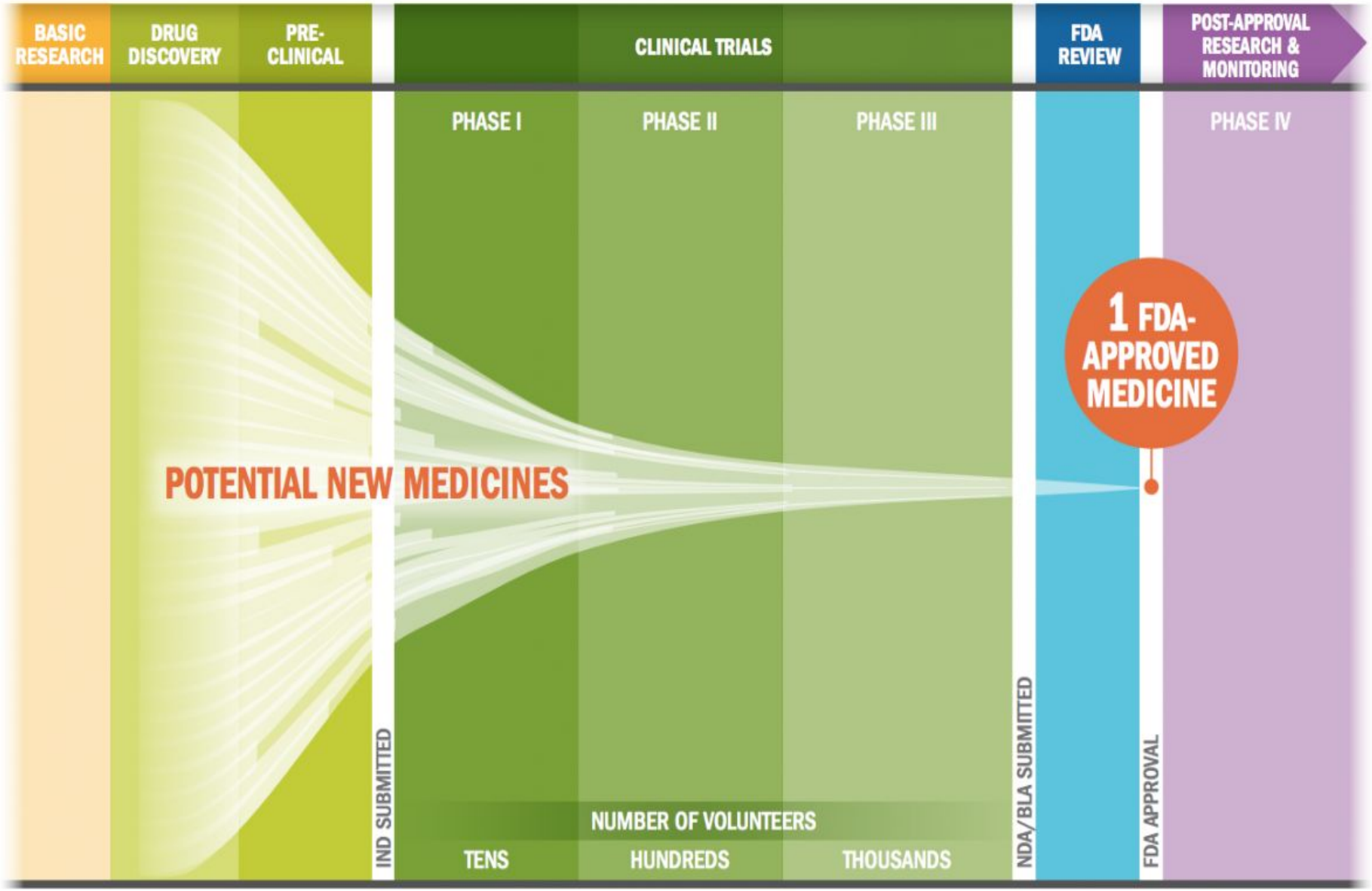
The efficiency of research and development (R&D), defined as the number of successfully approved drugs given the budget allocated to new drug development, has declined for decades. The cost of drug discovery and subsequent development is a massive challenge in the pharmaceutical industry.

A typical drug can cost upwards of $2.5 billion and can take a decade or more to identify and test a new drug candidate. Today, only about one in ten drugs that enter phase 1 clinical trials reaches patients. Drug makers need to find a more efficient way of developing medicines. AI can speed up drug discovery, cut R&D costs, decrease failure rates in drug trials and eventually create better medicines.



Source:http://blog.global.fujitsu.com/wp-content/uploads/2017/09/bock_humantech_blog.jpg

THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS



Source: Biopharmaceutical Research & Development, PRMA http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf

AI for Drug Discovery, Biomarker Development and Advanced R&D Landscape

Companies - 70
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Drug Discovery

Advanced R&D

Investors

AI Companies

Corporations

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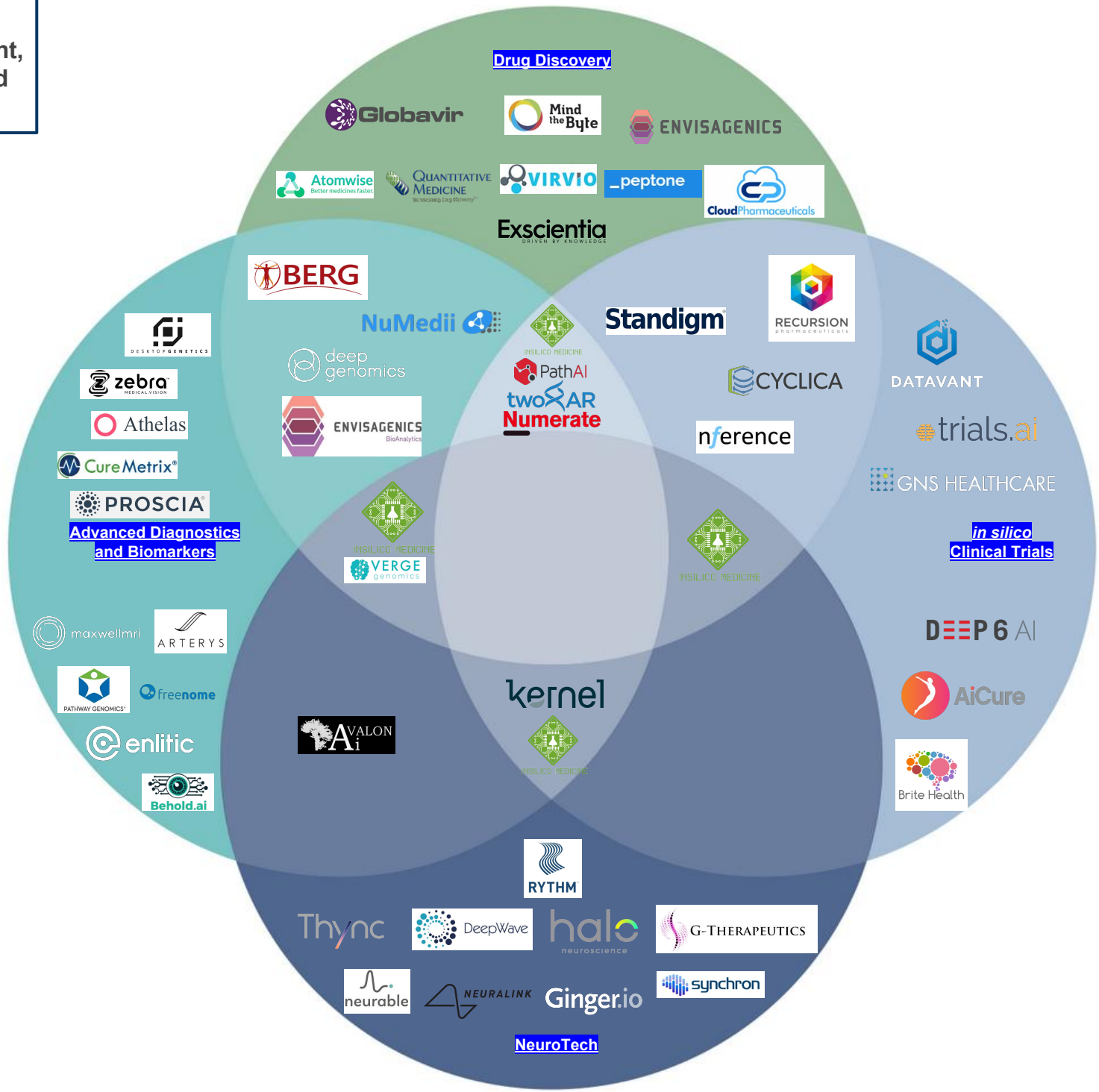
AI for Drug Discovery, Advanced Diagnostics and Biomarker Development, *in silico* Clinical Trials and NeuroTech 2017



DEEP KNOWLEDGE VENTURES

AI for Advanced R&D and Drug Discovery 2018 / Q1

BioPharma giants will need to commit significant resources (and perhaps even more importantly, significant will and the implementation of AI-focused strategies) to the acquisition of AI specialists and AI for drug discovery companies. However, several BioPharma giants have already began to do just this, and might jump ahead of other BioPharma companies in the AI race.

One prime example of the major changes that have occurred in just the past several months is the current state of what we referred to in our previous reports as the **Big Gap**, i.e., the fact that throughout 2016 and 2017 IT giants recognized and supported AI for healthcare startups, in terms of both investment and acquisitions, while BioPharma lagged behind, still skeptical of the impact that AI could make upon drug discovery, biomarker development and other BioPharma niches.

Our most recent analysis seems to indicate that this Big Gap is now to a large extent **neutralized**, and the BioPharma industry now has significant interest in AI, and belief in its ability to facilitate fundamental paradigm shifts in their traditional modes of operation.

Some BioPharma companies have now become actively involved in the AI for drug discovery sector, while others still lag behind, skeptical of the sector's potential for impact and disruption, or finding themselves unable to acquire or implement these novel technologies in any relevant capacity.

All indications point to the conclusion that 2018 will mark the year that will test the strength, resolve and foresight of BioPharma as a whole.

Those BioPharma companies that commit significant will and resources to acquiring strong AI specialists, technologies and acquisitions will flourish, and those that do not will stagnate, and by the time their profit margins force them to realize the disruptive potential of AI for drug discovery and other biomedical niches, they will have missed the boat, with the majority of talent, technology and companies having already been acquired by their competitors.

Meanwhile, within that last financial quarter, Chinese IT and Tech giants, such as Alibaba, Baidu and TenCent, have made significant investments and acquisitions in the AI for Drug Discovery sector, showing that the number of IT giants committing to the sector is growing not just regionally but also globally.

At the same time, the lack of AI specialists that was alluded to in our previous reports is still present. The majority of talented AI specialists in general have been acquired by traditional IT giants and have been applied for purposes other than AI in healthcare, creating a lack of enough specialists to support the activities of AI for drug discovery companies.

And it is not just traditional BioPharma companies that are suffering from this lack of specialists; indeed, even companies specializing specifically in **AI for drug discovery are feeling the effects of this lack, as can be seen on page 29 of this report, which shows that on average, AI specialists make up only 19.7% of such companies staff.** One of the central aims of this report is to summarize this gap, and chart the possible ways forward in order to neutralize it.

Overall, the AI in healthcare and BioPharma subsector is growing at an exponential rate, both in terms of new companies, investments and acquisitions, and in terms of the extent with which it is disrupting the traditional modes of operation on BioPharma as a whole.

What is now a subsector and niche is poised to grow into perhaps the leading subsector in BioPharma in the next 2-3 years, one that will have the greatest transformational impact on the industry, and one that will distinguish the leaders of the industry from the stagnators.

By the end of 2018, we can predict that there will be intensive competition between the largest BioPharma companies and the largest IT and tech giants for the acquisition of new AI specialists, technologies and startups, in much the same way that 2014 – 2016 saw intense competition between IT-giants and Tech corporations to acquire the best AI assets and resources.

The Application of AI for Advanced R&D

Generate Novel Drug Candidates

- Analyze data sets, form hypotheses and generate novel insights
- Identify novel drug candidates
- Analyze data from patient samples in both healthy and diseased states to generate novel biomarkers and therapeutic targets
- Predict binding affinity and other pharmacological properties of molecules
- Allow filtering for drug-like properties of molecules
- Reduce complexity in protein design

Aggregate and Synthesize Information

- Extract knowledge from literature
- Generate insights from thousands of unrelated data sources
- Improve decision-making
- Eliminate blind spots in research
- Identify competitive whitespace

Repurpose Existing Drugs

- Rapidly identify new indications for many known drugs
- Match existing drugs with rare diseases
- Conduct experimental biology at scale by testing 1000+ of compounds on 100+ of cellular disease models in parallel
- Generate novel biomarkers and therapeutic targets

Design and Run Preclinical Experiments

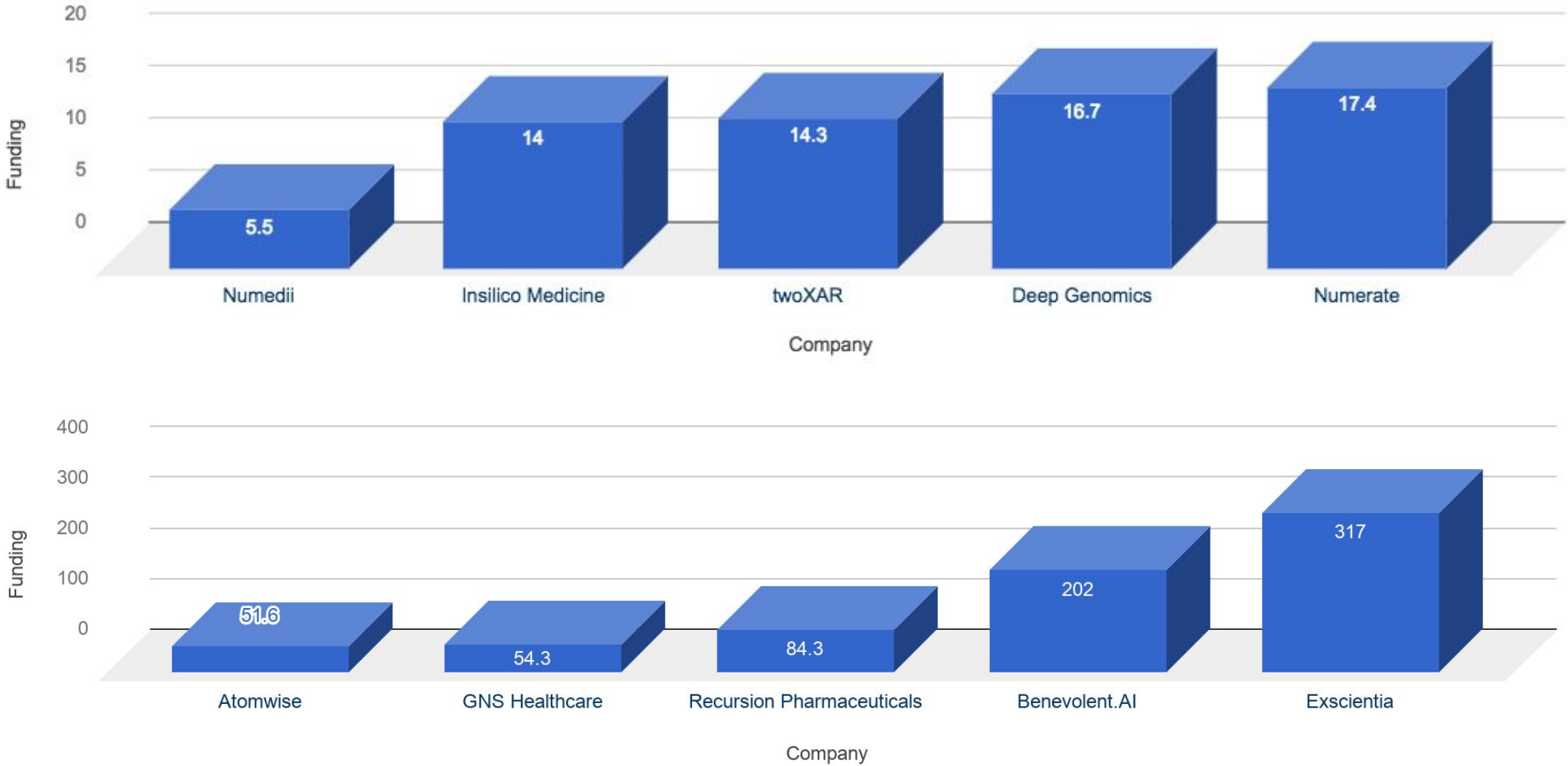
- Reduce time, money, and uncertainty in planning experiments
- Decode open- and closed-access data on reagents and get actionable insights
- Automate selection, manipulation, and analysis of cells
- Expedite development of cell lines and automate manufacturing of cellular therapeutics
- Automate sample analysis with a robotic cloud laboratory

Clinical Trials

- Optimize clinical trial study design
- Transform diverse streams of biomedical and healthcare data into computer models representative of individual patients
- Deliver personalized medicine at scale, by revealing optimal health interventions for individual patients
- Analyze medical records to find patients for clinical trials
- Automate matching cancer patients to clinical trials through personal medical history and genetic analysis
- Improve pathology analysis
- Identify patients that would benefit from novel therapies

Comparison of AI for Drug Discovery Companies

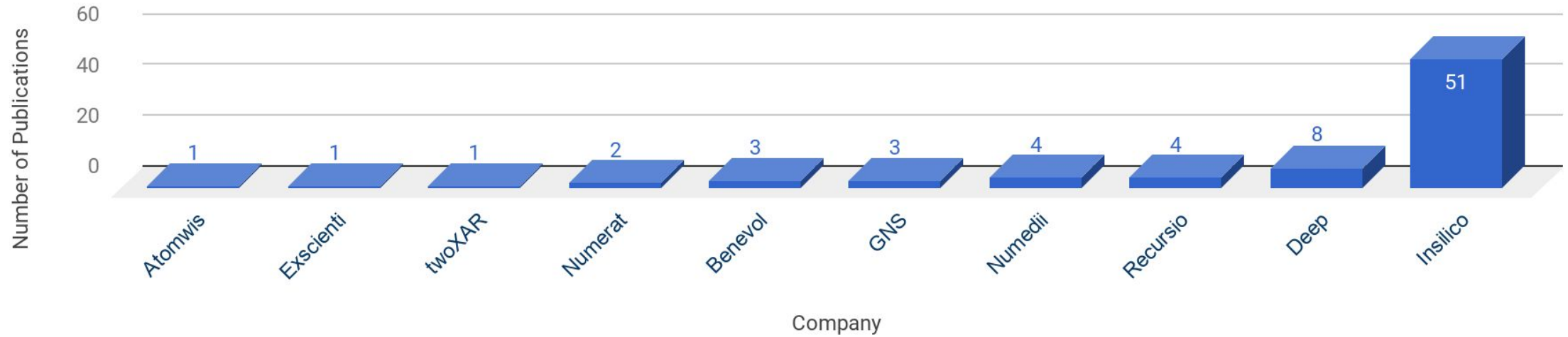
Funding*, $m



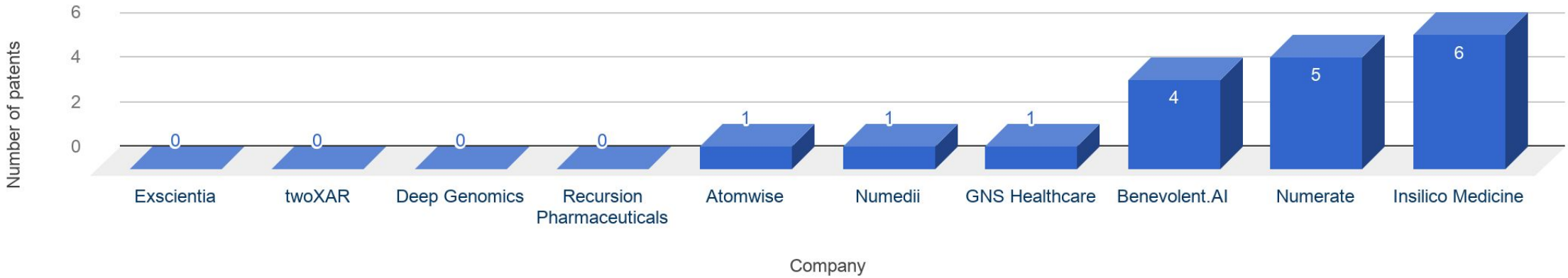
Source: Crunchbase or Company Website

Comparison of AI for Drug Discovery Companies

Number of Publications (PubMed)

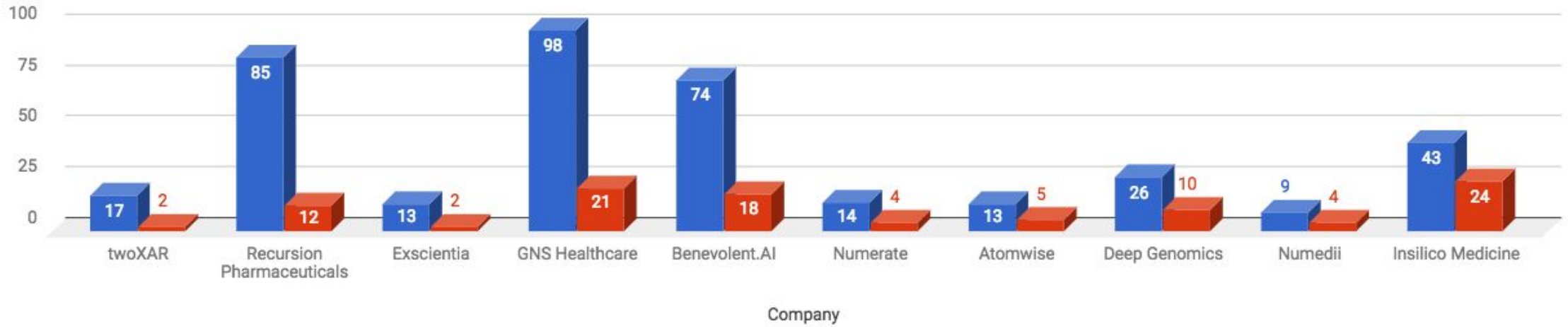


Number of Patents (Google Patents)



Source: patents.google.com // official websites

Total Number of Employees / AI experts



True AI companies
The ratio: AI experts vs Total Number of Employees

Source: Deep Knowledge Analytics
Crounchbase.com

Comparison of AI for Drug Discovery Companies

Company	Scientific publications covering AI for drug discovery	Number of AI experts in the team / total number of employees	Public talks on AI for drug discovery	Validation	Use GANs/RL
Atomwise	+	11/13	+	n/a	n/a
Cloud Pharmaceuticals	+	n/a	+	n/a	n/a
Benevolent.AI	+	18/74	+	n/a	n/a
Globavir	-	1/4	-	n/a	n/a
Envisagenics	-	n/a	+	n/a	n/a
Numerate	-	4/15	+	+	n/a
NuMedii	+	4/9	+	n/a	n/a
TwoXar	+	1/15	+	n/a	n/a
Exscientia	+	2/12	+	+	n/a
BioAge Labs	+	1/5	+	n/a	n/a
Insilico Medicine	+	24/43	+	+	+

Comparison of AI for Drug Discovery Companies

Company	Scientific publications covering AI for drug discovery	Number of AI experts in the team / total number of employees	Public talks on AI for drug discovery	Validation	Use GANs/RL
Cyclica	+	7/27	+		
Deep Genomics	+	10/26	-		
BioSymetrics	-	5/7	-		
e-therapeutics	+	4/25	-		
Healx	-	5/20	-		
GNS Healthcare	+	21/98	-		
AiCure	-	9/43	+		
PathAI	-	13/37	-		
Owkin	-	9/22	+		
Mendel.ai	-	6/8	-		
Insilico Medicine	+	24/43	+	+	+

AI in Healthcare & Drug Discovery

The most disruptive impacts of AIs will be on the business model of advanced R&D, biomarker development and drug discovery.

Specific attention should be paid to those projects capable of applying Next Generation Artificial Intelligence techniques, Deep Learning and in particular GAN's (generative adversarial networks) and reinforcement learning for:

- Drug Discovery and Drug Repurposing
- Biomarker Development
- Clinical Trials Predictors
- Aging Research
- AI Solutions in convergence with Blockchain

The leading players in this specific niche will become game changers for the entire market and significantly influence the capitalization of pharma companies.

The global healthcare AI market is highly fragmented and characterized by the presence of large number of industry players, while the AI for drug discovery segment has a comparatively lower level of competition because this market segment only accepts companies with very high levels of expertise.

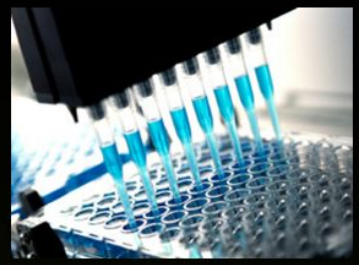
There are more than 100 AI in Healthcare companies, but only 10 of them are capable of entering the AI in Drug Discovery sector.

The breakthroughs in AI for drug discovery will change the R&D process of Bio Pharma, and will have tremendous impact on the whole biopharma industry. That is why the players from the AI for drug discovery market can become game changers and significantly influence the capitalization of pharma companies.

Computation-based Drug Discovery

Synthesize new Chemical Compounds

Millions of Compounds →



Robot-assisted screening
High Throughput Screening

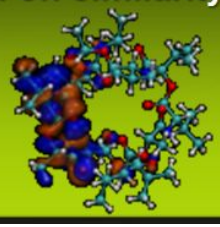
1000s of Compounds →

Testing for Efficacy, Side Effects, Safety

→ Clinical Trials FDA Approval Process

Computational Chemistry

- Synthesize compounds based on similarity

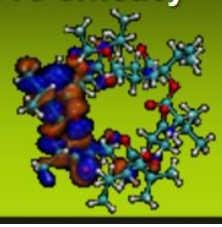


Virtual Screening

- Check if compounds bind to target proteins

Lead Optimization

- Modify chemicals to improve efficacy



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Source: https://blogs.nvidia.com/blog/2010/01/22/accelerating-the-pace-of-drug-discovery-using-gpus/

AI in BioPharma R&D: The big gap

This will have a domino effect, as biopharma budgets are significantly related to spending on R&D and failures in clinical trials, meanwhile the breakthroughs in the use of AI for drug discovery will have dramatic impact on not just Biopharma companies but all biotech startups and biotech VC funds. All of them will be disrupted. The major progress in these technologies is coming not from the biotech side but from the IT side.

Due to the lack of AI specialists and promising AI & Drug Discovery startups, only a select few BioPharma players will emerge as the leaders of the AI trend. Meanwhile others, even with substantial budgets and the will to succeed in this area, will fail if they are even one year late to the race, because all of the top AI specialists and AI in healthcare startups will have been acquired by then. The number of experts in the field of AI for drug discovery is insufficient to meet the demand of all big pharma companies, so only those few pharma companies and investors who will partner with the best AI for drug discovery companies in time will benefit from these collaborations and increase their capitalization accordingly.

Those Bio Pharma companies that create strong AI for R&D and drug discovery divisions and that will succeed to acquire the best AI startups will become the leaders of the field in as few as 3 to 5 years from now. *Consider the acquisition of DeepMind by Google for $0.5B in 2014*. Companies that invest heavily in AI for their drug discovery department will see their market capitalization skyrocket in coming years.

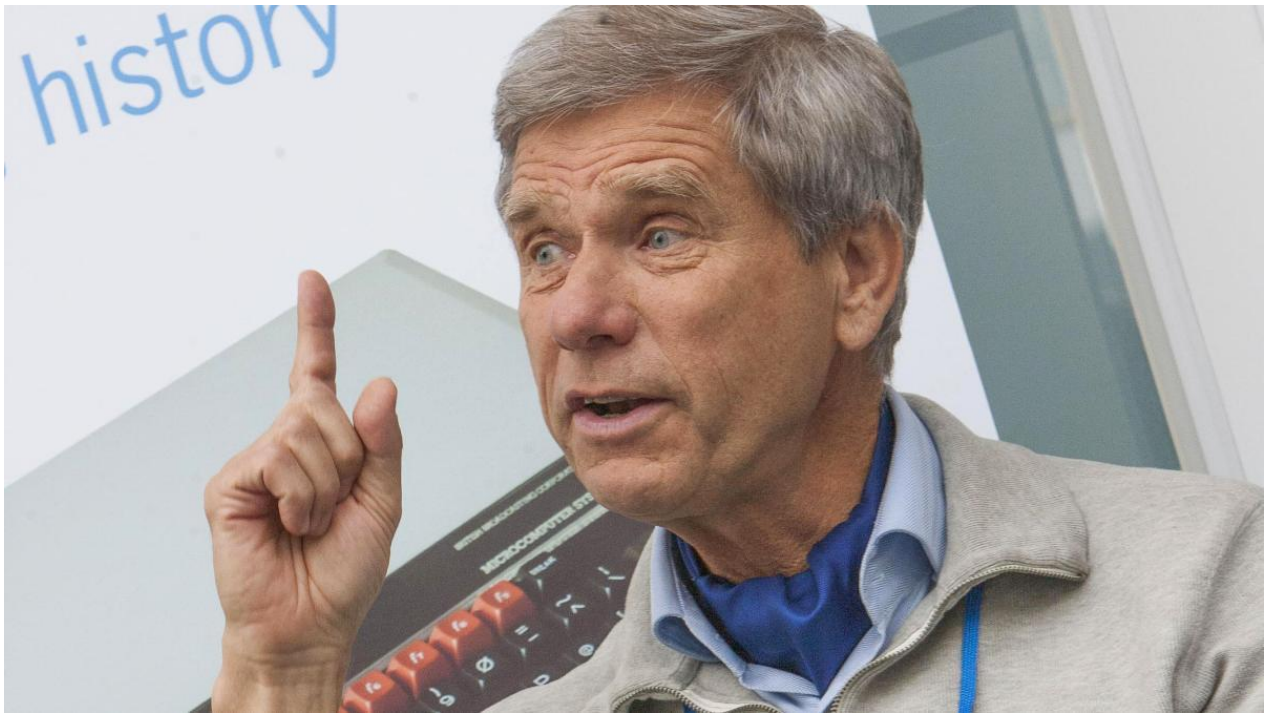
Bio Pharma companies that do not utilise AI will repeat the mistakes of Kodak. Once the leader of its industry, Kodak went bankrupt because it failed to embrace digital photography as the disruptive trend it was, despite the fact that the digital camera was invented inside Kodak labs. If Bio Pharma found the courage to spend 10% of their marketing budget on R&D in AI, they could blow IBM Watson out of the water, and by learning from their mistakes, reinvent themselves and come one step closer to halting the looming threat of the Silver Tsunami.

The Big Gap

Tech guru Hermann Hauser says drug giants are in denial.

The founder of ARM Holdings believes big pharma is poised for its own “Kodak moment” as healthcare moves away from drugs and towards artificial intelligence.

Big pharma was hardly reacting at all, and keeping its best people in developing new drugs. “They know this is coming, but their heart isn’t in it,” he said. “That’s why start-ups are so important, because many of these ideas are crazy and will fail. But that’s why we need more venture capitalists.



Source: The Sunday Times

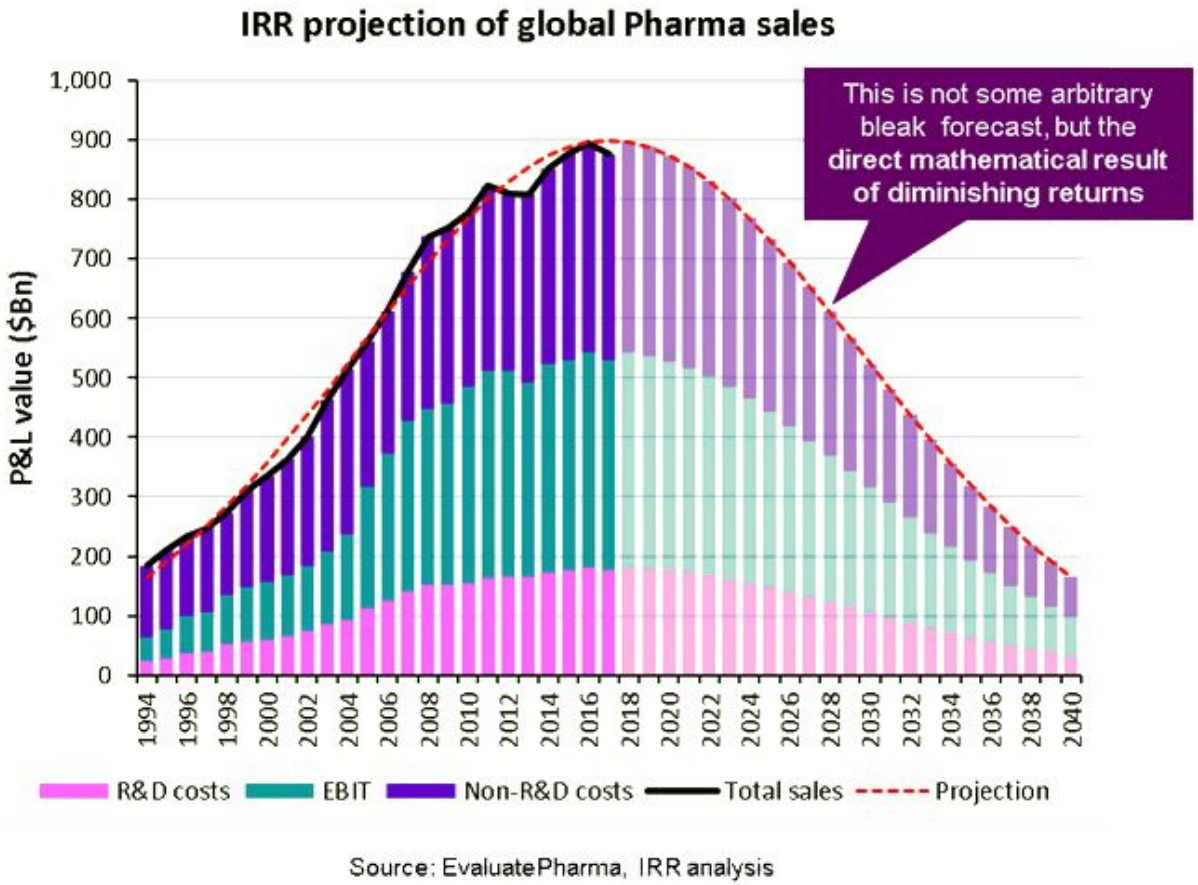
BioPharma's failure is strategy, not capital

The pharmaceutical industry has accumulated capital but remains conservative, bureaucratic and risk-averse in its investment strategy. As government budgets become ever more constrained, it is increasingly urgent that the roadblocks to medical advancement be eliminated.

This may reflect the inefficiency of the organizations themselves and capital-intensive barriers to entry, more than the intrinsic intractability of complex biological systems - indeed, the most successful drugs historically have been discovered serendipitously.

In any case, the sector shows signs of sluggishness: twenty years ago, 20% of Swiss GDP was derived from pharmaceuticals — now it is down to 5.7% of GDP.

Banks and IT giants are snapping up the best AI specialists and startups, and pharma will inevitably require the same scarce technology and talent.



Source: EvaluatePharma, IRR analysis

Geroprotectors

Some people call them "aging suppressants," "anti-aging drugs," "gerosuppressants," "longevity therapeutics," "senolytics," or "senotherapeutics." They include various foods, nutraceuticals supplements, and pharmaceutical drugs that target the root processes of aging, thereby increasing the healthy lifespan of an individual, and therefore belong to the traditional field of biomedical gerontology.

The maturity of the field means that this area of research has been wide open for many decades, during which hundreds of candidate geroprotective drugs have been tested, with some notable successes :

Known geroprotectors and their systemic effects

GEROPROTECTORS	
COMPOUND	**EFFECT**
Aspirin	Reduces inflammation
Bile Acids	Triggers longevity gene pathways
Curcumin	Blocks mTOR - Enhances insulin sensitivity
Estradiol	Rejuvenates skin and improves brain function
Everolimus	Reinvigorates the immune system
GH3/Gerivitol	Lowers cortisol levels
Melatonin	Powerful antioxidant
Metformin	Enhances insulin sensitivity
Protandim	Activates Nrf2 – a longevity regulating protein
Rapamycin	Delays onset of degenerative diseases
Resveratrol	Powerful antioxidant
Statins	Lengthens telomeres
TA-65	Lengthens telomeres
Thymus Extract	Restores immune function

"What we want to show is that if we delay ageing, that's the best way to delay disease. " ~ Dr. Nir Barzilia, Head of TAME trial for testing whether the drug metformin, a widely-used treatment for type 2 diabetes, can delay the onset of age-related diseases.

Source:
http://renegadehealth.com/blog/2015/01/30/can-these-compounds-help-you-live-longer-new-longevity-drugs

Geroprotectors are one of the most important technologies to be included in P3 Medicine and the longevity industry framework.

Currently known geroprotectors, although having narrow effects, are effective in increasing health- and lifespan both in animal models and in clinical trials

The personalized healthcare industry is able to put geroprotectors to their full potential. This happens due to the opened possibility of continued monitoring of biomarkers

This monitoring allows choosing specific geroprotector for each patient while avoiding unnecessary and harmful medications.

For example, if the patient has low enough levels of inflammation, regular aspirin intakes will bring only damage to the tissues by inhibiting healthy inflammation processes, therefore reducing lifespan instead of increasing it.

By using machine learning, big data, and other relevant technologies, P3 doctors will be able to create as efficient geroprotector therapies as possible.

In November 2017, researchers from the Biogerontology Research Foundation, Insilico Medicine, Life Extension and other institutions published a study showing that Metformin and Rapamycin had anti-aging and anti-cancer effects.

Researchers applied deep-learned neural networks to profile the safety and gene- and pathway-level similarity of more than 800 natural compounds to metformin and rapamycin, in an effort to identify natural compounds that can mimic the effects of these anti-cancer and anti-aging drugs while remaining free of the adverse effects associated with them.

Alex Zhavoronkov, PhD, co-author of the study and founder of Insilico Medicine commented "*Earlier this year we launched Young.AI, a comprehensive system utilizing the recent advances in deep learning for tracking a variety of aging biomarkers. I hope that the consumers using the Longevity A.I. will start using it. One of the goals of our group is to identify the combinations of molecules that achieve the desired effects*".

Alexey Moskalev, PhD, a co-author of the study, added: "Aging is not recognized as a disease, so we need strong potential geroprotectors of natural origin on the market. Supplements that slow down aging, affecting the key mechanisms of aging at the molecular and cellular level"

The following article was published in one of Britain's largest newspapers called *The Telegraph* on November 29, 2015:

November 29, 2015

The Telegraph

World's First Anti-Ageing Drug Could See Humans Live to 120

BY SARAH KNAPTON

The world's first anti-ageing drug will be tested on humans next year in trials which could see diseases like Alzheimer's and Parkinson's consigned to distant memory.

Scientists now believe that it is possible to actually stop people growing old as quickly and help them live in good health well into their 110s and 120s.

Although it might seem like science fiction, researchers have already proven that the diabetes drug metformin extends the life of animals, and the Food and Drug Administration in the US has now given the go ahead for a trial to see if the same effects can be replicated in humans.

If successful it will mean that a person in their 70s would be as biologically healthy as a 50 year old. It could usher in a new era of 'geroscience' where doctors would no longer fight individual conditions like cancer, diabetes and dementia, but instead treat the underlying mechanism – ageing.

Scottish ageing expert Professor Gordon Lithgow of the Buck Institute for Research on Ageing in California, is one of the study advisors.

"If you target an ageing process and you slow down ageing then you slow down all the diseases and pathology of ageing as well," he said "That's revolutionary. That's never happened before.

"I have been doing research into ageing for 25 years and the idea that we would be talking about a clinical trial in humans for an anti-ageing drug would have been though inconceivable.

"But there is every reason to believe it's possible. The future is taking the biology that we've now developed and applying it to humans. 20 years ago ageing was a biological mystery. Now we are starting to understand what is going on."

Ageing is not an inevitable part of life because all cells contain a DNA blueprint which could keep a body functioning correctly forever. Some marine creatures do not age at all.

However over our lifetime billions of cell divisions must occur to keep our bodies functioning

70 | LIFE EXTENSION | MARCH 2016

In March 2017 Life Extension, partnered with Insilico Medicine to identify specific nutrient combinations that function as geroprotectors, or agents capable of extending a healthy lifespan. The objective is to develop innovative ways to support healthy aging. To that end, Life Extension is introducing Ageless Cell, the first supplement in its GeroProtect line. The product delivers unique ingredients that inhibit cellular senescence, a natural part of the aging process where cells no longer function optimally.

“By rejuvenating near-senescent cells and encouraging the body’s healthy process for dealing with senescent cells, Ageless Cell turns back the clock at the cellular level,” said Michael Smith, MD, senior health scientist for Life Extension.

This scientific collaboration has resulted in the identification of a geroprotector formulation consisting of four nutrients with various complementary and reinforcing properties. “Clinical aging studies are extremely difficult, if not impossible, to perform at this time. Our collaboration with Insilico Medicine has allowed us to develop geroprotective formulations by using artificial intelligence to study very large data sets,” said Andrew Swick, PhD, senior vice president of product development and scientific affairs for Life Extension. Scientists from Life Extension and Insilico Medicine worked together to identify a subset of four specific nutrients—myricetin, NAC, gamma tocotrienol, and EGCG—all of which modify senescence-inducing pathways, inhibiting the development of senescent cells. The scientists found that the four nutrients work together, but in very different ways, to beneficially influence key anti-aging pathways. Together, they combat numerous aging factors throughout the body. These compounds all modulate specific biological pathways responsible for keeping people young and healthy.

“Combined, these ingredients promote anti-aging mechanisms at the cellular level throughout the body, acting by multiple pathways, some unique, and some overlapping,” said Alex Zhavoronkov, PhD, CEO of Insilico Medicine. *“Together, these four natural compounds represent the beginning of the future—anti-aging cocktails identified using artificial intelligence under expert human supervision.”*

https://www.eurekalert.org/pub_releases/2017-10/imi-aiu103017.php;https://www.eurekalert.org/pub_releases/2017-04/imi-gdu040417.php; https://www.healthline.com/health-news/drugs-help-us-live-longer; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4600621/

Wednesday, Oct. 25, 2017, Life Extension, in collaboration with Insilico Medicine, have employed artificial intelligence to develop a novel dietary supplement of plant extracts that can activate the body's own anti-aging pathways.

Insilico, a next-generation artificial intelligence company specializing in the application of deep learning proprietary technology for biomarker development and aging research, used pioneering high-performance computer simulations to probe of the effect of extracts on anti-aging pathways.

The resulting formulation, called Longevity A.I, is an innovative combination of three natural nutrients that mimic known metabolic regulators of the same anti-aging pathways targeted by calorie restriction mimetics, which have long been associated with increased life expectancy.

The active ingredients, Withaferin A, Ginsenoside Rg3 and Gamma linolenic acid, shown by recent scientific studies to increase longevity, were identified from combinations of thousands of other candidates using deep-learning technology which calculated the precise formula for maximum activation of the anti-aging pathways.

"GEROPROTECTTM Longevity A.I. is the only formulation to combine these three potential life-prolonging ingredients into a single supplement," said Andrew G. Swick, Ph.D., senior vice president, product development and scientific affairs at Fort Lauderdale, Fla.-based Life Extension. *"This unique formulation based on proprietary artificial intelligence technology contains these geroprotector ingredients in concentrations several magnitudes higher than conventional dietary supplements.*

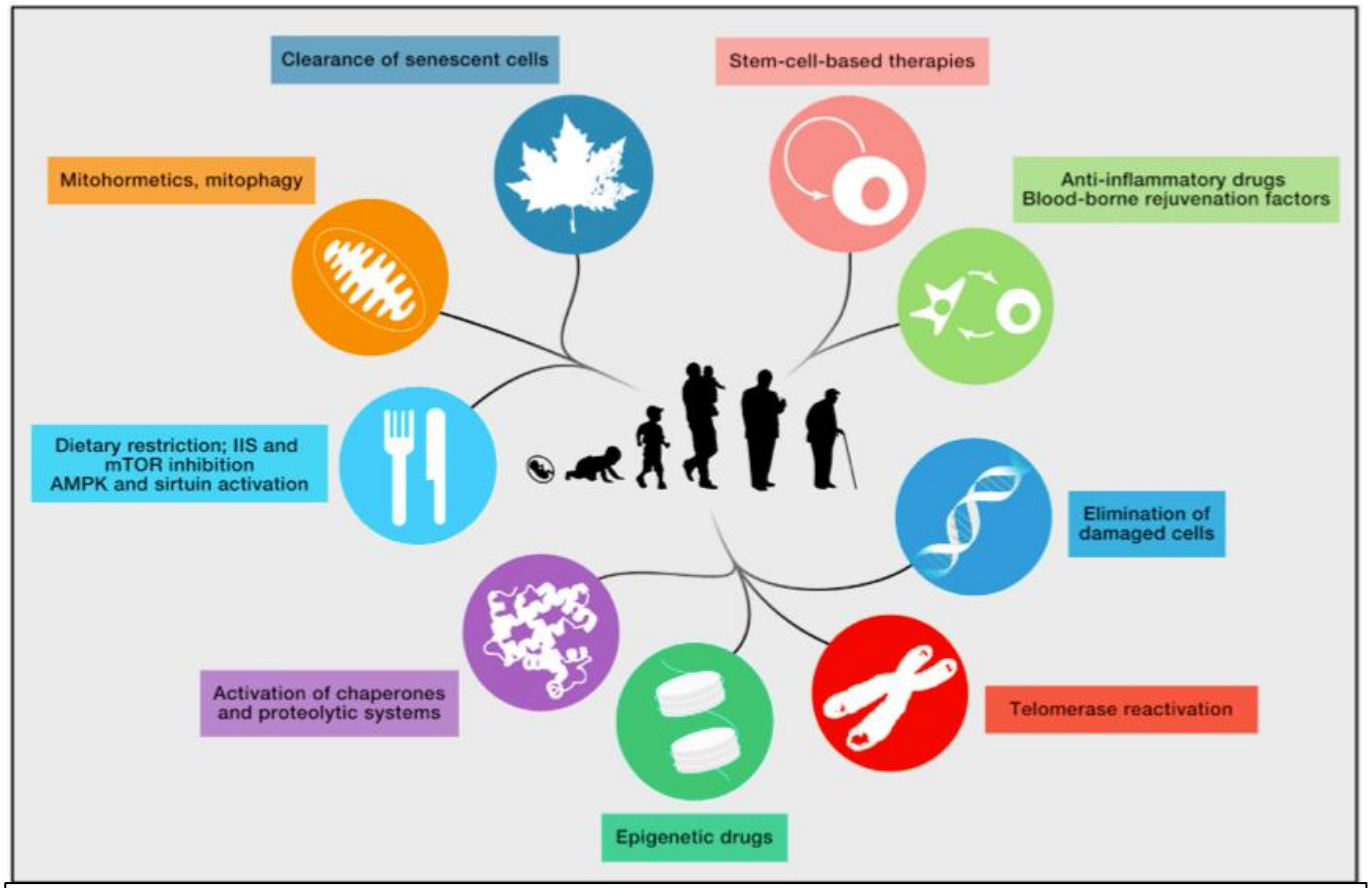
Regenerative Medicine

Regenerative medicine is a branch of translational research in tissue engineering and molecular biology which deals with the "process of replacing, engineering or regenerating human cells, tissues or organs to restore or establish normal function." Growing organs *ex vivo*, stem cell transplantation, and the re-activation of developmental repair programs are all within the scope of regenerative medicine.

Scientists in regenerative medicine often take inspiration from organisms like the Axolotl salamander, which can repeatedly regenerate a full limb after amputation.

As of 2018, the regenerative medicine industry is composed of 8 market segments, including:

- Stem cell therapies
- Cellular immunotherapies
- Gene Therapies
- Tissue engineering and biomaterials
- Cellular scaffolds and matrices
- Exosome therapies
- Direct cell reprogramming
- 3D bioprinting



Mason and Dunhill. "A Brief Definition of Regenerative Medicine." Regenerative Medicine, 2008, 3(1), 1–5 [47]

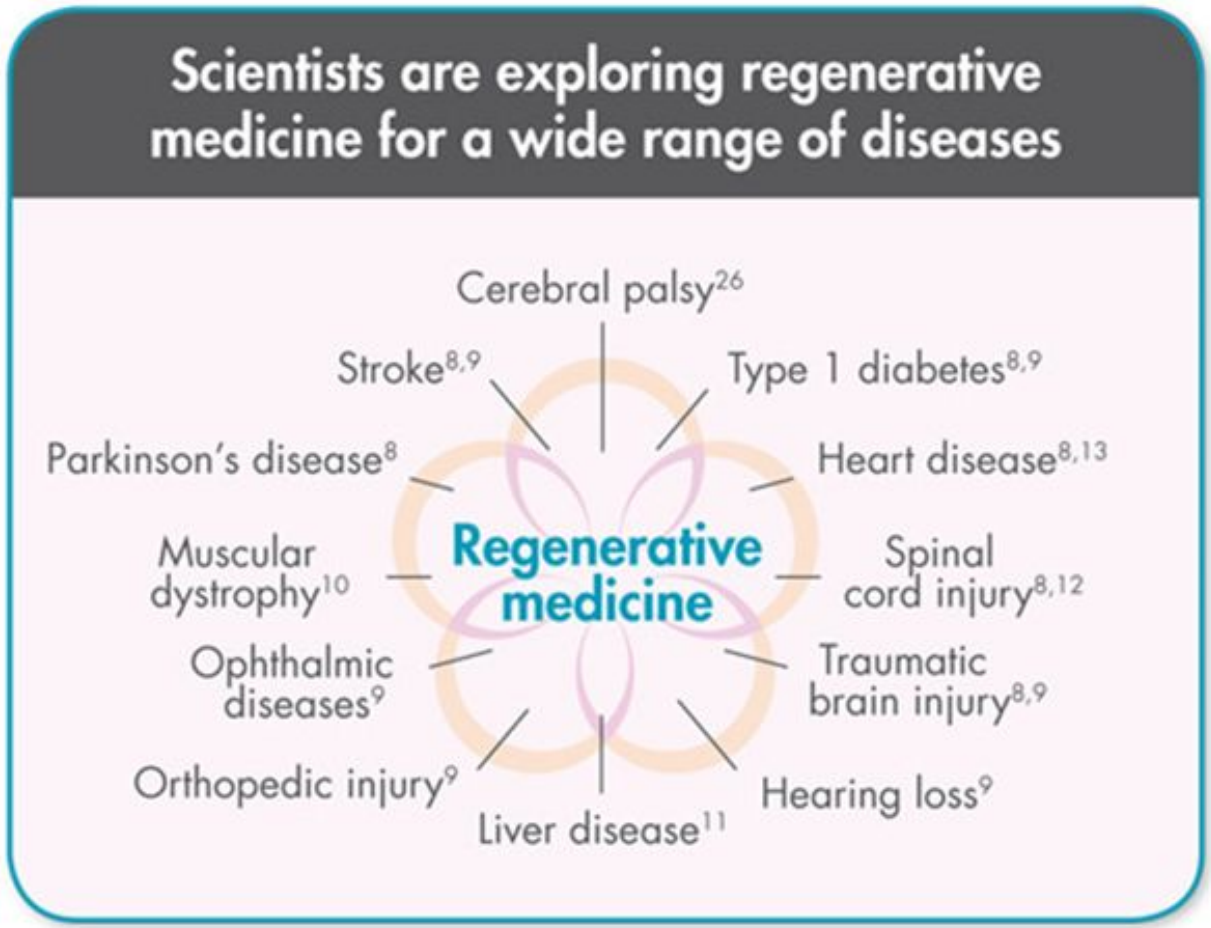
One of the most notable trends of the recent years in the field of modern medical research is regenerative medicine.

It is a translational science that studies how regenerative capabilities of the human body can be transformed into effective therapies. The regeneration is defined as the natural restoration of tissues and organs.

The regenerative medicine research revolves around using biological means to restore organs or tissues and to reverse adverse aging processes.

Remaining one of the pillars of the longevity research, regenerative medicine will most likely bring us the solution to a variety of different illnesses.

This is assured by a plethora of academic groups that dedicate great effort to pushing the research forward.



Source: https://www.reflexportland.com/regenerative-medicine-the-new-med-school/

Regenerative Medicine Overview

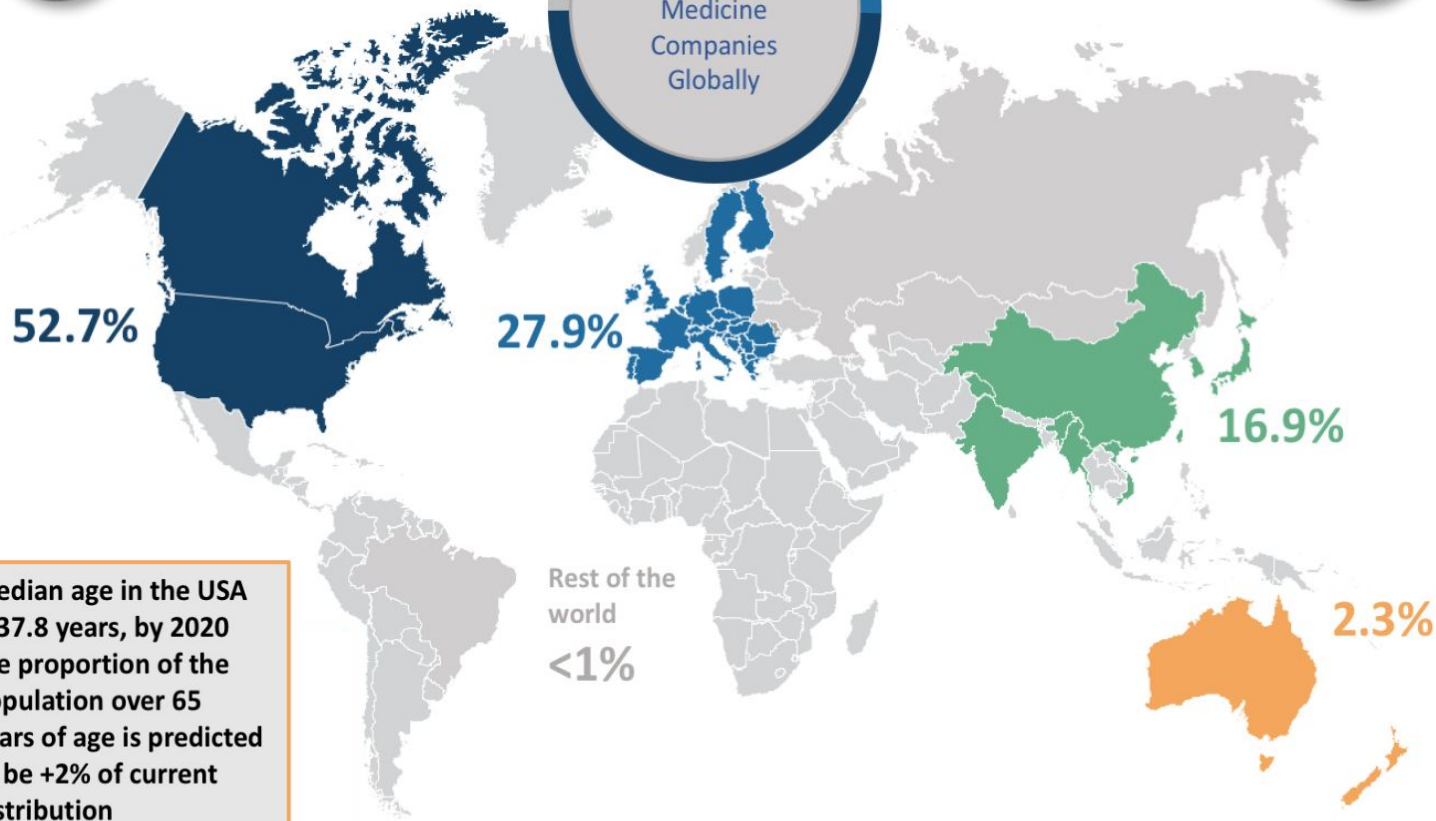
Hindered by costly drug approval regulations

Hindered by lack of skilled scientists

$11B Estimated gene-therapy market size by 2025

Estimated bioinformatics market size by 2020 $13B

>650 Regenerative Medicine Companies Globally

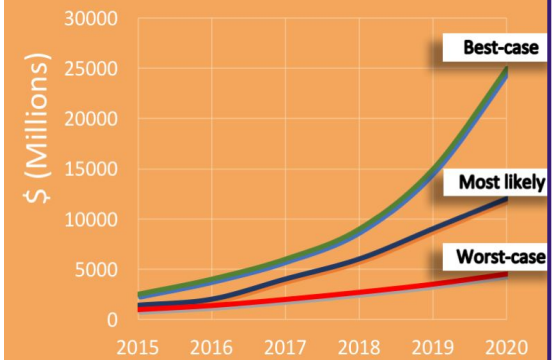


Median age in the USA is 37.8 years, by 2020 the proportion of the population over 65 years of age is predicted to be +2% of current distribution

Market Growth

- Gene Therapy estimated at 35.8% CAGR
- Bioinformatics estimated at 20.9% CAGR
- Stem Cell Therapy estimated at 39.5% CAGR
- Biopharmaceuticals estimated at 8% CAGR
- Growth will accelerate through the coming biotech revolution

REG. MED GROWTH OUTLOOK



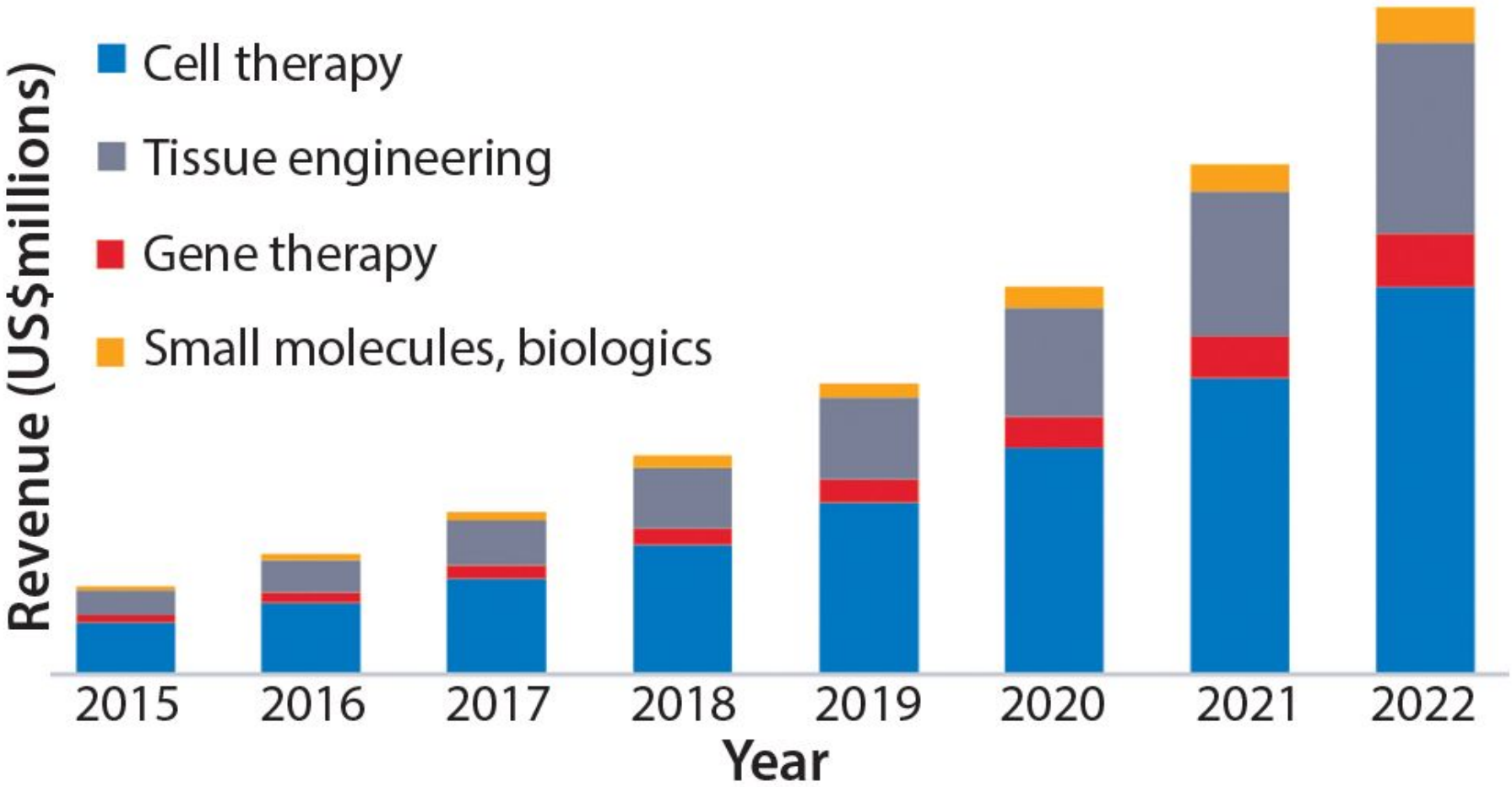


Figure 1: World regenerative medicine market by product type, 2015–2022

The 5 years following 2017 see a quadrupling of revenue of the global regenerative medicine market which is on course for exponential growth. This covers cell therapy, tissue engineering, gene therapy and small molecules and biologics equally.

The global market in regenerative medicine

The current global market for regenerative medicine is $36B and forecasted to grow to reach $49.41B by 2021.

- The current global market for cell therapy is $6B2 and the industry is expected to grow to over $8B by 2018 at an annual growth rate of 21 per cent.

- Approximately 100,000 patients will be treated with CAR-T immunotherapies by 2021.

- There are over 1,900 active cell therapy clinical trials, targeting indications such as cancer, heart disease, diabetes, chronic wounds, neurodegenerative disease, stroke, spinal cord injury, vision impairment and severe burns, amongst others.

- There are 574 active industry-sponsored cell therapy clinical studies, including 50 in Phase 3 development.

Source: https://www.bioinformant.com/product/regenerative-medicine-companies/

Rejuvenation biotechnology: regenerative medicine for aging

The form of regenerative medicine of specific relevance to the longevity industry is rejuvenation biotechnology, the application of regenerative medicine to aging.

Age, being an assortment of damages, is amenable to a diverse range of tools from the regenerative medical repair kit.

The term ‘rejuvenation biotechnology’ was coined in the late 00s during the period when a handful of regenerative medicine technologists, such as Tony Atala and Aubrey de Grey, grew aware that geroscience’s current knowledge of aging, though vastly incomplete, nonetheless contains within it a logically largely exhaustive damage report for the purposes the ‘repair approach’.

It was perhaps first used among colleagues and affiliates of the SENS Research Foundation, founded in 2009, of which Aubrey de Grey is chief science officer. “Rejuvenation biotechnology” has since been used as the title of a seminal industry conference series.

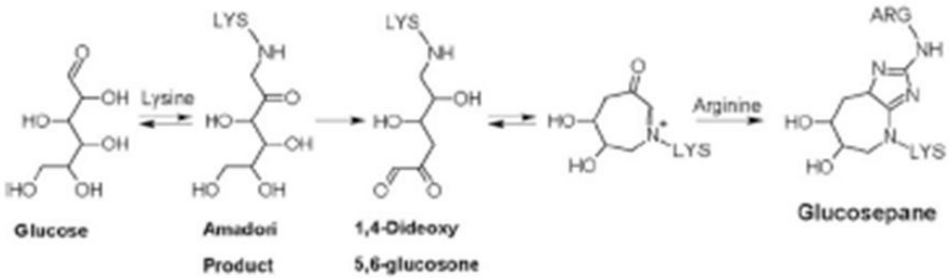
The rejuvenation biotechnology industry currently consists of a nexus of nonprofits acting as a catalyst for the fledgling industry.

Recent progress in rejuvenation biotechnology

This discipline aims to prevent and repair the fundamental damage that characterises aged tissues and organs, and necessarily includes the translational, clinical, and applied aspects of geroscience.. This damage can manifest as somatic DNA damage, telomere attrition, transposon-related genomic instability, reduced autophagy and protein turnover, epigenetic drift, stem cell exhaustion, advanced glycation endproducts, and more.

Over the past decade rejuvenation biotechnology has gone from a nascent to a fledgling industry. Although some necessary components of the technology, such as the use of stem cell therapy to replenish depleting cells, were advancing steadily even before the point of inauguration of rejuvenation biotechnology, this point has been followed by accelerated progress in this and other components. Thymus regeneration for instance, a previously neglected area of cell replenishment, has received serious attention and since taken off. And the overall rate of progress has received a huge boost from the newfound ability to synthesise glucosepane in the lab cheaply on demand for the purposes of researching methods for breaking glucosepane crosslinks.

Glucosepane Crosslink



- Forms from Glucose
- Links Lysine to Arginine

Sell DR, Biemel KM, Reihl O, Lederer MO, Strauch CM, Monnier VM. Glucosepane is a major protein cross-link of the senescent human extracellular matrix. Relationship with diabetes. J Biol Chem. 2005 Apr 1;280(13):12310-5.

This is of crucial importance as crosslinking increases mechanical stiffness of blood vessels, impairs functioning of kidney, heart, retina, and other tissues and organs, provokes tissue damage and cancers, and tightens up the extracellular matrix (ECM), hampering its natural self-replenishment.

The regenerative medicine industry rapidly expanded in 2017, making it a high-value, fast-growth market. With two approvals CAR-T cell therapies, which are crucial for restoring cancer immunity, as well as the first gene therapy and digital pill approvals in the United States, 2017 saw a lot of FDA "firsts."

The regenerative medicine market first gathered momentum when the Swiss pharmaceutical giant Novartis made history as the first company to win FDA approval for a CAR-T cell therapy in the U.S. in August 2017 (Kymriah). In October 2017, Kite Pharma became the second company to get FDA approval of a CAR-T cell therapy (Yescarta), further "snowballing" the effect.

With swelling momentum to support the CAR-T technology, there are now close to 40 companies developing redirected T cells or NK cells for therapeutic use.

On November 13, 2017, the FDA also approved Abilify MyCite as the world's first "digital pill." With 7 out of 10 Americans taking at least one prescription drug, approval of the antipsychotic medication represents a breakthrough in digital medicine. Made by Japan-based Otsuka Pharmaceutical, the tablet works by containing a sensor to track when and if patients take their medication. On December 19th, 2017, the FDA approved Spark Therapeutics' Luxturna, a novel gene therapy to treat patients with an inherited form of vision loss. The treatment is now priced at $425,000 per eye or $850,000 for both.

In addition to product approvals, there are now accelerated pathways for advanced therapy medicinal products (ATMPs) in several countries worldwide, including the U.S., Japan and South Korea. Legislation took effect in Japan in late 2014, in South Korea in 2016, and in the United States in 2017. Additionally, the EU has a program for product acceleration – the Adaptive Pathways. Although it is not explicitly for cell and gene therapies, it has been given a lot of attention by the group.

In the U.S., the 21st Century Cures Act (signed into law on December 13, 2016) is designed to accelerate regenerative medicine developments and bring new innovations to market. In late 2014, Japan passed two new laws that revolutionized the commercialization of cell therapies within the country, the Act on the Safety of Regenerative Medicine (Law No. 85/2013) and the Pharmaceuticals and Medical Device (PMD) Act (Law No. 84/2013).

These historic events demonstrate to investors, the public, and funding providers alike that regenerative medicine is a sector that has already emerged, and is no longer on the horizon.

Rejuvenation biotech startups and spinouts

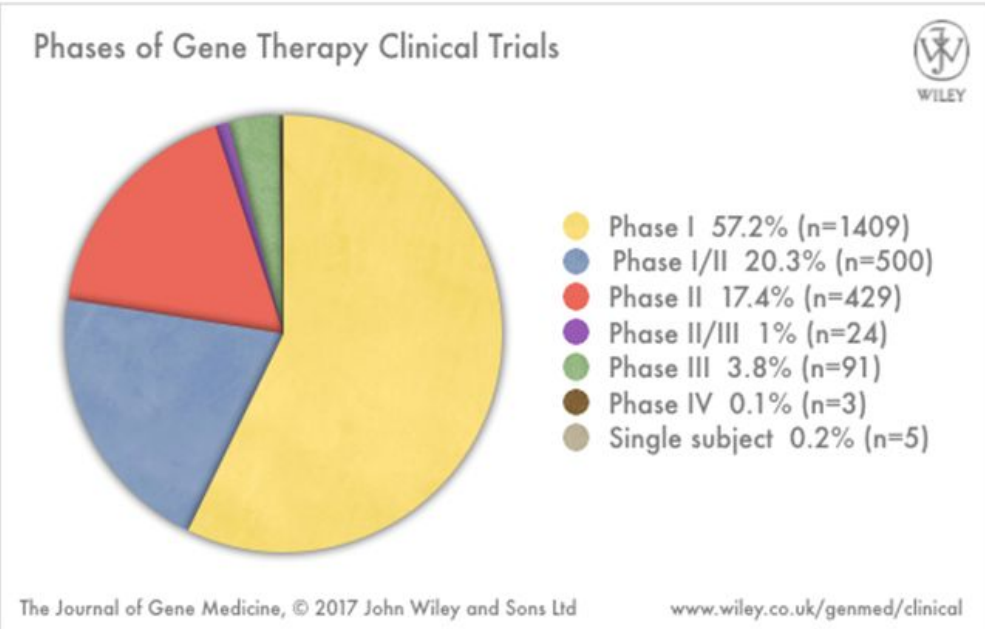
Rejuvenation biotechnology is emerging from a long period of reliance on philanthropic and government funding. The decade since the inception of rejuvenation biotechnology has seen the creation of a number of startups and spinouts whose missions statements include the regeneration of age-damaged tissues and organs.

2013 was the year this began in earnest. **Calico Labs**, mentioned earlier, founded that year by Google and Arthur D. Levinson with the goal of combating aging and associated diseases, has already partnered with MIT, Buck Institute, Harvard and others. Among their regenerative projects is a new class of drug based on Targeted Protein Degradation (TPD) to address a broad range of life-threatening and life-impairing age-damage. Bob Hariri, M.D., Ph.D., the former CEO of Celgene Cellular Therapeutics, and pioneer of the global cell-therapy industry, co-founded Human Longevity Inc, a genomics and cell-therapy diagnostics company focused on extending 'high-performance human lifespan'. The pharmaceutical platform company **Samumed**, also founded that year, has a regenerative medicine focus. And in 2017 Aubrey de Grey of the SENS Research Foundation also became Vice-President of Technological Discovery of the newly constituted **AgeX Therapeutics,** a subsidiary of BioTime Inc., its mission to apply the technology responsible to cell immortality and pluripotency to human aging and age-related disease.

Gene therapies

Gene therapy is one of the most discussed contemporary technologies with newest discoveries, such as CRISPR/Cas9 system, allowing for safer and more precise therapeutic procedures. Although the genetic therapeutic intervention was considered unattainable until recent times, more and more scientists and policy-makers are considering the possibility of this technology entering our everyday lives. This technology is gathering increasing interest in the longevity community.

Gene therapy is a rapidly developing area of life sciences. Between 1989 to 2017, over 24000 gene therapy clinical trials were conducted. While most of them are early-stage trials, the number of Phase II/III trials is increasing as the technology is maturing and becomes a viable prospective market option.



Source: http://www.abedia.com/wiley/phases.php

Gene therapy can be divided into the two broad areas depending on the type of cells that are used as a target for therapeutics. Somatic cell gene therapy (SCGT) is the mainstream of the modern gene therapy studies. All the therapies that target non-reproductive cells (i.e. gametes, germ, and stem cells) are considered SCGT. On the other side, there is an emerging field of germline gene therapies (GGT) that can bring new technologies to the market. There are two main differences are:

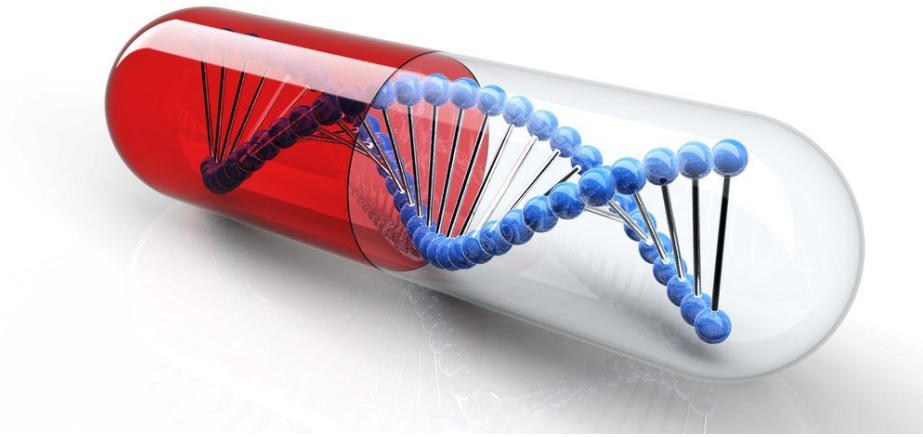
- GGT interventions are heritable, while SCGT can't be passed to the descendants of the target organism
- In contrast to the SCGT, GGT technologies cause each cell of the target organism to possess injected genetic information.
- GGT can't be applied to the fully formed organism

Gene therapy can be considered the embodiment of the ‘preventive’ part of P3 medicine: while conventional therapy acts on the protein level, leaving little hope for treating hereditary disorders, gene therapy aims to treat the source of such conditions by modifying the genome of the patient.

Such approach allows for the efficient preventive treatments that can, in some cases, fully treat the illness before it has managed to express itself.

Besides treating hereditary conditions, gene therapy can be applied to combat infections. For many contagious diseases, including HIV, there are rare mutations that give full or partial immunity to the disease. By successfully implementing gene therapies we can graft this immunity to the overall population, achieving the effect that is similar to the vaccination

Overall, gene therapy is one of the most important technologies in the P3 landscape that already delivers incredible results with promises of even greater miracles in the future.



Source:
https://www.healio.com/pediatrics/journals/pedann/1993-5-22-5/%7Bedcc526b-71f4-46fb-9666-0969cc0af9b1%7D/gene-therapy-a-primer

Despite some setbacks in the field, the gene therapy industry is flourishing. With an increasing amount of papers being published and discoveries being made that fueled investments and interest in the area, such as CRISPR/Cas9, gene therapy is making a name for itself. In July 2016, an ex vivo T-cell trial targeting lung cancer at Sichuan University's West China Hospital in Chengdu, received ethics approval, and is expected to be the first study to use CRISPR in humans.

Most clinical work using gene therapy has pursued disorders that are driven by rare mutations to a single known gene, such as diseases of the eye, the blood and the central nervous system. Spark Therapeutics demonstrated improved vision in a phase 3 trial of 31 patients in 2015 that had a form of inherited blindness driven by mutations in the RPE65 gene. Spark Therapeutics expects to file for FDA approval by the end of 2016.

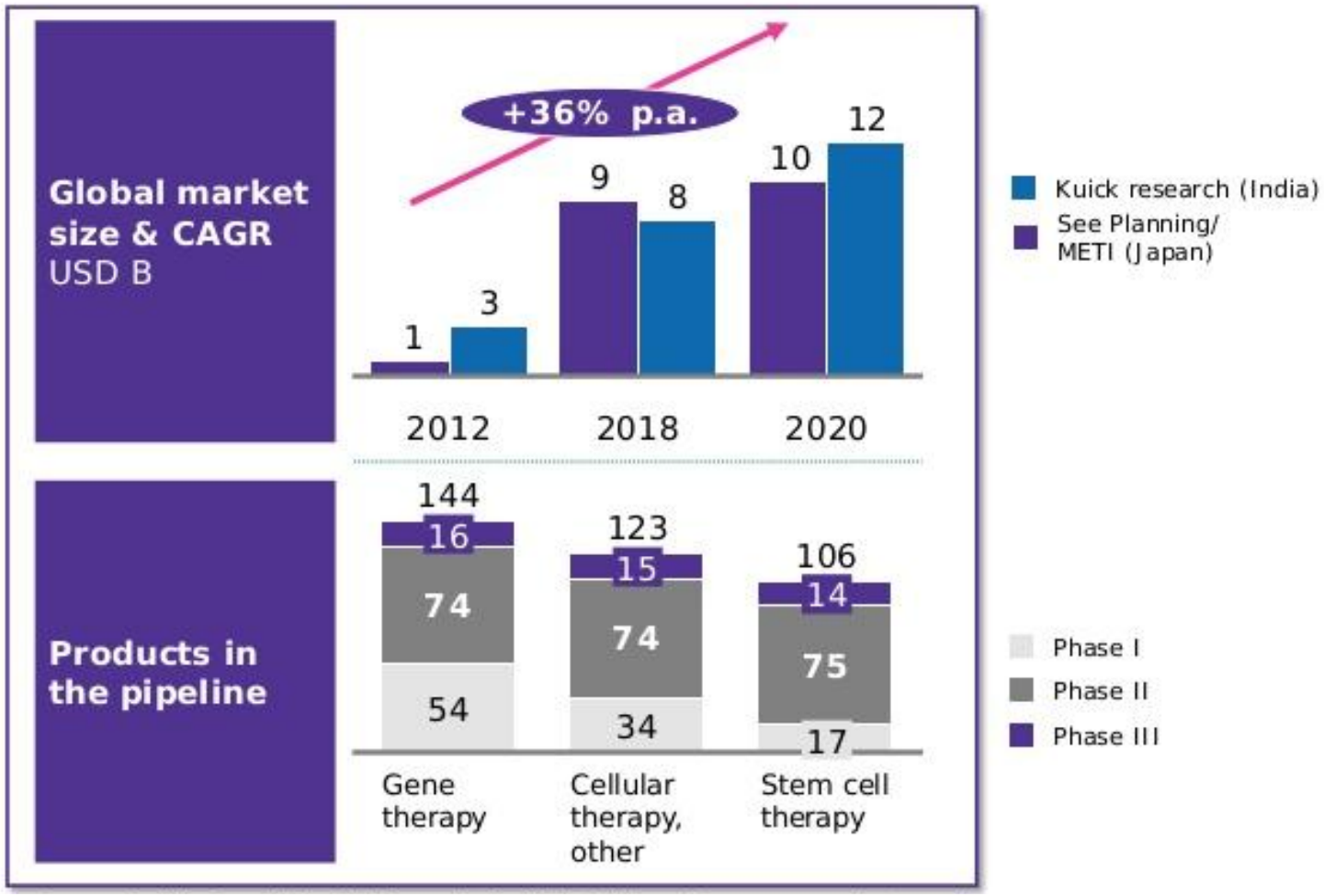
“This might be the first gene therapy approved in the United States, which would be very exciting, and would make a path for other people to develop treatments for other blinding diseases.”

- Jean Bennett, ophthalmologist at the University of Pennsylvania and head of the RPE65 study

Many other clinical studies are under way for genetic disorders of the central nervous system. AveXis, a biotech company based in Chicago, Illinois, for example, reported encouraging early results in May 2016 from a trial with 15 people with spinal muscular atrophy — a neuromuscular disease that is the leading genetic cause of infant death.

Current obstacles have still to be overcome, such as the difficulty of delivery to the cell of interest and the often high costs for gene therapy, but it is certain that gene therapy has great potential.

The cell & gene therapy market is poised for rapid growth with projections reaching ~ $10B in 5 years



Source: Seed Planning; METI; Kuick Research; Medmarket Diligence; Transparency market research

Immunotherapy for Cancer as a Propeller of Gene Therapies

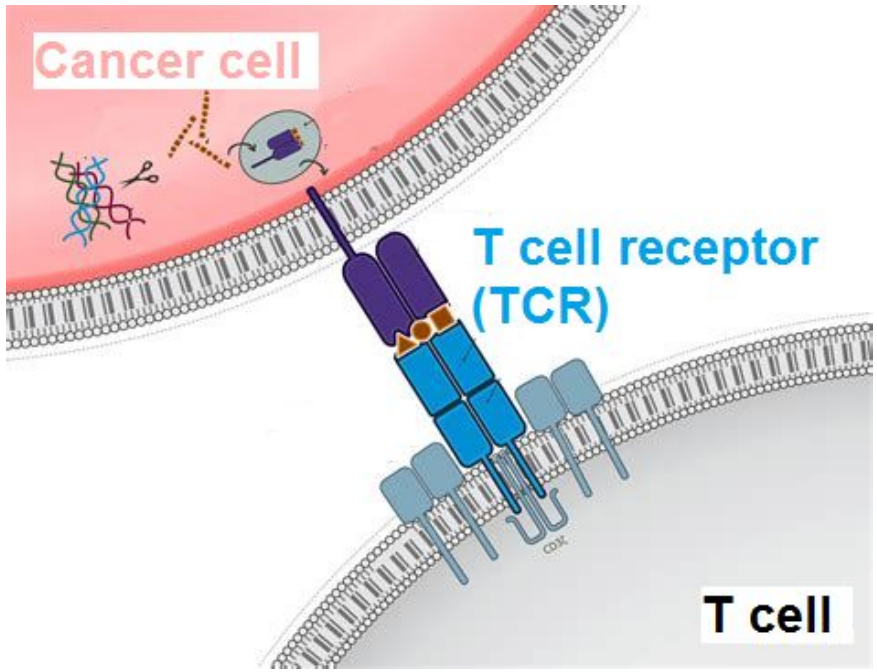
Immunotherapy to fight cancer primarily refers to activating the patient immune system against cancer cells by enabling the proper **recognition** of T cells against the **specific antigens** presented by cancer cells, while not targeting any other healthy cells.

Cancer cells develop methods of escaping the normal immune function that would otherwise eliminate them. Therefore, **gene therapies** can be implemented to reroute T cells towards the cancerous cells. By **genetically engineering** T cells, their immune function can successfully target cancerous cells and destroy them, thus implementing both immunotherapy and gene therapies in one treatment.

> **"2018 should be a watershed year for therapy of cancer with engineered T cells."**
> *— Dr. Phil Greenberg, immunotherapy researcher*

This has already been shown in blood cancers (acute myeloid leukaemia and myelodysplastic syndrome) and researched in glioblastoma, an aggressive form of brain cancer. In 2017 Cell Medica acquired Catapult Therapy TCR which developed WT1-TCR therapy against the aforementioned forms of blood cancer.

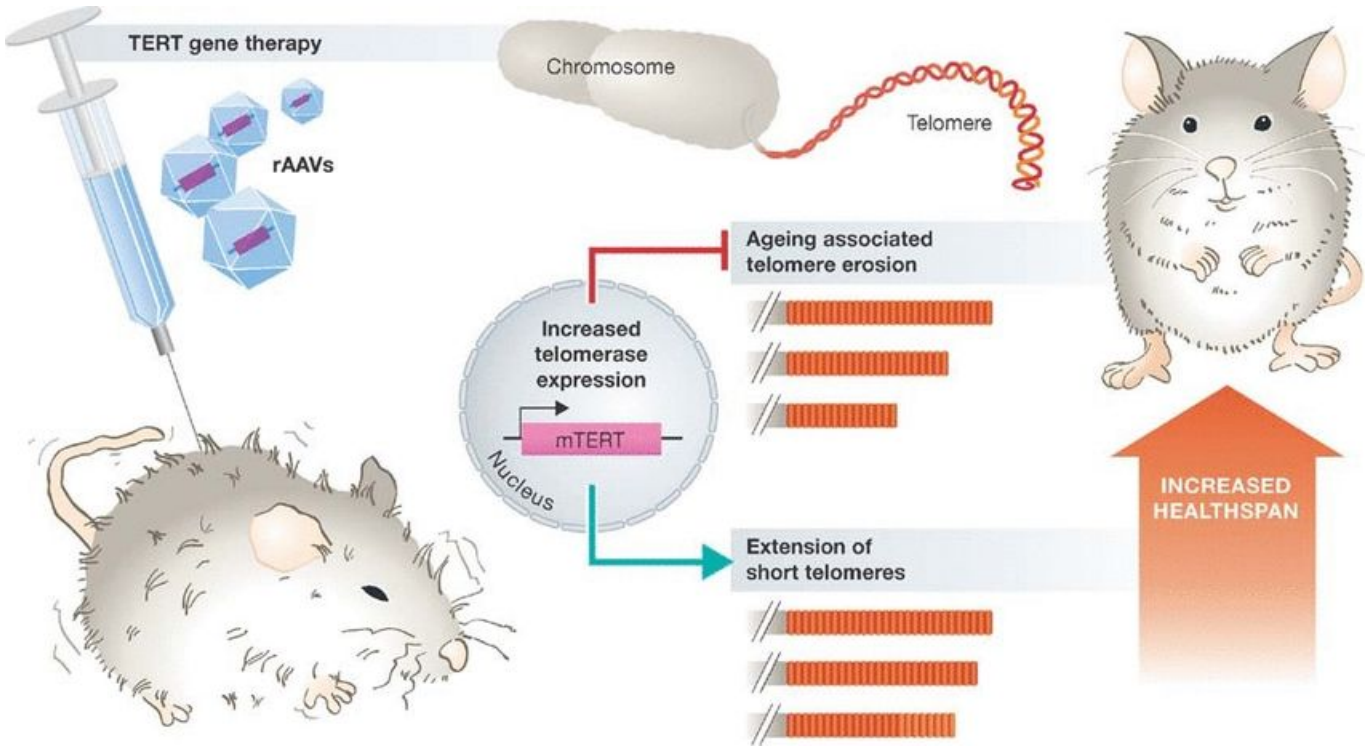
Immunotherapy is opening up a huge opportunity for the development of gene therapies alongside that can make a tremendous difference in terms of both cancer survival and longevity.



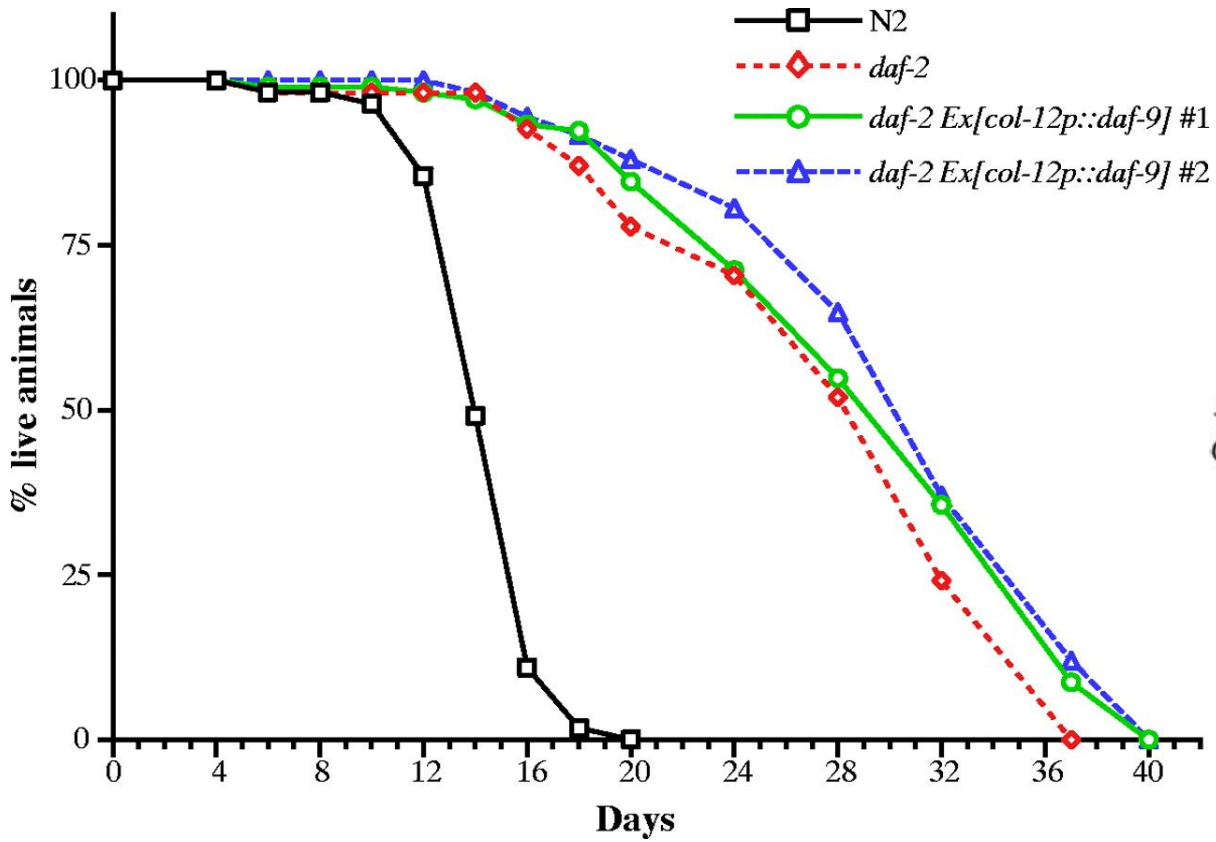
Anti-Ageing Gene Therapies

Gene therapies specifically targeting ageing have a broad range of actions and include lengthening the **telomeres** of chromosomes which experience attrition with each cell division, and muscle preserving gene therapy to target the muscle atrophy that occur with advancing age.

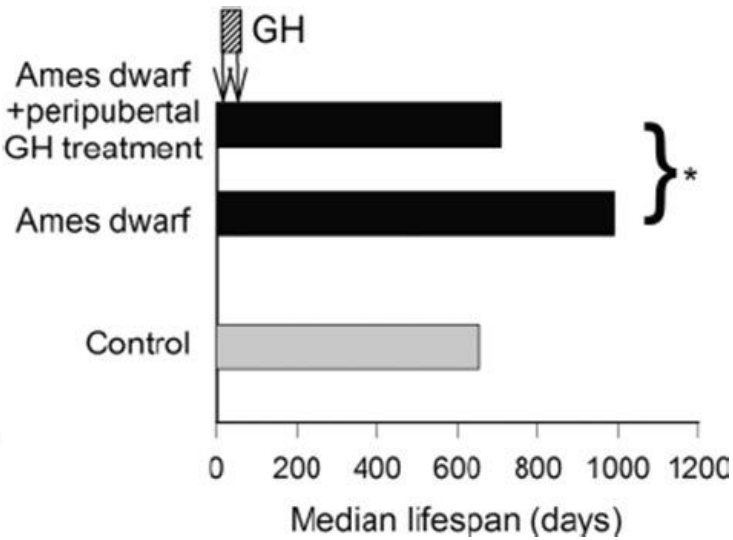
Tests revealed that her white blood cell telomeres had shortened considerably at her then-age of 45, and the gene therapy had successfully reverted their length by around **1,000 extra DNA base pairs**, equivalent to rejuvenation by 20 years. Cross-sectional scans of her thighs also revealed a maintenance of the muscle mass mass well as a decrease in the surrounding fat tissue. In animal models, **single gene manipulation** has so far been found to increase mouse lifespan by 150% and nematode life span by 1,000%.



http://onlinelibrary.wiley.com/doi/10.1002/emmm.201200246/abstract



Genetically engineered nematodes (*Caenorhabditis elegans*) experience vastly extended longevity compared to wild type. Some of the main loci, DAF-2 and DAF-16 are involved in metabolism and development.



Genetically engineered Ames and Snell **mouse models** do not produce growth hormones and experience an extended lifespan compared to wild type.

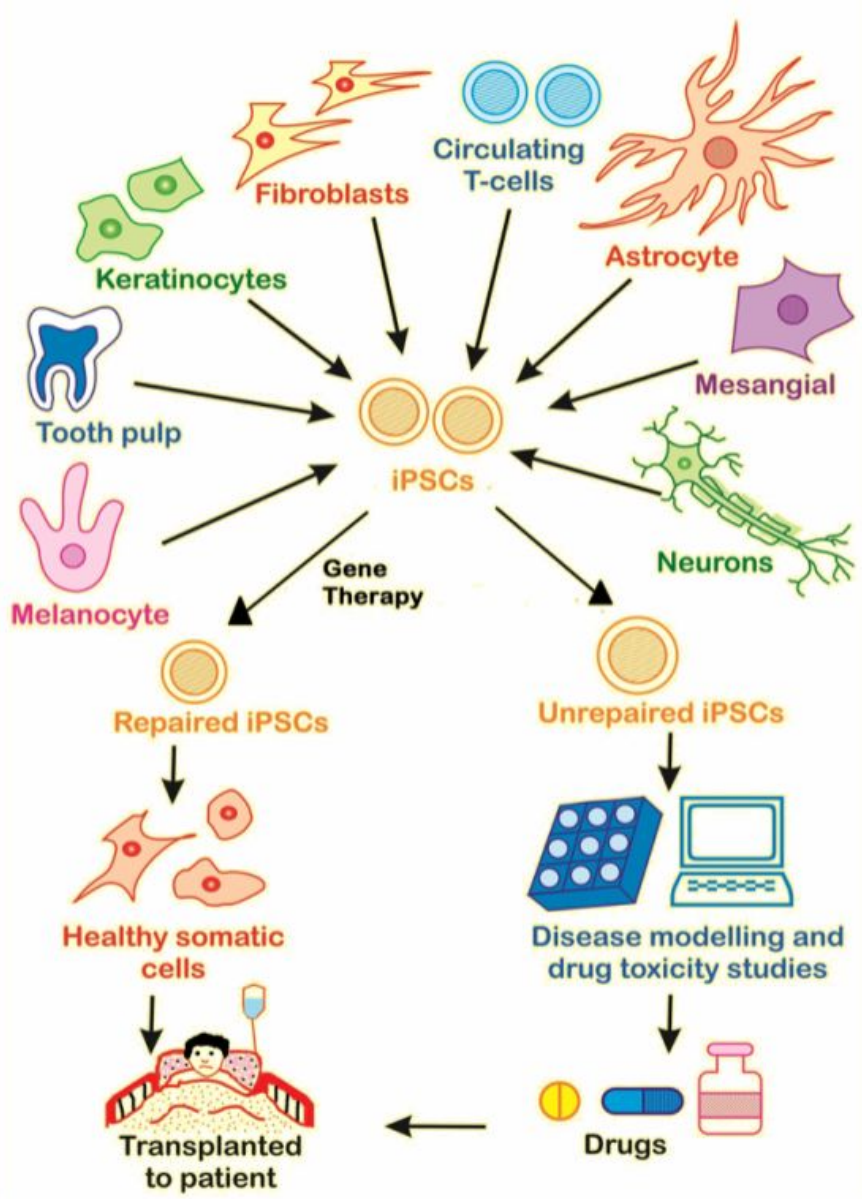
Cell Therapy

In 1981, the first successful derivation of embryonic stem cells (ESCs) was achieved by Nobel prize winners Martin Evans and Matthew Kaufman. In 1998, a technique was developed that enabled the isolation and growth of human ESCs in culture.

Following these two landmark achievements, stem cell research took off.

What makes stem cells so interesting for science and rejuvenation biotechnology? To begin with, these cells have the unique potential of self-renewal, or the theoretical characteristic of unlimited proliferation in-vitro. Second, stem cells are pluripotent, or have the ability to generate almost every adult cell type. This property of stem cells can enable cell replacement therapy, in which dead or damaged cells are replaced by injecting stem cells into the area of interest.

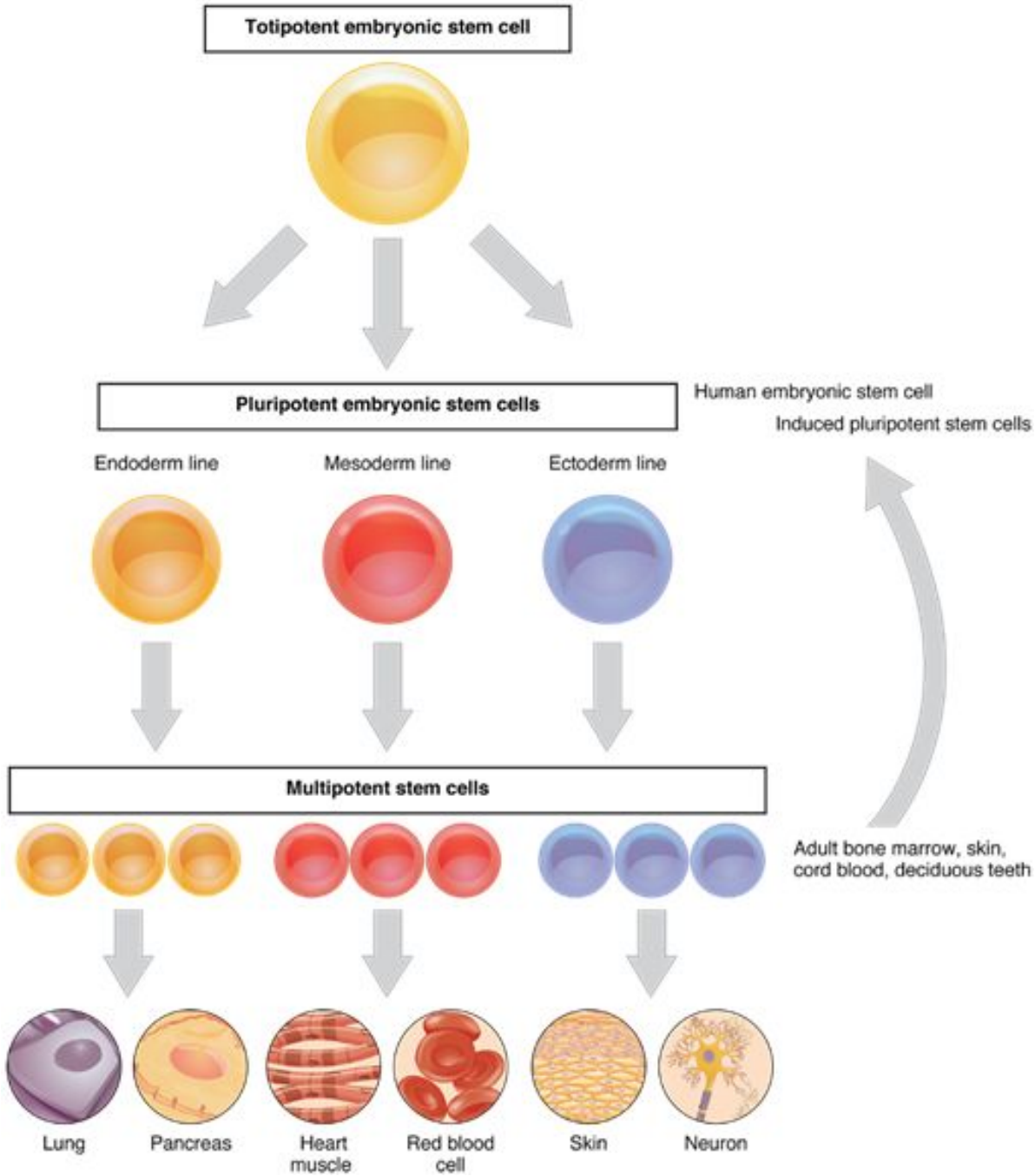
About a decade ago, another major breakthrough in stem cell research was achieved by Takahashi and Yamanaka. Takahashi and Yamanaka discovered and developed a technique that enabled adult cell conversion to generate induced Pluripotent Stem Cells (iPSCs), for which Yamanaka was awarded the Nobel Prize in 2012. In their research, Takahashi and Yamanaka were able to generate pluripotent stem cells from regular adult somatic cells, such as skin cells. This research overcame a number of major obstacles in ESC research, including immunorejection by patients, as well as the ethical issues being raised around the use of embryos for stem cell research.



Cell therapies are the group of methods that are based on the injection of the cellular material into the patient's organism. Although there are many types of cell therapies, the main ones revolve around stem cells, thus being the main way of administering regenerative medicine therapeutics.

There are a few ways that stem cells can be obtained for medical usage, each comes with certain advantages and disadvantages, both practical and ethical. Stem cells can be obtained as fetal, adult or induced pluripotent stem cells (iPSC), with the latter being the most advanced and developed technique.

Being the part of the regenerative medicine, cell therapies are naturally important for the P3 Medicine. The important distinction lies in the fact that some cell therapies can also treat contagious diseases, therefore being having broader field of application. Cell therapy as a term is also more often used when the goal of the therapy is to achieve systemic effect that isn't uniquely tied to the single organ.



Source: http://oerpub.github.io/epubjs-demo-book/content/m46036.xhtml

This major advance in the field revealed the true potential of stem cells and also indicated the great importance of iPSCs for regenerative medicine, disease modelling, and drug discovery. Although challenges remain, the future of iPSCs is bright. Its $853 million global market in 2012 grew to $1.2 billion in 2013 and is expected to reach $2.9 billion in 2018, with an average annual growth rate of 19.7% from 2013 to 2018.

Although cell replacement therapy is still a relatively new field of research, other major advances have already been made since Takahashi and Yamanaka developed their revolutionary technique about a decade ago. One such advancement was made by researchers at Utrecht University, who created a pancreas *organoid*, or a miniature version of the pancreas, from a patient's pancreatic cancer. This experiment provided valuable insight into the development of pancreatic tumors, which can now yield a number of new discoveries in pancreatic illness treatment.

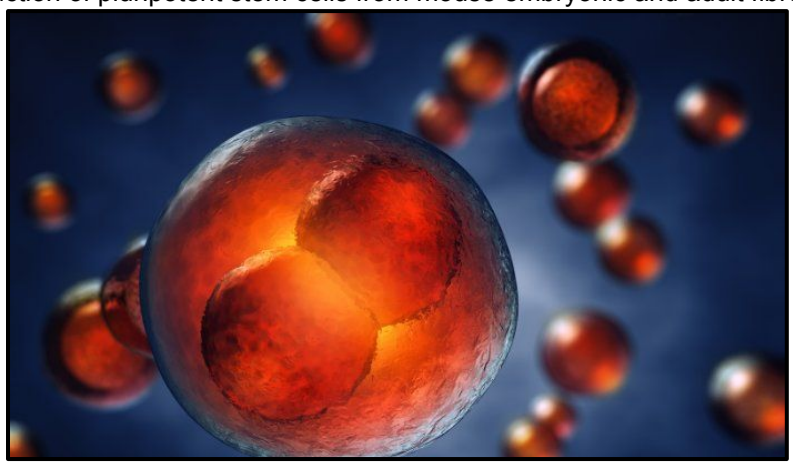
Bulterijs, S., Hull, R. S., Björk, V. C., & Roy, A. G. (2015). It is time to classify biological aging as a disease. *Frontiers in genetics*, *6*, 205.

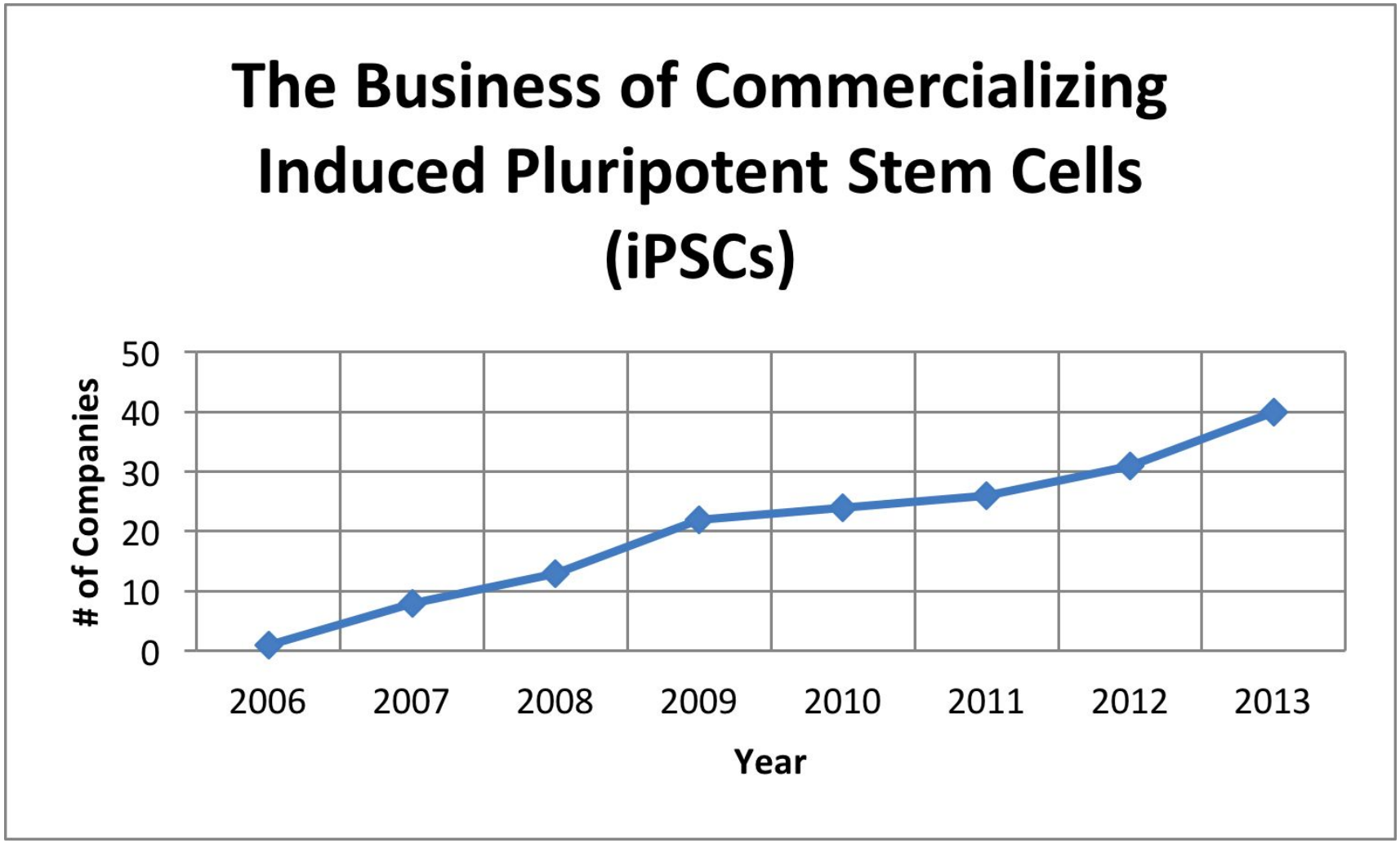
Zhavoronkov, A., & Bhullar, B. (2015). Classifying aging as a disease in the context of ICD-11. *Frontiers in genetics*, *6*, 326.

Smith, A. G., Heath, J. K., Donaldson, D. D., Wong, G. G., Moreau, J., Stahl, M., & Rogers, D. (1988). Inhibition of pluripotential embryonic stem cell differentiation by purified polypeptides. *Nature*, *336*(6200), 688-690.

Thomson, J. A., Itskovitz-Eldor, J., Shapiro, S. S., Waknitz, M. A., Swiergiel, J. J., Marshall, V. S., & Jones, J. M. (1998). Embryonic stem cell lines derived from human blastocysts. *science*, *282*(5391), 1145-1147.

Takahashi, K., & Yamanaka, S. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *cell*, *126*(4), 663-676.

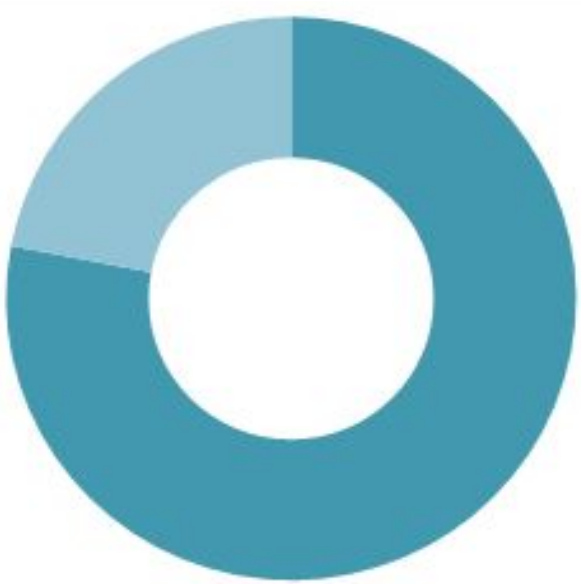




Number of Companies Offering iPSC Research Products, by Year

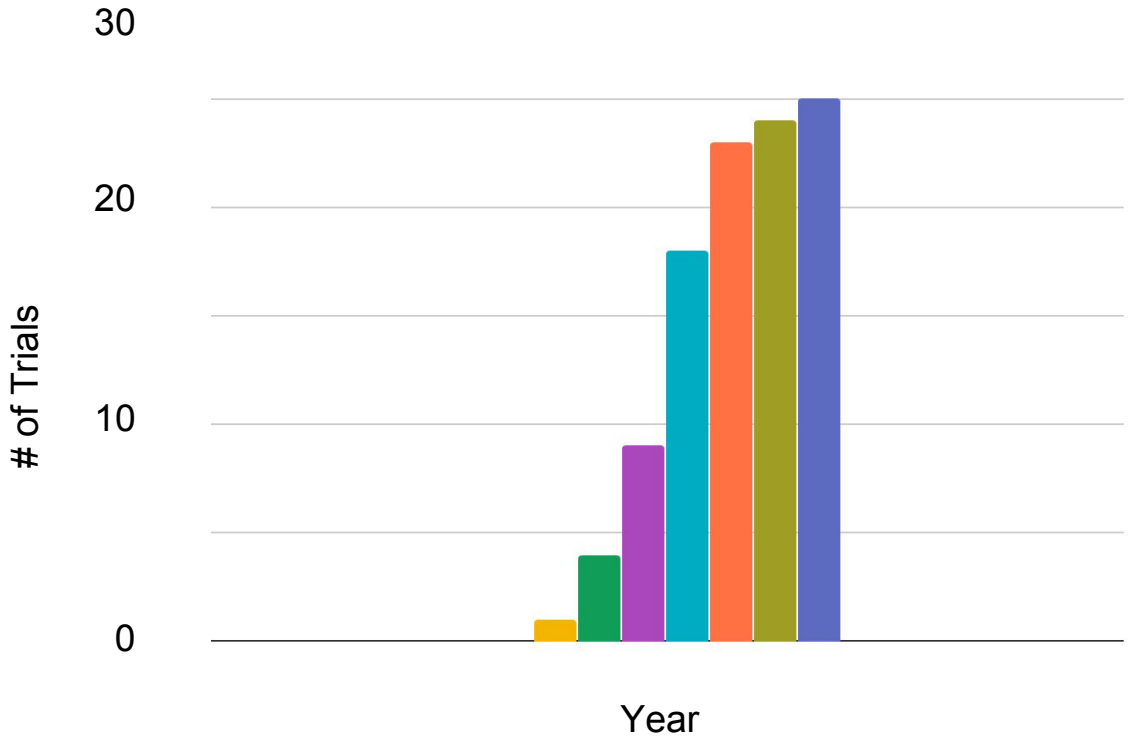
When iPSCs were discovered in 2006, there were only two companies selling iPSC research products. This number increased to seven by 2007 and then began increasing more substantially. A year-by-year breakdown is shown above to identify the rate of new market entrants and the current level of market competition for iPSC-specific research products.

Market Penetration Among Stem Cell Researchers



22% of all stem cell researchers now self –report having used iPSCs within a research project.

Clinical Trials Investigating iPSCs



# of Clinical Trials Investigating iPSCs

Currently, there are 26 clinical studies involving the creation and evaluation of iPSC lines for clinical purposes. None of these studies involve transplant of iPSCs into humans (cellular therapy).
[Visit ClinicalTrials.gov a list of current trials.]

Major Advances in Commercialization of iPSCs

AUGUST 2013:
1st time in which clinical research involving transplant of iPSCs into humans was initiated. Masayo Takahashi at RIKEN Center in Japan investigates safety of iPSC-derived cell sheets in patients with macular degeneration.

JULY 2013:
Cellular Dynamics International (CDI) went public with a offering that raised $43 million dollars, securing the company's position as the global leader in producing human iPSCs in industrial quantities.

MARCH 2013:
Cellular Dynamics International and Coriell Institute for Medical Research receive multi-million dollars grants from the California Institute for Regenerative Medicine (CIRM) for creation of iPSC lines from 3,000 healthy and diseased donors. It will create the world's largest human iPSC bank.

2013 was a major year for advances in iPSC clinical research applications, production and differentiation technologies, biobanking and more.

MARCH 2015:
Fujifilm Holdings Corporation acquires CDI for $307 million.

JUNE 2016:
RIKEN announces that it will resume its study in partnership with Kyoto University on retinal iPSCs.

JANUARY 2017:
Fujifilm Holdings Corporation acquires $4 million equity stake (10%) in Cynata Therapeutics who develop mesenchymal stem cells for human use by using CDI iPSCs.

NeuroTechnology

Arguably, the most profound and debilitating changes that occur with ageing are associated with defects in the nervous system. These include chronic pain, Parkinson's disease, Alzheimer's disease, age-related macular degeneration, hearing loss, etc. One of the strategies to combat nervous system disorders is by stimulating or suppressing nerve cell activity. In this section of the report we overview the major technologies used or in development for interacting with the nervous system and describe the most prominent examples of their use in details.

The classical proven and clinically available approach to stimulation of nerve cells is direct stimulation with electrodes (see Deep Brain Stimulation or DBS below), but this method involves complex brain surgery and bears the risk of damage by a foreign rigid body inside a soft organ like the brain. The clinical standard in non-invasive brain stimulation is transcranial magnetic current stimulation (TMS) which pulsates magnetic fields at high frequency into the brain, but its precision and depth of stimulation are severely limited, thus limiting its applications.

One technique called optogenetics involves genetically manipulating nerve cells to become excitable when exposed to light pulses; optic cables are less invasive than electrodes and it can potentially provide a high degree of specificity, but the experiments successfully done in rodents and monkeys have yet to be proven effective in humans. Finally, application of direct current through electrode pads through the skin/skull creates an electric field which can increase the excitability of, or silence neurons close to the electrode. This technique is non-invasive, and while it was shown to be safe and modestly effective for pain, its effectiveness for claimed cognitive enhancement remains a matter of debate.

Source: Famm, Litt, Tracey, Boyden & Slaoui, Nature, 2013

Major trends in neurostimulation

Arguably, the most profound and debilitating changes that occur with ageing are associated with defects in the nervous system. These include chronic pain, Parkinson's disease, Alzheimer's disease, age-related macular degeneration, hearing loss, etc. One of the strategies to combat nervous system disorders is by stimulating or suppressing nerve cell activity. In this section of the report we overview the major technologies used or in development for interacting with the nervous system and describe the most prominent examples of their use in details.

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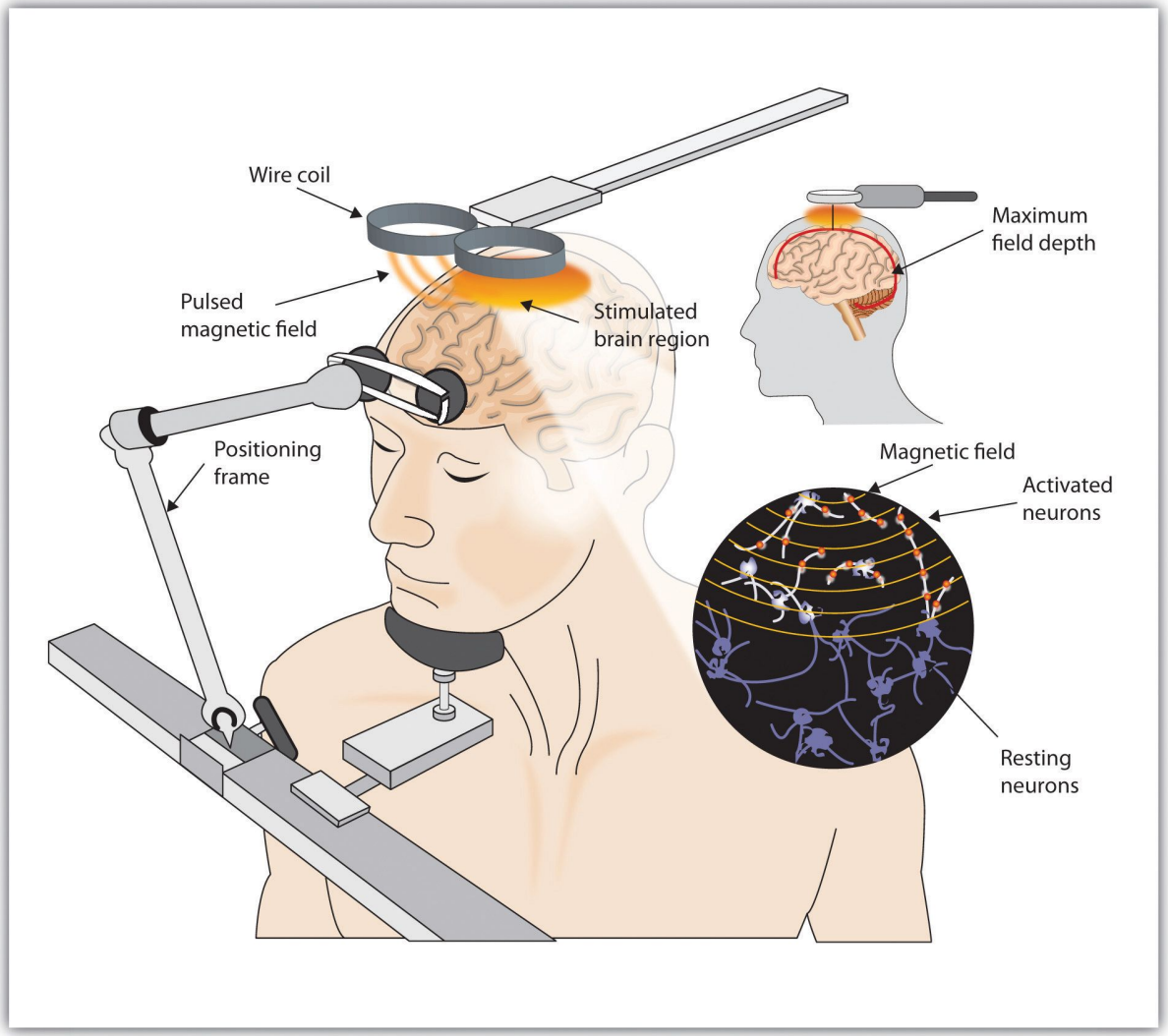


Transcranial Magnetic Stimulation (TMS)

Source: opentextbc.ca

Major trends in neurostimulation

The risk for developing chronic pain increases with ageing, particularly when associated with osteoarthritis, chemotherapy or other age-related diseases. Transcutaneous electrical nerve stimulation (or TENS) has been widely available over-the-counter for relief of chronic and acute pain. Systematic reviews, however, reveal a discrepancy in the studies raising the possibility that this treatment may not be equally effective for every case. A special case of TENS - (external trigeminal nerve stimulator), where the device is applied to the frontal lobe, has been approved by FDA for the treatment of migraine and these devices are available over-the- counter, which is a testament to their safety. A similar concept of applying current through the brain (called transcranial direct current stimulation) claims that when applied to particular areas and in certain doses, it can improve cognition, concentration and enhance athletic performance, but, again, the reported effects vary and studies require adequate blinding and placebo-control.

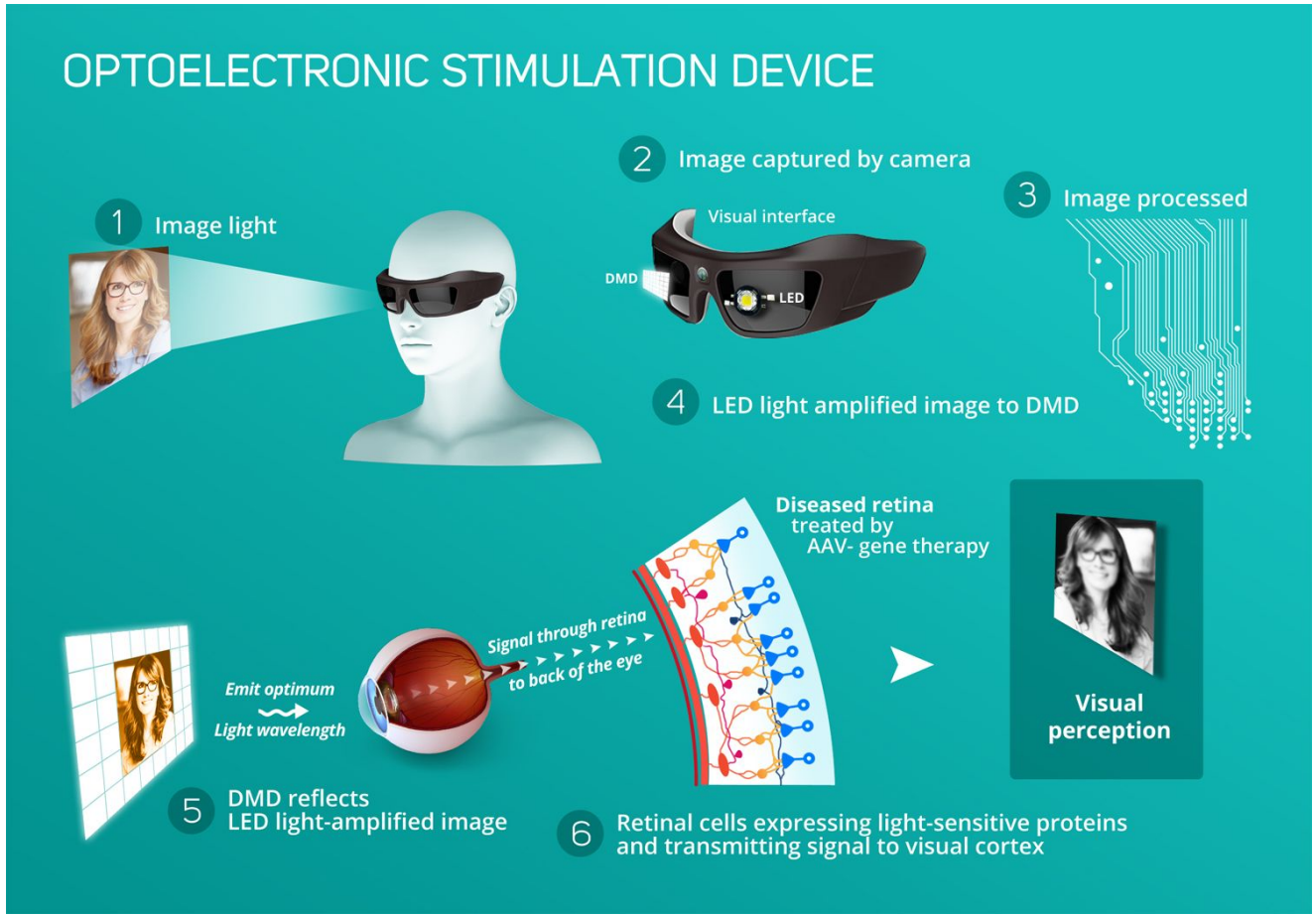
Parkinson's disease is more prevalent with ageing, it is characterised by the loss of dopaminergic neurons in a part of the midbrain (called substantia nigra) and the disease exhibits itself as uncontrollable tremor in patients, but other symptoms like depression and anxiety are common. The first line of treatment comes in the form of levodopa (L-DOPA) which works by increasing the availability of dopamine in the system. When this is unsuccessful, Deep Brain Stimulation (DBS) is currently the most effective treatment. Invasive brain surgery allows insertion of the stimulating electrode deep inside to bypass the dead area (substantia nigra).

The effect of the stimulation is instant and reversible, but the surgery and electrode insertion has the potential to irreversibly damage other areas of the brain. A recent development of non- invasive stimulation of deeper areas of the brain using temporal interference of electric fields (TI) brings the possibility of this becoming the first line treatment with no side effects of L-DOPA, nor DBS.

Major trends in neurostimulation

Age-related macular degeneration is characterised by a loss of light-sensitive cells in the centre of the visual field. The disease tends to occur more frequently in the ageing population and gets progressively worse over the years.

However, neurons, which convey the information between the retina and the brain remain intact. There is currently no approved treatment, but several avenues are being explored and are in their preclinical phases. One strategy delivers optogenetic genes (see above) into the remaining non-light sensitive neurons in order to turn them into light-sensitive ones and allow them to be stimulated by light.



Gensight Biologics

This optogenetic therapy is the first of its kind and if it becomes clinically successful, it would open the bottleneck in the development of optogenetic therapies for other neurological diseases.

The field of neurotechnology has been around for a long time but is nearing maturity in the last two decades. The advent of brain imaging revolutionized the field, allowing researchers to directly monitor the brain's activities during experiments. Neurotechnology has made a significant impact on society, although its presence is so commonplace that many do not realize its ubiquity. From pharmaceutical drugs to brain scanning, neurotechnology affects nearly all industrialized people either directly or indirectly, be it from drugs for depression, sleep, ADD, or anti-neurotics to cancer scanning, stroke rehabilitation, and much more. As the field's depth increases it will potentially allow society to control and harness more of what the brain does and how it influences lifestyles and personalities.

There are some technologies that are not considered as longevity subsectors *per se*, but their convergence and integration with proper longevity companies will enhance longevity. Some of these include gaming products, like BrainAge, and Fast ForWard, that aim to improve brain function. The technology relies on imaging of the brain, possible using Magnetoencephalography (MEG), Magnetic resonance imaging (MRI), functional MRI (fMRI), Computed tomography (CT), and Positron emission tomography (PET) scanning machines.

Transcranial magnetic stimulation (TMS) is essentially direct magnetic stimulation to the brain, transcranial direct current stimulation (tDCS) is a form of neurostimulation which uses constant, low current delivered via electrodes placed on the scalp. Cranial surface measurements using Electroencephalography (EEG) and Magnetoencephalography (MEG) are different methods to understand the electrical signaling in the brain during activation, including highly localized possibilities to better understand reactions and over-reactions (seizures) to stimulation.

Implant technologies provide neurodevices used to monitor or regulate brain activity. The most common neurodevices are deep brain stimulators (DBS) that are used to give electrical stimulation to areas stricken by inactivity. Neuromodulation is a relatively new field that combines the use of neurodevices and neurochemistry. The basis of this field is that the brain can be regulated using a number of different factors and that all these can be modulated by devices implanted in the neural network.

The number of patents filed in the field has grown by over 500% in the last decade, doubling the number of subclasses for patents, and it estimated at over $2 billion USD currently for IP alone. The devices market itself is projected to reach $12 billion USD by 2020. The overall financial impact of such neurotechnologies is tremendous. Overall, if you include the medical uses of NeuroTech, other devices, and all the businesses that can benefit from brain-related technologies, this is a field that's generating well over $150 billion in revenues annually.

As the costs of computing power, cloud accessibility and hardware sensors dwindle, brain health systems can leverage measurements taken from a far broader swath of the population than ever before possible.

Companies like CNS Response and Advanced Brain Monitoring are already deploying systems that harness the power of big data, allowing for better diagnoses and treatments.

Companies like Emotiv and NeuroSky are advancing the state of Brain-Computer Interfaces for better device control. Phillips has patents describing how ALS patients can control home appliances via BCIs.

- **$2B USD**

the value of **NeuroTech Patents in 2015** based on new and comprehensive SharpBrains analysis.

- **In 2000: 422 Classifications**
- **In 2014: 899 Classifications**

the number of unique USPTO Patent Subclasses reveals **NeuroTech is extending into more industries** than ever before.

- **8,000+ Active Patents and**
- **5,000+ Pending Applications**

The product of **500% growth in 10 years**, driven mostly by activity in the US and in the EU.

- **51% - large companies**
- **21% - small companies**
- **15% - universities or government organizations**

distribution of **NeuroTech IP ownership and licensing** by entity type.

Companies like Medtronic, Neuropace and St. Jude Medical, are developing systems to actively monitor brain activity and respond in real-time with appropriate treatments. Some monitoring systems are coupled with other assistive devices, such as robotic aids to enable patients suffering from neurological disorders (such as ALS) to regain lost motor control.

Systems employing neural detection devices to monitor vehicle operator alertness and take preventative measures with driver stimulation or vehicle autopilot/ shutdown systems are described by multiple patents. The US Army, automotive companies like Toyota, start-ups like Freer Logic, medical device makers and insurers are all patenting inventions addressing this concern. In 2017 a car was driven by thoughts alone, for the first time.

Medical tech companies such as Medtronic and Brainlab, and consumer research firms such as Nielsen are interested in using Virtual Reality, combined with EEG and transcranial direct current stimulation (tDCS), to treat mental illnesses such as PTSD, and to assist surgeons in the operating rooms.

Thync, an early-stage company, and St. Jude Medical, Brainlab and Neuronetics/NeuroStar are all pushing the boundaries of brain stimulation technology via magnetic fields or electrical impulses.

The Rise of Neurotechnology Science

Neurotechnology is used to understand and influence the brain and nervous system for the purposes of improving health, education, and cognition. It is a multidisciplinary field that is rapidly growing, and has more impact upon our lives with each passing day. It incorporates advancements in biology, neuroscience, medical imaging and computer science, providing many business opportunities for both established companies and startups.

Neurotechnology encompasses technologies such as diagnostic imaging and monitoring of the brain using fMRI or electroencephalography (EEG); neuropharmacology (drugs as antidepressants or painkillers); enhancements or replacements for sensory systems like cochlear implants or artificial eyes; brain-actuated limb prosthetics and neurostimulation (both invasive and non-invasive) to deliver stimulation to the nervous system like electrodes implanted deep in the brain of Parkinson's disease sufferers to help control some of their symptoms, and more.

The NeuroTech industry is growing rapidly, accounting for more than $172 billion in revenues in 2015, with 9% growth [1]. Venture capitalists invested more than $8.6 billion in new businesses in the sector, and more than 200 different investor groups participated in these financing deals.

Source: https://www.neurotechindustry.org/access-to-capital

The Rise of the Neurotechnology Industry

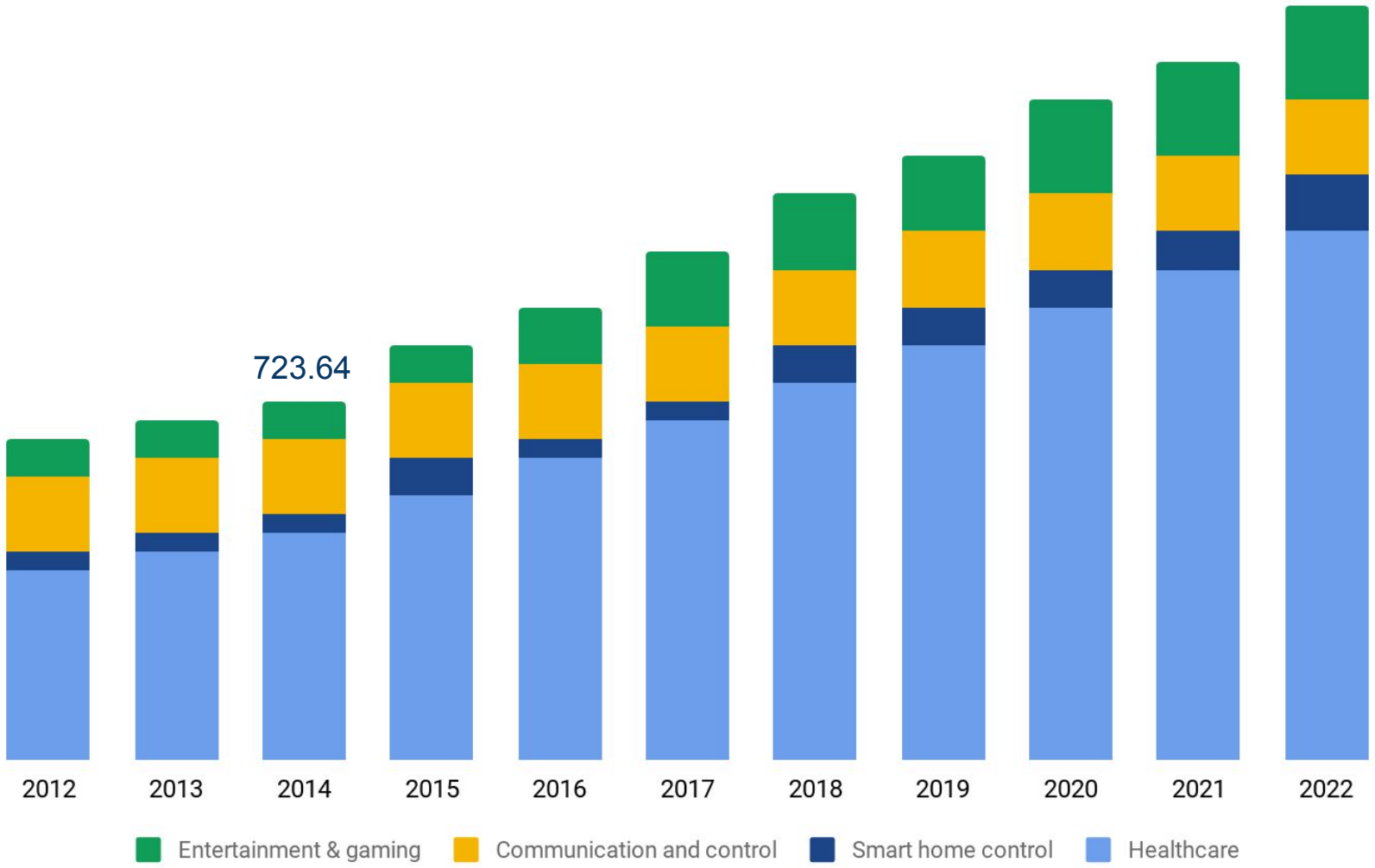
The growth of financing in neurotechnology is 31% while the average growth for life science investment in general is 12%. Private capital funds invested more than $19 billion in NeuroTech companies since the year 2000.

The investment in NeuroTech is relatively small in comparison with other areas of medicine and biotech but it can have a profound impact in our lives. Neurotechnology has existed for almost a century (EEG was discovered in the early 1930s) but has evolved rapidly in the last two decades. Brain imaging techniques like fMRI have brought a revolution by allowing monitoring the brain activity in almost real time during many experimental conditions.

Modern neurotechnology can image almost all aspects of brain activity and control to some extent certain functions: it can alleviate symptoms of depression, an increase or decrease of activation as experienced in ADHD, help with sleep deprivation and enhance sleep depth or ameliorate insomnia, reduce epileptic seizures or tremors in Parkinson's disease, assist with rehabilitation after a stroke and create a sensory-motor loop with brain controlled limb prosthetics.

The future of this industry will see advanced control of neurological disorders and conditions, modulation of brain states (from mood to attention to learning itself), and other applications that only time itself will reveal.

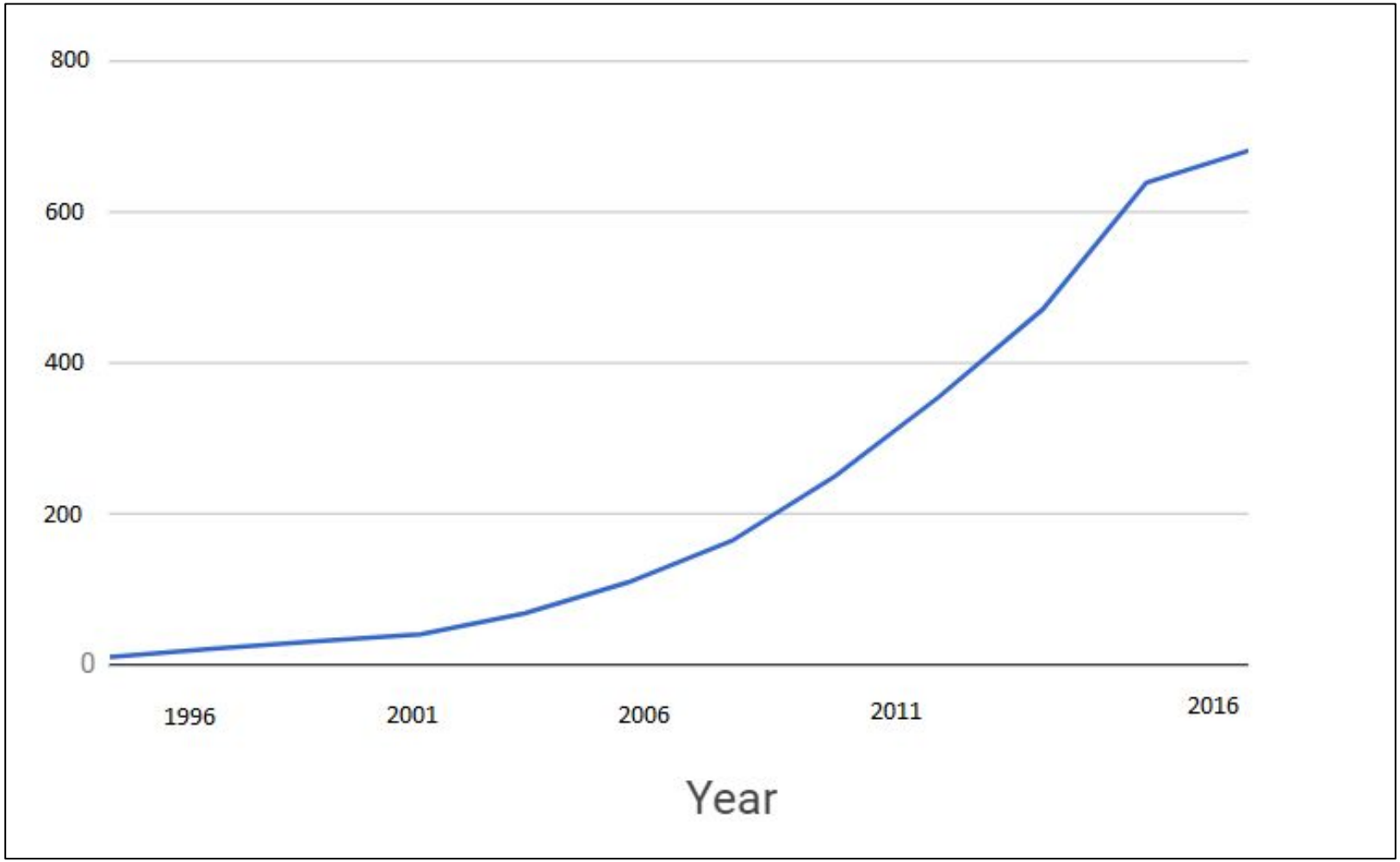
Global brain computer interface market, by application, 2012 - 2022 (USD Million)



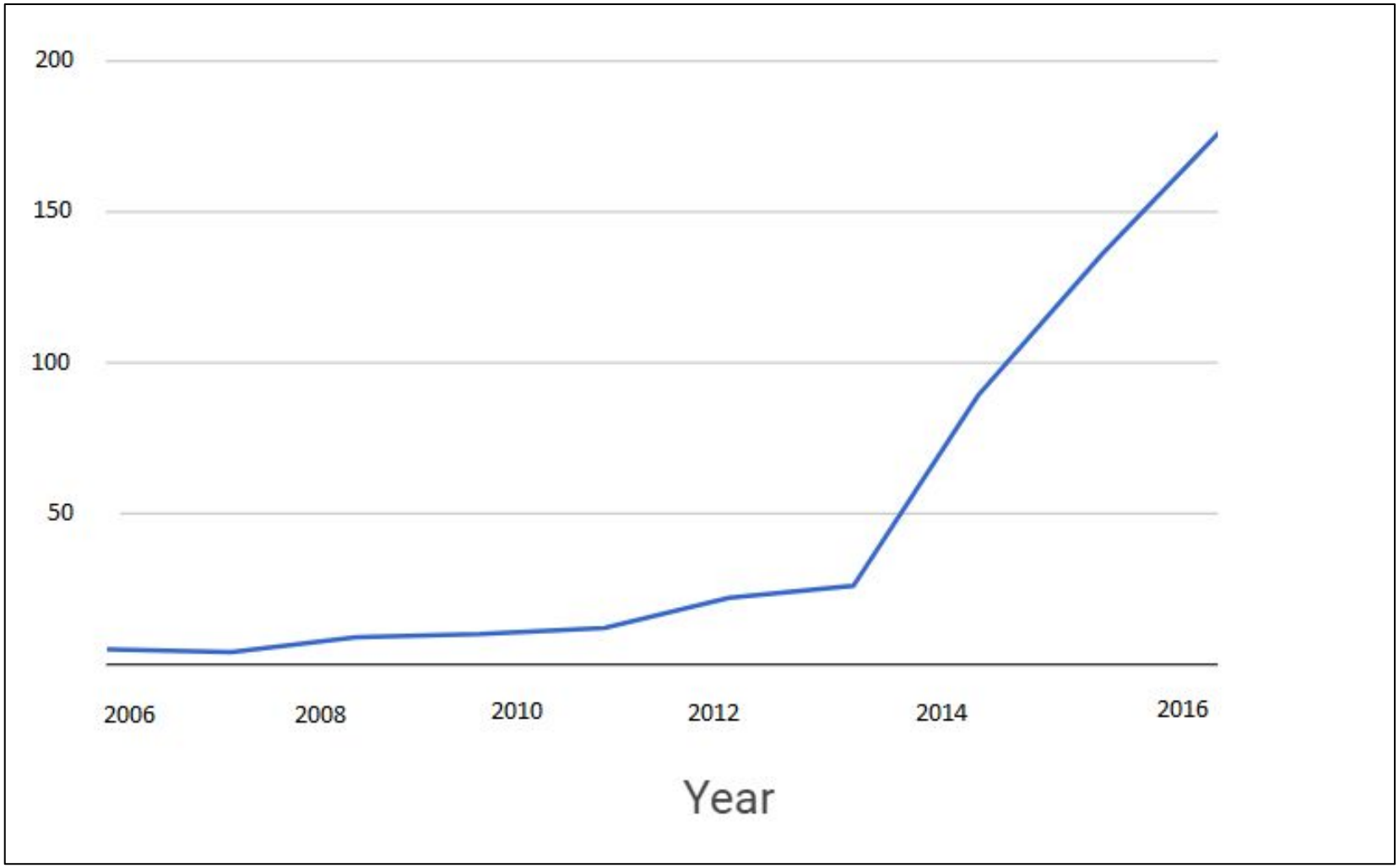
Source: https://www.grandviewresearch.com/industry-analysis/brain-computer-interfaces-market

Crowdfunding - BCI/EEG

2012:	InteraXon Muse	$288 000	(1,614 backers)	Meditation
2012:	NeuroDreamer	$66 500	(351 backers)	Sleep
2013:	Melon	$290 000	(2,723 backers)	Brain Insight
2013:	OpenBCI #1	$215 000	(947 backers)	Makers / Education
2013:	Emotiv Insight	$1 650 000	(4,459 bakers)	Brain Insight
2014:	FocusBand	$84 000	(210 backers)	Brain Insight
2014:	Aurora iWinks	$239 000	(1,428 backers)	Sleep
2015:	Kokoon	$1 900 000	(8,489 backers)	Sleep
2015:	OpenBCI #2	$169 000	(644 backers)	Makers / Education
2015:	Neuroon	$438 000	(1,944 backers)	Sleep
2016:	Neeuro	$80 730	(486 backers)	Brain Training
2016:	iBand+	€644 249	(3,958 backers)	Sleep
2016:	Sleep Shepherd	$864 089	(794 backers)	Sleep
2016:	Super Brain II	$70 000 x2*	(132 backers)	Sleep
2016:	Melomind	€169 420	(858 backers)	Relax / Stress
2016:	Aware	$150 952	(717 backers)	Hearable



Number of scientific papers on brain-computer interface on PubMed



Number of scientific papers containing the word "neurotechnology" on PubMed

SleepTech: a Growing Sector of NeuroTech

- One particularly powerful NeuroTech subsector emerging today is SleepTech.
- Sleep is the gateway to health, affecting myriad bodily processes, in particular memory, cognition, mood, and cardiometabolic health.
- While this subsector is still young, with relatively few key players and companies, it is a sector poised to experience massive growth over the next few years.

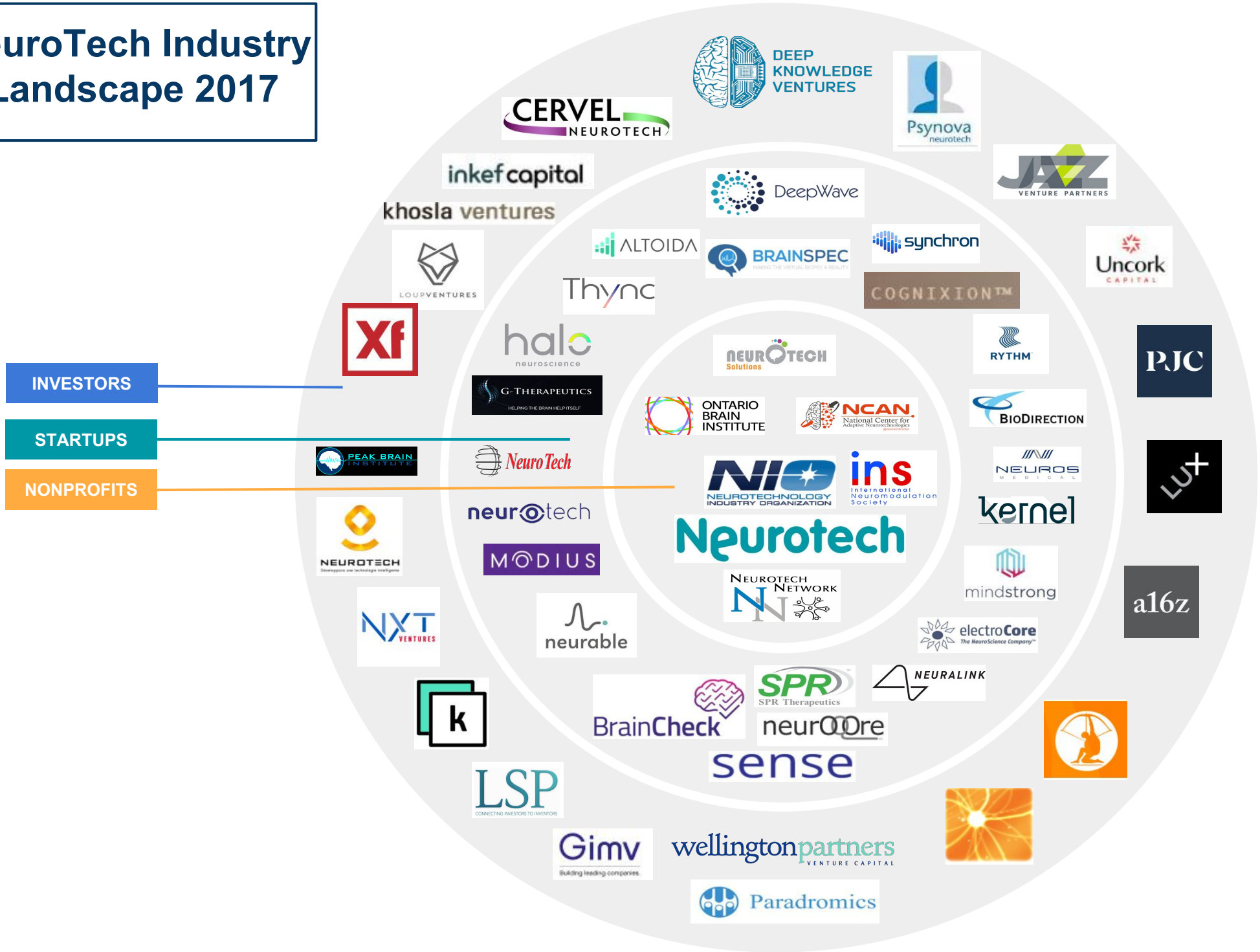
Major Benefits of Improved Sleep:

- Memory
- Learning
- Mood
- Alertness
- Focus

Comparison of NeuroTech Companies

Company	Scientific publications covering their core science	Clinical trials validating their product	Aspirations for medical devices market	Neuroscientists on management team	Total disclosed funding	Sleep Tech
Kernel	-	-	+	+	100M	-
G Therapeutics	+	+	+	+	40.8M	-
Rythm	+	+	-	+	22.5M	+
Thync	+	+	-	+	13M	+
Halo Neuroscience	-	-	-	+	10.7M	-
Synchron	+	+	+	+	10M	-
BrainCo	-	-	-	+	5.55M	-
Neurable	-	-	-	+	2.33M	-
Neuralink	-	-	-	+	27M	-
DeepWave Technologies	+	+	+	+	Seed	+

NeuroTech Industry Landscape 2017



Deep Knowledge Analytics: Neurotech Industry Landscape 2017

NeuroTech - What to Expect in the Next Few Years

- The global neurotechnology industry has witnessed the substantial expansion during the past five years, while in 2016-2017 there was a boom in powerful new techniques for imaging, analyzing and modulating neural activity.
- There are 2 major areas within the NeuroTech industry: brain-computer interfaces, which can be considered to be related to the IT & AI industries, and advanced NeuroTech approaches to HealthTech.
- In 2018-2020 we will observe the convergence of NeuroTech, AI, and SleepTech for personalized precision medicine.
- SleepTech is one of the most promising sectors of the NeuroTech industry and will have major impact on heart health, cardiometabolic health and diabetes.
- Many projects that had high level of consumer orientation 1-2 years ago now seem to be overestimated and failed to meet expectations.
- In 2018 we will see new NeuroTech industry players with strong scientific foundation, strong core IP, and achievable MVPs. The key players will be developing wearable devices enhancing sleep, cognition, and cardiometabolic health.
- Now is the best time for investors to enter the NeuroTech for advanced HealthTech industry.

Prosthetics

Replacement body parts are as old as ancient Egypt. But the exponential growth of technology in recent years has been driving progress in prosthetic tech at an ever increasing pace. No longer are scientists simply focused on mechanically replicating human body parts; recent advances promise prostheses that can be controlled by the brain. That, along with improved mechanics, sensory feedback, battery life, and AI, is closing the gap between prostheses and real body parts.

It is crucial to understand that the hindrances created by a missing limb are not limited to the loss of the functional aspects of the limb, but in fact grossly affect a person's health and well being. For example, the use of a prosthetic leg usually results in an unbalanced gait, which imposes stress on the skeleton, necessitating a surgery to replace a hip.

Designing the mechanical limb itself is still a challenge. But advances in of electric motors, particularly miniaturisation, along with advances in computing power are driving progress rapidly. Current day prostheses are adept at grabbing, twisting, and lifting objects, but there's still a lot of work to be done to make those tasks feel and look natural. A major issue facing scientists and engineers is proprioception, in other words, the ability to intuitively know where our extremities are without having to look.

When it comes to control, some of the prostheses available today have some degree of mental control through a phenomenon called myoelectricity: Sensors installed in the socket of a prosthesis can detect the electrical signals generated when the user tries to move a missing limb. The sensors that detect the signal must be placed on the correct area of the skin on the stump. It must be noted that the movement of the prosthesis may not reflect to the intended movement, but users can learn how to make the prosthetic behave in the desired fashion.

Using the same concept, researchers are figuring out how to transmit signals of pain, pressure, and heat to the brain. Simple sensors that detect temperature, pressure, and shear - a force lateral to the surface rather than perpendicular are placed onto the prosthesis. Their output, small electrical currents, is then applied to the skin of the stump.

Similarly here, each person might feel the sensations differently, for some it might feel like tickling, to others as scratching, but the brain can learn to interpret the sensation more accurately.

Meanwhile, scientists are exploring novel ways to give users more control over their artificial limb. A research team at Newcastle University has fitted a camera onto a prosthetic arm. The camera snaps photos of the objects present in its view and uses AI to execute actions, such grasping a glass of water and raising it to your face. In this case, the AI will help position the hand and the finger in optimal positions for the task. Some hand prosthetics now have air filled bubbles for fingertips, which enables them to handle delicate things. Those air-bubbled tips also render the user much more adept at typing on keyboards, a critical boon for a vast majority for people in the workplace nowadays.

The Linx, one of the most advanced artificial lower limbs available, uses 7 sensors and employs progressive machine learning tech to understands what the user is doing - sitting, walking, climbing, etc - and adjusts the stiffness of the prosthetic joint automatically based on the user's posture.

According to a new report by Grand View Research, Inc., the global robotic prosthetics market is expected to reach $1.76 billion by 2025, growing at a CAGR of 9.2% from 2017.

According to a new report by Grand View Research, Inc., the global robotic prosthetics market is expected to reach $1.76 billion by 2025, growing at a CAGR of 9.2% from 2017; Microprocessor controlled prosthetics held majority of the revenue share in 2016 and is estimated to generate revenue over $983 million by 2025.

Prosthetic limbs have existed for hundreds of years, but with recent advancements in converging technologies, they are providing advanced quality of life. 3D printing, AI, and brain-machine-interface technology have now made it possible to use robotic limbs with microprocessors and sensors that provide feedback.

The shame and stigma around prostheses is changing. As military-backed technology trickles down into the civilian healthcare system, and as more and more amputees see top-end limb replacements fitted to soldiers and elite athletes, the line between ‘able’ and ‘disabled’ begins to blur - for the user and the able-bodied public. There’s still no true replacement for a lost limb - but their prosthetic replacements are now functional and futuristic enough not to be hidden, but worn with pride.

In 2017 we’ve seen 21-year old Easton LaChappelle changing the lives of thousands of amputees around the world with a new robotic arm prosthetic that costs around $4,000. Carnegie Mellon University’s “assistive technologies” project designed a custom prosthetic designed specifically to play the cello. The cello-playing arm had a couple of benefits over a traditional prosthesis.

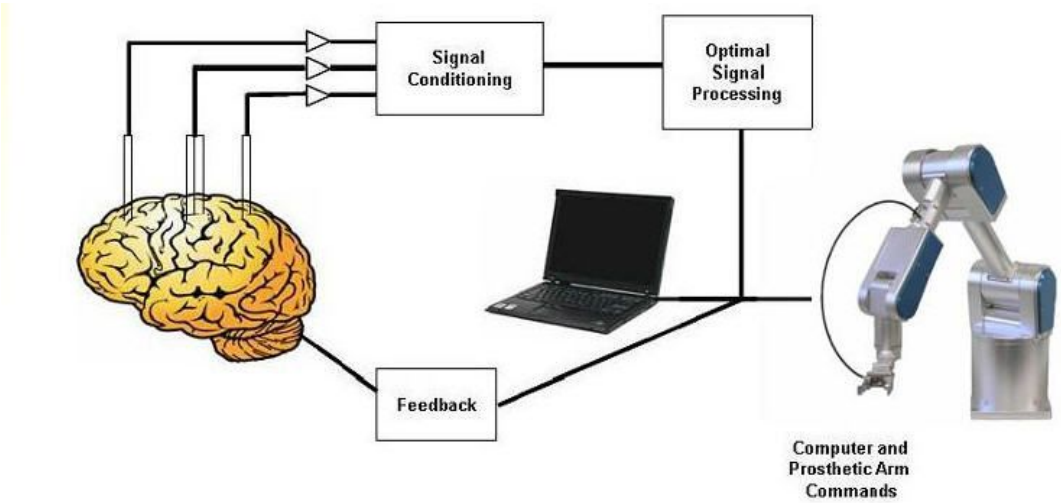
In the field of Brain-Machine-Interface there has been big progress as well. Facebook revealed they are working on a noninvasive “brain–computer speech-to-text interface”, and if it works, we’ll be able to “type” 100 words a minute just by thinking. Elon Musk declared he wants to connect our brains to computers with a mysterious device called “neural lace.” Scientists have made impressive progress uncovering, and even manipulating, the neural circuitry behind several brain functions.

During nearly 20 years of research, a biomedical engineer named Theodore Berger and his collaborators at USC and Wake Forest University developed a neuroprosthesis to improve memory in rats. The chip holds an algorithm that translates the firing patterns of neurons into a kind of Morse code that corresponded with actual memories.

The brain exchanges information through neural circuits, which have receptors to sense a stimulus, report this back to the nervous system and produce an appropriate response via motor neurons which lead to movement. Using a "biological amplifier" the muscle signals get amplified thousandfold by shifting the major nerves that normally go down the arm and letting them grow into the chest instead. When you think of closing your hand, a chest section will contract and electrodes will pick up those signals to tell the prosthetic arm to move.

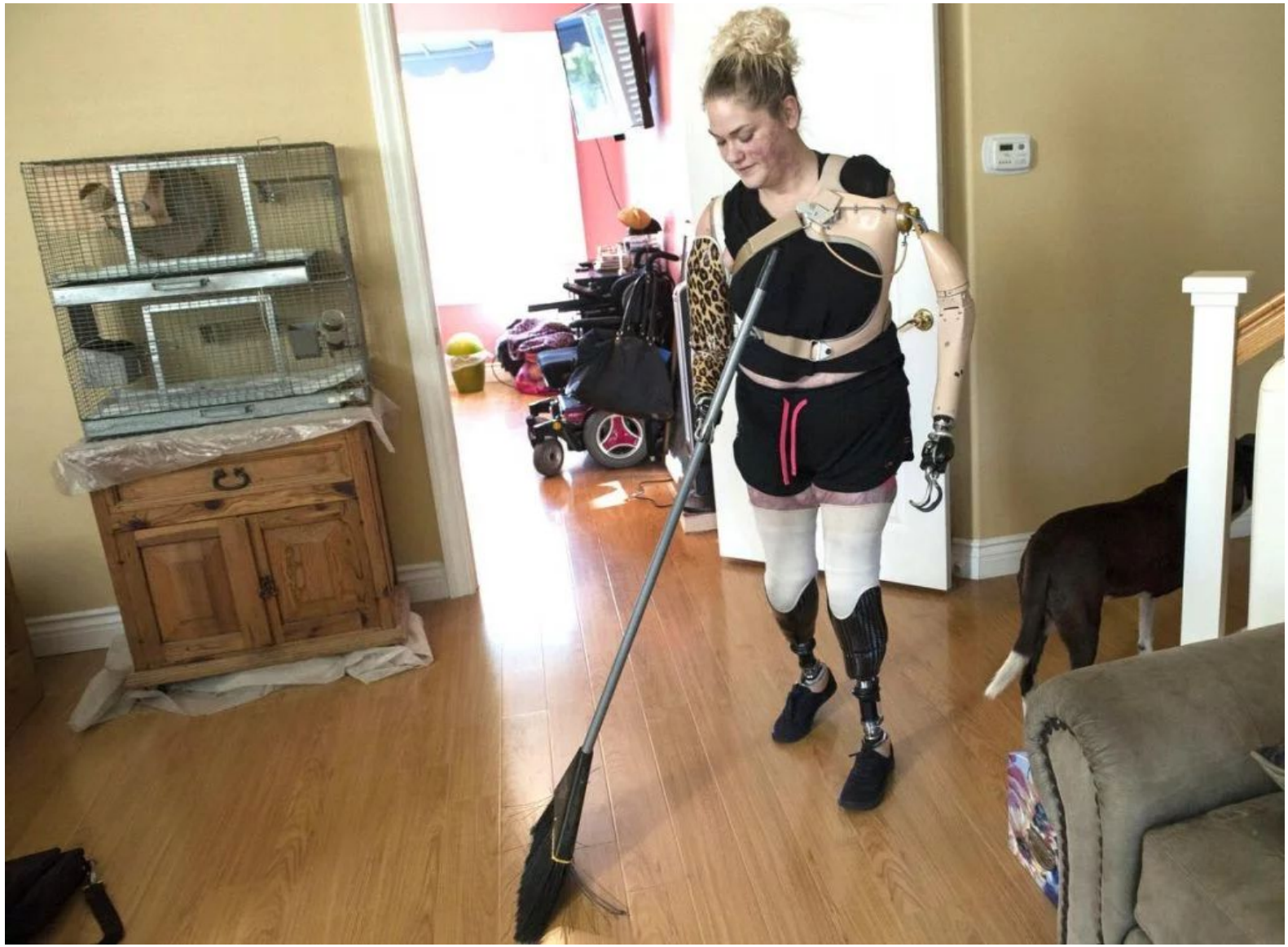
A touch on the chest would actually lead to the sensation of a touch on the patient's phantom arm, even their missing fingers. Sensations of hot, cold, as well as sharpness and dullness are all felt and provide a way to restore sensation using a prosthetic hand that “feels".

Financial analysts are forecasting a $27 billion market for neural devices within six years, and countries around the world are committing billions to the escalating race to decode the brain. The robotic prosthetic market is topping out at an estimated $2 billion within the same timeframe. By giving neuroscientists a vast new trove of data they can use to decode the workings of the brain, the level of sophistication needed to jump-start human evolution with a mind-enhancing neuroprosthesis is around the corner.



Dynamic Data-Driven Brain-Machine Interface (DDDBMI)

Nick Ackland (UK) lost his forearm in an accident and has been testing an advanced bionic arm and hand that is so precise he can use a keyboard



Quadruple amputee Kaitlyn Dobrow uses prosthetics to improve her mobility.

She underwent amputation of her limbs following bacterial meningitis complications which led her blood to clot and not reach her skin, causing damage equivalent to 3rd degree burns.

Source: https://www.everythinginspirational.com/quadruple-amputee-kaitlyn-dobrow/

Fantastic things are happening in neuroscience, like prosthetic legs controlled by thought and microchips connected to the visual cortex as scientists were learning to help the lame walk and the blind see.

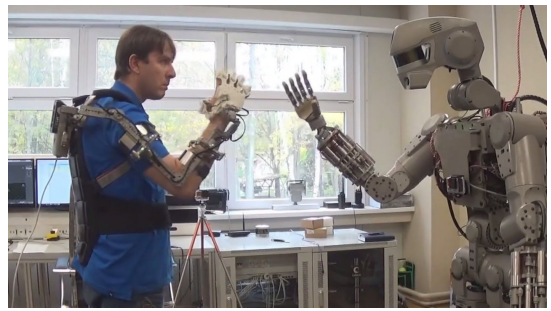
All of these neural implants and smarter prosthetic designs have lead to the overcoming of limb loss and paralysis and have taken us one step closer to our human-machine hybrid fantasy.

Now that humanity is learning how to reengineer its own capabilities, we really can choose how we evolve.

Prosthetics and aging

In 2017 scientists at Scuola Sant'Anna in Italy and EPFL (Ecole polytechnique fédérale de Lausanne) in Switzerland built a prototype of a smart, light-weight and easy-to-personalize exoskeleton that counteracts the loss of balance and promotes balance recovery after an accidental slip. This is a first in wearable machines, which are normally used to assist or enhance regular movement, instead of preventing an unexpected event like falling. The results are published on May 11th in Scientific Reports.

The exoskeleton was designed to help the elderly by preventing fall-related injuries, since seniors are involved in 40% of fatal injuries related to falling in Europe. But the exoskeleton could also be used as an aid for the physically impaired, amputees and those suffering from neurological disorders. It is technology that will actually help people with their daily activities.



https://i.ytimg.com/vi/oke01g1-H0s/maxresdefault.jpg

The exoskeleton is wearable from the waist down, and is vastly different from the armored stuff you see in today's science fiction movies.

"Our smart exoskeleton is lightweight and extremely easy to personalize," says Silvestro Micera, professor at EPFL and Scuola Sant'Anna and Bertarelli Foundation Chair in Translational Neuroengineering. For this first prototype, the exoskeleton requires only a few minutes to adapt to a given patient, which involves adjusting the size for a particular user and learning the user's gait.

Open Bionics started as a prototype project developed by 25-year-old robotics graduate Joel Gibbard, can be 3D-printed in 40 hours and costs less than other prosthetics.

De Oliveira Barata is a sculptor by trade who started the Alternative Limb Project in 2011 after working for medical prosthetic providers for nearly a decade.

Touch Bionics is a provider of world-leading prosthetic technologies and supporting services designed to ensure the best possible outcomes for people with upper limb deficiencies.

Freedom Innovations is solely focused on developing world-class lower limb prosthetic solutions in close collaboration with prosthetists and amputees.

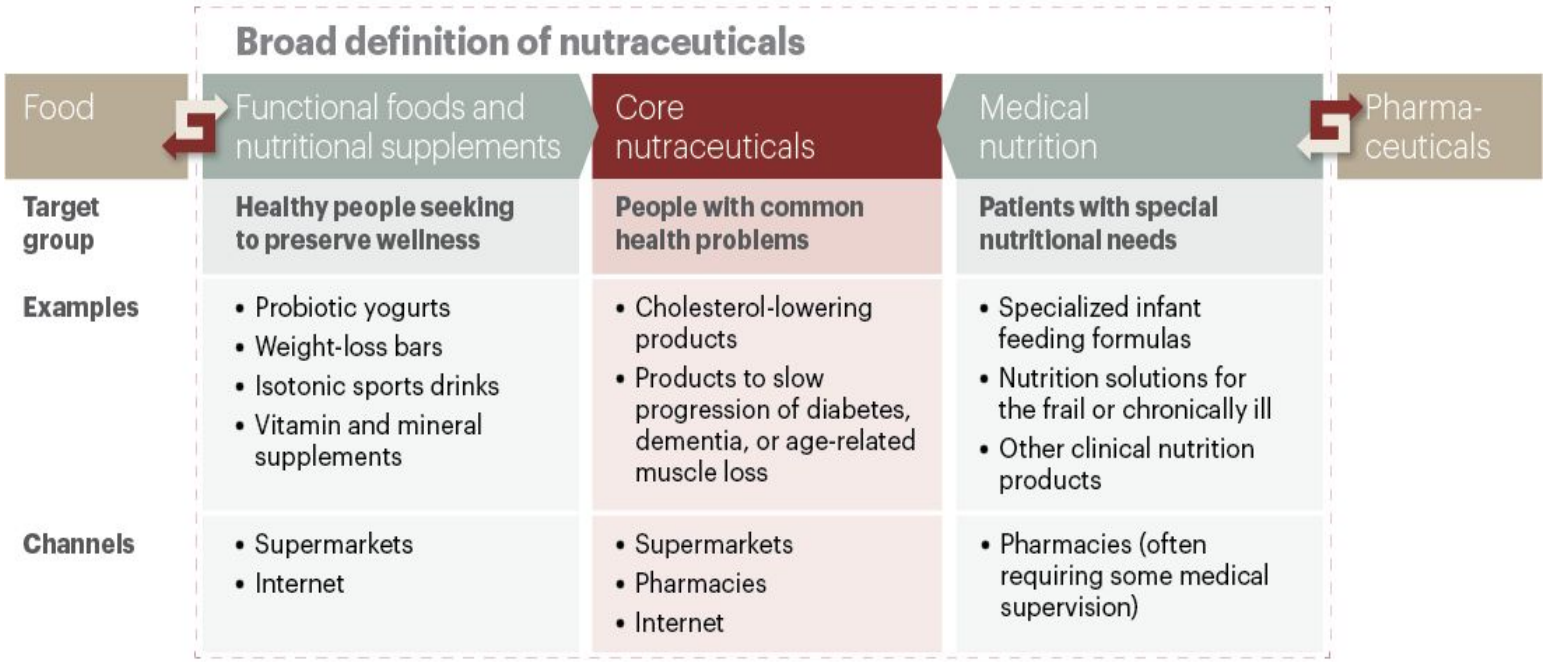
Ottobock is a German prosthetics company situated in Duderstadt. It has been responsible for several innovations in prosthetics, like a computerized knee that adaptively varies its passive resistance to suit the patients' different walking gaits, and a fully articulated robotic hand prosthesis.

Nutraceuticals

According to a new report by Grand View Research, Inc., the global nutraceuticals market is projected to reach USD 578.23 billion by 2025, with rising health concerns as the main driver. Dietary supplements particular, a subsegment of nutraceuticals, is expected to grow at a CAGR of over 9.7%, mainly due to rise in demand from Brazil, China, India, South Korea, Poland and Mexico.

Nutraceutical, a concatenation of “nutrition” and “pharmaceutical,” is a broad term that describes a range of products derived from food sources with extra health benefits. It covers products such as dietary supplements, functional foods, botanicals and herbals, vitamins and minerals, amino acids, proteins, and peptides.

The philosophy behind nutraceuticals is to focus on prevention. To be classified as a nutraceutical, a product must have physiological benefits or provide protection against chronic disease. They may be used to improve health, delay the aging process, and increase life expectancy.



Recent studies have shown promising results for nutraceuticals in various complications including allergies, Alzheimer's, cardiovascular diseases, cancer, diabetes, eye disorders, immune system status, inflammations, Parkinson's disease as well as obesity.

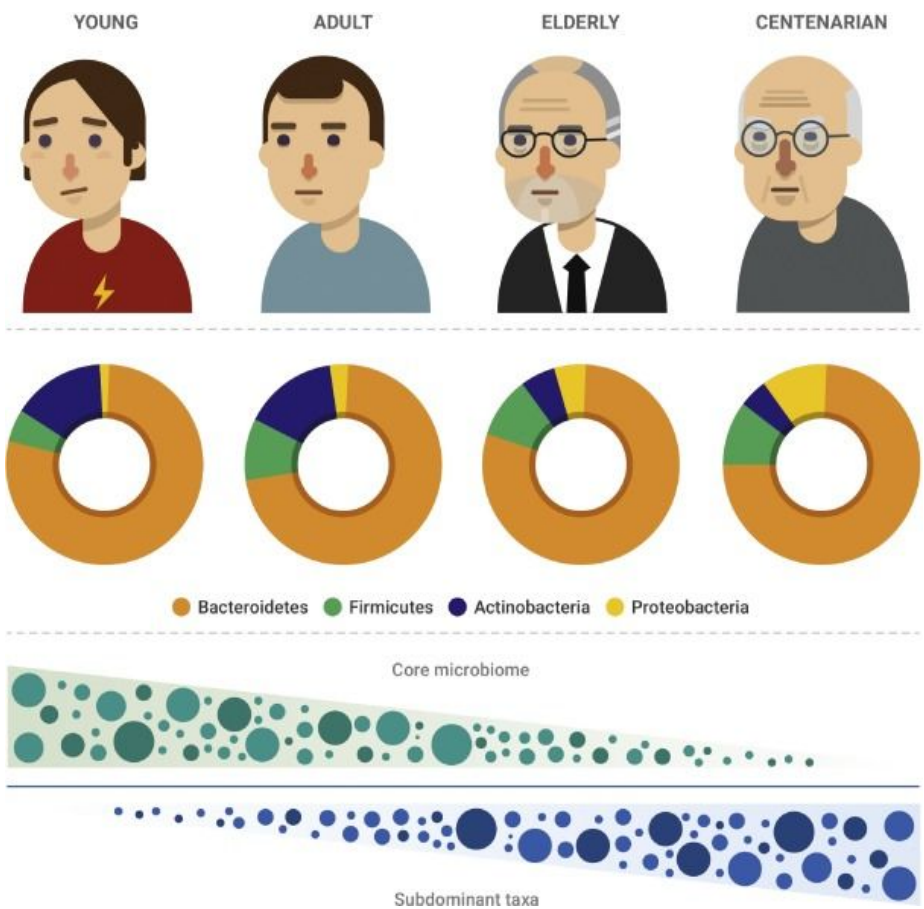
The antidiabetic drug metformin and the immunosuppressant rapamycin are both FDA-approved mTOR, or mechanistic target of rapamycin, inhibitors that multiple animal studies have shown may have anticancer and antiaging properties beyond their licensed clinical applications. However, the potential to use these drugs for off-label, prophylactic use to prolong a healthy lifespan is hampered by their side effects.

An international research team (Insilico Medicine) has now applied deep-learning neural networks to identify natural, and potentially far less toxic, mimetics of rapamycin and metformin, which could springboard the development of antiaging nutraceuticals that aren't subject to FDA regulation.

Currently there are already 2 anti-aging nutraceuticals identified by AI available on the market.

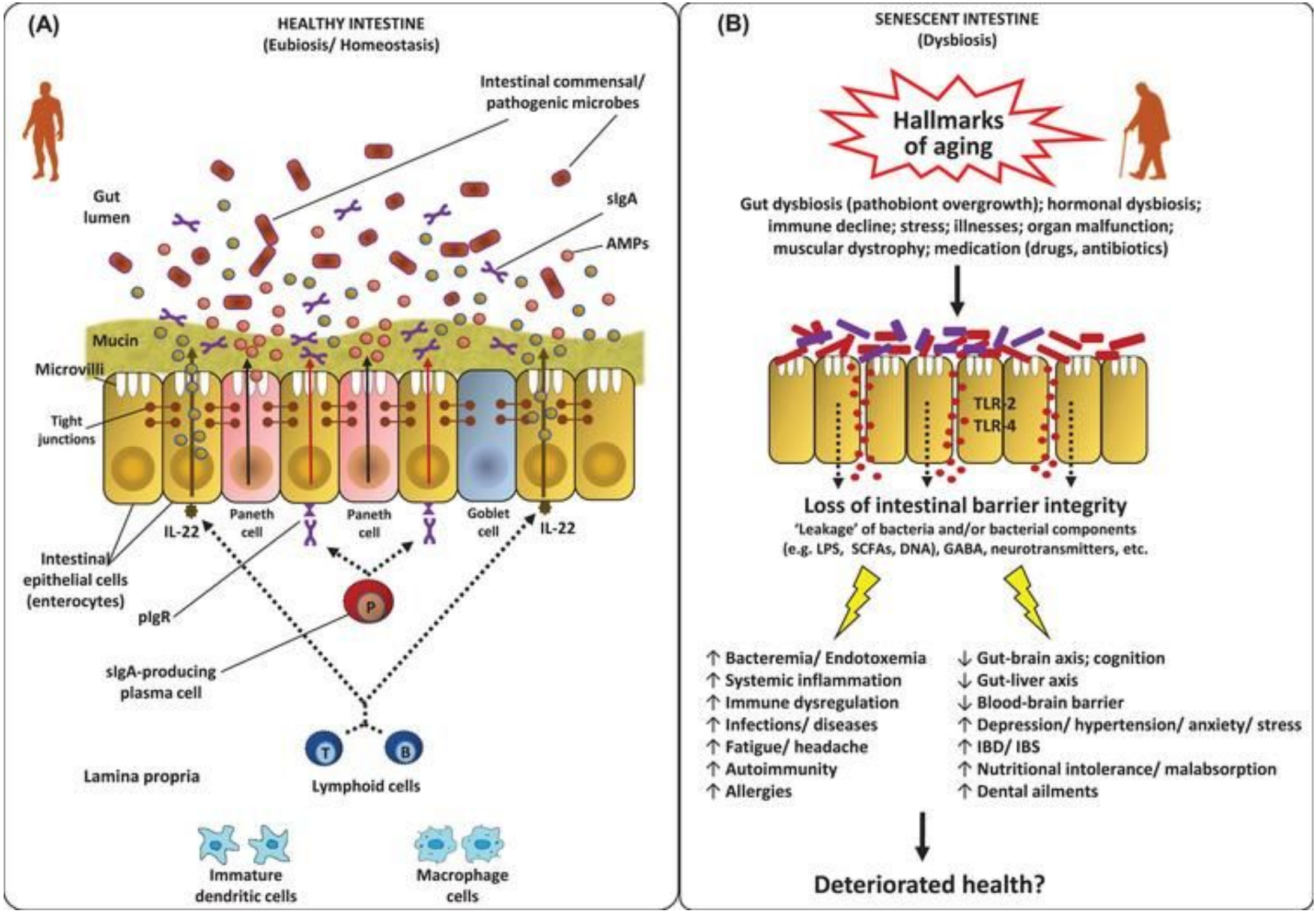
Microbiome

The microbiome is a collection of microbial life in the gut, known as the microbiota, and could be considered an accessory organ of the gastrointestinal tract. It is a self-contained, multi-cellular, biochemically active mass with specialized functions. Some functions are important for life such as **vitamin K synthesis**, an essential molecule in blood clotting. Others are responsible for training and maintaining a healthy **immune system** or **digesting** indigestible food products such as insoluble fiber. Like other organs, the microbiota has physiologic reserve (i.e., the capacity to regenerate). It may be harvested from one host for transplant into another. It is thus no surprise that as our other organs age, such as our heart, brain, and kidneys, our **gut microbiota ages**, too.



Aging-associated alterations in composition, diversity and functional features of intestinal microbiota are well-described in the modern literature. They are suggested to be caused by an age-related decline in immune system functioning (**immunosenescence**) and a low-grade chronic inflammation (**inflammaging**), which accompany many aging-associated pathologies.

Microbiota-targeted **dietary and probiotic interventions** have been shown to favorably affect the host health and **aging** by an enhancement of antioxidant activity, improving immune homeostasis, suppression of chronic inflammation, regulation of fat deposition and metabolism and prevention of insulin resistance. In 2017 researchers at the Max Planck Institute for Biology of Ageing in Cologne, Germany, showed for the first time that older fish live longer after they consumed microbes from the faeces of younger fish.

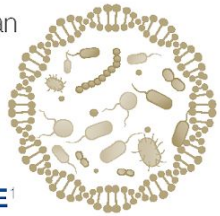

(A)
HEALTHY INTESTINE
(Eubiosis/ Homeostasis)
Intestinal commensal/
pathogenic microbes
Gut
lumen
sIgA
AMPs
Mucin
Microvilli
Tight
junctions
Paneth
cell
Paneth
cell
Goblet
cell
IL-22
IL-22
Intestinal
epithelial cells
(enterocytes)
pIgR
P
sIgA-producing
plasma cell
T
B
Lymphoid cells
Lamina propria
Immature
dendritic cells
Macrophage
cells
(B)
SENESCENT INTESTINE
(Dysbiosis)
Hallmarks
of aging
Gut dysbiosis (pathobiont overgrowth); hormonal dysbiosis;
immune decline; stress; illnesses; organ malfunction;
muscular dystrophy; medication (drugs, antibiotics)
TLR-2
TLR-4
Loss of intestinal barrier integrity
'Leakage' of bacteria and/or bacterial components
(e.g. LPS, SCFAs, DNA), GABA, neurotransmitters, etc.
↑ Bacteremia/ Endotoxemia
↑ Systemic inflammation
↑ Immune dysregulation
↑ Infections/ diseases
↑ Fatigue/ headache
↑ Autoimmunity
↑ Allergies
↓ Gut-brain axis; cognition
↓ Gut-liver axis
↓ Blood-brain barrier
↑ Depression/ hypertension/ anxiety/ stress
↑ IBD/ IBS
↑ Nutritional intolerance/ malabsorption
↑ Dental ailments
Deteriorated health?

The human gut microbiota: stability and diversity

Medicine

There are more than **3 MILLION MICROBIAL GENES** in our gut microbiota

150 TIMES more genes than in the **HUMAN GENOME**[1]



2kg APPROXIMATE WEIGHT OF THE TOTAL **GUT MICROBIOTA**[1]

OUR GUT MICROBIOTA EVOLVES THROUGHOUT OUR ENTIRE LIFE and is the result of a variety of influences:[1-2]

GENETICS · STRESS · HYGEINE PRACTICES · MODE OF DELIVERY · DRUGS/ ANTIBIOTICS · DIET · INFECTIONS · SURGERY · ENVIRONMENT

The composition of **GUT MICROBIOTA IS UNIQUE** to each individual, **just like our FINGERPRINTS**[1]

EFFECT OF ANTIBIOTICS ON GUT MICROBIOTA[1-12]

The **GUT MICROBIOTA** is the name for the microbe population living in the intestine. It is estimated to contain at least 1800 genera and 15,000-36,000 species, most of which have never been successfully cultured.

The gut microbiota has co-evolved with its host over millenia and provides benefits to its host including digestion, nutrient production, detoxification and immunity.

One of the ways pathogens and commensals interact with their host is via the expression of microbe-associated molecular patterns (MAMPs) which diffuse through the mucus layer and stimulate pattern-recognition receptors (PRRs) of dendritic cells, M cells and intestinal epithelial cells (IECs). In normal healthy individuals the gut microbiome is diverse and with an abundance of beneficial bacteria which promotes protective intestinal immune responses.

INTESTINAL EPITHELIAL CELLS (IECs) act as a physical barrier that prevents commensals from entering the lamina propria and integration of microbial signals. Tight junctions form a continuous intercellular barrier between IECs and regulate selective movement of solutes across the epithelium.

GOBLET CELLS secrete mucin (Muc2). They respond to the gut microbiome by increasing mucin production, increasing Muc2 sulfate incorporation (increase resistance to enzymatic degradation of mucus) and inhibit pathogen adherence.

MUCUS LAYER is a major mediator of IEC–commensal interactions. It consists of two layers of secreted mucin. The inner layer is sense and devoid of commensal bacteria. The outer layer is more loose and houses commensal bacteria and antimicrobial proteins. The mucus layer prevents IECs from direct contact with commensal bacteria and their molecular components.

Commensals promote strengthening of the mucus barrier.

GUT MACROPHAGES develop a non-inflammatory profile and do not produce pro-inflammatory cytokines in response to MAMPs.

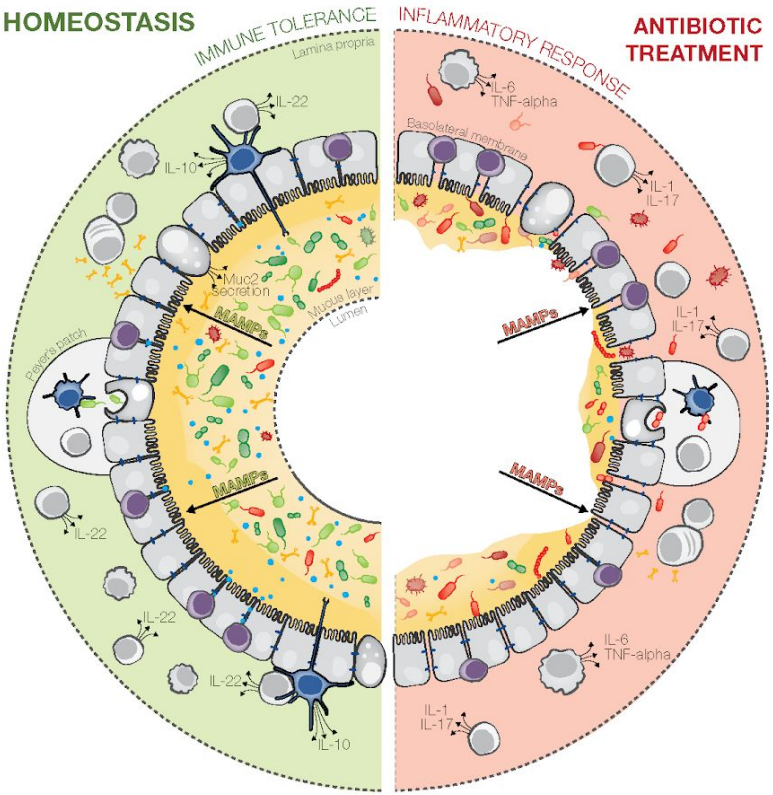
DENDRITIC CELLS protect against infection while maintaining immune tolerance by producing high levels of anti-inflammatory cytokines, e.g. IL-10.

MICROFOLD CELLS (M cells) transport bacteria and bacterial antigens to immune cells.

INTRAEPITHELIAL LYMPHOCYTES are influenced by the gut microbiota via MAMPs and secrete antimicrobial proteins, e.g. defensins, cathelicidins, C-type lectins.

T CELLS produce protective cytokines, e.g. IL-22.

PLASMA CELLS produce large amounts of secretory IgA, which impairs pathogenic bacterial attachment to mucosal epithelium, therefore interfering with pathogenicity.



Antibiotic administration results in significant reduction in **GUT MICROBIOTA** size and diversity. This is seen as increased colonisation by antibiotic-resistant bacterial species, e.g. *Clostridium difficile*, *Candida albicans*, salmonella, *C. perfringens* type A, *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus pneumoniae*, and reduction in butyrate-producing species, e.g. *Faecalibacterium*, *Subdoligranulum*, and uncultered *Ruminococcaceae*, *Roseburia*, *Coprococcus* and *Lachnospiraceae*.

Studies have shown that while much of the diversity eventually recovered, there were still several species that failed to recover after four years, suggesting that even a short course of antibiotics may cause permanent changes to gut microbiome.

Health implications for low-diversity gut microbiota include inflammatory bowel disease, autoimmune disease, allergies, obesity, cancer, mental illness and autism.

INTESTINAL EPITHELIAL CELL (IEC) barrier function is altered due to changes in MAMP concentrations.

Reduced expression of tight junction proteins leads to increased intestinal permeability and enhanced bacterial penetration into the lamina propria. This can set off a vicious cycle of inflammation and pro-inflammatory immune responses leading to destruction of tight gap junctions and IEC apoptosis, increased permeability and more inflammation.

Shifts in the the intestinal microbiota induce defects in mucin production and alterations in MAMP concentrations.

A defective **MUCUS LAYER** can lead to increased MAMP diffusion, commensal contact with IECs and commensal translocation to underlying lamina propria.

Hyper-stimulation of IECs and commensal translocation lead to further disruption of intestinal homeostasis and further host pathology and inflammation.

GUT MACROPHAGES adopt an inflammatory phenotype and produce IL-6 and TNF-alpha which drives inflammation and cell damage.

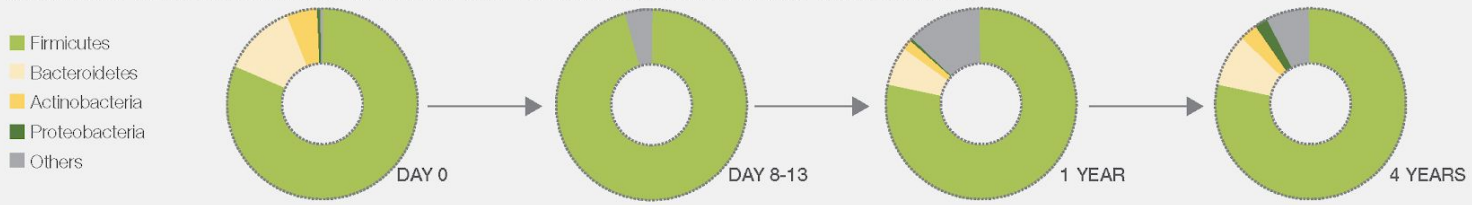
INTRAEPITHELIAL LYMPHOCYTES respond to changes in MAMP concentrations through decreased secretion of antimicrobial proteins. This may promote inflammation and increased susceptibility to intestinal diseases.

T CELLS decrease secretion of protective cytokines and increase secretion of pro-inflammatory cytokines

DENDRITIC CELLS protect against infection while maintaining immune tolerance by producing high levels of anti-inflammatory cytokines, e.g. IL-10.

MICROFOLD CELLS (M cells) transport pathogenic bacteria and bacterial antigens to immune cells which promotes an inflammatory immune response.

OVERVIEW OF RELATIVE ABUNDANCE OF KEY PHYLA OF GUT MICROBIOTA IN ANTIBIOTIC TREATED ADULTS[11-13]



The gut microbiota of individuals who have been treated with antibiotics experiences massive shifts in diversity, which may cause permanent changes to phyla distribution.

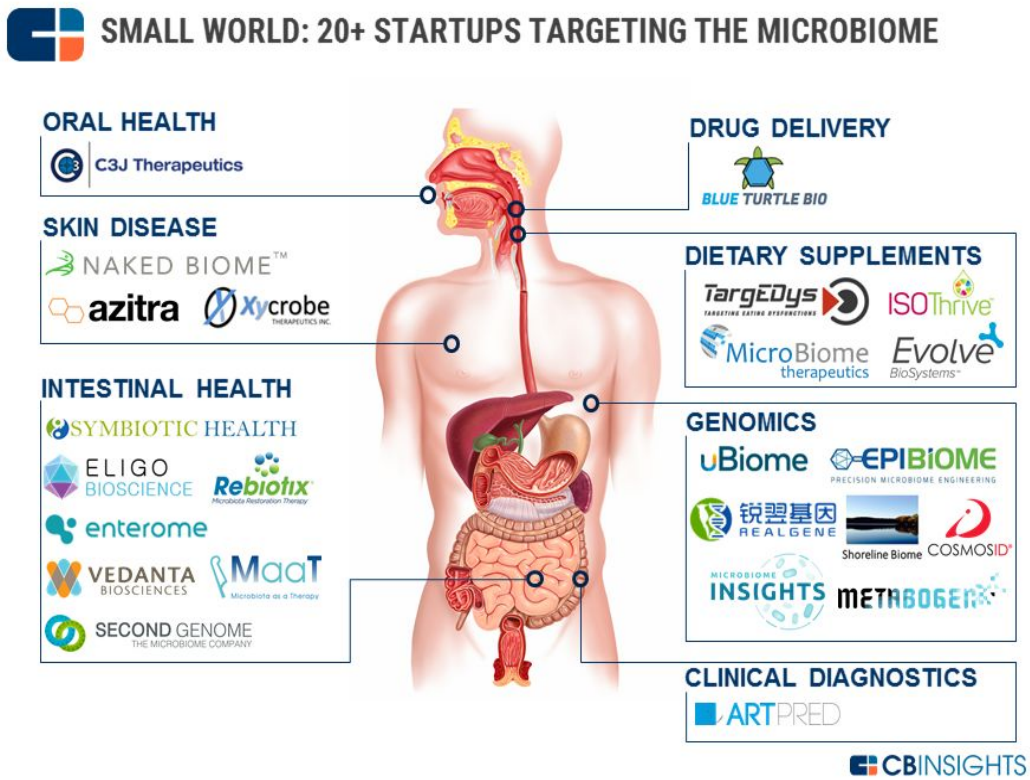
Dramatic decline in bacteroidetes and actinobacteria can be observed immediately after antibiotic treatment.

Even after four years, the microbiota is yet to recover its former diversity and distribution.

Interestingly, there is a significant increase in proteobacteria. All proteobacteria are gram-negative, with an outer layer of lipopolysaccharides which is strongly associated with inflammation. Members of the Proteobacteria phylum include escherichia, salmonella, vibrio, helicobacter, and yersinia.

Artificial intelligence and the microbiome

Microbiome or microbiota is defined as ‘an ecological community of commensal, symbiotic and pathogenic microorganisms’. This term is used to describe the vast majority of microorganisms that dwell in other hosts. Human microbiome was an area of interest for medicine since its advent. From supporting the beneficial bacteria via probiotics to treating infectious diseases, each microbiome-associated discovery leads to great improvement in the quality of life. Antibiotics can serve as a prime example: even simplest, mundane medical procedures are potentially deadly without them.

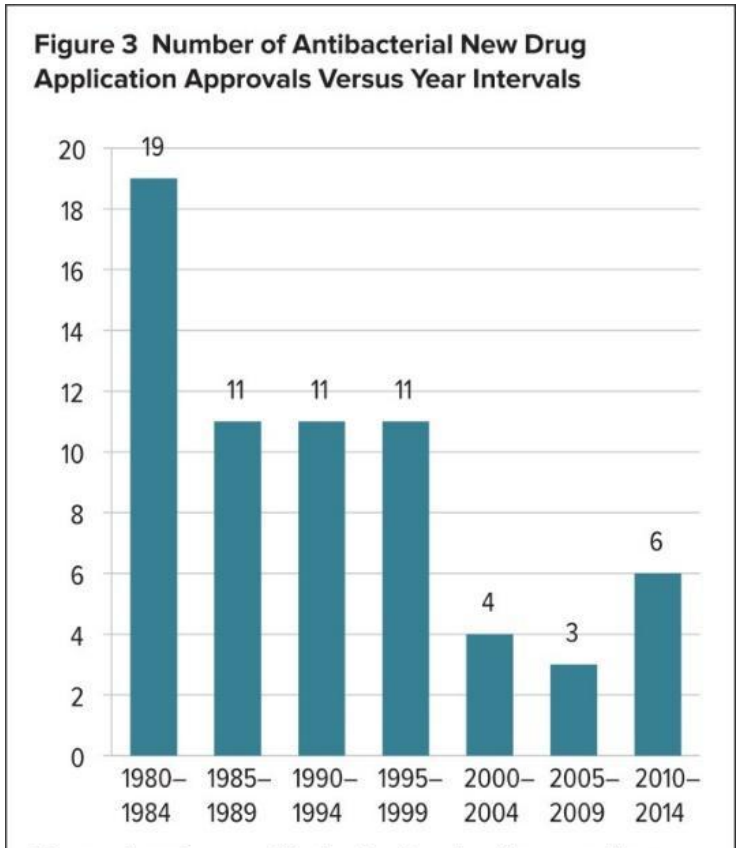


The main problem of human microbiota research is the sheer complexity of it. There are over 1000 species that live in and on the regular human with a total number of their cells reaching trillions. It is estimated that microbe cells outnumber human ones in 3 to 10 times. It is extremely hard to collect and process this amount of data in a conventional way.

However, with the development big data and artificial intelligence in the recent years, this task becomes more and more manageable. Current big data technologies allow collecting and categorizing large chunks of data received by researchers. Neural networks can effectively find connections between microorganisms living in the human body in order to find optimal solutions to various problems. As healthcare becomes the dominant trend in AI, many aspiring entrepreneurs present innovative technologies in various life sciences domains, including microbiology.

Another major technological breakthrough that allowed implementation of AI technologies in microbial research is whole genome sequencing (WGS). While the first major WGS, The Human Genome Project, is estimated to cost from $500 billion to $1 trillion, now there are multiple companies that provide WGS at a price of $1000.

The interest for microbiome is on the spike. CB Insights analytical agency has made a publication concerning prospects of microbiota industry. Their research has shown that there are multiple new generation companies that aim to use microbiome as a target for their research. The area of their operations ranges from oral and intestinal health to drug delivery and genomics.



Besides companies that work to treat specific diseases, there are also microbiome companies that seek to complete much more large-scale projects. Healthcare is currently on the verge of unprecedented crisis. While less and fewer antibiotics are discovered each year (and most of them are extremely toxic, which makes them viable only in extreme cases), antibiotic resistant bacteria are seen more often. Those bacteria can effectively throw humanity back to the pre-antibiotic era and make multiple deadly diseases return.

This trend has spiked interest in novel antimicrobial therapies. The most prominent technology so far is the use of phage lysin enzymes, also known as enzybiotics. While phage research is currently mostly academic topic, several companies are working in this area. The most prominent of them is Eligo Bioscience, a French startup that strives to produce new generation antimicrobials that are able to overcome antibiotic resistance.

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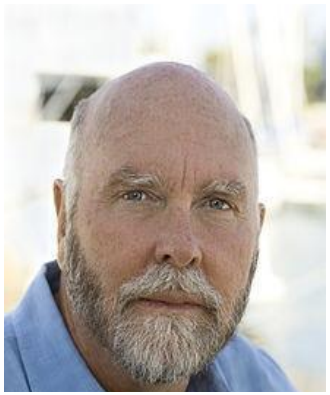
One of the main problems of phage-derived therapeutics lies in a fact that therapeutic needs to match the specific strain of bacteria. Using AI-mediated technologies, whole genome sequencing and synthetic biology itis possible to overcome this hindrance and enable continued functioning of modern healthcare.

One of the most promising researches on the topic comes from J. Craig Venter Institute (JCVI). His institute is working on a project to apply machine learning to microbial studies. JCVI scientists (then Celera Genomics) were the ones to finish The Human Genome Project and have recently created first fully synthetic organism, Mycoplasma laboratorium. In collaboration with UCSD, JCVI has recently published a paper concerning the implementation of machine learning in human gut microbiome research. This paper shows the effect that AI technologies can bring to microbiota



We need 10,000 genomes, not 100, to start to understand the link between genetics, disease and wellness". ~Craig Venter

Microbiome studies are extremely complex and are in need of multiple enabler technologies to reach their full potential. Artificial intelligence is one of them, along with whole genome sequencing, big data, and synthetic biology. However, when realized correctly, it has the potential to forever revolutionize the healthcare system and create innovative multi-billion industry.

AgeTech

AgeTech refers to technology developed specifically to **support the elderly** in their daily lives around their specific healthcare needs as well as productivity, work and ability to accomplish what they want without the effects of ageing interrupting them.

AgeTech will be covered in depth in a future case study. Here, however, we will highlight the use of AgeTech to enhance mobility

Mobility is a key aspect of daily life that may be impeded in OAPs, both in terms of increasing disability in carrying out tasks they were previously able to do, as well as diseases and injuries that may suddenly prevent them from carrying out the lifestyle they had before (Association, 2015).

With the ageing population increasing worldwide, Japan is at the front of this rapid change. Therefore, it is unsurprising that some of the tech advances targeting the elderly were trialled here.

One of these focuses on mobility and is termed **Hybrid Assistive Limb** (HAL). It facilitates limb movement by sensing current changes on the skin when a user initiates movement, and robotically supporting that movement (Murgia, 2015).

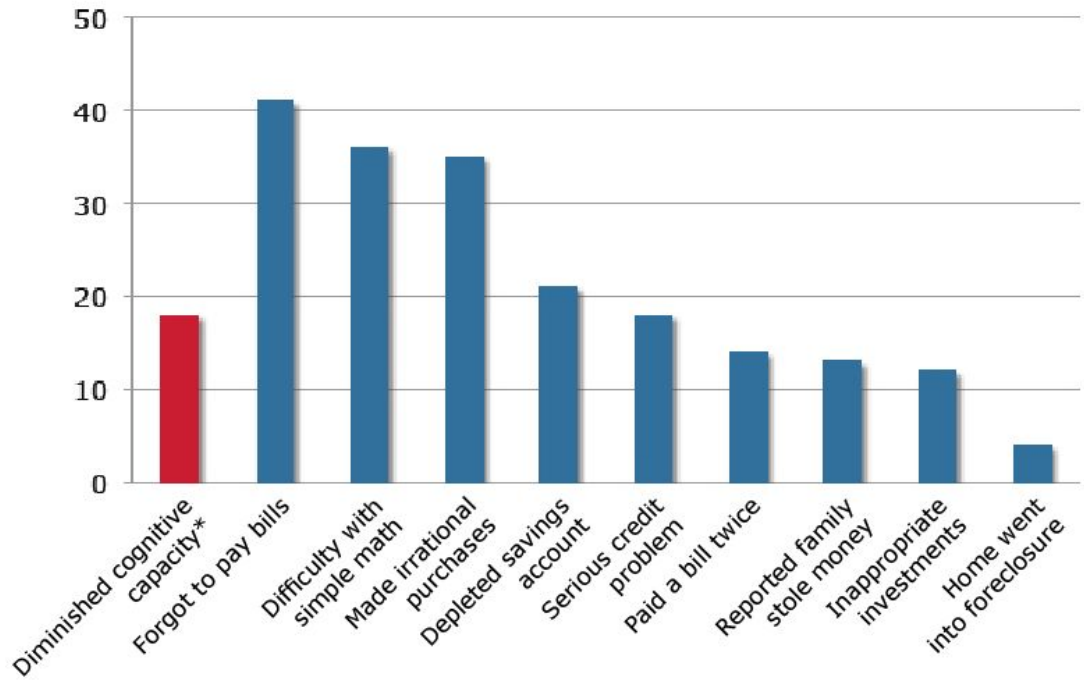
Information technology is also a main focus for adapting to the needs of the ageing population. **Apple** has developed an iPad tailored specifically to older people, with easier to read interfaces, simpler apps and a greater focus on healthcare-related services (Spencer, 2015).

This also falls under the **NextGen mobile apps for elderly** section of AgeTech, and ties in with **FinTech** for the elderly as new ways of managing their wealth emerge, including ahead of retirement through **novel retirement plans**.

Other areas of focus for AgeTech include **Continuing Education** and **Cognitive Enhancement**. Both areas highlight the extended potential for an active mind and work in older age as well as circumventing any age-related damage to cognitive function such as working memory, focus, etc.

Increasing age is associated with physical decline related to the function and structure of the brain, as well as the much earlier decline in cognitive exercise associated with being part of formal education in the younger years.

Why Cognitive Decline Matters



* 18% of older people or a family member said they had diminished capacity in financial decision making or were uncertain if capacity was diminished.
Source: National Endowment for Financial Education.

Cognitive function is also tightly connected to an elderly person's ability to manage their **wealth and financial activities**.

Cognitive decline results in issues such as forgetting to pay bills, making irrational purchases including inappropriate investments or being susceptible to scams, overpayments and being vulnerable to abusive family members.

Technologies such as NextGen Apps and cognitive enhancers can solve these issues, as well as open the door to increased productivity and pleasure for the elderly. The latter covers the final element of AgeTech - **Entertainment for Elderly**.

EdTech

There is a general consensus that sending people to retirement leads to a sharp decrease in the demand for some of their key functions - intellectual, physical, and communicative.

Aging is an objective process built into our body, and the question is the causes of this process, which can be divided into several categories:

Factors we can call genetic - either a predisposition to drug resistance or the presence of certain diseases - and ways of life and thinking - external factors that can produce unfavorable effect on the body's functions - which we call social aging.

It should be taken into account that there are two opposing processes that happen simultaneously in the body: maintenance and degradation - both at the functional and at the cellular level. In turn, any function of the body is an adaptive response, i.e. functions are developed and honed for achieving a certain goal or maintaining a process inside the body.

If a level of a function does not match the query, it can be classified as maladaptation. The body then begins to build up the function in response. For example, if we increase load on a muscle, its volume begins to grow to a level where this load is perceived as regular for the muscle. The opposite is also true. If a function is not in demand, then its entire infrastructure in the body begins to degrade to the level of demand or dysfunction.

To sum up, the state of the body and its functions depend both on the factors of time (objective aging) and on the level of demand for functions, incl. Cognitive.

To combat the social aging, AgeTech can be utilized to continually re-educate elderly citizens.

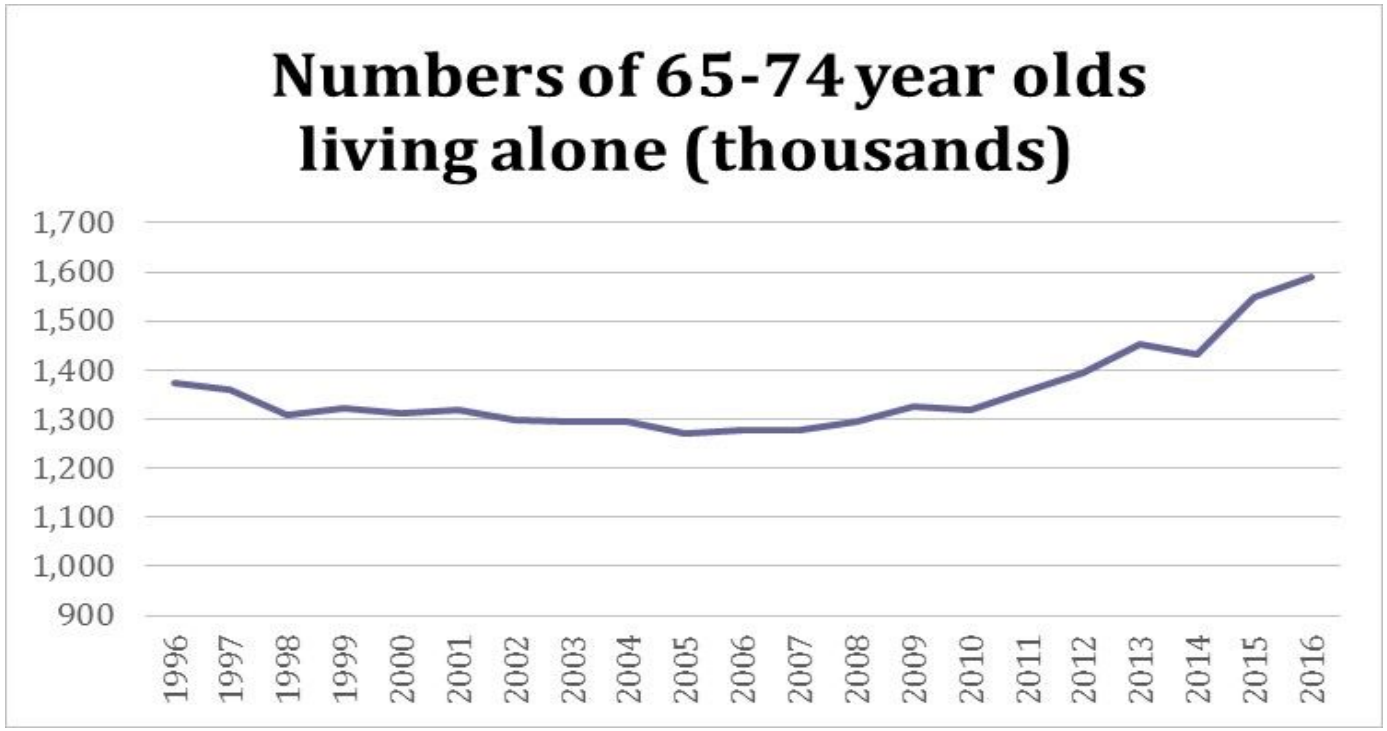
Unfortunately, there isn’t much research dedicated specifically to the effects of immersive technology on the elderly. Focus has so far been on younger subjects and informal learning in general. What we do know is that generally, Immersive technologies allow for physical or cognitive envelopment of one's attention.

"Absent significant brain disease, the gains that come with age can functionally offset the declines that typically occur."

— Laura Carstensen

-Milken Institute, *Silver to Gold*

One of the major facets of aging is psychological aging, and one of the major factors in that is loneliness.



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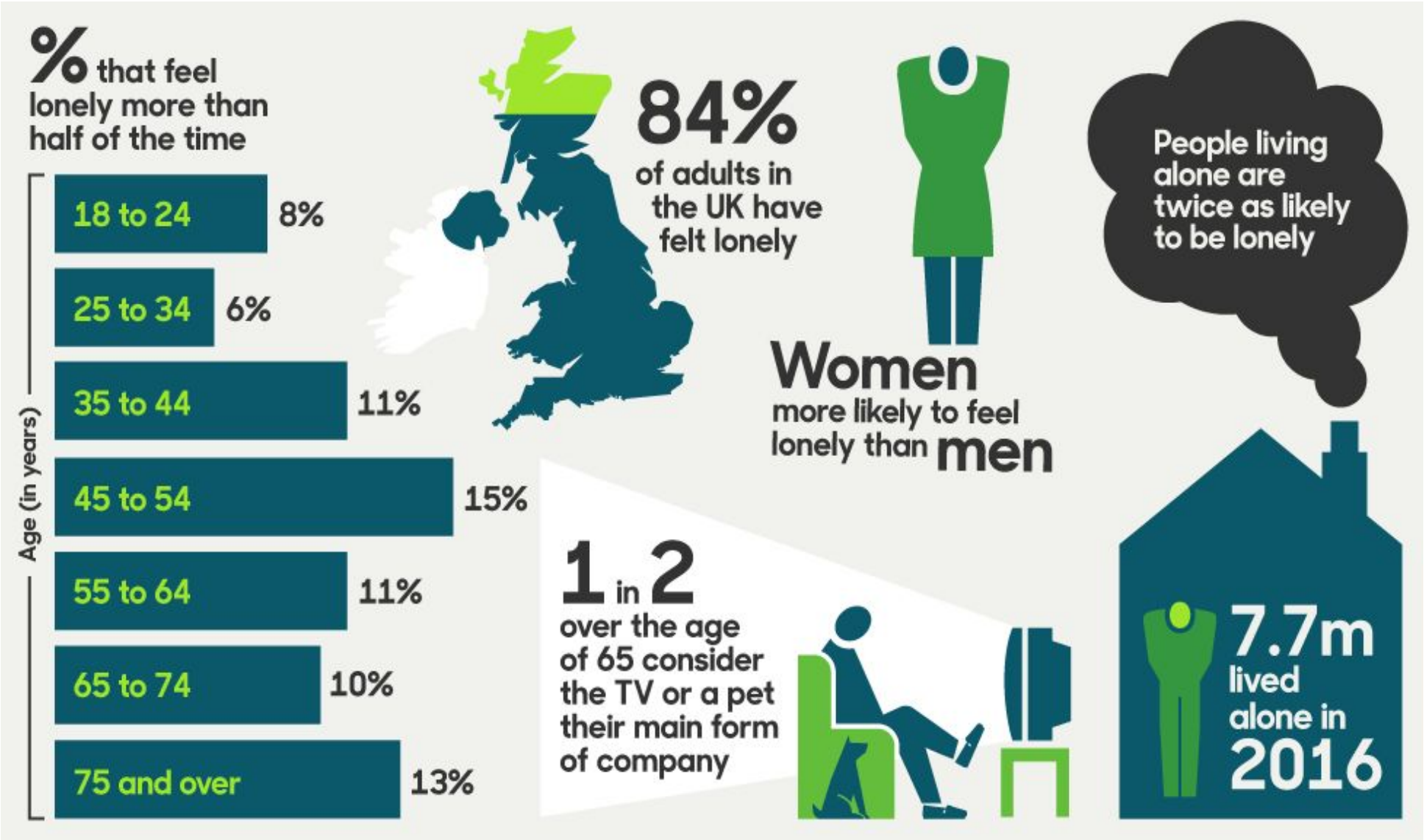

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Scientifically validated lifestyle recommendations

Throughout history the longevity industry has consisted not only of the development of technologies but the development of advices and devices for improving personal lifestyle for maximal health.

As geroscience has grown more advanced, this advice has grown more effective.

Much of this body of technique, traditionally communicated verbally and in popular literature, has now become technology in its own right, and can even be found in the form of various automated wearable devices.

The wearable fitness device market is estimated to be worth around $13.2B, with healthcare amongst its fastest growing segments.

Today's health and fitness device makers fall into 4 categories:

- **Lifestyle** - the most advanced segment includes fitness, activity and sports trackers is increasingly beginning to merge with the health sector, offering a wider range of measurements.
- **Diagnostics** - non invasive devices that provide health information; monitoring includes glucose, cardiovascular, event, pregnancy, obstetrics, fetal, sleep and neurological.
- **Therapeutics** - wearables are capable of monitoring disease states, and health activity, but also storing data and providing feedback e.g. respiratory information, insulin and pain management.
- **Injury prevention** - this can include measuring body movements, wearable sensing garments, fall detection. Can also include rehabilitation.

Thanks to the progress and commercialisation of modern tech products, consumers are increasingly comfortable relying on wearable devices to help recover from illnesses, maintain a healthy lifestyle and record daily activities.

It would be easy to assume that because these technologies are backed by science which already looks very comprehensive, such as the science of health and nutrition, that there would be little room left for improvement.

However, many monitoring devices such as Fitbit, Mapmyrun etc. tend to be **simplistic** or have a single focus such as step counters or heart rate monitors - compromising their value to the modern consumer. They are designed to carry out a single function and often lack the capability to provide more sophisticated health monitoring and recommendations about diet, fitness regimes, and particularly longevity.

But as the science behind these devices is based on medical data, it follows that there should be a second body of data to draw from - the user's unique personal data.

Moreover, in today's world, nearly every company is looking to compile as much data on their "customers" as possible, from health institutions, to the food and drink industry. But all too often the companies are unable to make the data work for them, lacking the ability to use AI and machine learning algorithms to generate **useful, accurate information**. Device makers of the future could add data into their platform, storing it effectively and efficiently using **blockchain technology**, and combining it with user data and personal information in an anonymised, secure way to create recommendations, diagnoses, health and fitness plans, product recommendations and more.

https://sa1s3.patientpop.com/assets/images/provider/photos/1608397.png

Such science-backed lifestyle technology is opening up the following doors:

- Device makers can market themselves to a wider, more sophisticated audience, becoming an indispensable part of their health and fitness regimes. They could interpret and process user data alongside the latest medical research and make **personalised adjustments** to users' daily activities.

- Companies wish to know about their employees and create a more **holistic health program**. Examples of companies already offering digitised, wearable driven corporate wellness programs include YouEarnedIt, Fitbit and Peerfit - however these are early stage companies that offer no rigorous medical backing.

- **Typical example:** A retirement home may wish to plan a year's worth of nutritional, healthy meals in advance and order the most appropriate goods in advance. This home could provide invaluable guidance, assessing the entire communities' needs in one go and calculating precisely the amounts and combinations required, wasting nothing; or devise personalised health plans and diets for a corporate member of staff recovering from a serious illness to hasten their recovery.

- Remote patient monitoring is the latest innovation in the healthcare industry, as it allows patients to keep a check on their own conditions, eliminating the need for repeated visits to the physician's office. The precision of such devices have the potential to improve diagnosis, and provide a more customized treatment or post-treatment recuperative plan. The most significant growth driver for the markets is the increasing role these devices play in diagnosis and treatment plans of chronic diseases such as diabetes, arthritis, and osteoporosis.

Conclusion

P3 medicine is in a relatively advanced state, with many technologies already on the market.

The problem is that medical clinics are around 5 - 10 years behind the latest practical innovations.

The source of these problems is in many ways the **business model of clinics**, which are not directly incentivised via profit to provide the most modern and efficient services and products.

The main issue therefore is ready availability of the technology, and the work that takes place in clinics to bring it to fruition.

Even in the most advanced clinics, managers are not assembling the best services into an integrated pipeline that can deliver the most competent and cutting-edge healthcare that P3 medicine could feasibly provide to patients today.