Imagining the future of Precision Medicine

‘Re-imagine, re-think, re-build’ - Seminar

12 October 2021

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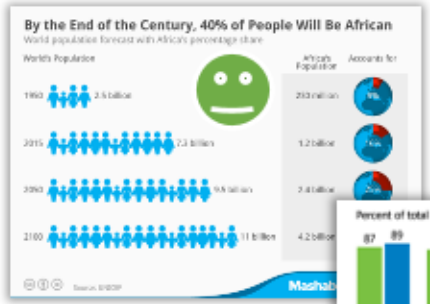
Bigger Picture:

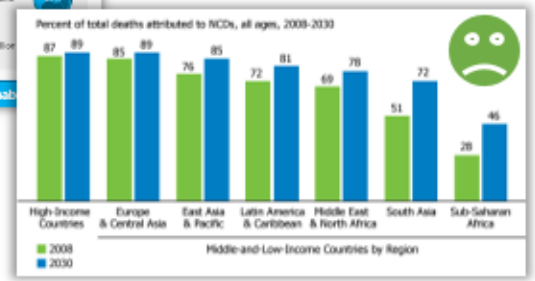
Grounding Precision Medicine in a national or regional context

Politics

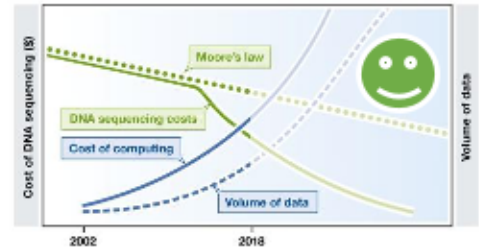
Society



- Population growth
- Rise in NCDS
- Epi/pandemics
- 4IR changes



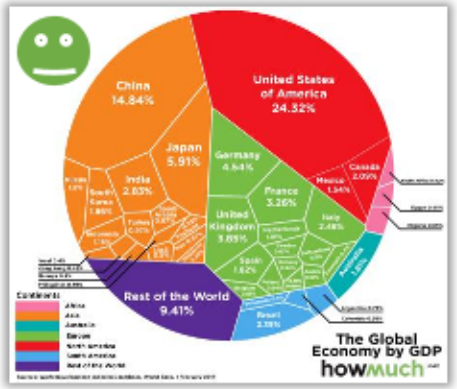
Technology

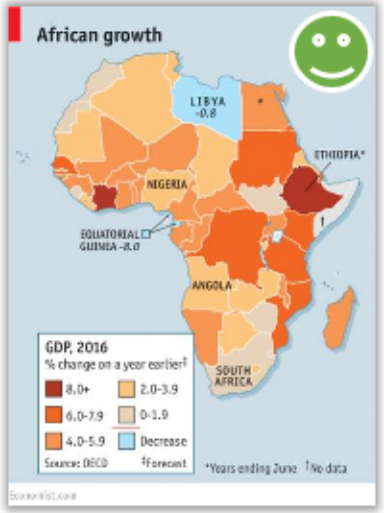


- CRISPR
- 3D printing
- AI

} Expo-nential. tech

Economy





Environment

- Droughts
- Extreme weather
- Food security

Legal/regulatory

- Import regulations
- Sample transfer
- Data utilisation
- Education (HPCSA)
- Medicine regulations (SAHPRA)
- AI & AI (4IR) impact (automation)

The impact of research spending at the national level

Chart of the Week

A GLOBAL LOOK AT R&D SPENDING

The companies and nations that are leading the way in innovation and research

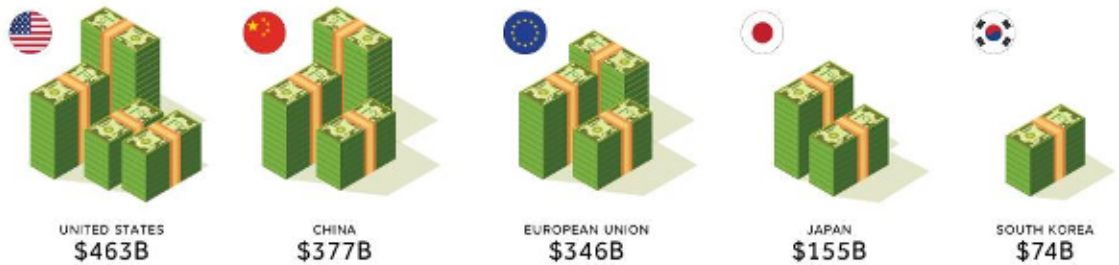
The G20 accounts for **92%** of global spending on research

94% of patents granted by the US Patent and Trademark Office stem from G20 countries

R&D Expenditure as a percentage of GDP

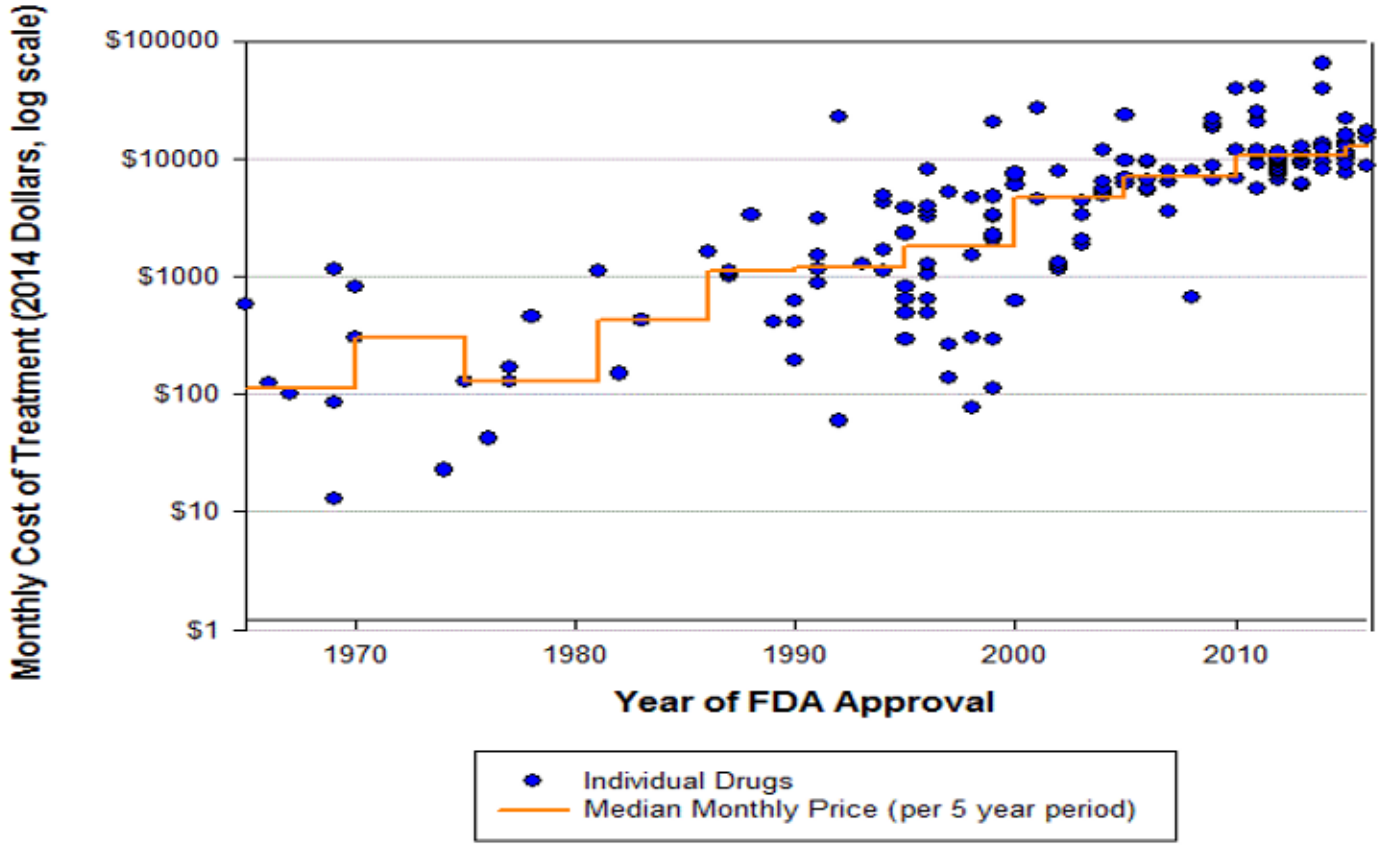
Select G20 countries; 2015

Top 5 Jurisdictions by R&D Expenditure (2015)



- SA's GERD (Gross Expenditure on R&D) has been stagnating over the last few years; is currently in a 0,75% bracket
- Is low relatively to other economies and low in absolute terms
- Plans are to **up it to 1,5%**, but feasibility is doubtful given overall fiscal constraints and slow-growth economy

Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval 1965-2016



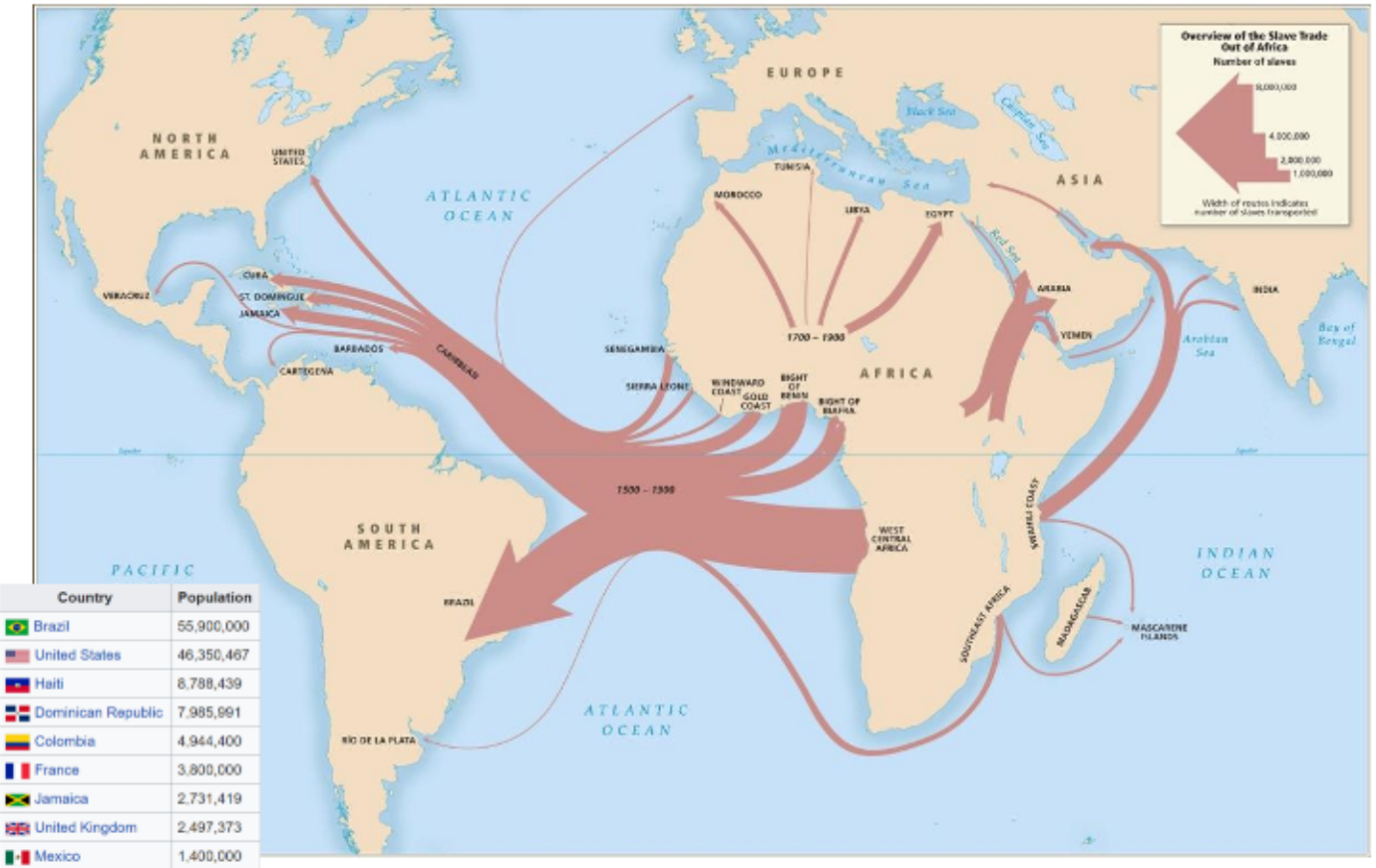
Source: Peter B. Bach, MD, Memorial Sloan Kettering Cancer Center

- >95% of pharma R&D done in developed nations
- 2/3 of global value of pharmaceutical products are produced in 5 countries: USA, Japan, France, Germany and UK. Japan and USA jointly contributed to 47% of global production value in 1999
- **Africa gets less than 2% of the global share (most of this goes to SA)**
- Clinical trial activity in SA has been falling (= regulatory framework issue)

- Little local pharma R&D means that medical issues aren't addressed and new medicines will not be available
- Strategic 'data production' initiatives could boost attractiveness of SA and Africa as a whole

1. https://www.mskcc.org/research-areas/programs-centers/health-policy-outcomes/cost-drugs#sthash.8G9ihkit.dpuf
2. https://www.ft.com/content/935e6ebe-29a1-11e7-9ec8-168383da43b7
3. https://www.abpi.org.uk/facts-and-figures/science-and-innovation/worldwide-pharmaceutical-company-rd-expenditure-by-country/

Integrated Precision Medicine vision: Global integration & positioning *vis-à-vis* global patient communities

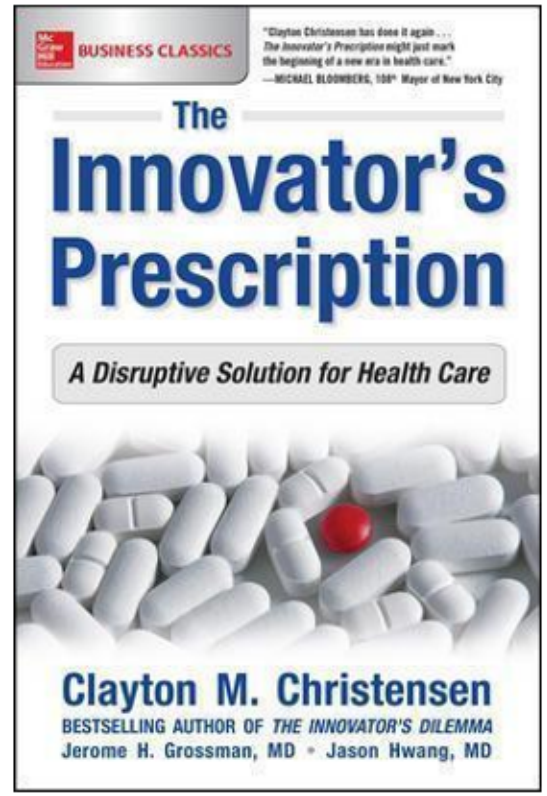


Country	Population
Brazil	55,900,000
United States	46,350,467
Haiti	8,788,439
Dominican Republic	7,985,991
Colombia	4,944,400
France	3,800,000
Jamaica	2,731,419
United Kingdom	2,497,373
Mexico	1,400,000
Cuba	1,126,894
Italy	1,100,000
Puerto Rico	979,842
Peru	875,427
Germany	817,150
Canada	783,795
Spain	690,291
Ecuador	680,000
Trinidad and Tobago	607,472

http://www.un.org/en/events/africandescentdecade/slave-trade.shtml;
https://en.wikipedia.org/wiki/African_diaspora

- Owing largely to the slave trade from the 1500s, people of African descent were dispersed all over the world, mostly – however – to the Americas, Northern Africa and Asia.
- This gave rise to dispersed Populations of African descent (eg the African American community) as well as mixed ancestral populations.
- Given the poorly understood complexity of 'African genetics' and the paucity of dedicated research, effective medical solutions for corresponding patient groups are lacking.
- There is a big opportunity to use data generated in Africa to boost medical R&D globally, notably for people of African descent.

Precision Medicine | Attempting a definition



Precision Medicine = a data-driven approach to enhance **prevention > detection > diagnosis > treatment** of disease

It is currently dominated by Genomics & Genetics but it ought to encompass data very broadly to be effective (-> link to digitisation and continuum of care, 'big data')

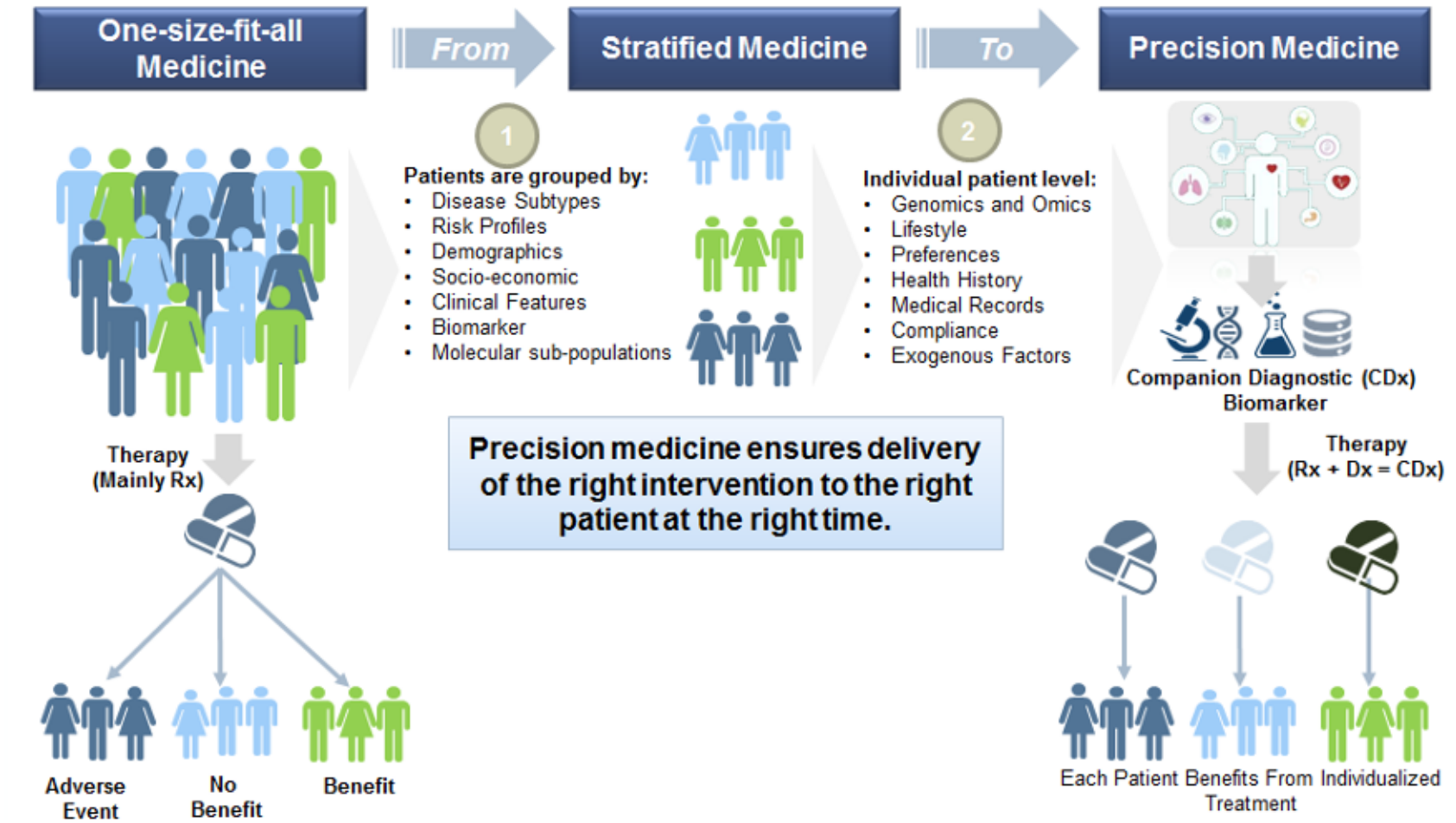
In contrast to traditional (= 'one size fits all') medicine it develops in 2 stages:

- Stratified Medicine (= data-based sub-characterisation of patients)
- Personalised Medicine (= development of individualised treatments)

https://med.stanford.edu/dean/healthtrends.html

New Paradigm Shift in Treatment

Transitioning From the 'one-size-fits-all' to 'precision medicine' model with multi-level patient stratification.

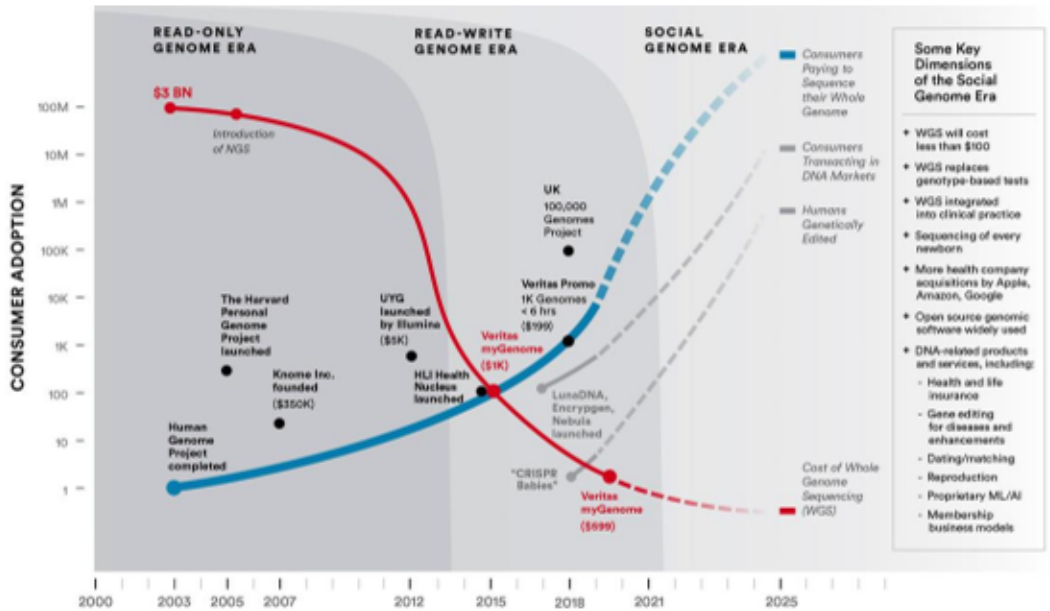


https://www.forbes.com/sites/reenitadas/2017/03/08/drug-development-industry-bets-big-on-precision-medicine-5-top-trends-shaping-future-care-delivery/?sh=1388bcb35d3a

Middle of 90s to beginning of the 00s: *First Human Genome*

The Human Genome Project cost an estimate USD 3,5 bn

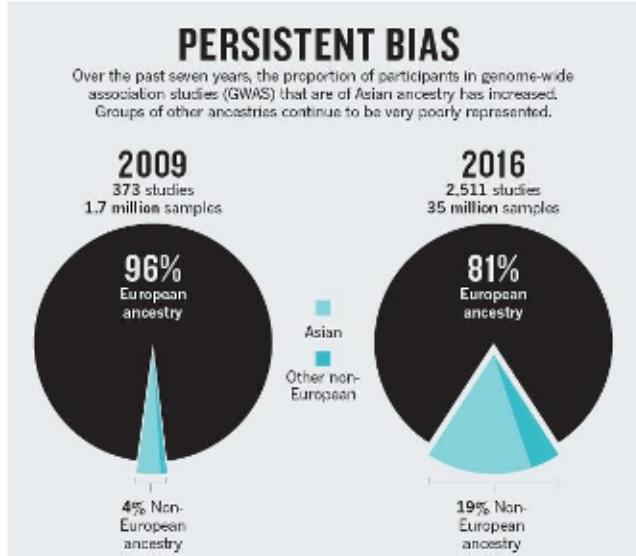
Beginning of the 00s until today: *Dramatic reduction in sequencing cost / dramatic increase in data generation / emergence of the 'Social Genome'*



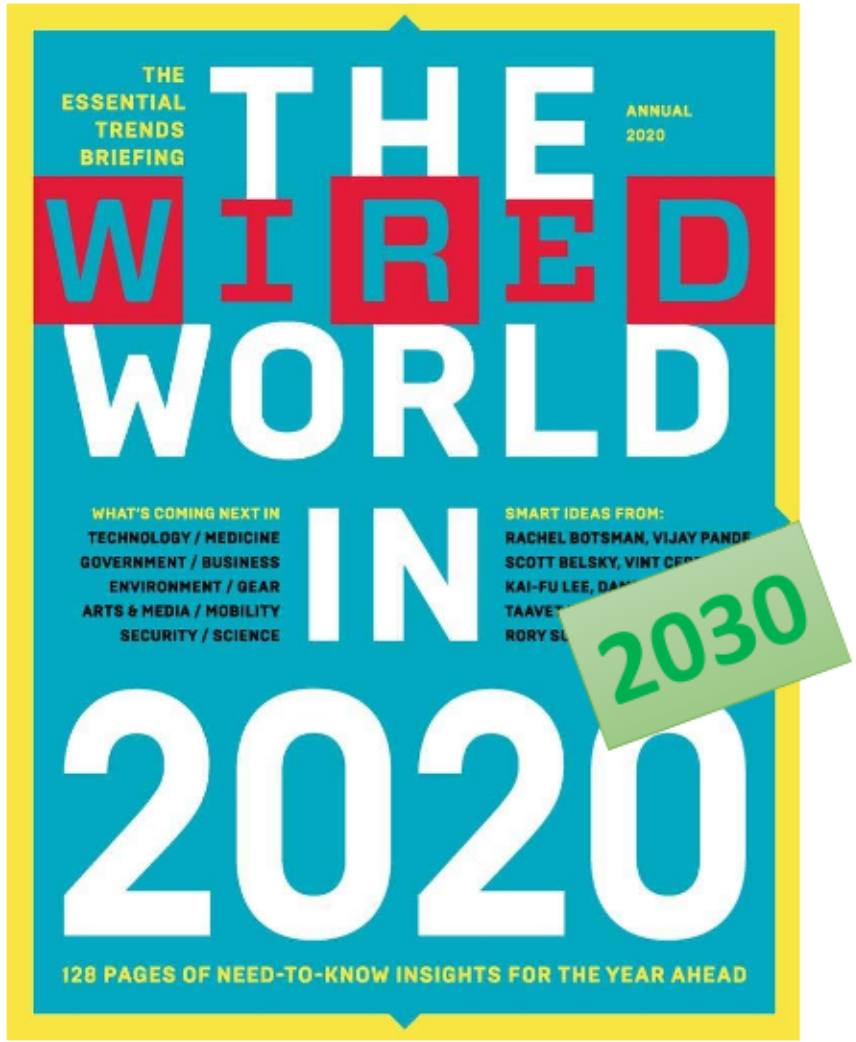
Population-based sequencing projects in more than a dozen countries, including the US, are expected to produce 60 million genomes by 2025.

By 2030, China hopes to add another 100 million from its own precision medicine initiative.

Present situation: Lack of Non-European individuals in global genome data repositories



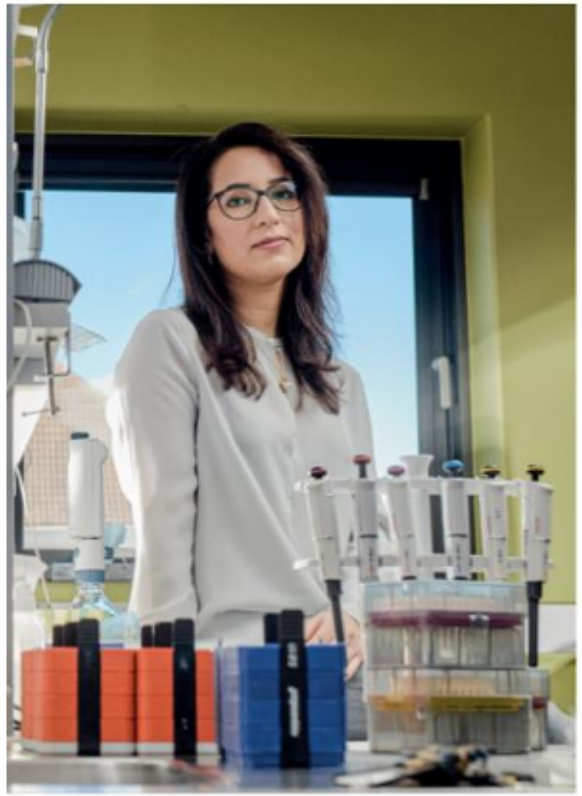
Only 3% of the total currently derived from African populations



https://www.wired.com/story/heres-what-the-world-will-look-like-in-2030-right/

- Population-based sequencing projects in more than a dozen countries, including the US, are expected to **produce 60 million genomes by 2025.**
- **By 2030, China hopes to add another 100 million** from its own precision medicine initiative.

Example: Estonia population genomics project



A BANKER OF GENOMIC POTENTIAL

At the Estonian Genome Centre, Lili Milani and her team are investigating the impact of genetic variations on drug metabolism and adherence to prescriptions. She spoke with Bec Crew.

The Estonian Genome Centre at the University of Tartu is one of the largest biobanks in Europe, containing biological samples and personal health information volunteered by more than 150,000 people, over 20% of the country's adult population. This trove of data and materials is emblematic of Estonia's ambitious personalized medicine programme and drive to be one of the world's most advanced digital societies. It is a resource for genome-wide association studies to identify genetic variations linked with disease detection, treatment and prevention.

At the heart of the Estonian initiative is geneticist Lili Milani, group leader in pharmacogenomics at the biobank and one of the leading biomedical researchers by article count in the Nature Index.

Which conditions are you investigating?
My group focuses on adverse reactions to drugs, as well as on problems with adherence — patients not taking their medications as prescribed. These issues are seriously underreported, so we need to be creative in trying to discover genetic variants that are associated with poor treatment response or side-effects.

We are using biobank samples to look at the genetic effects and associations that may cause discontinuation of medications such as antidepressants or statins. We can do this in Estonia because we have such rich electronic health records. We're working on this with colleagues from Finland and Norway, and feeding a lot of information into the Estonian National Personalised Medicine Initiative.

What have your studies revealed?
A person's specific genetic variants affect how quickly he or she metabolizes certain drugs. These results are being published by the Clinical Pharmacogenetics Implementation Consortium, an international group of volunteers that provides recommendations for healthcare professionals on dosing or drug selection based on genetic variants. Our latest study took these guidelines and genotype data in the biobank, and translated them into specific plans of action for the participants. In one case, a biobank volunteer had been prescribed two different antidepressants and had experienced serious side-effects. She got her genetic report and discovered that she's actually a very slow metabolizer of both medications, and needed much smaller dosing. Prior knowledge of this information could have really helped.

How does the biobank inform research?
Our data reflect the general population, which is why we deal mostly with common disorders such as cardiovascular disease and type 2 diabetes. We work with many international consortia, including the UK Biobank, which has about 500,000 samples, and deCODE in Iceland, with roughly 130,000. Sweden and Finland and the other Nordic countries also have a lot of clinical biobanks, and those collections are also valuable.

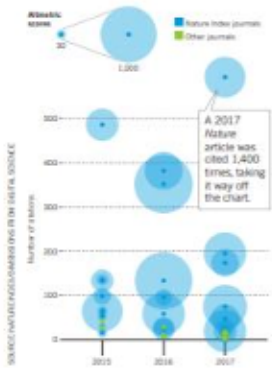
Why is the Estonian biobank so large, relative to its population?
Since the launch of the Estonian biobank in 2000, we have been using the genotype and health data of the first 50,000 participants for large genomic studies. We've been very active in communicating the results to the general population through the media, which has created great awareness and interest in genomics.

With a lot of excellent IT systems in place, and with genetic findings that could be used to improve health care, Andres Metspalu, director of the Estonian Genome Centre, came up with a vision about five years ago for implementing personalized medicine to prevent common complex diseases. After a few years of studies showing the increased incidence of disease among individuals with a high genetic risk, the Ministry of Social Affairs decided to fund the biobank with €5 million in 2018 to increase the sample size with 100,000 new participants, and to launch the national programme for the implementation of personalized medicine.

Can you elaborate on how the biobanks around Europe work together?
Our team mostly collaborates through the BBMRI-ERIC, which brings together researchers, biobankers, industry and patients from 20 countries, making it one of the largest research infrastructures in Europe. Meanwhile, scientists mostly collaborate directly. If I'm working on a specific phenotype, I will look for scientists with similar data sets. Usually we build capacity by running analyses locally, and then running meta-analyses together.

RESEARCH RECORD

Lili Milani's publication history. Each small dot represents one paper published in one of the journals tracked by the Nature Index. Some dots overlap. Citation figures correct as at 12 April 2019.



Different consortia have different routines. There are regular teleconferences and webinars, but usually we interact with the writing groups — the papers' lead authors. They have the task of specifically sharing the analysis plans and interacting with all the analysts to get the results, that is, the input on cohort and data that should be reported back. Then a draft of the manuscript is circulated. My record is running such studies with two or three cohorts and 15 to 20 co-authors. I found that challenging, so I really admire the principal investigators who are managing more than 100 co-authors. Although most of the communication and collaboration is done via e-mail, chats and video/teleconferences, the highlight is always meeting up at conferences, such as the American Society of Human Genetics annual conference.

How did you get into the field?
I've always found genetics fascinating. I started as a student in gene technology at the University of Tartu, and ended up doing my PhD in molecular medicine at Uppsala University in Sweden. The advances in technology over the past 20 years have been amazing. In 2005 we were printing our own microarrays and trying to simultaneously sequence hundreds of SNPs — single nucleotide polymorphisms, the most common type of genetic variation. Then in 2006, Illumina came to the market with machines that allowed us to analyse hundreds of thousands of SNPs in parallel on a single microarray. I'm just as excited now as I was when I started.

What has your experience been like as a woman in the field?
I've been lucky. My mentor and supervisor during my PhD studies, Ann-Christine Syvänen, was one of the few women in the field back then. My postdoc supervisor at the Estonian biobank was also very supportive when I was raising small children. He once asked me to go to a conference and I said, "I can't go; my son is nine months." He said, "Don't say you can't go. Just tell me what you need to make it possible."

He said the institute would send a babysitter with me and cover the costs, and it showed me that there is always a way. I felt empowered. And although I did not want the institute to pay, I realized that I could take my dad along with me and pay for his ticket myself. It was such an easy solution and it was an excellent conference that gave me lots of new ideas and enthusiasm.

What is your ultimate research goal?
I used to be more interested in molecular mechanisms and functional studies around genomics. Since we launched the personalized medicine initiative, I'm very motivated to run research projects with results that can be implemented in the near future. With all the outreach that we've done, in the hopes of getting general support for increased scientific funding and our work in general, I feel a responsibility to deliver some kind of scientific output that people will benefit from sooner. ■

Leading authors

Based on article counts higher than 50 between 2015 and 2017 in biomedical sciences in the Nature Index

KARL DEISSEROTH
Bioengineer, neuroscientist
Stanford University

Credited with developing neuroscience techniques, including optogenetics, which uses light to control cells such as neurons in living tissue, lauded as the most precise known method for studying the brain.

STEVEN P GYGI
Cell biologist
Harvard Medical School

Develops and applies new technologies in mass spectrometry and proteomics (the large-scale study of proteins). Jointly credited for the BioPlex network, with 9,000 proteins the largest open access resource for studying protein interactions.

ALBERT HOFMAN
Epidemiologist
Harvard T.H. Chan School of Public Health

A world leader in the epidemiology of common neurologic and vascular diseases, such as dementia and stroke; author of influential studies on the role of vascular factors in Alzheimer's disease.

KÁRI STEFÁNSSON
Geneticist
University of Iceland

Has published widely on the genetics of common and complex diseases and is a leading figure in the identification of genetic risk variants in the genome.

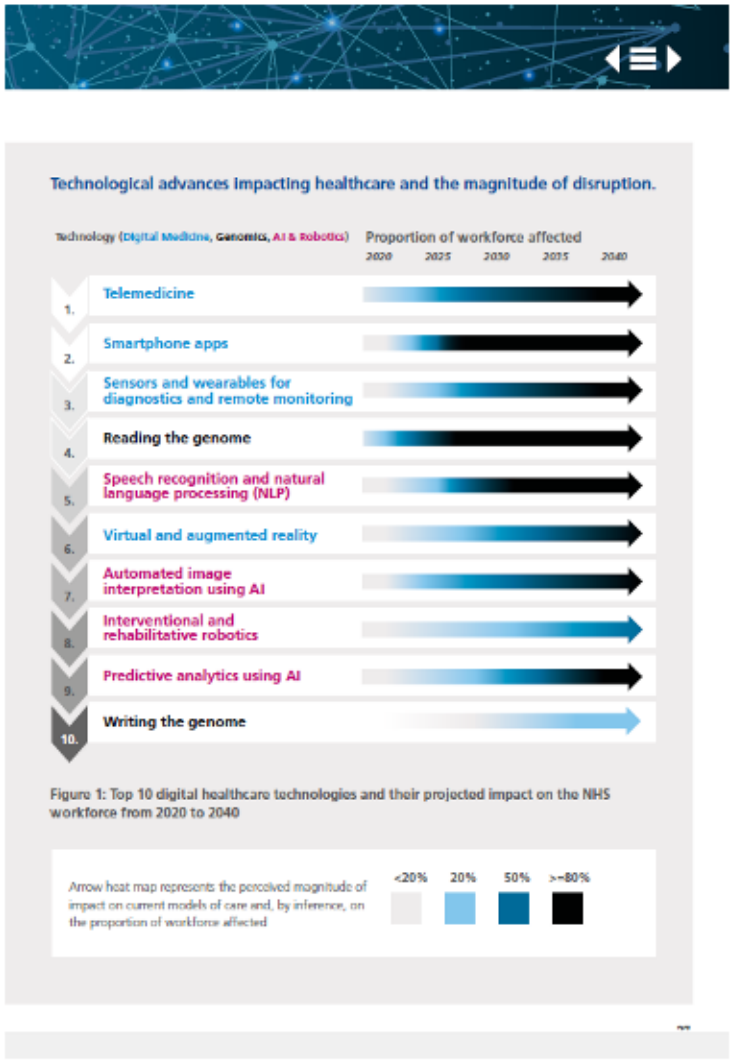
BO TANG
Chemist
Shandong Normal University, China

Research on application of nanomaterials and molecular probes in biochemical analysis, clean synthesis of chemicals, and technologies for solar power generation and storage. ■

- **Systematic** genetic testing of the entire population (1,3M)
- **Population** Genomic program (health & research impact)
- Pharmacogenetics and disease **risk (feedback** to individuals with consent)
- **PRS (Polygenic Risk Scores)** in development
- Imbedded in comprehensive **national data repository**
- **Strong trust** in government-led initiative

Reference: https://media.nature.com/original/magazine-assets/d41586-019-01440-y/d41586-019-01440-y.pdf

The workforce must be ready…



https://www.hee.nhs.uk/our-work/topol-review

The suffix -ome as used in molecular biology refers to a totality of some sort;

Simplistically, it refers to the technical ability to capture and analyze (nearly) all biological markers of a particular type (eg genes or proteins) at once.

Metabolomics

Microbiome

Genomics

Transcriptomics

Proteomics

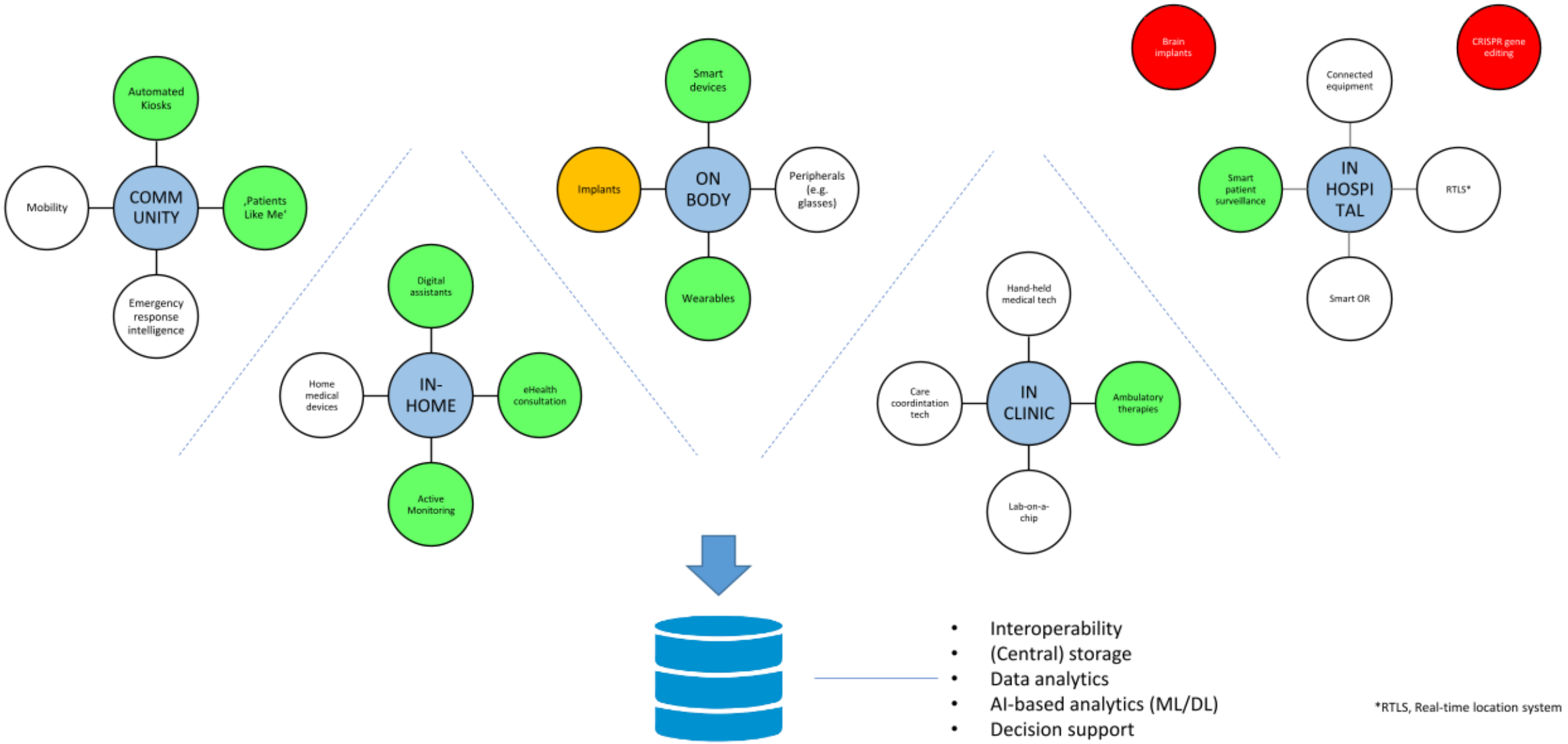
Bioinformatics

Data aggregation

Artificial Intelligence

Blockchain

Precision Medicine & the Internet of Things (IoT) – Link to the Continuum of Care



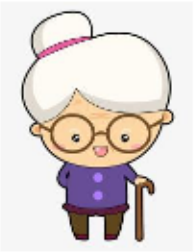
Modified after: http://healthcarethinktank.org/wp-content/uploads/2016/12/Business-Model-Briefing.pdf

Use case

Patient description

Patient description

- Female individual, 80 years of age, born and living in Austria; 60 km north of Vienna, rural area with moderate access to public transportation, patient relies on husband for commutation
- Co-morbid patient with a diversity of conditions, including rheumatoid arthritis, osteoporosis, hypothyroidism, recently (2 years ago) diagnosed dementia of Alzheimer's type (table refers)



Condition	ICD-10	Link
Coronary Heart Disease with AP	I25 119	Link
percutaneous coronary intervention	Z98.61	Link
Left bundle branch block (LBBB)	ICD I44	Link
Hypercholesterolemia	E78	Link
Rheumatoid arthritis	M06.9	Link
Degenerative spine / disc disease	M51.36	Link
Osteoporosis	M81.0	Link
Hashimoto Thyroiditis	E06.3	Link
Substituted hypothyroidism	E03.9	Link
Chronic reflux	K21.9	Link
SDAT (Senile dementia of the Alzheimer's type)	G30.1	Link

Some observations

- Medical records not available to patient or family members (to understand or get a second opinion)
- What is available is often not legible, time-consuming to interpret
- GP not available for discussion; specialist certainly not available for discussion

Medication related information

#	Medication	Dose	Dosage	Link	Report	Use	Alternative name
1	Aprednislon TBL	5mg	1/2-0-0	Link	Yes	Rheumatic arthritis	Glucocorticoid
2	Bisoprol San FTB	2.5mg	1/2-0-1	Link	Yes	Blood pressure	Ziac
3	Calciduran FTBL	500mg/800IE	1-0-0	Link	No		Vitamin D
4	Cipralex	10mg	1/2-0-0	Link	No	Depression?	Escitalopram
5	Exelon (dermal patch)	4.6mg/24h		Link	Yes	Dementia	
6	Pantoprazol SAN MSR TBL	40mg	1-0-0	Link	Yes	Gastric	Protonix
7	Paspertin FTBL		1-1-1	Link	No	Gastric	Metoclopramide, Reglan
8	Simvastatin SAN FTBL	40mg	0-0-1	Link	Yes	Cholesterol	Zocor
9	Thyrex TBL	100mcg	1-0-0	Link	No	Thyroid function	Levoxyo, Euthyrox
10	Vertirosan		0-1-0	Link	No		Vitamin B6

Observations

- Challenges noted above for the collection of information about the patient's medical condition apply here too.
- The patient doesn't have easily accessible information to explain the choice of a medication over another.
- The reason for taking Cipralex wasn't clear to the patient nor to the family members. The patient has always been good natured and never had any known episodes of worry, anxiety or depression. We surmised that the medication was prescribed owing to the diagnosis with dementia.
- The patient has been complaining about lethargy and fatigue, which is a problem because she is not as active as she should be, negatively impacting her overall condition, mentally as well as physically.
- Has complained about nausea repeatedly and was hospitalised several times after being unconscious for several minutes

Interventions to date (genetic testing)

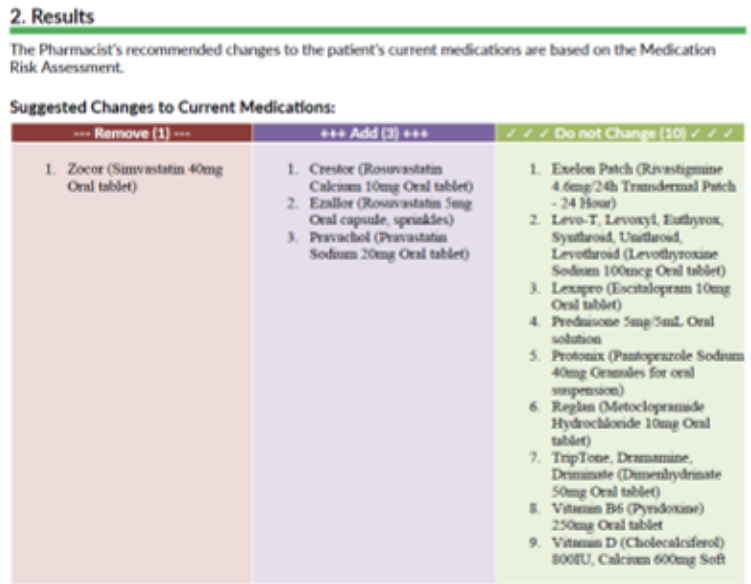
- Performed two types of tests, one nutrigenetic, and the other a PGx (pharmacogenetic) test, for the following reasons:
  - To unravel the effect of the patient's genetic makeup on nutrition, and *vice-versa*, and concomitant side effects;
  - To identify genetic risks associated with the medication the patient is taking

- After another episode with unconsciousness, GP decided to cancel all drugs except for Eltroxin / Euthyrox

Nutrigenetics

Condition / gene	Finding	Prospective intervention
Lactose intolerance	Both alleles present; manifests as digestive issues - poor digestion, bloating, gas etc. but can also have immune consequences such as allergies and eczema	Reduce cheese and milk products, monitor change in self-reported nausea (= not regular, intermittent)
FUT2 (link)	Likely increased B12 need. This is due to "secretor" status which interferes with gut bacteria needed to produce intrinsic factor which is needed for vitamin B12 absorption. Recommend B12 injection to bypass digestive system. Symptoms are tiredness / fatigue.	Get a prescription/discuss with doctor. Will otherwise be difficult to adjust diet. Will monitor change in activity levels.
VDR (link)	Increased need for vitamin D. Receptivity to vitamin D is lower so levels needs to remain consistently high. Recommend supplementation, particularly through Autumn / Winter / Spring	Taking on a script already. Should check need for adjusting dosage.

Pharmacogenetics



2. Results

The Pharmacist's recommended changes to the patient's current medications are based on the Medication Risk Assessment.

Suggested Changes to Current Medications:

--- Remove (1) ---	+++ Add (3) +++	✓ ✓ ✓ Do not Change (10) ✓ ✓ ✓
1. Zocor (Simvastatin 40mg Oral tablet)	1. Crestor (Rosuvastatin Calcium 10mg Oral tablet) 2. Ezallor (Rosuvastatin 5mg Oral capsule, sprinkles) 3. Pravachol (Pravastatin Sodium 20mg Oral tablet)	1. Exelon Patch (Rivastigmine 4.6mg/24h Transdermal Patch - 24 Hour) 2. Levo-T, Levoxyl, Euthyrox, Synthroid, Unithroid, Levothroid (Levothyroxine Sodium 100mcg Oral tablet) 3. Lexapro (Escitalopram 10mg Oral tablet) 4. Prednisone 5mg/5mL Oral solution 5. Protonix (Pantoprazole Sodium 40mg Granules for oral suspension) 6. Reglan (Metoclopramide Hydrochloride 10mg Oral tablet) 7. TripTone, Dramamine, Dramamate (Dimenhydrinate 50mg Oral tablet) 8. Vitamin B6 (Pyridoxine) 250mg Oral tablet 9. Vitamin D (Cholecalciferol) 800IU, Calcium 600mg Soft

Imagining the future

Family WGS

Sleep, heart rate, etc

Comprehensive PGx

Wearable

Movement / frailty analysis

Disease stratification

Alarm system

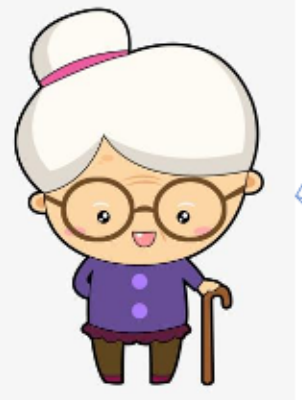
Home sensor system

Diet

Whole genome sequencing (WGS)

Voice analysis (mood, etc)

Cognitive stimulation

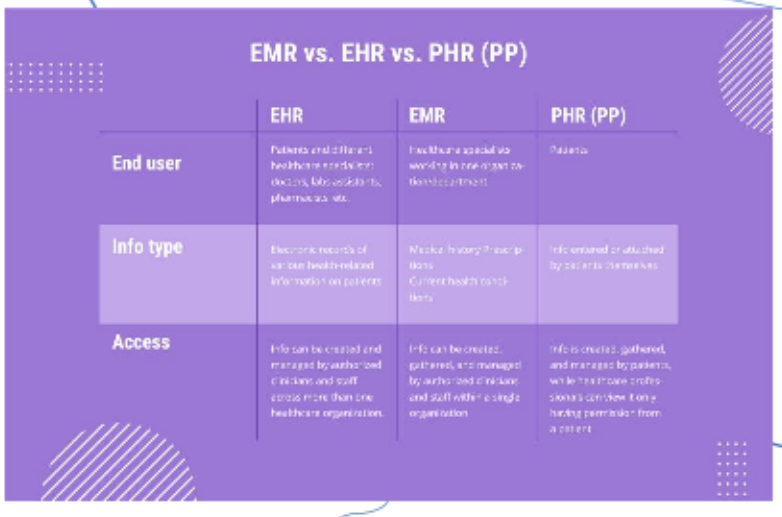


Fully-fledged PHR*

AI-aided pre-diagnosis

eHealth (mobile device)

Remote expert consultation



Real-time dashboard (feedback)*

Brain implant

Monthly biomarker analysis

Implants

Smart tatoo

Smart food delivery

mobile device

Regular (gut) microbiome analysis

Time horizon

- Green = Now
- Yellow = 1-5 years
- Red > 5 years

https://emerline.com/blog/ehr-vs-emr-vs-phr-vs-pp

*available to other family members with authorisation

Discussion

Imagining the future of Precision Medicine

‘Re-imagine, re-think, re-build’ - Seminar

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