Back to the future: pathology

MOLECULAR DRIVEN ONCOLOGY: FUTURE DIRECTIONS

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Disclosure of Interest

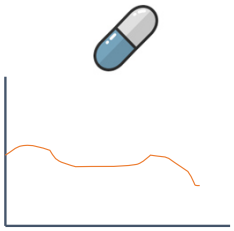
Travel support from MSD, Illumina
Honoraria from: Veeva, GSK, MSD, Altems

PRESENT TIME

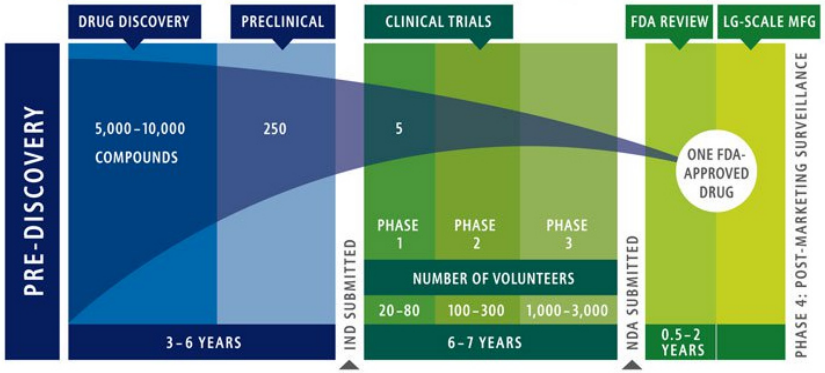
IMPRECISION MEDICINE

Slow, expensive, ineffective and wasteful

ONE SIZE FITS ALL



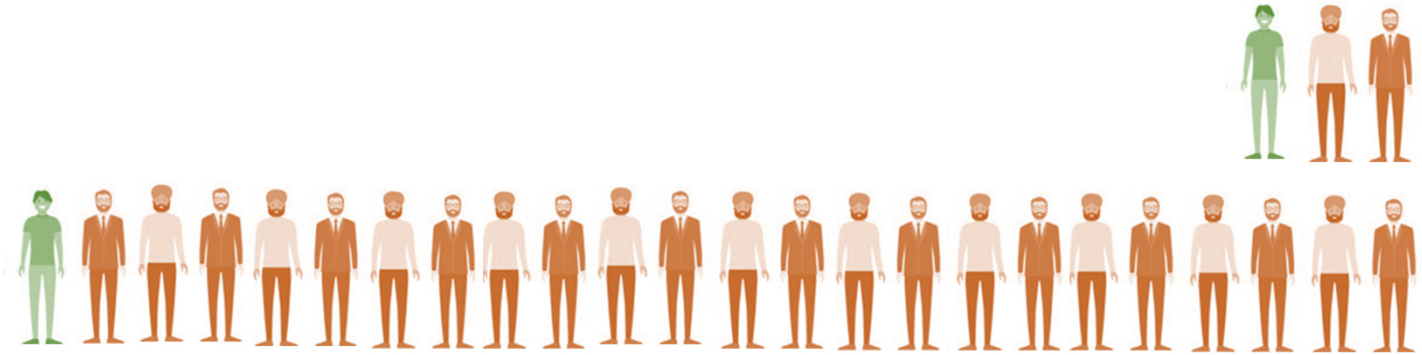
Effect



15 years

2018	1,064 $ million	446 $ million	2 $ million
2022	1,255 $ million	526 $ million	3 $ million

$1.8B



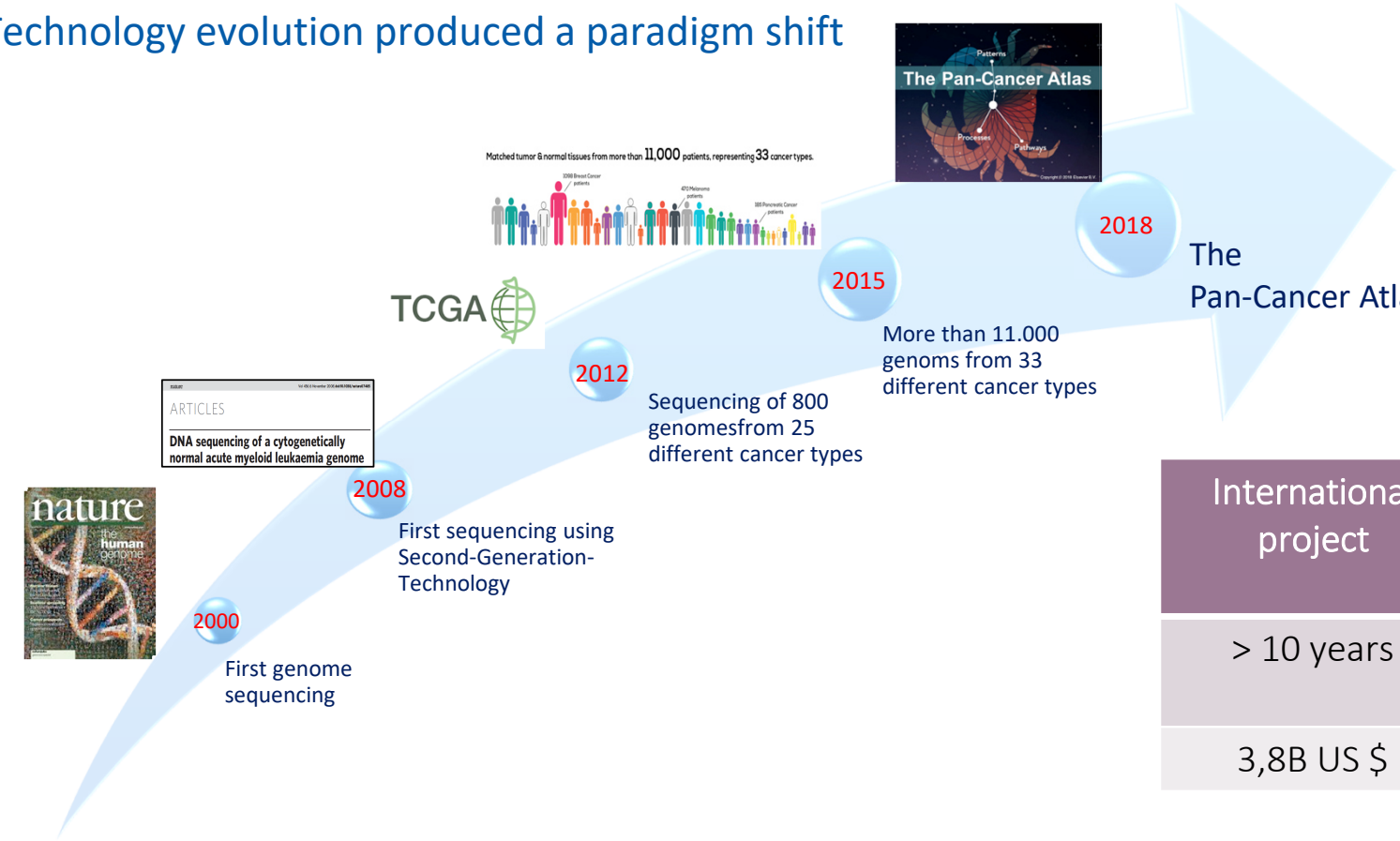
Best case 1/3

Worst case 1/24

Nature, 2015
source: Pharmaceutical Research and Manufacturers of America
FTLO Science
Washington DC: Foundation For Biomedical Research
Wong, C. Biostatistics, 2018.
Mestre-Ferrandiz, J .2012
Paul S.M., et al, Nature reviews Drug discovery 2010

PRECISION MEDICINE

Technology evolution produced a paradigm shift

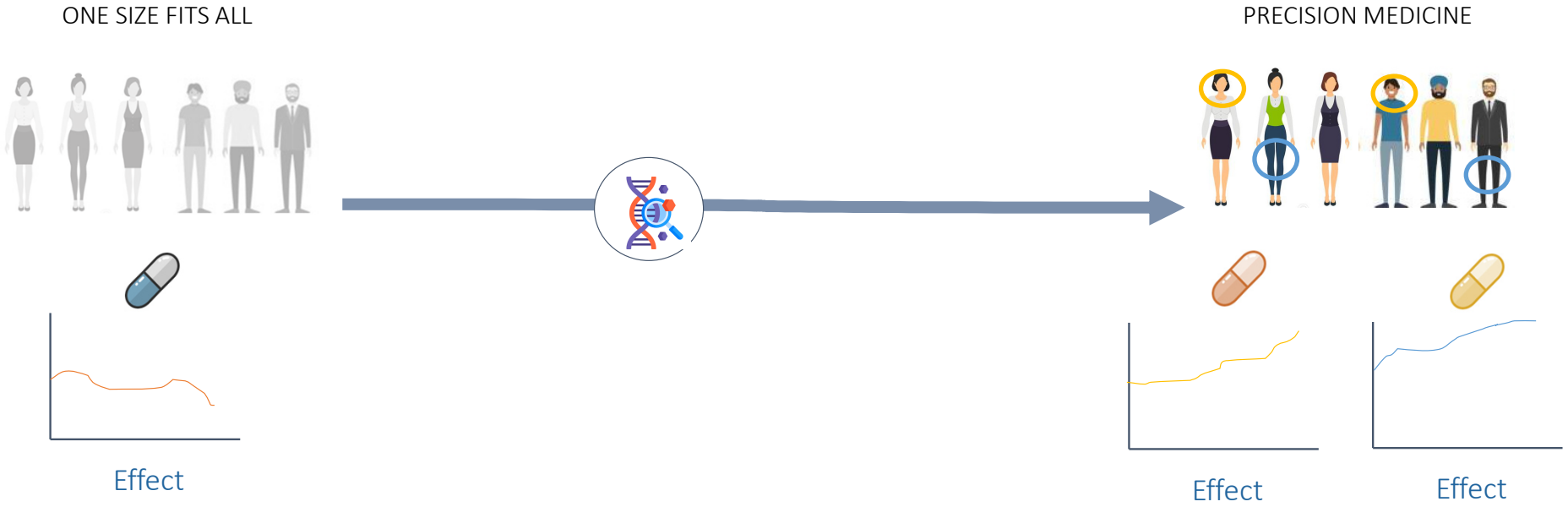


International project	One center
> 10 years	Few hours
3,8B US $	<1000 US $

18 YEARS

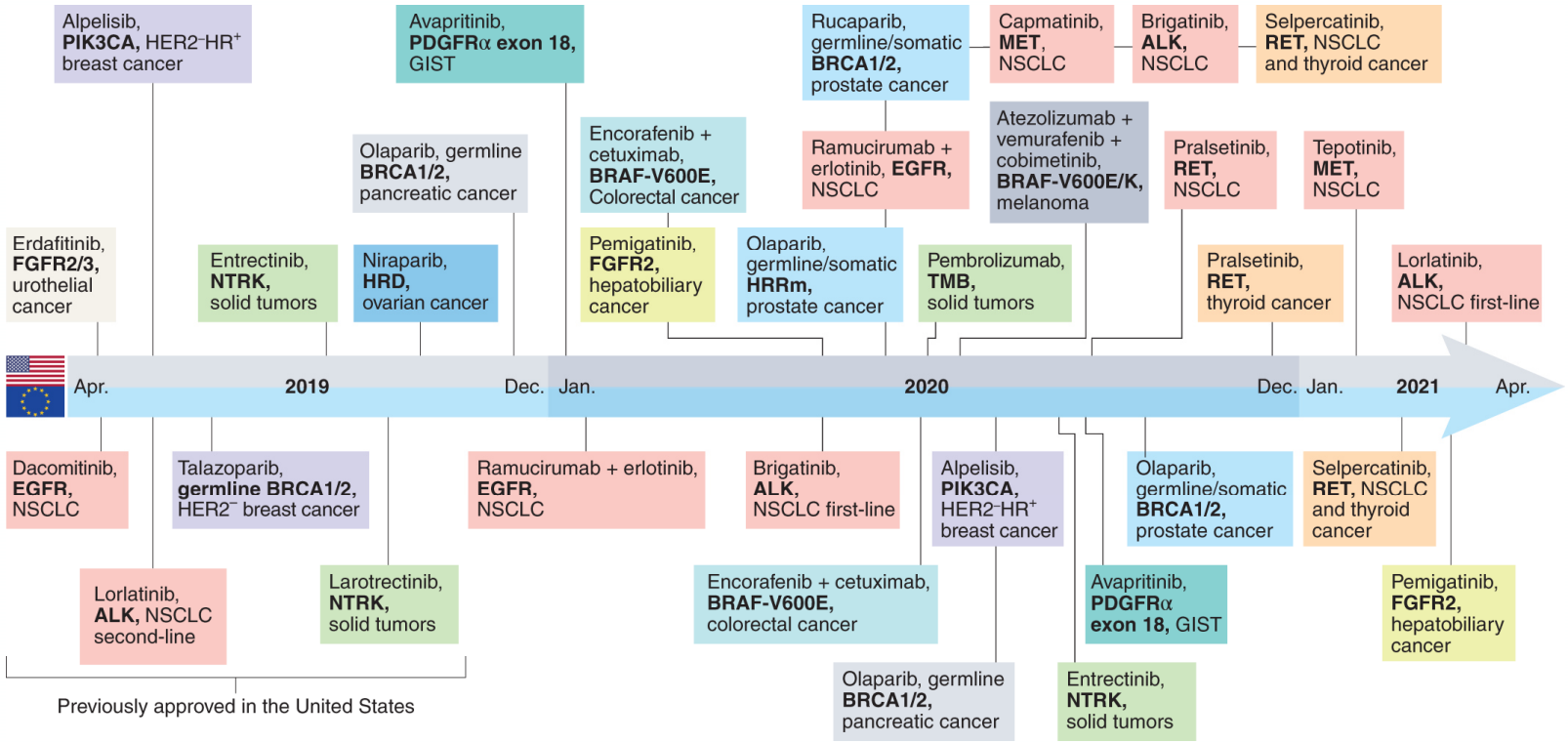
PRECISION MEDICINE

Genomics in healthcare: clinical utility



PRECISION MEDICINE

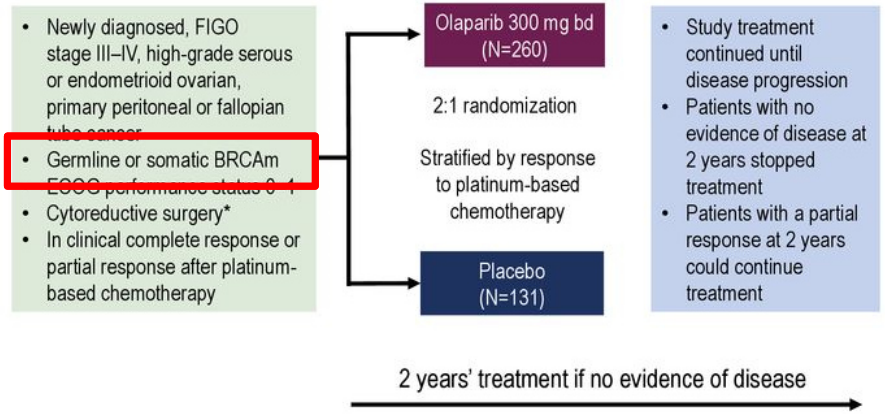
Clinical utility: target therapies

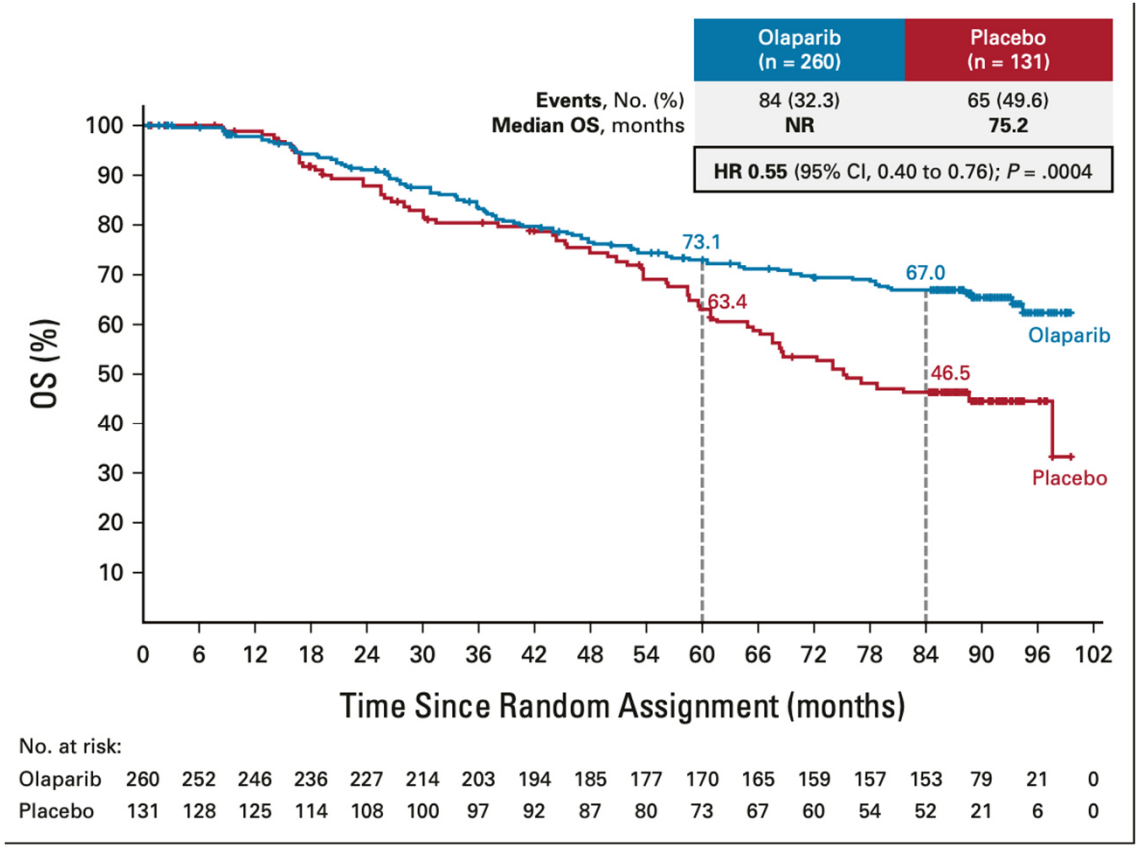


J. Mateu et al, Nature 2022

PRECISION MEDICINE

Clinical utility: the case of ovarian cancer



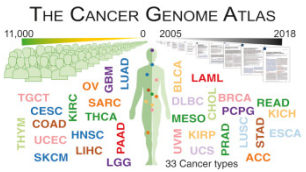


Jdi Silvestro et al, JCO 2023

PRECISION MEDICINE

Clinical utility: the case of endometrial cancer

Integrated genomic characterization of EC



From NGS to IHC and additional prognostic markers

2013

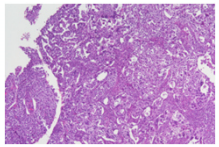
2015-2019

1983

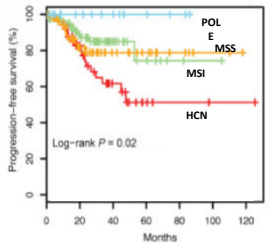
2015

2020

Two pathogenetic types



External validation of TGCA classification



ESMO/ESTRO/ESP 2020 Recommendations and ESMO 2022

Bokhman, Gynecol Oncol 1983
TGCA, Nature 2013
Stelloo, Clin Can Res 2016

PRECISION MEDICINE

Clinical utility: the case of endometrial cancer

Table 2. EC risk groups

Risk group	Description[a]
Low risk	Stage IA (G1-G2) with endometrioid type (dMMR[b] and NSMP) and no or focal LVSI Stage I/II *POLE*mut cancer; for stage III *POLE*mut cancers[c]
Intermediate risk	Stage IA G3 with endometrioid type (dMMR and NSMP) and no or focal LVSI Stage IA non-endometrioid type (serous, clear-cell, undifferentiated carcinoma, carcinosarcoma, mixed) and/or p53-abn cancers without myometrial invasion and no or focal LVSI Stage IB (G1-G2) with endometrioid type (dMMR and NSMP) and no or focal LVSI Stage II G1 endometrioid type (dMMR and NSMP) and no or focal LVSI
High-intermediate risk	Stage I endometrioid type (dMMR and NSMP) any grade and any depth of invasion with substantial LVSI Stage IB G3 with endometrioid type (dMMR and NSMP) regardless of LVSI Stage II G1 endometrioid type (dMMR and NSMP) with substantial LVSI Stage II G2-G3 endometrioid type (dMMR and NSMP)
High risk	All stages and all histologies with p53-abn and myometrial invasion All stages with serous or undifferentiated carcinoma including carcinosarcoma with myometrial invasion All stage III and IVA with no residual tumour, regardless of histology and regardless of molecular subtype[b]

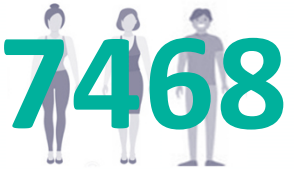
Oaknin A. et al Ann Oncol 2022

NEXT FUTURE

PREVENTION IS BETTER THAN EARLY DETECTION

Genomics profiling as an opportunity for cascade prevention

- **13.3%** PGVs found using **CGP**
- **48.4%** of them would not have been detected by phenotype or family history–based testing criteria using the 2018 NCCN, NSGC, or ACMG guidelines
- **17.6%** with PGVs had family members undergoing no-cost cascade FVT



- **2.22%** PGVs in in moderate risk **breast and ovarian** cancer susceptibility genes found using **CGP**
- **45.3%** of them would not have eligible for germline testing
- **51.5%** of the ones undergoing germline testing (40% of the identified) had germline confirmation

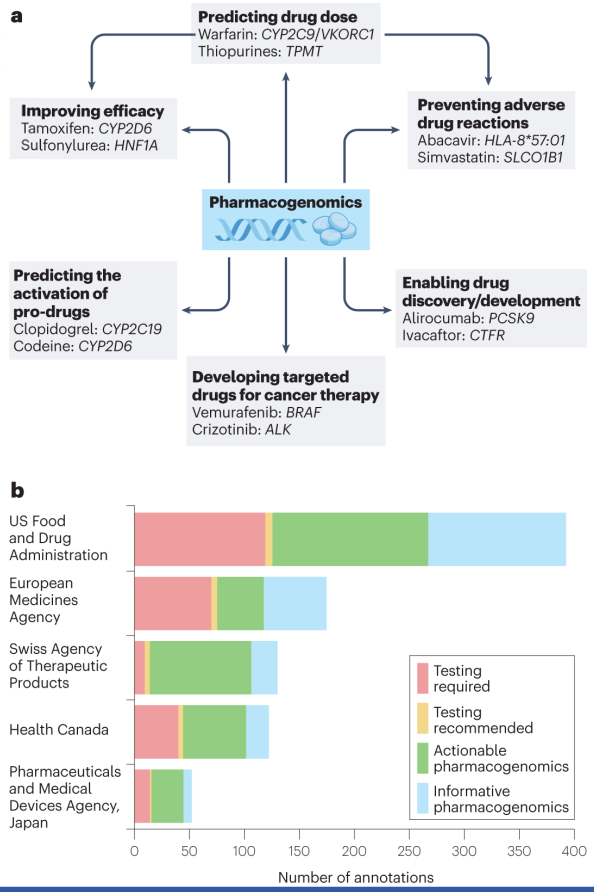
- **11.2%** PVGs found using **CGP**
- **9.2%** PVGs found using **standard approaches**

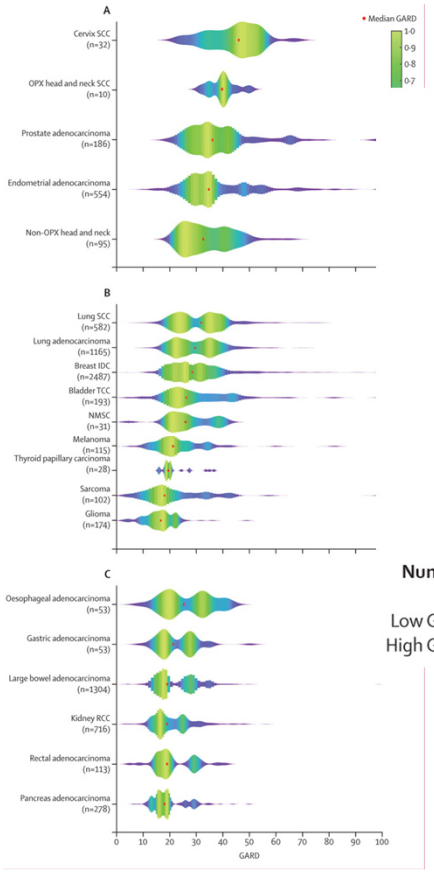
MRO.ART
MODERN RADIATION ONCOLOGY

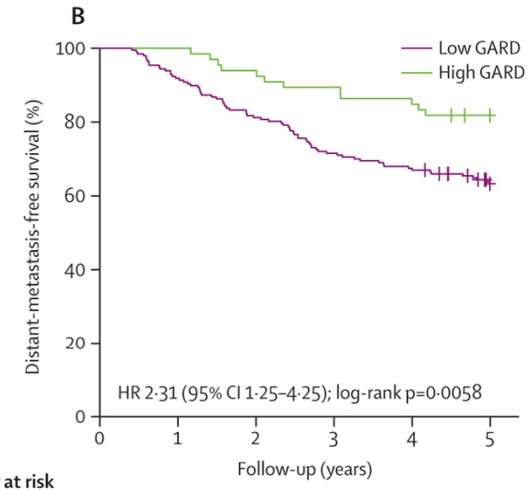
N.J. Samadder et al., JAMA oncol 2021
Llorin H et al, Cancer Genet. 2022
N. Normanno et al, EJC 2023

TAILORING DOSE AND TREATMENTS

Pharmacogenomics and genomic-adjusted radiation dose







Number at risk (censored)

Low GARD group	66 (0)	66 (0)	62 (0)	59 (0)	56 (0)	52 (54)
High GARD group	197 (0)	181 (0)	160 (0)	141 (0)	133 (0)	177 (125)

M. Pirmohamed,et al.,. Nature Reviews Genetics 2023
Scott JG et al., Lancet Oncol. 2017

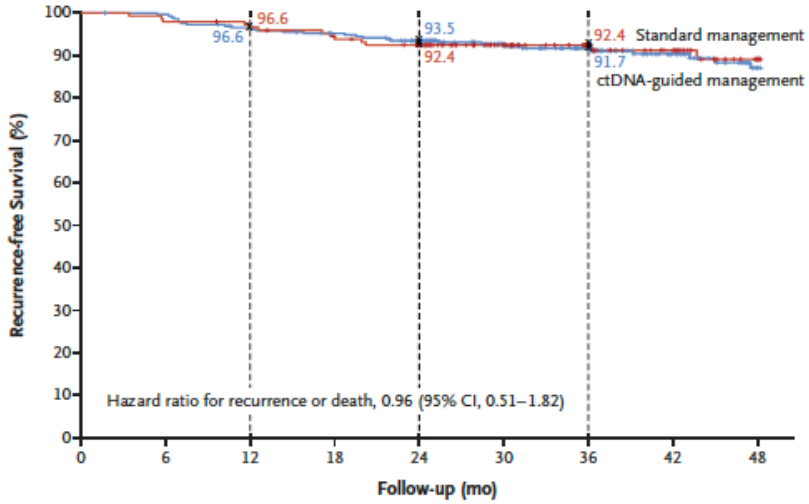
DECISION MAKING

The role of liquid biopsy in minimal residual disease assessment

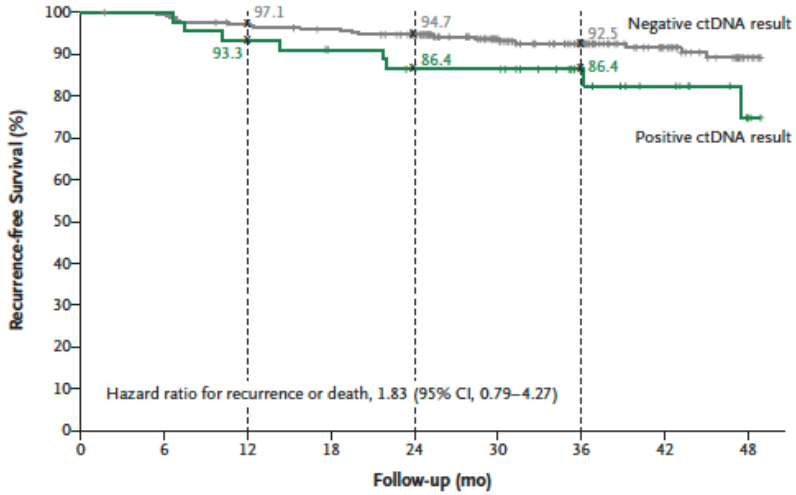
Stage II colon cancer

2:1

- Adjuvant treatment decision guided by ctDNA
- Adjuvant treatment decision guided by standard clinicopathological features

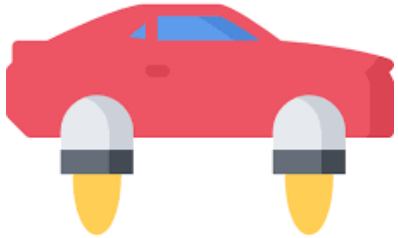


No. at Risk									
Standard management	147	144	142	136	128	97	78	57	33
ctDNA-guided management	294	292	281	273	259	207	155	109	64



No. at Risk									
Negative ctDNA result	246	244	236	231	220	169	131	93	55
Positive ctDNA result	45	45	42	39	36	36	22	16	9

L Tie et al. NEJM 2022

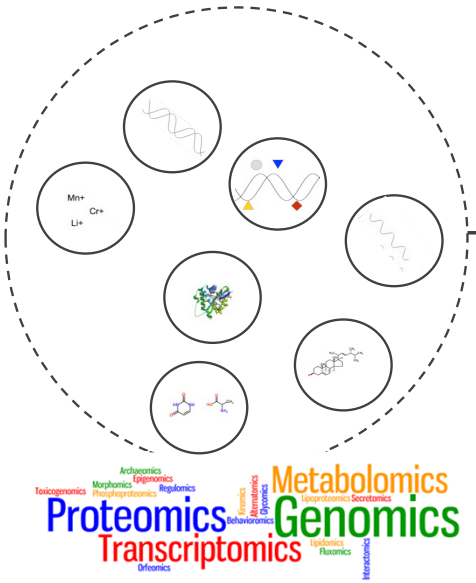


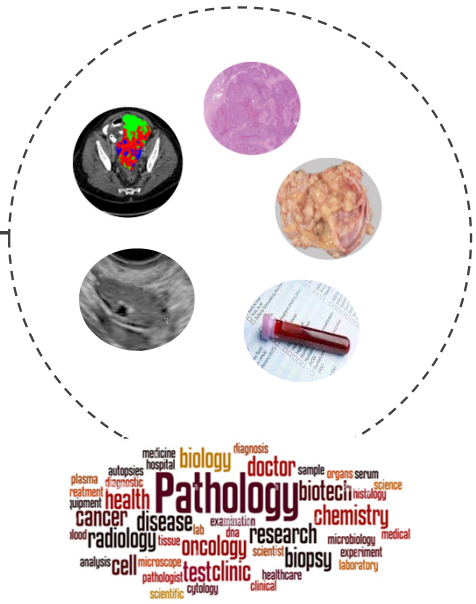
FAR FUTURE

TORWARDS PERSONALIZED MEDICINE

Integrated Multi-omics longitudinal profiling

CLINICAL
DATA 2.0

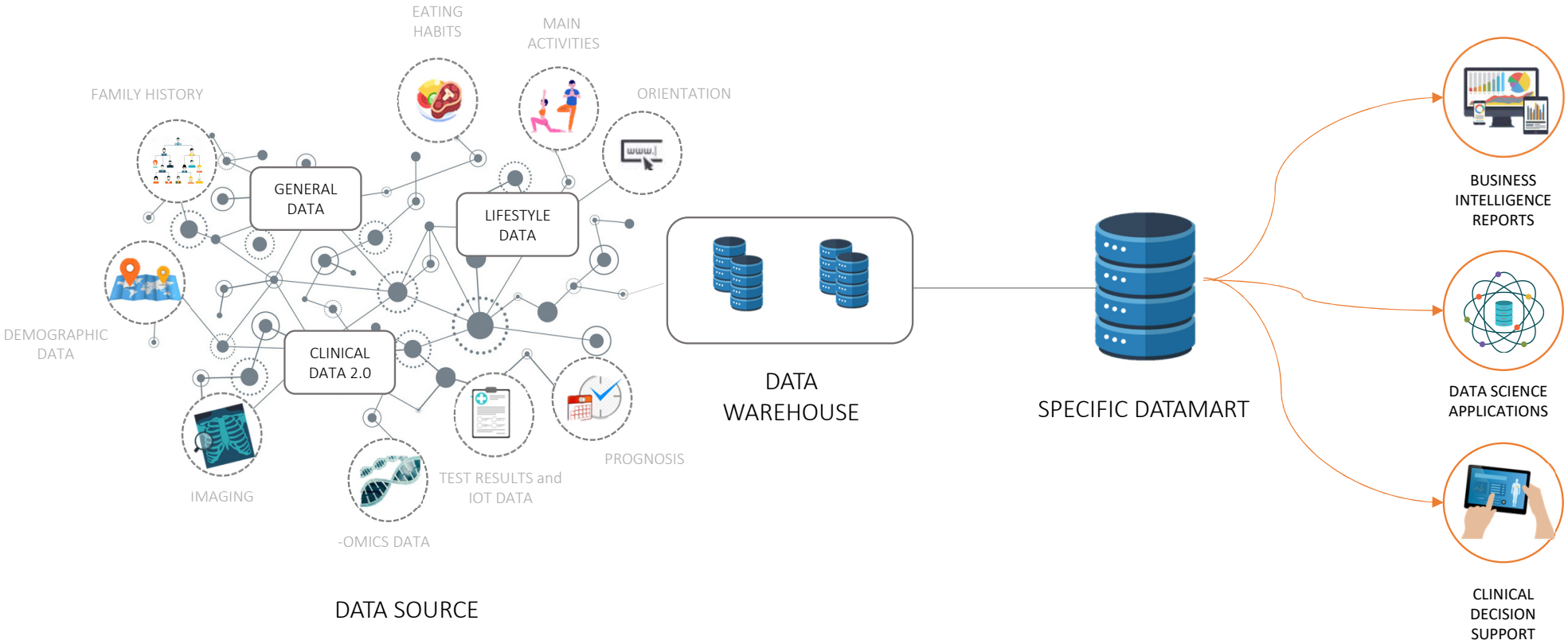




OVER TIME

TORWARDS PERSONALIZED MEDICINE

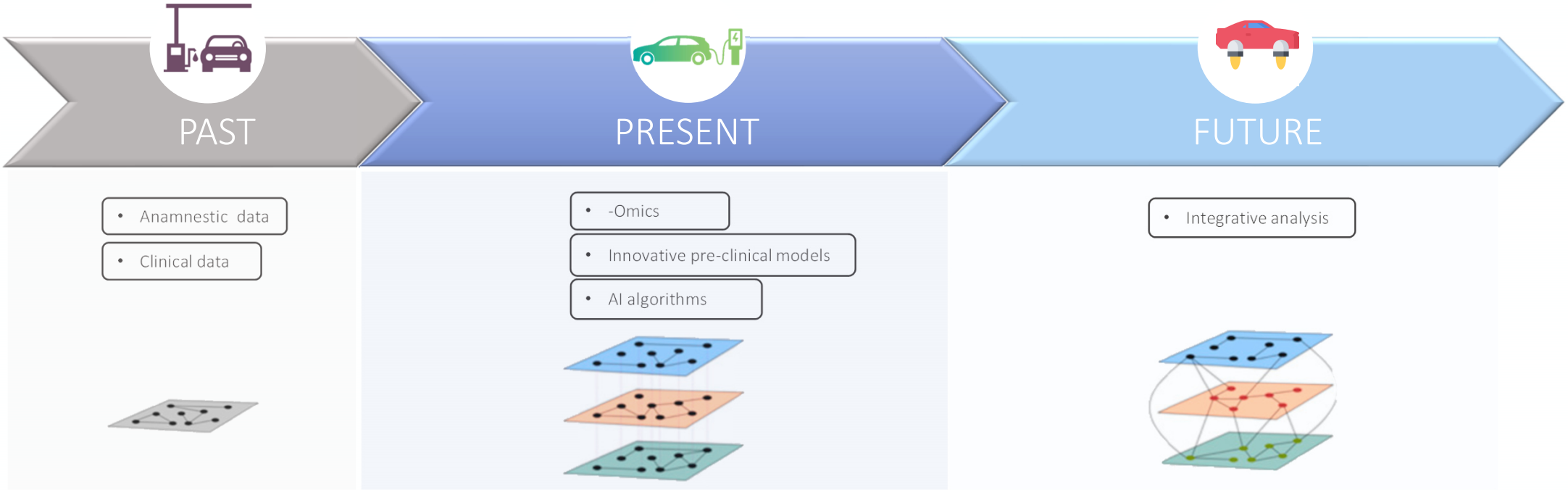
From data to information



TAKE HOME MESSAGE

CHALLENGES

Complex data analysis and integration



UNSELECTED RANDOMIZED CLINICAL TRIALS

TRADITIONAL PRE-CLINICAL MODELS

COMPLEX PRE-CLINICAL MODELS

TARGET DRUGS

INTEGRATED NOMOGRAMS

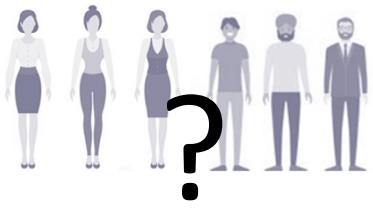
AI-DRIVEN CLINICAL TRIALS

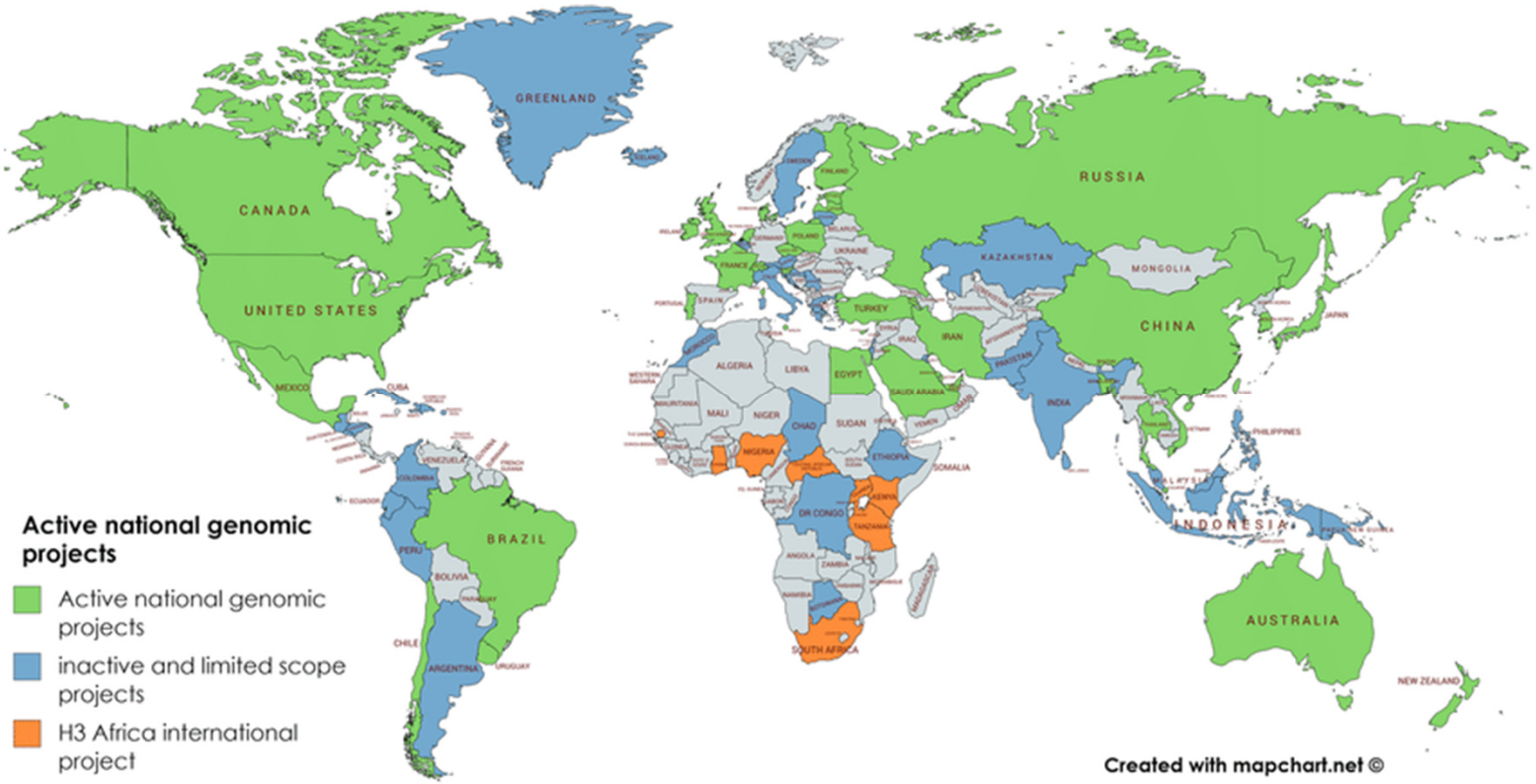
HEALTH DIGITAL TWIN

PERSONALIZED CELLULAR THERAPIES

CHALLENGES

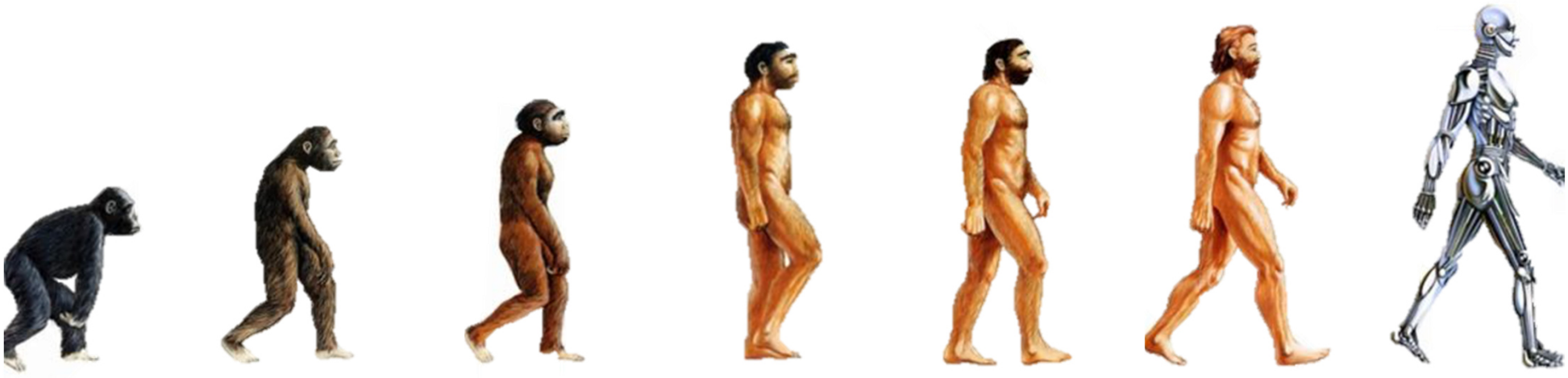
Demand and access





MOLECULAR DRIVEN ONCOLOGY

Inevitable evolution



BASIC → SIMPLE FORECASTING → STATISTICAL FORECASTING → DEMAND PLANNING → DEMAND MODELLING → REALITY → MACHINE LEARNING, DEEP LEARNING, AI

Hominidos | Australopithecus | H. abilis | H. erectus | H. sapiens | Machine

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